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Kaempferol Inhibits Lipid Accumulation in HepG2 Cells through AMPK-Mediated Autophagy

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ABSTRACT: Metabolic dysfunction-associated steatotic liver disease (MASLD) is closely associated with metabolic syndrome. Currently, it is considered as a global health concern. Kaempferol (a flavonoid) exhibits extensive pharmacological properties, including anti-inflammatory, antioxidant, anticancer, and neuroprotective effects. In the present study, we investigated the effects of kaempferol on free fatty acid (FFA)-induced lipid accumulation in HepG2 cells. To establish an *in vitro* model of MASLD, we treated the human hepatocellular carcinoma cell line HepG2 with FFAs. Subsequently, we performed Western blot analysis to analyze the expression levels of essential proteins associated with lipogenesis and autophagy. Vital lipogenesis-related proteins (e.g., acetyl-CoA carboxylase, fatty acid synthase, sterol regulatory element-binding protein-1c, CCAAT/enhancer-binding protein alpha, and peroxisome proliferator-activated receptor gamma) were downregulated by kaempferol treatment. Concurrently, the expression of proteins involved in fatty acid oxidation (e.g., carnitine palmitoyltransferase 1 and peroxisome proliferator-activated receptor alpha) was upregulated. These changes indicate that kaempferol promotes a shift toward enhanced fatty acid oxidation and reduced lipogenesis, thereby mitigating lipid accumulation in liver cells. Our findings suggest that kaempferol exerts a protective effect against MASLD by modulating lipid metabolism via autophagy activation.

Keywords: AMP-activated protein kinases, autophagy, kaempferol, metabolic dysfunction-associated steatotic liver disease

INTRODUCTION

The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic syndrome is increasing worldwide (Than and Newsome, 2015). MASLD is strongly associated with obesity, type 2 diabetes mellitus, hypertension, and abnormal lipid metabolism (Hashimoto et al., 2013). This condition occurs because of the excessive consumption of high-calorie diets, particularly those that are rich in carbohydrates and fats, and inadequate physical activity. At the metabolic level, MASLD leads to the excessive synthesis and accumulation of fatty acids in hepatocytes, whereas oxidation is diminished. Excess carbohydrates are converted into fat in the liver when energy intake exceeds expenditure. Initially, carbohydrates are metabolized to acetyl-CoA through glycolysis, which then enters the fatty acid biosynthesis pathway, leading to the synthesis of fatty acids. Increased blood glucose levels stimulate insulin secretion, which enhances glucose uptake and lipogenesis. Furthermore, insulin and glucose promote lipogenesis through the activation and mRNA expression of sterol regulatory element-binding protein 1 (*SREBP-1*), an essential gene involved in fat production (Foretz et al., 1999).

To alleviate MASLD, strategies to enhance lipolysis in adipose tissues and to increase fatty acid oxidation in the liver need to be developed. The regulation of fat-producing transcription factors, induction of autophagy, and modulation of related hormones (e.g., insulin and leptin) are some approaches that have been adopted to treat MASLD (Kersten, 2001). Moreover, antioxidant control via mitochondria and reduction in carbohydrate intake have been considered. Lipogenesis and oxidation-related proteins regulate hepatic lipid metabolism. In particular, the activation of AMP-activated protein kinase (AMPK) may promote lipid degradation by inducing autophagy and directly regulating lipid-metabolizing proteins (Zhang et al., 2017). However, an ideal treatment strategy for

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MASLD has not yet been identified.

As a naturally occurring flavonoid found in various fruits, vegetables, and medicinal plants (Yao et al., 2024), kaempferol exerts anti-inflammatory properties, which are effective against acute and chronic inflammatory diseases (Park et al., 2009). Moreover, kaempferol has been studied for its antioxidant (Wang et al., 2006), anticancer (Imran et al., 2019; Amjad et al., 2022), and neuroprotective properties (Filomeni et al., 2012). Notably, it has been used in *in vitro* and *in vivo* studies related to liver conditions, including hepatocellular carcinoma (Mylonis et al., 2010), liver damage (Du et al., 2020), liver fibrosis (Xu et al., 2019), liver cancer (Huang et al., 2013), and MASLD (Liu et al., 2021; Li et al., 2023).

However, *in vitro* studies on the inhibitory effects of kaempferol on hepatic fat accumulation via autophagy are limited. Therefore, the present study aimed to investigate whether kaempferol inhibits lipid accumulation by inducing AMPK-mediated autophagy in free fatty acid (FFA)-induced HepG2 cells.

MATERIALS AND METHODS

Culture of HepG2 cells

HepG2 cells (a human liver cancer cell line) were obtained from the American Type Culture Collection and cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum and 1% antibiotics at 37°C and 5% CO_2.

Cell counting kit-8 (CCK-8) assay

To create the FFA stock solution, 1 M oleic acid and 0.5 M palmitic acid stock solution was dissolved in isopropanol at 37°C and mixed in a 1:1 ratio. Then, the FFA stock solution was diluted to 0.5 mM with 1% bovine serum albumin (BSA) in serum-free DMEM. The HepG2 cells were seeded at a density of 2×10^4 cells per well in a 96-well plate. After 24 h, the cells were treated with various kaempferol concentrations (0–80 μM) with and without 0.5 mM FFA and then incubated for an additional 24 h. The medium in each well was replaced with CCK-8 (Dojindo Molecular Technologies) reagent solution in DMEM. Subsequently, the plates were incubated for 2 h. The absorbance at 450 nm was measured using a microplate spectrophotometer (Bio-Rad).

Oil Red O staining

The HepG2 cells were seeded at a density of 4×10^5 cells per well in a six-well plate and incubated with 0.5 mM FFA and various kaempferol concentrations (0, 5, 10, 20, and 40 μM) in 1% BSA serum-free medium. The positive control group was cultured in the same medium without FFA or kaempferol. The HepG2 cells were fixed with 4% paraformaldehyde, stained with Oil Red O solution, and incubated in the dark for 30 min. Afterward, they were rinsed with phosphate-buffered saline (PBS) until no impurities were detected. The lipid accumulation in the cells was observed using an inverted microscope, and the absorbance at 500 nm was determined after dissolving the dye in 100% isopropanol.

Western blot analysis

The cells were washed with PBS and lysed using a protein lysis buffer with phosphate inhibitors, and the proteins were extracted. About 40 μg of protein was quantified and separated by size on a 10% sodium dodecyl sulfate-polyacrylamide gel via electrophoresis and then transferred to a polyvinylidene fluoride membrane. After blocking using 5% skim milk, the membrane was incubated overnight with primary antibodies at 4°C. Subsequently, the membrane was washed three times and incubated with secondary antibodies at room temperature for 1 h. The protein bands were visualized using an enhanced chemiluminescence reagent and imaged using the ImageQuant™ LAS500 system (Amersham Pharmacia). All bands were quantified relative to β-actin. The following primary antibodies were used: p62 (1:1,000), LC3B (1:500), phosphorylated mechanistic target of rapamycin (p-mTOR) (1:1,000), mTOR (1:1,000), Bax (1:1,000), Bcl2 (1:1,000), Beclin1 (1:1,000), pAMPK (1:1,000), AMPK (1:1,000), phosphorylated acetyl-CoA carboxylase (pACC) (1:1,000), ACC (1:1,000), fatty acid synthase (FAS) (1:1,000), carnitine palmitoyltransferase 1 (CPT1) (1:1,000), peroxisome proliferator-activated receptor alpha (PPARα) (1:1,000), PPARγ (1:1,000), CCAAT/enhancer-binding protein alpha (C/EBPα) (1:1,000), SREBP-1c (1:1,000), and β-actin (1:5,000).

Statistical analysis

Comparisons between groups were performed using one-way analysis of variance followed by Tukey's post hoc test using GraphPad Prism 9 software (GraphPad Software Inc.). Statistical significance was considered at $P<0.05$. All experimental data are expressed as the mean±standard error of the mean obtained from each measurement in triplicate.

RESULTS

Effects of kaempferol and FFA on the cell viability

We performed CCK-8 assay to evaluate the effects of kaempferol and FFA on the viability of HepG2 cells (Fig. 1). Kaempferol concentrations up to 40 μM did not significantly affect the cell viability after 24 h of treatment. However, a significant reduction in cell viability was observed at 80 μM, the highest kaempferol concentration

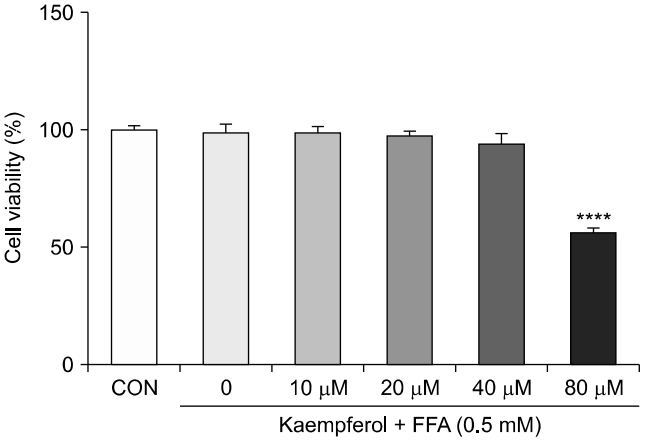

Fig. 1. Effects of kaempferol and free fatty acids (FFAs) on the cell viability. The HepG2 cells were incubated in various kaempferol concentrations with 0.5 mM FFA for 24 h. Meanwhile, the control (CON) cells were incubated with 1% fat-free bovine serum albumin. All experiments were performed in triplicate, and the data are presented as the mean±standard error of the mean. ****P<0.0001 vs. CON.

used in this study, compared with the control group. Therefore, the experiments were performed at concentrations (0, 5, 10, 20, and 40 μM) where more than 80% of the cells could survive.

Kaempferol reduces lipid accumulation in FFA-induced HepG2 cells

The effects of kaempferol on lipid metabolism in HepG2 cells were assessed by measuring the degree of lipid accumulation in each treatment group using Oil Red O staining (Fig. 2). The lipid droplets in HepG2 cells were stained red. The FFA-treated HepG2 cells showed increased lipid accumulation but decreased cellular lipid accumulation after kaempferol treatment compared with the control group. This finding suggested that kaempferol effectively reduced lipid accumulation in HepG2 cells. Similarly, Tie et al. (2021) demonstrated that kaempferol treatment reduced oleic acid-induced hepatic fat accumulation in HepG2 cells.

Effects of kaempferol on the expression of cell lipogenesis-related proteins

To confirm the effects of kaempferol on fat accumulation, the expression of lipogenesis-related factors was analyzed using Western blot analysis in FFA-induced HepG2 cells (Fig. 3). As shown in Fig. 3A and 3B, the protein expression of pACC was significantly decreased, whereas that of FAS was significantly increased in cells treated with 0.5 mM FFA compared with control cells. However, after kaempferol treatment for 24 h, the expression of pACC increased, whereas that of FAS decreased in a concentration-dependent manner. On the other hand, in Fig. 3C and 3D, the expression levels of PPARα and CPT1 were significantly decreased in FFA-treated cells than in control cells. However, the expression of both proteins increased in a concentration-dependent manner upon kaempferol treatment. In addition, Fig. 3E–3G show that kaempferol treatment decreased the expression of SREBP-1c, PPARγ, and C/EBPα compared with that in FFA-treated cells. These findings suggest that kaempferol can inhibit FFA-induced lipid accumulation by downregulating fatty acid synthesis and adipocyte differentiation and upregulating fatty acid oxidation.

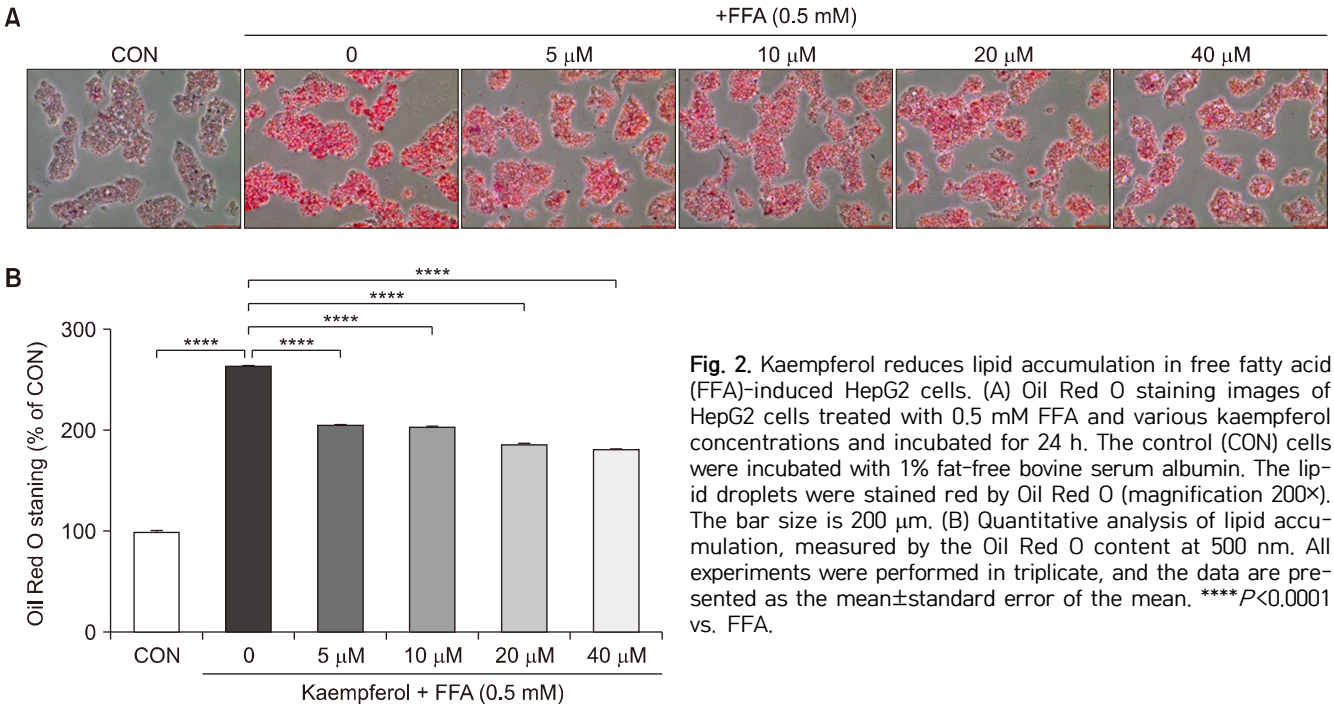

Fig. 2. Kaempferol reduces lipid accumulation in free fatty acid (FFA)-induced HepG2 cells. (A) Oil Red O staining images of HepG2 cells treated with 0.5 mM FFA and various kaempferol concentrations and incubated for 24 h. The control (CON) cells were incubated with 1% fat-free bovine serum albumin. The lipid droplets were stained red by Oil Red O (magnification 200×). The bar size is 200 μm. (B) Quantitative analysis of lipid accumulation, measured by the Oil Red O content at 500 nm. All experiments were performed in triplicate, and the data are presented as the mean±standard error of the mean. ****P<0.0001 vs. FFA.

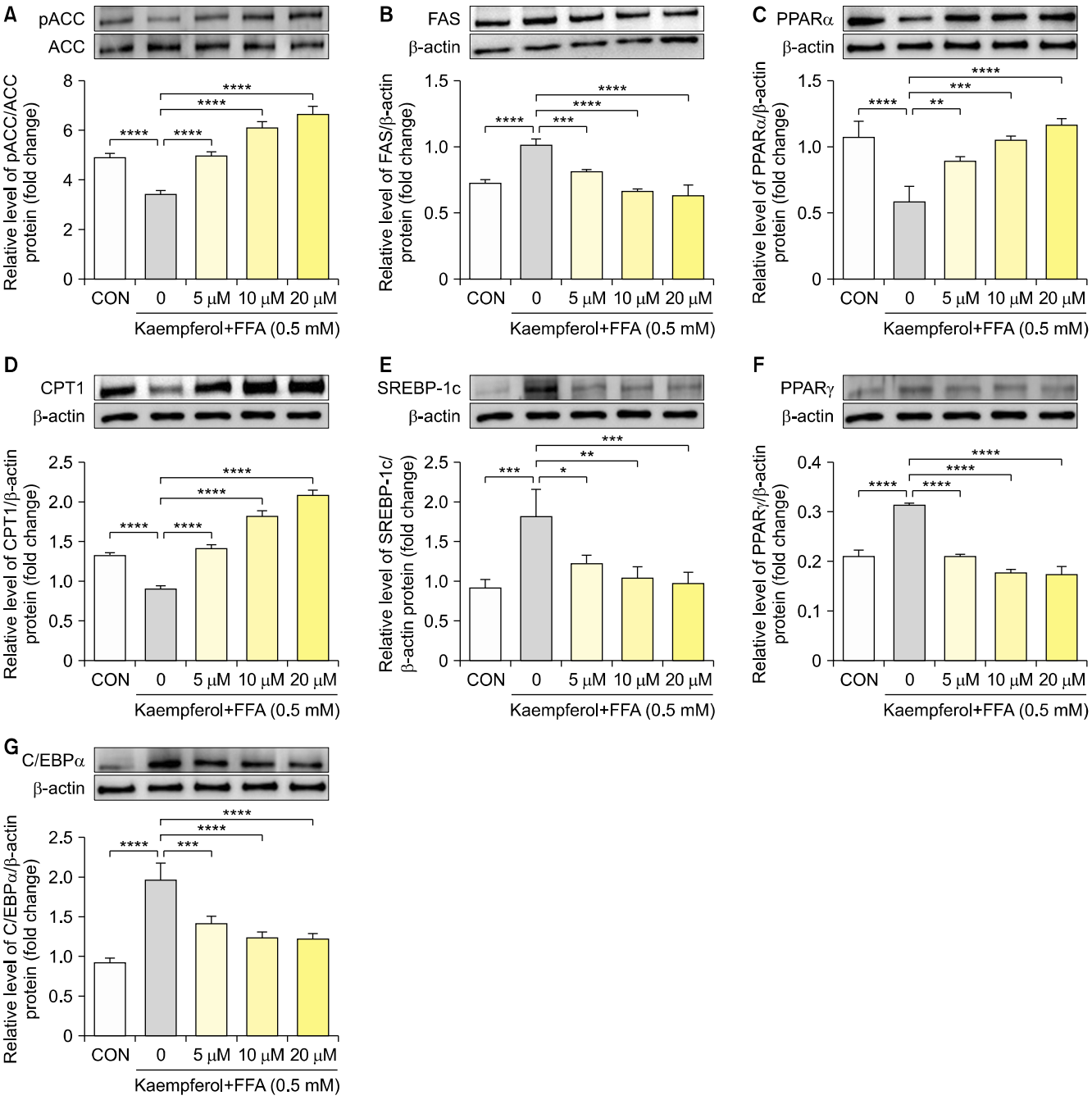

Fig. 3. Effects of kaempferol on the expression of cell lipogenesis-related proteins. The HepG2 cells were treated with various kaempferol concentrations with 0.5 mM free fatty acids (FFAs) for 24 h. Meanwhile, the control (CON) cells were incubated with 1% fat-free bovine serum albumin. (A) The protein levels of phosphorylated acetyl-CoA carboxylase (pACC)/ACC, (B) fatty acid synthase (FAS), (C) peroxisome proliferator-activated receptor alpha (PPARα), (D) arnitine palmitoyltransferase 1 (CPT1), (E) sterol regulatory element-binding protein (SREBP)-1c, (F) PPARγ, and (G) CCAAT/enhancer-binding protein alpha (C/EBPα) were analyzed using Western blot analysis. ACC was used as the control for pACC, whereas all other protein markers were quantified with β-actin as control. All experiments were performed in triplicate, and the data are presented as the mean±standard error of the mean. *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001 vs. FFA.

Effects of kaempferol on the expression of cell autophagy-related proteins

The protein expression of AMPK and its sub-factors, which are significant regulators of autophagy, was analyzed to examine the effects of kaempferol on autophagy (Fig. 4). Fig. 4A shows that AMPK phosphorylation significantly decreased when HepG2 cells were treated with FFA; however, it significantly increased after kaempferol treatment. In addition, the occurrence of autophagy was confirmed by the expression levels of mTOR, Beclin1, p62, and LC3B-II/LC3B-I ratio, all of which are regulated by AMPK (Fig. 4B–4E). In FFA-treated cells, mTOR phosphorylation and p62 expression were increased; however, they were significantly decreased after kaempferol treatment. Meanwhile, the expression of Beclin1 and the LC3B-II/LC3B-I ratio showed the opposite trend,

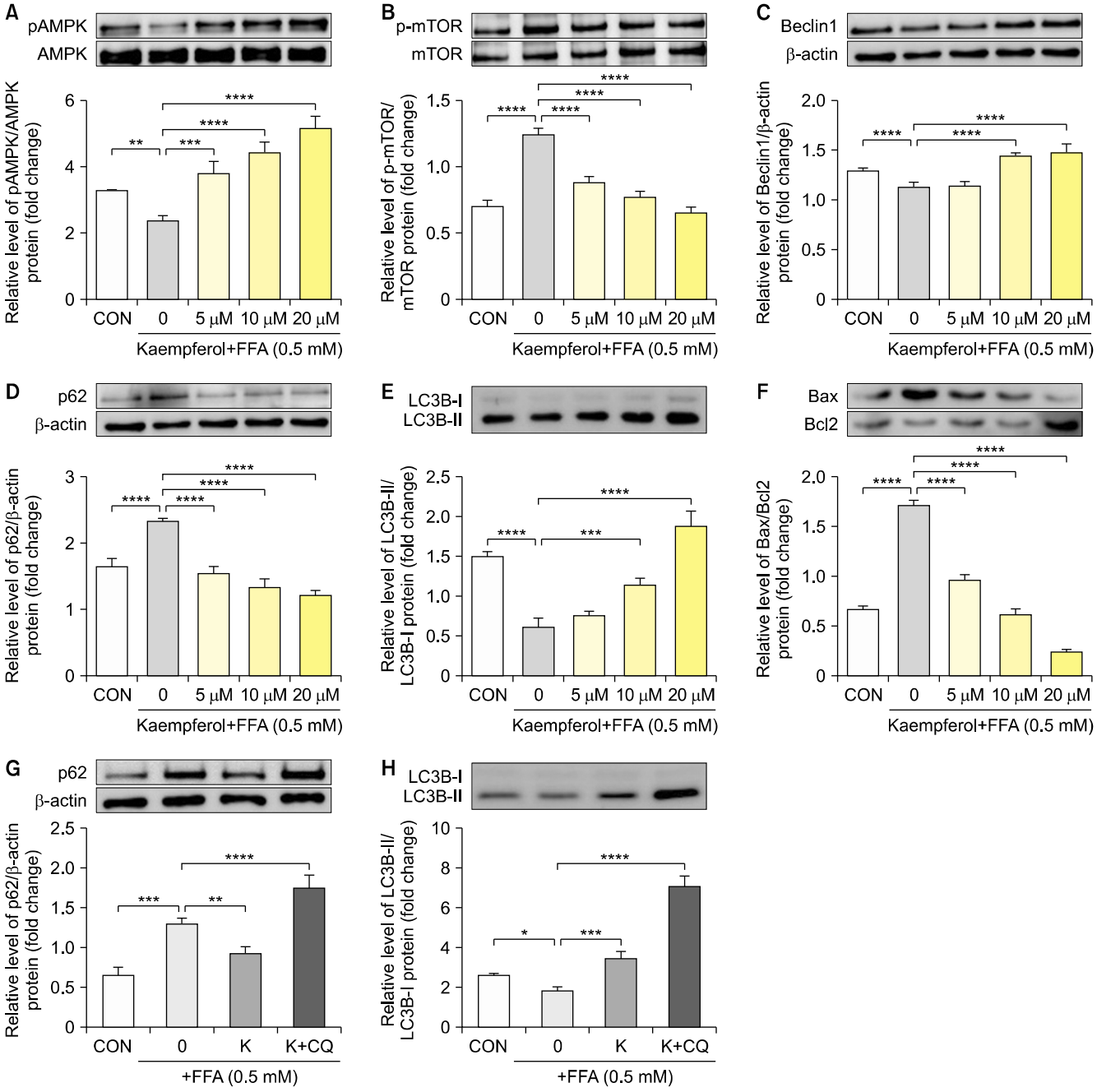

Fig. 4. Effects of kaempferol on the expression of cell autophagy-related proteins. (A-F) The HepG2 cells were treated with various kaempferol concentrations with 0.5 mM free fatty acids (FFAs) for 24 h. Meanwhile, the control (CON) cells were incubated with 1% fat-free bovine serum albumin. (A) The protein levels of phosphorylated AMP-activated protein kinase (pAMPK)/AMPK, (B) phosphorylated mechanistic target of rapamycin (p-mTOR)/mTOR, (C) Beclin1, (D) p62, (E) LC3B-II/LC3B-I, and (F) Bax/Bcl2 were analyzed using Western blot analysis. (G, H) HepG2 cells were treated with 20 μM kaempferol (K) and 10 μM chloroquine (CQ) with 0.5 mM FFA for 24 h. (G) p62 and (H) LC3B-II/LC3B-I were analyzed using Western blot analysis. AMPK and mTOR were used as controls for pAMPK and p-mTOR, respectively, whereas other protein markers were quantified with β-actin as control. All experiments were performed in triplicate, and the data are presented as the means±standard error of the mean. *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001 vs. FFA.

with increased levels in kaempferol-treated cells than in FFA-treated cells. These findings suggest that kaempferol activates autophagy by promoting AMPK phosphorylation and inhibiting p-mTOR. As excessive autophagy can lead to apoptosis, the expression levels of proapoptotic Bax and antiapoptotic Bcl2 were examined and expressed as ratios (Fig. 4F). In FFA-treated cells, apoptosis appeared to be activated because of the high Bax/Bcl2 ratio. However, kaempferol treatment significantly reduced the Bax/Bcl2 ratio, indicating a protective effect against apoptosis. Furthermore, the HepG2 cells were treated with chloroquine (CQ), an autophagy inhibitor, along with kaempferol to confirm whether kaempferol specifically induces autophagy (Fig. 4G and 4H).

DISCUSSION

MASLD is a chronic disease caused by excess fat accumulation in liver cells, leading to severe complications, including cirrhosis and liver cancer (Li et al., 2023). Therefore, reducing fat accumulation in the liver is crucial for preventing and treating MASLD. In the present study, we treated HepG2 cells with oleic acid and palmitic acid to induce lipid accumulation and create an MASLD cell model. Moreover, we evaluated the effects of kaempferol on MASLD by specifically focusing on the AMPK pathway.

As a natural flavonoid, kaempferol modulates autophagy and fat metabolism in various types of cells, including 3T3-L1 adipocytes, pancreatic β-cells, and HepG2 hepatocytes (Yao et al., 2024). The present study aimed to explore the effects of kaempferol on lipid metabolism and its underlying mechanisms, particularly in the context of FFA exposure. When the HepG2 cells were co-treated with 0.5 mM FFA and various kaempferol concentrations, the cell viability was maintained up to a concentration of 40 μM, indicating that kaempferol is not cytotoxic at this concentration. Considering that kaempferol can be used at effective concentrations without adversely affecting the cell viability, this is crucial for its potential therapeutic use. The results of Oil Red O staining also demonstrated a concentration-dependent reduction in triglyceride accumulation upon kaempferol treatment. This finding confirmed kaempferol's lipid-lowering effects, which is consistent with previous reports highlighting its role in the management of lipid metabolism. Moreover, we treated the cells with kaempferol at concentrations of 5, 10, and 20 μM in the presence of FFA. This treatment resulted in significant changes in AMPK phosphorylation and expression levels of several key metabolic regulators. Kaempferol-induced AMPK phosphorylation downregulates SREBP-1c, C/EBPα, and PPARγ, indicating reduced adipocyte differentiation. Moreover, the expression levels of CPT1 and PPARα increased, whereas the phosphorylation of ACC and the expression of FAS decreased, suggesting reduced fatty acid synthesis and increased fatty acid β-oxidation. Thus, we found that kaempferol inhibits lipid accumulation by regulating AMPK expression.

AMPK is activated under energy deficiency conditions, including low glucose levels or increased adenosine monophosphate/adenosine triphosphate ratios. Once activated, AMPK plays a pivotal role in cellular energy homeostasis by modulating several metabolic pathways (Hardie et al., 2012). AMPK restricts lipid accumulation by suppressing FAS and promoting fatty acid oxidation while simultaneously inducing autophagy through the inhibition of mTOR (Zhang et al., 2017), thereby playing a pivotal role in maintaining cellular energy balance and homeostasis. In particular, the activation of AMPK leads to the phosphorylation and subsequent inhibition of ACC and FAS, which are critical enzymes in the lipogenic pathway. This suppression reduces the synthesis of fatty acids and triglycerides in the liver. AMPK enhances fatty acid oxidation by increasing the expression of CPT1 and PPARα. CPT1 is a rate-limiting enzyme in the transport of fatty acids into the mitochondria for β-oxidation, whereas PPARα regulates the genes involved in fatty acid metabolism.

The activation of AMPK also inhibits mTOR, a critical negative regulator of autophagy (Zhang et al., 2017). The suppression of mTOR promotes autophagy, a process of cellular degradation that breaks down and recycles cytoplasmic components, including lipid droplets. Furthermore, autophagy reduces lipid accumulation in hepatocytes (Singh et al., 2009; Byrnes et al., 2022; Yang et al., 2022). To confirm this, we analyzed the expression of mTOR, Beclin1, and p62 and the LC3B-II/LC3B-I ratio in HepG2 cells treated with kaempferol. Because of the concentration-dependent suppression of mTOR, the expression of Beclin1 and the LC3B-II/LC3B-I ratio increased, whereas the expression of p62 decreased. This finding suggests that kaempferol-induced autophagy in HepG2 cells. To confirm this, we treated the cells with CQ, an autophagy inhibitor, and observed the expression of p62 and the LC3B-II/LC3B-I ratio. In the presence of CQ, the expression levels of p62 significantly increased compared with those in the kaempferol-only group. Moreover, the LC3B-II/LC3B-I ratio dramatically increased in the CQ-treated group, likely because LC3B-II accumulated without binding to the autophagosome membrane, as CQ inhibits the breakdown of the autophagosome. These findings indicated that kaempferol induces autophagy, which contributes to its lipid-lowering effects in HepG2 cells.

Previous studies found that kaempferol effectively promoted AMPK-mediated autophagy (Han et al., 2017) and reduced lipid accumulation (Zhao et al., 2023). However, our study further elucidated the role of AMPK-mediated autophagy in reducing lipid accumulation by demonstrating that kaempferol affects lipogenesis- and autophagy-related protein markers under MASLD-like conditions. Therefore, these findings suggest that kaempferol is a promising therapeutic agent for MASLD because it modulates lipid metabolism by promoting autophagy and activating the AMPK pathway.

Despite our findings, this study has several limitations. Although the study identified vital pathways, including AMPK activation and autophagy induction, it did not fully explore other potential mechanisms and signaling pathways through which kaempferol may modulate lipid metabolism. Although we confirmed autophagy activation using CQ, further studies are needed to determine whether this process directly contributes to reduced lip-

id accumulation. Moreover, no clinical data were provided to support the translation of these *in vitro* findings for potential therapeutic use in patients with MASLD. Thus, further research is needed, including *in vivo* studies and clinical trials, to validate the therapeutic potential of kaempferol in MASLD treatment.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: MP, HJL. Analysis and interpretation: SP. Data collection: SP. Writing the article: SP. Critical revision of the article: MP, HJL. Final approval of the article: HJL. Statistical analysis: SP. Obtained funding: HJL. Overall responsibility: HJL.

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