Honokiol reverses alcoholic fatty liver by inhibiting the maturation of sterol regulatory element binding protein-1c and the expression of its downstream lipogenesis genes

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A B S T R A C T

Ethanol induces hepatic steatosis via a complex mechanism that is not well understood. Among the variety of molecules that have been proposed to participate in this mechanism, the sterol regulatory element (SRE)-binding proteins (SREBPs) have been identified as attractive targets for therapeutic intervention. In the present study, we evaluated the effects of honokiol on alcoholic steatosis and investigated its possible effect on the inhibition of SREBP-1c maturation. In in vitro studies, H4IIEC3 rat hepatoma cells developed increased lipid droplets when exposed to ethanol, but co-treatment with honokiol reversed this effect. Honokiol inhibited the maturation of SREBP-1c and its translocation to the nucleus, the binding of nSREBP-1c to SRE or SRE-related sequences of its lipogenic target genes, and the expression of genes for fatty acid synthesis. In contrast, magnolol, a structural isomer of honokiol, had no effect on nSREBP-1c levels. Male Wistar rats fed with a standard Lieber–DeCarli ethanol diet for 4 weeks exhibited increased hepatic triglyceride and decreased hepatic glutathione levels, with concomitantly increased serum alanine aminotransferase and TNF-α levels. Daily administration of honokiol (10 mg/kg body weight) by gavage during the final 2 weeks of ethanol treatment completely reversed these effects on hepatotoxicity markers, including hepatic triglyceride, hepatic glutathione, and serum TNF-α, with efficacious abrogation of fat accumulation in the liver. Inhibition of SREBP-1c protein maturation and of the expression of SREBP-1c and its target genes for hepatic lipogenesis were also observed in vivo. A chromatin immunoprecipitation assay demonstrated inhibition of specific binding of SREBP-1c to the Fas promoter by honokiol in vivo. These results demonstrate that honokiol has the potential to ameliorate alcoholic steatosis by blocking fatty acid synthesis regulated by SREBP-1c.

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Introduction

Steatosis, or fatty liver, is an early-stage liver pathology induced by ethanol, drugs and abnormal metabolic states including disturbed triglyceride cycle and insulin resistance. Depending on the dose and duration of exposure, chronic consumption of ethanol can cause cumulative liver damage ranging from steatosis to end-stage liver disease. Ethanol induces fatty liver by enhancing hepatic fatty acid synthesis (Lieber et al., 1966), reducing fatty acid oxidation (Rabino-witz et al., 1991), and inhibiting lipoprotein secretion from the liver (Venkatesan et al., 1988). Although hepatic fatty infiltration was once considered a benign and fully reversible condition, it is now known to be an important pathogenic factor in the development of alcoholic liver disease (Feinman and Lieber, 1999; You and Crabb, 2004b). Clinical studies have provided evidence that alcoholic fatty liver, which was widely assumed to be benign, may lead to cirrhosis if left untreated (Sorensen et al., 1984; Teli et al., 1995). Nevertheless, no effective treatment options based on solid molecular mechanisms have been established.

Sterol regulatory element (SRE)-binding proteins (SREBPs) are membrane-bound transcription factors that are members of the basic helix–loop–helix leucine-zipper family (Brown and Goldstein, 1997). They are expressed at high levels in the liver and adipose tissue, and they regulate lipid homeostasis by controlling the expression of genes for lipid metabolism. Insulin-induced gene (INSIG) proteins and SREBP cleavage-activating protein (SCAP) are major regulatory proteins that control the activation of SREBP. In sterol-depleted cells, SCAP escorts SREBP from the endoplasmic reticulum to the Golgi apparatus, where mature forms of SREBP are released by the site-1– and site-2–proteases (Bose-Boyd et al., 1999). The mature form of SREBP translocates to the nucleus (nSREBP) where it transcriptionally regulates lipogenic genes such as those for ATP-citrate lyase (Acly), acetyl CoA carboxylase (Acac), fatty acid synthase (Fas) and stearyl CoA desaturase-1 (Scd-1).
Acly and Acc are enzymes responsible for the synthesis of cytosolic acetyl-CoA and carboxylation of acetyl-CoA to produce malonyl-CoA, respectively. Fas synthesizes the long-chain fatty acids from acetyl-CoA and malonyl-CoA, which are unsaturated by Scd-1 (Kathleen et al., 2006). Ethanol metabolism was reported to increase hepatic lipogenesis by activating SREBP-1, which might promote the development of alcoholic fatty liver (You et al., 2002).

Using microarray analysis, we recently found that acute ethanol treatment increases the level of mature SREBP-1c protein in rat liver nuclear extract and the binding to SRE and SRE-related sequences of the lipogenic target genes (Yin et al., 2007). Honokiol and magnolol are biphenolic structural isomers isolated from the stem bark of Magnolia officinalis. They possess potent antioxidant, anti-inflammatory, anti-bacterial and anti-thrombotic properties (Chang et al., 2003; Lin et al., 2007; Park et al., 2004; Hu et al., 2005). Because it exhibits diverse pharmacological effects without remarkable toxicity, M. officinalis has been used in traditional medicine for the treatment of various disorders of the digestive system (Liu et al., 2007). The results of in vitro studies have suggested that honokiol offers protective effects against hepatocyte injury caused by tert-butyl hydroperoxide, d-galactosamine, carbon tetra-chloride, and hypoxia/reperfusion (Chiu et al., 1997; Park et al., 2003; Cao et al., 2005). However, the effects of honokiol on ethanol-induced fatty liver have not been described.

In the present study, we evaluated the effects of honokiol on alcoholic steatosis and elucidated its possible mechanisms of action in terms of the inhibition of SREBP-1c maturation. This study demonstrates that honokiol inhibits SREBP-1c maturation and binding to the promoters of the target genes for hepatic lipogenesis, thereby reducing lipid accumulation, in H4IIEC3 cells as well as in rats fed a standard Lieber–DeCarli liquid ethanol diet.

Materials and methods

Materials and cell culture. The rat hepatoma H4IIEC3 cells were maintained in the logarithmic phase of growth in Dulbecco’s modified Eagle’s medium (GIBCO BRL, Grand Island, NY) supplemented with heat inactivated 10% fetal bovine serum (GIBCO BRL) at 37 °C in a 5% CO2–95% air humidified incubator. Honokiol and magnolol (Fig. 1) were obtained from Wako Pure Chemical Industries, Ltd. (Japan). All other chemicals used were of the highest pure grade available. SRE-luc plasmid was a kind gift from Dr. Lee MO (Seoul National University, Korea).

Cell viability assay. Cell viability was measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell proliferation assay. Briefly, 1 mg/mL MTT solution was added to each well of plate, and incubated at 37 °C under 5% CO2 for 3 h. The formazan product was dissolved in dimethyl sulfoxide and the optical density was measured at 540 nm.

Fig. 1. Structures of honokiol and magnolol.
Western blot analysis. Nuclear extracts from the liver homogenate were prepared using a commercially available kit (BioVision, Mountain View, CA) according to the manufacturer’s instructions. Forty micrograms of the protein were separated by 10% SDS-polyacrylamide gel electrophoresis, transferred to a nitrocellulose membrane and immunoblotted with rabbit polyclonal SREBP-1 (Cat# ab28481, Abcam, Cambridge, MA) and Lamin A antibody (Cat# ab8980, Abcam, Cambridge, MA). Detection was performed by enhanced chemiluminescence Western Blotting Detection Reagents (Amersham, Abcam, Cambridge, MA) and Lamin A antibody (Cat# ab8980, Abcam, Cambridge, MA). Detection was performed by enhanced chemiluminescence Western Blotting Detection Reagents (Amersham, Piscataway, NJ).

Reverse transcription-polymerase chain reaction (RT-PCR). Total RNA was prepared using the Easy-blue Total RNA Extraction Kit (Intron Biotechnology, Seongnam, Korea) and single-stranded cDNA was synthesized from the RNA by using oligo (dT) primer and the Superscript III reverse transcriptase supplied with the Superscript First-Strand Synthesis kit (Invitrogen, Carlsbad, CA). For in vitro samples, Semi-quantitative PCR was performed with gene specific primers designed using Oligo 6.0 software (Table 1). For in vivo samples, quantitative real-time PCR amplifications were performed using Fast Start DNA Master SYBR Green I Mixture Kit (Roche Diagnostics, USA) in a Light Cycler system (Roche Diagnostics, USA) following the manufacturer’s protocol. To determine the specificity of amplification, melting curve analysis was applied to all final PCR products.

Chromatin Immunoprecipitation (ChIP) assay. ChIP assay was performed as described elsewhere (Nelson et al., 2006) with some modifications. Briefly, liver tissue homogenate was fixed with 1% formaldehyde in PBS and the cross-linking was stopped with 125 mM glycine at room temperature. Chromatin was sheared by sonication and immunoprecipitated with anti-SREBP1 antibody (Santa Cruz Biotechnology, Santa Cruz, CA) or non-immune IgG antibody at 4 °C. Immune complexes were collected with protein A-Sepharose beads (Amersham Biosciences). Total DNA was purified by Chelex 100-based method (Nelson et al., 2006). Primers used to amplify FAS promoter regions was the SRE/E-box site at −65 (−109 to +63 was amplified), sense, 5′-GACGCTATTGGCCTGG; antisense, 5′-CTCTGGAGGCAGACGACAAG.

Statistical analysis. Statistical analysis was performed using Student’s t test (in vitro data) or one-way analysis of variance (ANOVA) test (in vivo data) followed by the Newman–Keuls multiple ranges test. Differences between groups were considered to be statistically significant at p<0.05.

Results

Honokiol inhibits ethanol-induced lipid accumulation and activation of SREBP-1c in H4IIEC3 cells

In the course of a search for novel compounds with therapeutic potential against alcoholic steatosis, we first tested the effects of a number of natural compounds on ethanol-induced lipid accumulation in H4IIEC3 cells stained by Nile Red. The percentage of Nile Red-positive cells was significantly higher among ethanol-treated cells than among control cells. However, co-treatment with honokiol (10 μg/mL) reduced lipid synthesis substantially, bringing it down to the control level (Figs. 2A, B).

Based on the evidence that SREBP-1c is involved in hepatic lipid homeostasis, we tested the effects of honokiol on the maturation and nuclear translocation of SREBP-1c in H4IIEC3 cells. After the cells were incubated with or without honokiol (0–10 μg/mL) for 24 h, we measured the levels of SREBP-1c in the nuclear fractions isolated from the total cell lysates. Western blot analysis indicated that honokiol markedly decreased the level of nSREBP-1c in a dose-dependent manner. In contrast, magnolol, the structural isomer of honokiol, increased the level of nSREBP-1c (Fig. 3A).

Honokiol inhibits the binding and transcriptional activity of SREBP-1c in H4IIEC3 cells

To examine whether honokiol also affects the transcriptional activity of SREBP-1c, we transfected a Fas-promoter luciferase-reporter gene construct into H4IIEC3 cells. As shown in Fig. 3B, the luciferase activity of the Fas promoter was decreased by honokiol treatment in a dose-dependent manner. We subsequently examined whether honokiol inhibited the expression of SREBP-1c target genes that are involved in fatty acid synthesis. When the levels of the Acly, Fas, and Scd-1 gene transcripts were measured by RT-PCR using gene-specific primers, we found that mRNA expression of the genes was decreased significantly in honokiol-treated cells. But the expression levels of Srebf1c, Acc gene were not changed significantly by honokiol treatment (Fig. 3C). Taken together, these data suggest that honokiol inhibits the maturation and transcriptional activity of SREBP-1c in H4IIEC3 rat hepatoma cells.

Honokiol inhibits fatty liver in rats fed a Lieber–DeCarli ethanol diet

To assess whether the effect of honokiol would also be observed in vivo, rats were fed a standard Lieber–DeCarli liquid diet supplemented with ethanol for 4 weeks to induce fatty liver. Since steatosis was evident after 2 weeks in our previous study (Yin and Lee, 2008),

Table 1: Gene specific primers used PCR amplification

<table>
<thead>
<tr>
<th>Gene</th>
<th>NCBI RefSeq</th>
<th>Forward primer (5′–3′)</th>
<th>Reverse primer (5′–3′)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ack</td>
<td>NM_022193</td>
<td>TGAGGAGGACCGCATTTATC</td>
<td>GAAGCTTCCTTCGTGACCAG</td>
</tr>
<tr>
<td>Acly</td>
<td>NM_016987</td>
<td>CAAGAGGGATTACGAGTGAG</td>
<td>GGATGTCGGCTGAAGAG</td>
</tr>
<tr>
<td>Gapdh</td>
<td>NM_017008</td>
<td>AACATCATCCCTGCATCCAC</td>
<td>CTGCTTCACCACCTTCTTG</td>
</tr>
<tr>
<td>Fas</td>
<td>NM_007332</td>
<td>CCGAGTGGCTGGGTATTCTTT</td>
<td>AGGGAGCTGTGGATGATGTTA</td>
</tr>
<tr>
<td>Srebf1c</td>
<td>XM_1264946</td>
<td>TGGACTACTAGTGTTGGCCTG</td>
<td>ATCCAGGTCAGCTTGTTTGCGAG</td>
</tr>
<tr>
<td>Scd-1</td>
<td>NM_133912</td>
<td>CCTCTATTGCACACACCAT</td>
<td>AGCCAAACGGCTGAGACAA</td>
</tr>
<tr>
<td>Srebf1c</td>
<td>XM_1264946</td>
<td>TGGACTACTAGTGTTGGCCTG</td>
<td>ATCCAGGTCAGCTTGTTTGCGAG</td>
</tr>
<tr>
<td>Acc</td>
<td>NM_022193</td>
<td>TGAGGAGGACCGCATTTATC</td>
<td>GAAGCTTCCTTCGTGACCAG</td>
</tr>
<tr>
<td>Gapdh</td>
<td>NM_017008</td>
<td>AACATCATCCCTGCATCCAC</td>
<td>CTGCTTCACCACCTTCTTG</td>
</tr>
</tbody>
</table>
Honokiol (10 mg/kg body weight) was orally administered to the rats beginning at the third week. At the end of the treatment period, the liver samples were stained with hematoxylin and eosin and Oil Red-O and examined by microscopy. Both staining methods clearly demonstrated that fatty infiltration, which was commonly observed in the ethanol-fed rats, was completely reversed by honokiol treatment. In the honokiol-only treatment group, no pathologic changes were observed. (Figs. 4A, B).

Biochemical analyses of the serum ALT and liver triglyceride levels corroborated the histopathologic findings. Honokiol administration was found to significantly attenuate the effects of ethanol on hepatocyte triglyceride accumulation and ALT release (Fig. 4C). Glutathione (GSH), a thiol-containing tripeptide, plays the major antioxidant and detoxification role in the liver. The hepatic GSH content of the ethanol-treated rats was substantially lower than that of the control rats. Treating the rats with honokiol restored GSH to its original level. Honokiol also substantially decreased the level of serum TNF-α (Fig. 4C).

**Honokiol inhibits binding of SREBP-1c to the Fas promoter and expression of its downstream target genes in rats fed a Lieber–DeCarli ethanol diet**

To determine whether honokiol induces the inhibition of SREBP-1c binding to the promoter in vivo, we measured the maturation and translocation of SREBP-1c, the level of Srebflc mRNA, and the levels of SREBP-1c responsive genes. Binding of SREBP-1c to the Fas promoter was assessed using a ChIP assay. Treatment of both ethanol- and pair-fed rats with honokiol significantly inhibited the maturation of SREBP-1c protein and reduced the Srebflc transcript levels (Fig. 5B) in rat liver nuclear extracts (Fig. 5A). The levels of Acc and Acly mRNA also changed, in a pattern similar to that of Srebflc (Fig. 5B). But the elevated levels of Acly and Scd-I mRNA were not significantly changed by honokiol treatment in ethanol fed rats. The DNA immunoprecipitate obtained with SREBP-1c antibody was significantly enriched for DNA containing the Fas promoter, as compared to the immunoprecipitate obtained with control antibody (normal IgG). Further enrichment was observed in the extracts from the ethanol-fed rats; this enrichment was significantly attenuated by honokiol treatment (Fig. 5C).

**Discussion**

In this study we evaluated the ability of honokiol, a biphenolic compound isolated from the stem bark of *M. officinalis*, to inhibit alcoholic steatosis. In *in vitro* studies using H4IEC3 rat hepatoma cells, honokiol treatment inhibited the activation and translocation of SREBP-1c to the nucleus, decreased the reporter activity of the Fas promoter, and consequently inhibited the expression of genes involved in fatty acid synthesis. Rats fed a standard Lieber–DeCarli ethanol diet for 4 weeks exhibited increased hepatic triglyceride levels and decreased GSH content with concomitant increases in serum ALT and TNF-α. Supplementation of the diet with honokiol for the final 2 weeks of the treatment period completely reversed the changes in hepatotoxicity markers and effectively abrogated fat accumulation. Honokiol-induced inhibition of SREBP-1c maturation, and nSREBP-1c binding to the Fas promoter was also observed in vivo.
Alcohol abuse is a leading cause of morbidity and mortality worldwide. Depending on the dose and duration of exposure, chronic consumption of ethanol is detrimental to the central nervous system and many organs, including the liver. Hepatocytes exposed to ethanol in vitro undergo structural and functional changes ranging from fatty infiltration, inflammation, and focal necrosis to terminal venular sclerosis that can ultimately develop into cirrhosis. Although alcoholic steatosis has been widely assumed to be benign, with very low risk of progression, clinical studies have provided evidence that it is an important pathogenic factor in the development of end-stage liver disease (Teli et al., 1995). Therefore, efficacious therapeutics for prevention and treatment of alcoholic fatty liver are urgently needed. Using drugs, chemicals, and natural products derived from medicinal plants, researchers have made many attempts to develop effective therapeutics for the disease. Although the mechanisms by which ethanol causes fatty liver appear to be complex and multifactorial, enhanced lipogenesis has long been proposed as an important biochemical mechanism underlying the development of alcoholic fatty liver (Lieber et al., 1966; You and Crabb, 2004a).

AMP-activated protein kinase (AMPK), a heterotrimeric enzyme complex, is the key regulator of cellular energy metabolism. The energy-sensing motif of the enzyme monitors cellular energy status and is regulated by phosphorylation at Thr 172 (Hawley et al., 1996). In the liver, activation of AMPK phosphorylates and inactivates the rate-limiting enzymes of lipogenesis, including acetyl-CoA carboxylase (Acc) (Davies et al., 1990). A relationship between AMPK and SREBP has been proposed by Zhou et al. (2001), who described the mechanisms by which metformin lowers levels of hypoglycemic and hepatic lipids. In studies performed with isolated hepatocytes and rat skeletal muscles, they demonstrated that metformin leads to activation of AMPK, inhibition of lipogenesis, and suppression of SREBP-1 expression. Although SREBP-1c is not a direct downstream target of AMPK, AMPK activation has been shown to downregulate SREBP-1c expression. The role of SREBP in hepatic steatosis was verified by Shimano et al. (1997), who found that transgenic mice overexpressing SREBP-1a or SREBP-1c produced massive fatty livers. The central role of SREBP in alcoholic fatty liver has been investigated in vitro as well as in mice fed an ethanol-containing diet (You et al., 2002). In view of the importance of SREBP in the development of alcoholic steatosis, inhibition of maturation, binding to SRE of the promoters of the lipogenic genes and transactivation of SREBP-1c by honokiol in hepatoma cells as well as in animal models of ethanol-induced steatosis may represent an important feature with regard to the inhibition of fatty liver.

Although honokiol and magnolol are structural isomers, they exhibited differential pharmacological effects in many studies. Bai et al. (2003) reported that honokiol, but not magnolol, induced apoptosis at 10 μg/mL in SVR cells. Honokiol was more specific for blocking NMDA-induced Ca²⁺ influx than magnolol (Lin et al., 2005). They also

Fig. 4. Honokiol reverses fatty liver in rats fed a Lieber–DeCarli ethanol diet. Male Wistar rats were fed a standard Lieber–DeCarli ethanol diet for 4 weeks with or without a daily dose of honokiol (10 mg/kg body weight) administered by gavage for the final 2 weeks. A cross-section of the left lateral lobe of the liver was fixed in 10% neutral buffered formalin. The liver tissues were dehydrated, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin (A). Frozen liver sections were stained with Oil Red O (B) (400× magnification). Hepatic triglycerides and glutathione and serum alanine aminotransferase and TNF-α were quantified as described in the Materials and methods section. Data shown represent the means±SEM from four rats. Values sharing a common subscript letter are not statistically different (p<0.05) (C). C, Pair-fed control group; H, Pair-fed control group supplemented with honokiol; E, ethanol-fed group; E/H, ethanol-fed group supplemented with Honokiol.
showed that the inhibitory effect of honokiol on LPS-mediated pro-
inflammatory response by macrophages was more potent than that of
magnolol (Kim and Cho, 2008). In the present study, magnolol has no
inhibitory effect on SREBP1 maturation while honokiol suppresses the
SREBP1 maturation in a dose-dependent manner.

Several lines of evidence suggest that oxidative stress and toxic
cytokines contribute to alcoholic liver disease. Ethanol increases
intracellular levels of reactive oxygen species and depletes mitochon-
drial GSH content (Fernandez-Checa et al., 1997). Although the
importance of cytokines in ethanol-induced steatosis was not widely
recognized until Yin et al. (1999) reported that TNFR1 knockout almost
completely blocks development of ethanol-induced fatty liver.
Moreover, ethanol induced cytochrome P450 2E1 enzyme
activity was not decreased by honokiol treatment (Supplementary
data). So, the effect of honokiol on ethanol-induced steatosis was not
due to the decreased ethanol oxidation.

The role of TNF-α in alcoholic liver disease is well characterized in
terms of its direct inflammatory and cytotoxic properties. However, the
importance of cytokines in ethanol-induced steatosis was not widely
recognized until Yin et al. (1999) reported that TNFRI knockout almost
completely blocks development of ethanol-induced fatty liver. This
result was in accordance with those of earlier studies showing that TNF-
α increases free fatty acid release from adipocytes, stimulates
lipogenesis in hepatocytes, and inhibits β-oxidation of free fatty acids
(Feingold and Grunfeld, 1987; Hardardottir et al., 1992; Nachiappan et
al., 1994). TNF-α also induces hepatic lipid accumulation indirectly by
stimulating pro-oxidant production; the resulting lipid peroxidation
leads to the impairment of mitochondrial lipid metabolism. Studies in
ethanol-fed rats have shown that TNF-α inhibition decreases the
formation of fatty liver. Moreover, in a recent report, TNF-α was

Fig. 5. Honokiol inhibits binding of SREBP-1c to the Fas promoter and expression of the SREBP-1c downstream target genes in rats fed a Lieber–DeCarli ethanol diet. Male Wistar rats
were fed a standard Lieber–DeCarli ethanol diet with or without honokiol as described in Fig. 4. Western blot analysis using a specific antibody was used to examine the expression of
nSREBP-1c protein in nuclear extracts of the rat liver homogenates. Band densities were determined using an image analysis system, normalized to that of Lamin A, and expressed as a
percentage of the vehicle-treated control (A). Srebf1c, Acc, Fas, Acly, and Scd-1 transcript levels were analyzed using real-time PCR (A–E). Binding of SREBP-1c to the endogenous
promoter in liver nuclear extracts was examined using a ChIP assay. The Fas promoter region in DNA isolated from immunoprecipitated chromatin was amplified using real-time PCR.
Specific SREBP-1c immunoprecipitates are compared to those obtained with IgG antibody (C). Data shown represent the mean±SEM from four rats. Values sharing a common
subscript letter are not statistically different (p>0.05). C, Pair-fed control group; H, Pair-fed control group supplemented with honokiol; E, ethanol-fed group; E/H, ethanol-fed group
supplemented with honokiol.

not been reported previously. Our results indicate that an improve-
ment in the intrinsic antioxidant capacity of ethanol-fed rats via
repletion of the hepatic GSH pool may underlie the potential
therapeutic value of honokiol in the treatment of alcoholic liver
disease. Moreover, ethanol induced cytochrome P450 2E1 enzyme
activity was not decreased by honokiol treatment (Supplementary
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leads to the impairment of mitochondrial lipid metabolism. Studies in
ethanol-fed rats have shown that TNF-α inhibition decreases the
formation of fatty liver. Moreover, in a recent report, TNF-α was
suggested to increase intrapulmonary fat deposition by affecting hepatic lipogenic metabolism involving SREBP-1c (Endo et al., 2007). In view of the importance of TNF-α in the development of alcoholic steatosis, the suppressive effects of honokiol on cytokine secretion may contribute to its overall therapeutic value in alcoholic liver disease. Although the mechanism by which ethanol induces hepatic steatosis is complex, a variety of molecules have been proposed as targets for therapeutic intervention. In this study, we found that honokiol is effective in reversing alcoholic fatty liver in rats. Honokiol treatment restored hepatic GSH content and inhibited TNF-α secretion in chronic ethanol-fed rats. By inhibiting the maturation of SREBP-1c and the binding of nSREBP-1c to the promoters of the target genes for hepatic lipogenesis, honokiol inhibited lipid accumulation in these rats. An important issue in the management of alcoholic liver disease is controlling the progression of simple steatosis to steatohepatitis. In this context, honokiol is a promising candidate for the development of therapeutics for alcoholic fatty liver.

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References


