Preventative activity of kimchi on high cholesterol diet-induced hepatic damage through regulation of lipid metabolism in LDL receptor knockout mice

Minji Woo¹ · Mijeong Kim¹ · Jeong Sook Noh² · Chan Hum Park³ · Yeong Ok Song¹

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Abstract This study investigated the effect of kimchi on hepatic lipid metabolism and inflammatory response. Low-density lipoprotein receptor knockout mice fed high cholesterol diet (HCD) with an oral administration of kimchi methanol extracts (KME, 200 mg kg bw⁻¹ day⁻¹) or distilled water for 8 weeks (n = 10 per group). Compared with the control group, plasma and hepatic lipid concentrations were lower in the kimchi group ($p < 0.05$), which was confirmed with hepatic histological examination by Oil Red O staining. Hepatic expressions for fatty acid synthesis were downregulated whereas those for beta-oxidation were upregulated in the kimchi group ($p < 0.05$). Hepatic expressions for cholesterol synthesis were decreased but those for cholesterol export was increased in the kimchi group ($p < 0.05$). Moreover, kimchi intake

reduced expression for inflammatory cytokines ($p < 0.05$). Kimchi exerted beneficial effects on HCD-induced hepatic damage by suppressing lipid synthesis and inflammation, and facilitating fatty acid oxidation and cholesterol excretion.

Keywords Kimchi · High cholesterol diet · Lipid metabolism · Inflammation · Liver disease

Introduction

Hepatic steatosis or steatohepatitis are characterized by the excessive lipid accumulation and inflammation in the liver, which can progress into fibrosis and cirrhosis. These diseases are mainly caused by abnormality of lipid metabolism in the liver [1–3]. Homeostasis of lipid metabolism in the liver is controlled by key transcriptional factors such as sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptor alpha (PPAR- α) [4]. SREBP-1 upregulates triglyceride synthesis related genes such as fatty acid synthase (FAS) and acetyl-CoA carboxylase alpha (ACC α). SREBP-2 involved in the regulation of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) for cholesterol synthesis. In contrast, PPAR- α promotes the fatty acid oxidation by upregulating target genes such as carnitine palmitoyltransferase I (CPT1) and acetyl-CoA oxidase 1 (ACOX1). Therefore, numerous researches have focused on regulation of factors related to fatty acid and cholesterol synthesis to improve the abnormal lipid metabolism in a defected liver [4, 5].

Numerous studies have interested in searching for functional foods or ingredients with anti-oxidative or lipid-lowering effects to diminish the fatty liver disease [6]. Kimchi, a Korean traditional fermented vegetable, is made

✉ Yeong Ok Song
yosong@pusan.ac.kr
Minji Woo
woo07140@pusan.ac.kr
Mijeong Kim
mijeongkim@pusan.ac.kr
Jeong Sook Noh
jsnoh2013@tu.ac.kr
Chan Hum Park
ptman123@korea.kr

¹ Department of Food Science and Nutrition and Kimchi Research Institute, Pusan National University, 2, Busandaehak-ro 63beon-gil, Geumjeong-gu, Busan 46241, Republic of Korea

² Department of Food Science and Nutrition, Tongmyong University, Busan 48520, Republic of Korea

³ Department of Medicinal Crop Research, National Institute of Horticultural and Herbal Science, Rural Development Administration, Eumseong 55365, Republic of Korea

with brined cabbage and kimchi condiments prepared with red pepper powder, garlic, ginger, green onion, and fermented fish sauce. Kimchi has been appreciated as a functional food owing to its lipid lowering [7], anti-inflammatory [8, 9], antioxidative [10, 11], anticancer [12], and antiatherogenic effects [13, 14]. In addition, our previous study reported that the presence of ascorbic acid, capsaicin, 3-(4-hydroxyl-3,5-dimethoxyphenyl) propionic acid (HDMPPA), quercitrin, and quercetin in kimchi methanol extracts (KME) with appreciable amount [10]. Hypolipidemic effects of quercetin [15], capsaicin [16], ascorbic acid [17], and HDMPPA [13, 14] are also well known. Further, lactic acid bacteria (LAB) produced during kimchi fermentation demonstrated plasma cholesterol lowering effects [18]. However, benefits of kimchi consumption on attenuation of fatty liver disease induced by high cholesterol diet (HCD) have yet studied extensively and its related mechanism study is lacking.

Materials and methods

Preparation of kimchi methanol extracts

Korean cabbage cut into pieces (3×5 cm) were brined in 10% (w/w) salt solution for 3 h. Brined cabbage was washed and water was drained for 1 h. For kimchi making, kimchi condiments prepared with red pepper powder (2.6%), garlic (2.5%), green onion (2.3%), ginger (0.5%), fermented fish sauce (3.0%), sugar (0.5%), and glutinous rice paste (3.7%) were mixed with the brined cabbage (84.9%) [19]. Kimchi was stored at 10 °C for a day followed by storage at 0 °C for 14 days in a kimchi refrigerator (R-K182PM; LG, Seoul, Korea). The ripened kimchi (pH 4.3 ± 0.1 , acidity $0.7 \pm 0.1\%$) was freeze-dried (SFDSM06; Samwon Freezing Engineering Co., Busan, Korea) and then extracted three times with 10 volumes of 70% methanol for 24 h at room temperature. The KME was concentrated using a rotary evaporator (R-200; Buchi, Flawil, Switzerland), freeze-dried, and stored at -80 °C until use. The KME yield was 7.75%.

Animal study

Low-density lipoprotein receptor knockout (LDLr KO) mice (male, 5 weeks old) purchased from Jackson Laboratories (Bar Harbor, ME, USA) were raised individually under controlled room temperature (23 ± 1 °C) and humidity ($50 \pm 5\%$) with a 12 h light–dark cycle. After an acclimatization period of 1 week, the mice were divided into two groups based on body weight. The HCD was prepared by adding 1.25% cholesterol [19] and stored at -20 °C. The diet compositions were as follows (w/w):

casein, 7.5%; soy protein 13.0%; DL-methionine, 0.3%; corn starch, 42.5%; sucrose, 5.3%; cellulose, 9.0%; lard, 10.0%; cocoa butter, 4.0%; coconut oil, 2.0%; mineral mix, 3.5%; vitamin mix, 1.0%; choline bitartrate, 0.2%; cholesterol, 1.25%; sodium cholic acid, 0.5%. Mice were provided the HCD with oral administration of KME at a dose of $200 \text{ mg kg bw}^{-1} \text{ day}^{-1}$ (kimchi group, $n = 10$) or distilled water as a vehicle (control group, $n = 10$) for 8 weeks. Oral administration was performed by using gavage. The KME concentration for oral administration was based on a previous study [20]. The mice had free access to the diet and water. The diet intake was checked daily and the body weight was measured every week. After the 8 weeks, the mice were fasted for 12 h and then sacrificed. Blood was obtained and the liver was excised after perfusion with ice-cold phosphate-buffered saline (10 mM, pH 7.2). The samples were stored at -80 °C until use. The animal study was approved by the Pusan National University Institutional Animal Care and Use Committee (PNU-IACUC, approval number: PNU-2016-1063).

Aminotransferase activity and lipid concentration

Aspartic acid transaminase (AST), alanine transaminase (ALT), triglyceride (TG), and total cholesterol (TC) levels were measured using the indicated commercially available kits (AM101-K, AM157S-K, and AM202-K; Asan Pharmaceutical Co., Seoul, Korea).

Histological analysis

The liver was fixed in 4% formalin and then frozen into blocks, using an optimal cutting temperature compound (Tissue-Tek OCT compound; Miles Inc., Elkhart, IN, USA). Liver tissues sections ($7 \mu\text{m}$ thick), cut with a microtome (CM1510S-3; Leica, Wetzlar, Germany), were stained with Oil Red O on a coated glass slide and observed under a light microscope ($\times 100$; Nikon ECLIPSE Ti; Nikon Corp., Tokyo, Japan).

Western blot analysis

The western blot assay was performed as previously described [19]. Protein expression was visualized by the enhanced chemiluminescence, detected using CAS-400 (Core Bio, Seoul, Korea), and then evaluated by ImageJ software (National Institutes of Health, Bethesda, MD, USA). Protein expression was normalized to that of α -tubulin. The primary antibodies used in this study; α -tubulin (ab52866) and fatty acid synthase (FAS, ab22759) were purchased from Abcam Inc. (Cambridge, UK). The others were from Santa Cruz Biotechnology (Santa Cruz, CA, USA) including SREBP-1 (sc-8984), ACC α (sc-

26817), PPAR- α (sc-9000), CPT1 (sc-139482), ACOX1 (sc-98499), SREBP-2 (sc-5603), HMGCR (sc-33827), cytochrome P450 family 7 subfamily A member 1 (CYP7A1, sc-25536), nuclear factor kappa B (NF- κ B, sc-109), cyclooxygenase 2 (COX-2, sc-1747), inducible nitric oxide synthase (iNOS, sc-651), tumor necrosis factor- α (TNF- α , sc-1351), and interleukin-1 β (IL-1 β , sc-1252). The secondary horseradish peroxidase-conjugated antibodies (all from Abcam Inc.) were rabbit anti-goat IgG H&L (ab6741), donkey anti-rabbit IgG H&L (ab6802), and rabbit anti-Mouse IgG H&L (ab6728).

Statistical analysis

Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). Values were presented as the mean $\pm$ standard deviation. Data were analyzed by the Student's *t* test and significance was considered at $p < 0.05$.

Results and discussion

Decrease in plasma and hepatic lipid levels by kimchi

The average liver weight of mice in the kimchi group was significantly lower than that of the control group (Table 1, $p < 0.05$). The AST and ALT activities of the kimchi group were significantly reduced by 18.85 and 19.53%, respectively, relative to that of the controls ($p < 0.05$).

Table 1 Liver weight, body weight gain, food efficacy ratio, and plasma biochemical analysis of LDLr KO mice fed a high cholesterol diet for 8 weeks

Group ^a	Control	Kimchi
Liver weight (g)	1.58 $\pm$ 0.15	1.44 $\pm$ 0.09*
Body weight gain (g)	2.83 $\pm$ 1.26	3.76 $\pm$ 0.97 ^{NS}
Food efficacy ratio ^b	0.68 $\pm$ 0.39	0.98 $\pm$ 0.31 ^{NS}
AST (IU/L)	219.55 $\pm$ 58.53	178.17 $\pm$ 52.97*
ALT (IU/L)	79.48 $\pm$ 17.31	63.96 $\pm$ 23.46*
TG (mg/dL)	207.62 $\pm$ 42.81	138.41 $\pm$ 30.81**
TC (mg/dL)	1568.44 $\pm$ 126.44	1342.17 $\pm$ 102.56**

Data are the mean $\pm$ SD (n = 10 each group)

^aThe control group was fed a high cholesterol diet (HCD) with oral administration of distilled water for 8 weeks. The kimchi group was fed a HCD with oral administration of kimchi methanol extracts (200 mg/kg bw⁻¹ day⁻¹) for 8 weeks

^bTotal weight gains were divided by total food intakes. Significant difference between the two groups was analyzed by Student's *t* test; * $p < 0.05$; ** $p < 0.01$

^{NS}Data between the two groups are not significantly different

However, there were no significant differences between the two groups in terms of body weight gain and food efficacy ratio. Compared with the control group, plasma TG and TC concentration significantly decreased in the kimchi group by 33.3 and 14.4%, respectively ($p < 0.01$).

Excessive intake of dietary cholesterol might disturb hepatic lipid metabolism [1, 2], which subsequently causes liver disorders [3]. Several studies have reported that LDLr KO mice fed HCD developed a nonalcoholic fatty liver disease or steatohepatitis [21–23]. HCD-fed LDLr KO mice showed remarkably hepatic steatosis with severe inflammation, which was linked to increased plasma TG, TC, and free fatty acid levels [21]. In addition, compared with the C57BL6 mice and apoE knockout mice, hepatic inflammation, fibrosis, and apoptosis were increased in only LDLr KO mice fed HCD [23]. These evidences suggest that HCD-fed LDLr KO mice model is a suitable as an evaluation for hepatic damage. In this study, the kimchi group showed the lower aminotransferase activity. Moreover, kimchi intake had the lipid-lowering effects, which was consistent with earlier studies of kimchi from animals [19] and human [7]. Daily intake of 210 g kimchi for 1 week by health young adults whose average age of 23-year-old revealed beneficial effects on lowering plasma TG and TC concentration, in particular, LDL-C concentration of the participants whose LDL-C level higher than 130 mg/dL was significantly decreased [7]. Participants stayed at dormitory during the clinical experiment and three meals, drinks, snacks, and kimchi were provided by researchers. Bioactive compounds in kimchi such as capsaicin, quercetin, ascorbic acid, and phenolic compounds might be attributed to these effects [13–17]. In our previous study, ascorbic acid, capsaicin, HDMPPA, quercitrin, and quercetin were detected from KME used in this study, which were 280, 270, 40, 30, and 20 μ g/g-KME, respectively [10]. Total phenolic contents of KME were 15.75 $\pm$ 3.91 mg of gallic acid equivalents/g extracts. And, *lactobacillus* and *leuconostoc* spp. concentration in KME were 8.03 and 6.82 log CFU/mL, respectively.

Inhibitory effects of kimchi on the hepatic lipid accumulation

Histological analysis of the liver tissue revealed a remarkable decrease of fat deposition in the kimchi group, compared with that in the control group (Fig. 1(A)). The concentrations of hepatic TG and TC in the kimchi group were lower than that in the control group by 26.34% (Fig. 1(B), $p < 0.05$) and 38.89% (Fig. 1(C), $p < 0.01$), respectively. The histological data were in line with the reduced liver TG and TC contents in the kimchi group.

Unburnt energy from the consumption of excessive calories is converted into fat, the liver accumulation of

Fig. 1 Histological analysis and lipid concentration in the liver of LDLr KO mice fed a high cholesterol diet for 8 weeks. **(A)** Representative liver sections stained with Oil Red O. Magnification: 100 $\times$. **(B)** Hepatic triglyceride concentration. **(C)** Hepatic total cholesterol concentration. See the legend in Table 1 for the experimental groups. Data are the mean $\pm$ SD ($n = 10$ each group). Significant difference between the two groups was analyzed by Student's *t* test

which leads to what is known as a “fatty liver” [4]. Moreover, a disturbance of lipid metabolism by liver diseases decreases the ability for burning energy, leading to lipid storage in liver cells. In this study, plasma and hepatic TC and TG concentrations in the kimchi group were lower than those in the control group, indicating that elevated lipids levels by HCD were reversed by KME administration. In addition, histological results by oil red O staining showed that hepatic lipid accumulation was less severe by kimchi intake. These results are in line with previous animal studies shown that kimchi supplementation to high-fat diet significantly reduced hepatic lipid concentrations [24, 25]. Numerous studies suggested that bioactive compounds such as ascorbic acid, capsaicin, β -sitosterol, indole compounds, gingerol, allyl compounds, chlorophyll, and thiocyanate are present in kimchi [11, 18]. These compounds have been well-established to inhibit lipid synthesis and enhance the lipolytic activity [8]. Therefore, KME suppressed the elevation of lipid accumulation in the liver based on these mechanisms.

Regulatory effects of kimchi on hepatic fatty acid metabolism

As shown in Fig. 2, protein expression of SREBP-1 (mature) was 22.23% lower in the kimchi group than in the control group ($p < 0.05$). The protein expression levels of the lipogenic enzymes such as ACC α and FAS, were decreased by 13.19 and 17.60%, respectively, in the kimchi group relative to that in the control group ($p < 0.05$). Compared with the control group, protein expression of PPAR- α (involved in β -oxidation) was increased by 130.87% in the kimchi group (Fig. 3, $p < 0.05$). Similarly, the protein expression levels of CPT1 and ACOX1 were 115.86 and 120.55% higher, respectively, in the kimchi group ($p < 0.05$).

Impairment of fatty acid metabolism promotes lipid accumulation in the liver [26]. Upregulation of SREBP-1 that regulates lipogenic enzyme expression such as FAS and ACC α [27] and downregulation of PPAR- α that facilitates lipolytic enzymes regulation such as CPT1 and ACOX1 [28] have been observed in hepatic steatosis [29]. In the current study, SREBP-1, ACC α , and FAS were downregulated in kimchi group with concomitant increase

Fig. 2 Expression of proteins involved in fatty acid synthesis in the liver of LDLr KO mice fed a high cholesterol diet for 8 weeks. See the legend in Table 1 for the experimental groups. Data are the

mean $\pm$ SD ($n = 10$ each group). Significant difference between the two groups was analyzed by Student's t test

Fig. 3 Expression of proteins involved in β -oxidation in the liver of LDLr KO mice fed a high cholesterol diet for 8 weeks. See the legend in Table 1 for the experimental groups. Data are the mean $\pm$ SD

($n = 10$ each group). Significant difference between the two groups was analyzed by Student's t test

of PPAR- α , CPT1, and ACOX1 expression. Our results are in good agreement with previous study in which kimchi starter inhibited fatty acid synthesis by decreasing the SREBP-1, FAS, and ACC α levels in hepatic steatosis-induced mice, while promote β -oxidation by increasing the CPT1 level [25]. In addition, consumption of capsaicin prevented fatty liver disease and promoted the lipid catabolism in the body by increasing and expenditure of energy [30]. These results imply that kimchi apparently improves hepatic lipid metabolism through suppression of fatty acid synthesis, but elevation of β -oxidation.

Beneficial effects of kimchi on hepatic cholesterol regulation

Compared with the control group, protein expression of SREBP-2 (mature) and its target gene, HMGCR, was significantly decreased by 20.91 and 15.50%, respectively, in the kimchi group (Fig. 4, $p < 0.05$). In contrast, the protein expression of CYP7A1 was significantly elevated by 117.13% in the kimchi group ($p < 0.05$).

Cholesterol synthesis is mediated through HMGCR that is regulated by SREBP-2 [30]. In contrast, CYP7A1 cooperate cholesterol into bile acid synthesis. In addition, PPAR- α activation leads to SREBP-2 downregulation, which consequently reduces hepatic cholesterol synthesis [31]. In patients with nonalcoholic fatty liver disease, upregulation of SREBP-2 and HMGCR are commonly observed [32]. In the present study, kimchi suppressed SREBP-2 and HMGCR expression but the expression of CYP7A1 was elevated. Previous studies with kimchi starter or LAB demonstrated that SREBP-2 [24] and HMGCR [24, 33] expressions in the liver decreased while CYP7A1 expression was increased, compared with high-fat diet only fed mice [33]. These results suggest that kimchi affect cholesterol metabolism through decrease of cholesterol synthesis and increase of cholesterol export.

Anti-inflammatory effects of kimchi in the liver

As shown in Fig. 5, for the kimchi group, the protein expression levels of NF- κ B and its transcription factor, COX-2 and iNOS significantly decreased by 9.08, 4.80,

Fig. 4 Expression of proteins involved in cholesterol metabolism in the liver of LDLr KO mice fed a high cholesterol diet for 8 weeks. See the legend in Table 1 for the experimental groups. Data are the

mean $\pm$ SD (n = 10 each group). Significant difference between the two groups was analyzed by Student's *t* test

Fig. 5 Expression of proteins involved in inflammation in the liver of LDLr KO mice fed a high cholesterol diet for 8 weeks. See the legend in Table 1 for the experimental groups. Data are the mean $\pm$ SD

(n = 10 each group). Significant difference between the two groups was analyzed by Student's *t* test

and 15.03%, respectively, compared with the control group ($p < 0.05$). Protein expression of IL-1 β in the kimchi group was significantly reduced by 22.94% compared with that in the control group ($p < 0.05$). Although the protein expression of TNF- α was also lower in the kimchi group, the difference was not significant.

Inflammation and lipid concentration are strongly associated with chronic diseases such as obesity, atherosclerosis, and fatty liver disease [34]. Hepatic inflammation plays vital role in the progression of fatty liver, steatohepatitis, fibrosis, and finally cirrhosis [2, 4]. Because an elevation in the lipid concentration increases the vulnerability of the liver to inflammatory insults, which can potentially contribute to a progression to more advanced stages of hepatic damage [34]. Inflammatory transcription factor, NF- κ B is deeply involved in the development of numerous pathological states through upregulating the inflammatory enzymes or cytokines including iNOS, COX-2, and IL-1 β [35]. In this study, kimchi suppressed hepatic NF- κ B, iNOS, COX-2, and IL-1 β expression. These results are line with our previous study demonstrated that HDMPPA isolated from kimchi downregulated NF- κ B, iNOS, and COX-

2 in lipopolysaccharide-stimulated cells [9] and in the aorta of apoE knockout mice [14]. These results suggest that KME could have effect on suppressing the progression to steatohepatitis by inhibition of inflammation.

Taken the current study results together, kimchi are responsible for revealing lipid-lowering and anti-inflammatory effects. KME exerted beneficial effects on HCD-induced hepatic damage by suppressing synthesis of fatty acid and cholesterol, and facilitating fatty acid oxidation and cholesterol excretion. Furthermore, KME suppressed hepatic inflammation, a critical condition for hepatic damage. These effects might be responsible for bioactive compounds in kimchi. Subsequently, the current study suggests that the intake of kimchi might help to improve hepatic lipid metabolism and inflammation. Our study has a limitation not having a chow diet-fed mice group. However, previous animal studies demonstrated that liver diseases such as hepatic steatosis and hepatitis were successfully induced by HCD [1, 22, 23]. In further study, the mechanism involved in lipid metabolism and anti-inflammatory reaction of individual active compound in kimchi should be studied.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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