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Fagopyrum dibotrys extract improves nonalcoholic fatty liver disease via inhibition of lipogenesis and endoplasmic reticulum stress in high-fat diet-fed mice

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Abstract

Objective The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing, presenting a treatment challenge due to limited options. Endoplasmic reticulum (ER) stress and associated lipid metabolism disorders are main causes of NAFLD, making it important to inhibit ER stress for effective treatment. *Fagopyrum dibotrys* has hypolipidemic, anti-inflammatory and hepatoprotective properties, showing promise in treating NAFLD. However, its effects on ER stress in NAFLD remain unclear. This study used a high-fat diet (HFD) to establish NAFLD mouse models and supplemented with *Fagopyrum dibotrys* extract (FDE) to evaluate its therapeutic effect and underlying mechanisms.

Results We showed that FDE supplementation reduced the severity of hepatic steatosis and lowered triglycerides (TG) and total cholesterol (TC) levels in NAFLD mice. At the molecular level, FDE supplementation reduced hepatic lipid deposition by downregulating lipogenic markers (SREBP-1c, SCD1) and upregulating fatty acid oxidase CPT1α expression. Additionally, FDE treatment inhibited the overexpression of ER stress markers (GRP78, CHOP, and P-EIF2α) in NAFLD mice livers, and blocked the activation of the PERK-EIF2α-CHOP pathway, demonstrating its role in maintaining ER homeostasis. Considering that activation of the PERK pathway could exacerbate lipid deposition, our findings suggest that FDE has a protective effect against hepatic steatosis in NAFLD mice by attenuating ER stress, and the potential mechanism is through inhibiting the PERK pathway.

Keywords Nonalcoholic fatty liver disease, *Fagopyrum dibotrys* extract, High-fat diet, Endoplasmic reticulum stress, Lipid metabolism

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as the predominant chronic hepatic disorder globally, affecting approximately one-third of adults and 10% of children and adolescents [1, 2]. The incidence of NAFLD continues to increase due to the increasing number of patients with metabolic syndrome, obesity, and diabetes mellitus [3], resulting in a heavy disease burden [4]. Modern medicine suggests that the pathogenesis of NAFLD is multifaceted, with various factors such as excessive nutritional density in the liver (carbohydrate/lipid), activation of the hepatic immune system, lipotoxicity, stress response, and genetic susceptibility collectively contributing to its development [5, 6]. In this process, endoplasmic reticulum (ER) stress, which acts as a convergence point for various detrimental factors, including hepatic inflammatory response, lipid deposition, and hepatocyte apoptosis, plays a crucial role in the development of NAFLD [3, 7]. For example, the activation of ER stress induces an inflammatory response by activating nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) in NAFLD cell models [8, 9]. In contrast, the addition of an ER stress inhibitor, like tauroursodeoxycholic acid, effectively suppresses NF-κB pathway activation and mitigates inflammation [10]. Additionally, all three ER stress pathways can regulate hepatic steatosis development. Specifically, activation of the protein kinase RNA–like ER kinase (PERK) pathway increases lipogenesis gene expression [11], leading to excessive hepatic lipid accumulation. Conversely, blocking eukaryotic translation-initiation factor 2α (EIF2α) phosphorylation reduces hepatic lipogenesis and protects against high-fat diet (HFD)-induced steatohepatitis in mice [12]. Furthermore, activation of activating transcription factor 6 (ATF6) promoted the translocation of sterol regulatory element binding protein 1c (SREBP-1c) into the nucleus, thereby inducing hepatic adipogenesis in a cell model of NAFLD. However, treatment with berberine reversed ER stress-induced lipogenesis by modulating the ATF6/SREBP-1c pathway [13]. It is evident that targeting ER stress represents a promising therapeutic approach for improving NAFLD.

Despite the widespread attention that NAFLD has garnered, there remains a lack of recognized pharmacological interventions [14]. Hence, it is imperative to develop safe and efficacious pharmacotherapies. *Fagopyrum dibotrys* (D. Don) Hara is a valuable resource plant with abundant nutrients that is widely distributed in Asian countries [15]. Previous studies have demonstrated that *Fagopyrum dibotrys* exhibits a wide range of pharmacological effects, including hypolipidemic, anti-inflammatory, antioxidant, hepatoprotective, and antidiabetic properties [16, 17], suggesting its potential health benefits for various diseases. Our previous study confirmed that supplementation with *Fagopyrum dibotrys* extract (FDE) reduces obesity, improves insulin resistance and hepatic steatosis in HFD-fed mice, and these effects are achieved through the activation of autophagy and reversal of intestinal flora dysbiosis in NAFLD mice [18]. Additionally, *Fagopyrum esculentum* Moench. also improved dyslipidemia in mice fed a high-fat, high-cholesterol diet by regulating bile acid metabolism. Therefore, dietary intervention with *Fagopyrum esculentum* Moench. is considered a nutritional strategy for preventing dyslipidemia and the development of NAFLD [19]. However, it remains unreported whether *Fagopyrum dibotrys* can ameliorate NAFLD by alleviating ER stress, necessitating further investigations.

Methods

Fagopyrum dibotrys extract preparation

The preparation procedure was the same as that described elsewhere [18].

Animal model and experimental protocol

Twenty-four male C57BL/6J mice, aged 7 weeks and weighing between 18 and 22 g, were procured from Kunming Medical University (Kunming, China). The mice were housed in Science and Technology's Experimental Animal Center under controlled environmental conditions: relative humidity was maintained at 55–70%, temperature at 22–25℃, and a 12-hour light/dark cycle was implemented. They had unrestricted access to food and water. After one week of acclimation, the mice were randomly assigned to four groups: control group (receiving a normal diet), HFD group (receiving a HFD, 4.7 kcal/gm, 48.5% energy as fat, 19.8% protein, and 31.7% carbohydrates) (BiotechHD Co., Ltd, Cat#HD001b, China), control+FDE group (receiving a mixture of normal diet and FDE at a mass ratio of 9:1), HFD+FDE group (receiving a mixture of HFD and FDE at a mass ratio of 9:1). After a 14-week dietary intervention, the mice underwent a 12-hour fast. Subsequently, they were anesthetized by intraperitoneal injection with 1% sodium pentobarbital solution (50 mg/kg) and sacrificed by cervical dislocation. Tissue samples were collected for future experimentation. The experimental protocol was approved by the Institutional Animal Care and Use Committee of Kunming Medical University (approval number kmmu20211584).

Histological analysis

Fresh liver tissue samples were fixed in 4% paraformaldehyde for 24 h, embedded in paraffin and sectioned into 5-μm thick slices. For hematoxylin and eosin (H&E) staining, the sections were stained with hematoxylin and eosin solution (Solarbio, Cat#G1120, China), followed by microscopic examination to assess morphological alterations. For the Oil Red O experiment, frozen liver tissue sections were incubated with Oil Red O staining solution

(Solarbio, Cat#G1261, China) for 30 min and then counterstained with hematoxylin to visualize lipid deposition in hepatocytes. Images of pathological sections were captured using a Leica Aperio CS2 system. The degree of hepatic lipid deposition and Oil Red O positive area were quantified using ImageJ software.

Measurement of triglyceride (TG) and total cholesterol (TC) in the liver

Mouse liver tissue (0.1 g) was precisely weighed and 0.9 ml of anhydrous ethanol was added at a ratio of 1:9. The tissues were homogenized on ice and then centrifuged to collect the supernatant for TG and TC content determination following the protocol instructions (Jiancheng Bioengineering Institute, Cat#A-110-1-1, Cat#A-111-1-1. China).

Immunofluorescence assays

The in situ expression of target proteins was detected using immunofluorescence staining with specific antibodies. Paraffin sections (5-μm thick) were cut, baked at 65 °C for 3 h, and subsequently deparaffinized by immersion in xylene. The slices were hydrated in gradient alcohol, washed with PBS three times, blocked with goat serum to prevent nonspecific antibody binding, and then incubated overnight at 4 °C with specific primary antibodies against GRP78 (Cell Signaling Technology, Cat#3177, USA; 1:200). The following day, after three washes with PBS, the slices were incubated with a fluorescent secondary antibody at room temperature for 1 h in the dark. The cell nuclei were stained with DAPI and sealed with anti-fluorescence quenching sealing solution. Fluorescence microscopy was used to capture images.

Western blotting

The expression of target proteins in liver tissues was evaluated via Western blotting. Liver tissues were lysed using RIPA lysis buffer (Solarbio, Cat#R0010, China) and homogenized on ice. Subsequently, the supernatant was collected after centrifugation. The protein concentration was quantified using a BCA Protein Assay Kit (Beyotime Biotech, Cat#P0010, China), after which the proteins were separated by SDS-PAGE and transferred to PVDF membranes. Nonspecific binding proteins were blocked with TBST containing 5% nonfat dry milk at room temperature for 2 h, and then incubated overnight at 4 °C with specific primary antibodies. The next day, the membranes were washed three times with TBST and subsequently incubated with a secondary antibody at room temperature for 2 h. Protein bands were visualized using an enhanced chemiluminescence (ECL) kit (Thermo Scientific Science, Cat#32109, USA) and captured on a ChemiDoc XRS imaging system (Bio-Rad, USA). Quantification analysis was performed utilizing ImageJ software.

Statistical analysis

Quantitative data are expressed as the mean ± SEM. The normality of the data was assessed using the Shapiro-Wilk test, and variance equality was evaluated using the Brown-Forsythe test. Individual group comparisons were performed utilizing one-way analysis of variance (ANOVA). A statistically significant difference was defined as $P<0.05$. Statistical analysis was performed using GraphPad Prism 9.0 software.

Results

FDE supplementation improves hepatic steatosis in HFD-induced NAFLD mice

The animal experiment protocol is shown in Fig. 1A. To evaluate the effects of FDE supplementation on hepatic lipid accumulation, we performed H&E and Oil Red O staining on mouse liver tissues. FDE supplementation effectively mitigated hepatic steatosis and lipid accumulation in HFD-fed mice (Fig. 1B-E). Because abundant extracellular lipids may obscure intracellular lipid staining, we additionally quantified lipid content using commercial kits. Similarly, both TG and TC levels in the liver of the HFD group were decreased by FDE (Fig. 1F and G).

FDE supplementation ameliorates abnormal lipid metabolism in HFD-induced NAFLD mice

To investigate the molecular mechanism underlying FDE-mediated attenuation of hepatic lipid accumulation in HFD-induced NAFLD mice, we used Western blotting to evaluate the expression levels of lipometabolism-related proteins. Interestingly, key lipid synthesis enzymes, including SREBP-1c and stearoyl coenzyme a desaturase-1 (SCD1), were upregulated in the HFD group but downregulated with FDE supplementation. Furthermore, supplementation with FDE significantly increased the protein level of CPT1α, a mitochondrial enzyme involved in fatty acid β-oxidation (Fig. 1H and I).

FDE supplementation attenuates hepatic ER stress in HFD-induced NAFLD mice

Prolonged ER stress is implicated in lipid metabolism and lipotoxicity in peripheral tissues [20]. To further elucidate the potential mechanisms underlying the beneficial effects of FDE on NAFLD, we examined its impact on ER stress. The results demonstrated that FDE significantly decreased the protein levels of glucose-regulated protein 78 (GRP78) and C/EBP homologous protein (CHOP) induced by HFD (Fig. 2C, D and E). Additionally, we performed immunofluorescence staining for GRP78 and found that the results were consistent with its Western blot analysis (Fig. 2A and B).

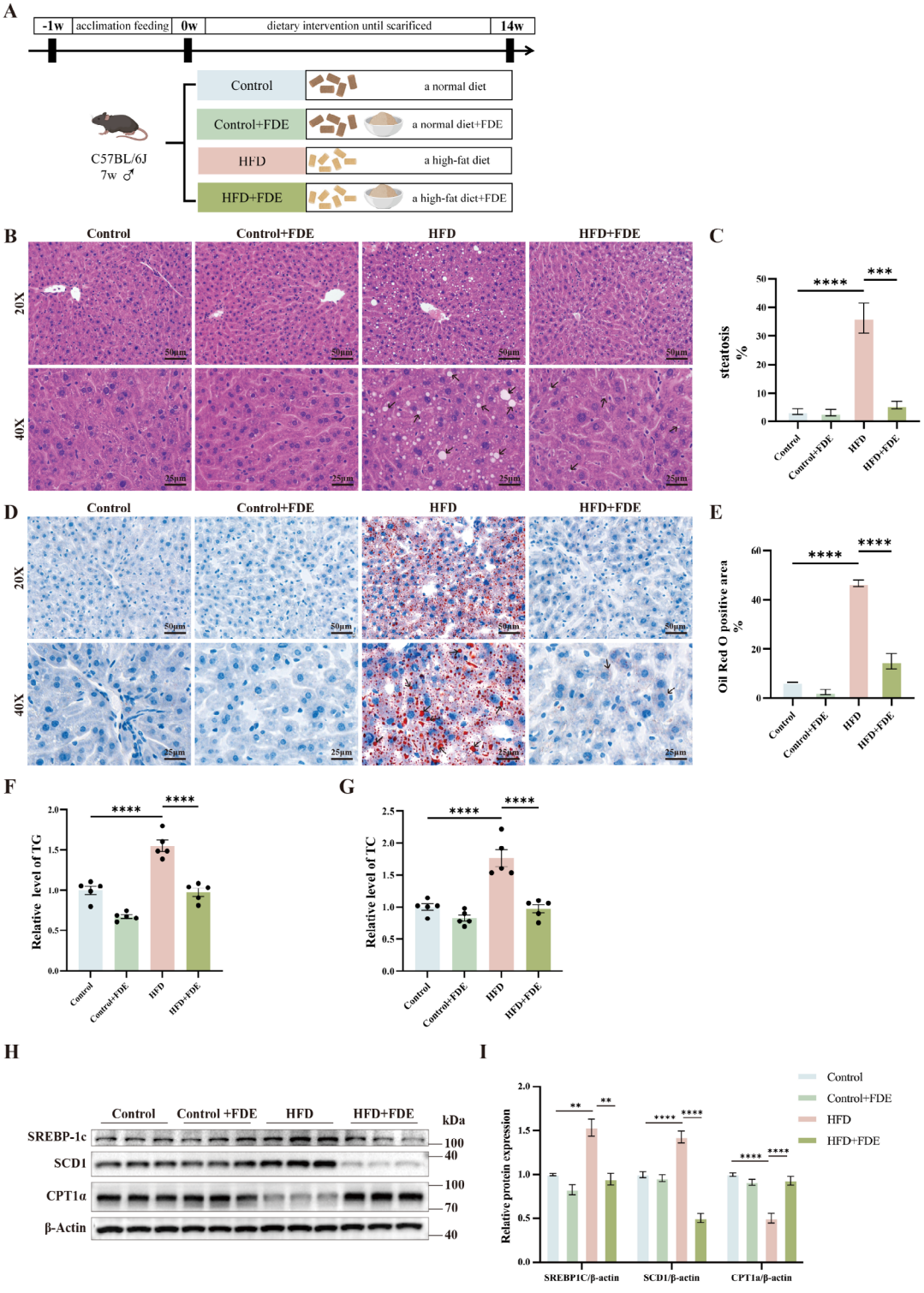

Fig. 1 FDE protects against hepatic steatosis and lipid deposition in HFD-fed mice. (**A**) Graphical protocol of the animal experiment. (**B**) Representative images of H&E staining of liver tissue sections (magnification 200× and 400×; scale bar, 50 μm and 25 μm). (**C**) Quantification of steatosis area. (**D**) Representative images of Oil Red O staining of liver tissue sections (magnification 200× and 400×; scale bar, 50 μm and 25 μm). The arrows denote the presence of adipose vacuoles or lipid droplets. (**E**) Quantification of Oil Red O positive area. Quantification of hepatic (**F**) TG content and (**G**) TC content. (**H**) Protein expression of SREBP-1c, SCD1 and CPT1α determined by Western blot. (**I**) Quantification of protein expression. Control, normal diet group; Control + FDE, normal diet + *Fagopyrum dibotrys* extract; HFD, high-fat diet group; HFD + FDE, high-fat diet + *Fagopyrum dibotrys* extract. The presented data represent the mean ± SEM ($n = 6$). $^{**}p < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$

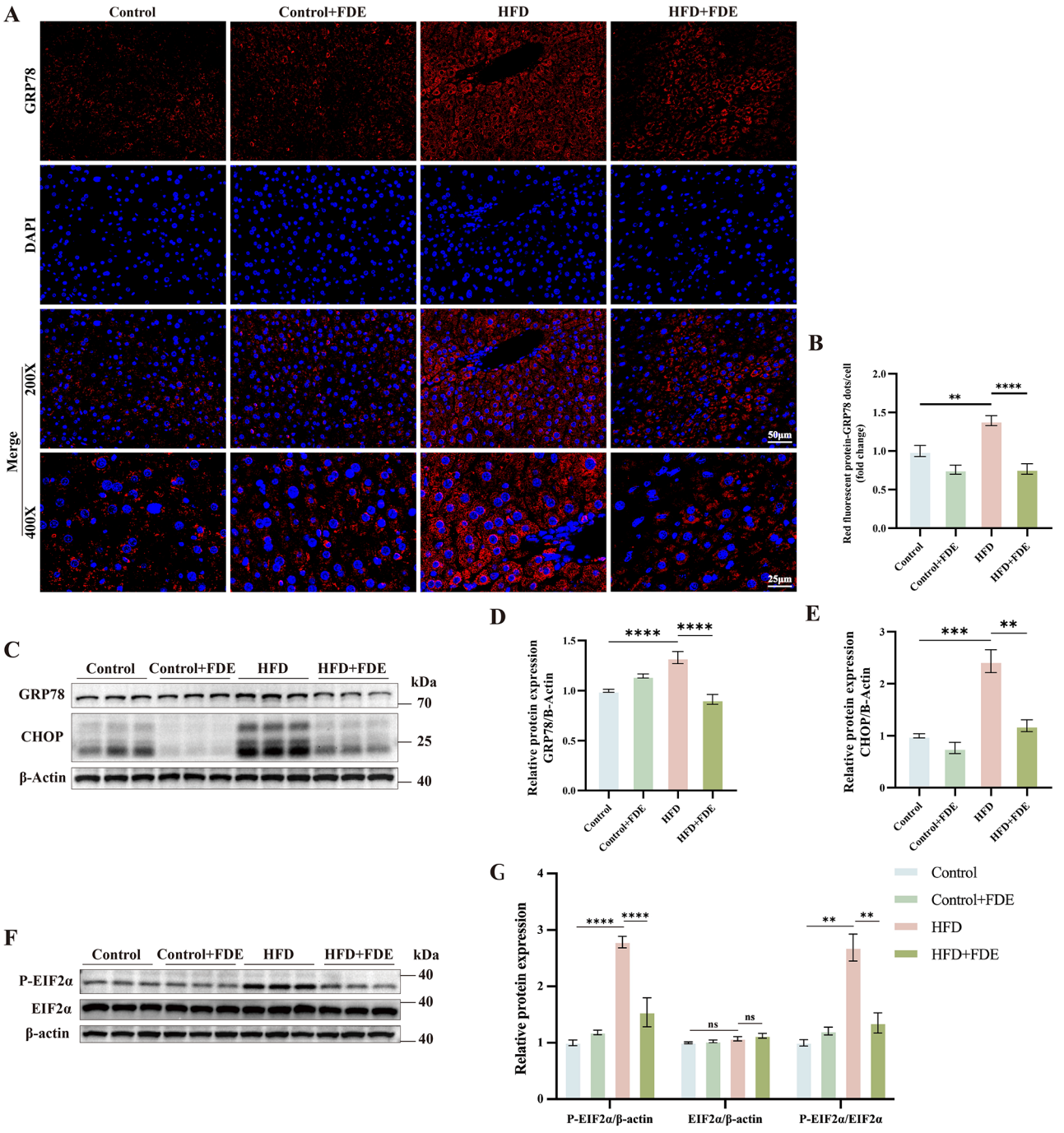

Fig. 2 FDE attenuates hepatic ER stress and inhibits activation of PERK pathway in HFD-fed mice. (**A**) Representative images of immunofluorescence staining for GRP78 in the livers of mice (magnification 200× and 400×; scale bar, 50 μm and 25 μm). (**B**) Quantification of GRP78 fluorescence intensity. (**C**) Protein expression of GRP78 and CHOP determined by Western blot. (**D**, **E**) Quantification of protein expression. (**F**) Protein expression of P-EIF2α and EIF2α determined by Western blot. (**G**) Quantification of protein expression. Control, normal diet group; Control + FDE, normal diet + *Fagopyrum dibotrys* extract; HFD, high-fat diet group; HFD + FDE, high-fat diet + *Fagopyrum dibotrys* extract. The presented data represent the mean ± SEM ($n = 6$). $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$

FDE supplementation inhibits the activation of PERK pathway in HFD-induced NAFLD mice

To further elucidate the potential mechanism underlying FDE-mediated regulation of ER stress, we investigated the expression of proteins associated with PERK pathway. The phosphorylation status of EIF2α, a downstream target of PERK, is commonly assessed to monitor PERK activity [21]. Our findings demonstrated that HFD

feeding induces EIF2α phosphorylation, indicating activation of the PERK pathway, while FDE supplementation restored the EIF2α phosphorylation level to a normal level compared to that in the control group (Fig. 2F and G). Moreover, CHOP acts as a crucial downstream effector of the PERK-EIF2α pathway [22], and supplementation with FDE effectively reduced the HFD-induced upregulation of CHOP expression. These results indicate that supplementation with FDE inhibited the activation of the PERK-EIF2α-CHOP pathway.

Discussion

In the present study, we investigated the efficacy of supplementation with FDE in treating NAFLD by establishing a HFD-induced mouse model. Interestingly, our experimental evidence demonstrated that FDE supplementation can reduce hepatic lipid accumulation in HFD-fed mice by inhibiting de novo synthesis (DNL), promoting fatty acid β-oxidation, and improving ER function (Fig. 3). These findings provide novel insights into the mechanism underlying FDE supplementation for improving NAFLD.

The liver functions as the central hub for lipid metabolism and exerts precise control over lipid homeostasis through a myriad of complex biochemical reactions, signaling pathways, and cellular communication. Under normal circumstances, the liver stores only small amounts of fatty acids as TG, and its content is less than 5% [23]. However, dysregulation of hepatic lipid metabolism, including excessive activation or inhibition of fatty acid uptake, DNL, β-oxidation, and export, can lead to excessive accumulation of lipids and their metabolites within hepatocytes. This cascade can trigger lipotoxicity, inflammation, apoptosis, and other abnormal cell signaling pathways [24], ultimately promoting NAFLD development. Therefore, the key to effectively treating NAFLD is reducing hepatic lipid accumulation. Hepatic lipogenesis is primarily regulated by SREBP-1c, which is activated by HFD and plays a crucial role in NAFLD development [25]. Therefore, inhibiting SREBP-1c expression is beneficial for treating NAFLD. Our study confirmed that FDE supplementation significantly reversed the overexpression of SREBP-1 C and its downstream target SCD1 induced by HFD. Furthermore, FDE increased the expression of CPT1α compared to the HFD group, which is known to promote fat uptake and mitochondrial fatty acid β-oxidation. These findings suggest that the protective effect of FDE against NAFLD may be attributable to reduced lipid acquisition and increased lipid disposal.

In eukaryotic cells, the ER is an important organelle for protein folding and lipid synthesis. Various perturbations, such as HFD consumption, inflammation, viral infections, and drug exposure, can disrupt ER homeostasis, leading to unfolded protein response (UPR) signaling

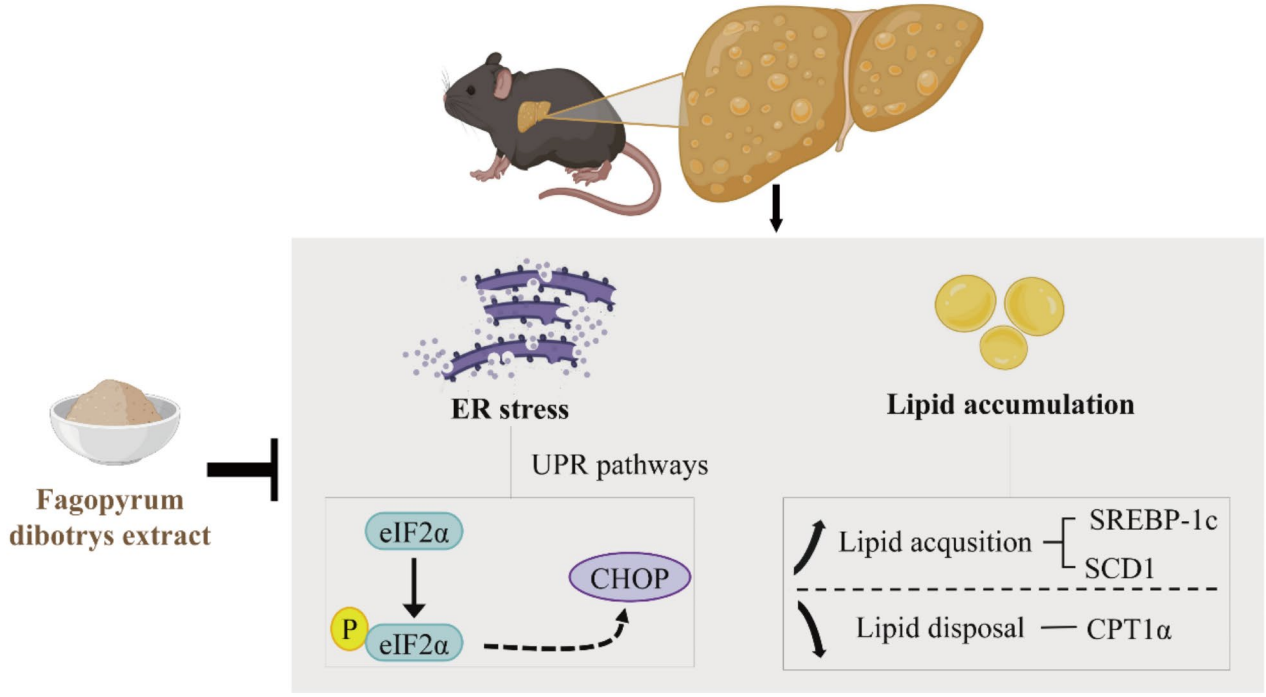

Fig. 3 Schematic model of FDE improving NAFLD. ER stress and lipid metabolism disorders play crucial roles in the development of NAFLD. Supplementation with FDE can alleviate NAFLD by improving lipid metabolism disorders, including reduced lipid synthesis and enhanced fatty acid β-oxidation, as well as by attenuating ER stress, mainly through inhibiting the activation of PERK-EIF2α-CHOP pathway in the livers of NAFLD mice

pathway activation and subsequent downstream events [26, 27]. Our study demonstrated that supplementation with FDE reduces the expression of HFD-induced ER stress markers, such as GRP78 and CHOP. These findings suggest that FDE has the potential to inhibit ER stress. To further elucidate the mechanism of FDE on ER stress, we investigated ER stress-related pathways. In early stage of ER stress, the PERK pathway is initially activated. This activation leads to EIF2α phosphorylation, and selectively promotes the translation of certain genes [28]. It has been reported that there is crosstalk between the PERK pathway and molecules involved in lipid metabolism, and high levels of PERK-EIF2α contribute to lipid accumulation by activating SREBP-1c, as well as inhibiting very low-density lipoprotein (VLDL) secretion [29, 30]. Therefore, inhibiting the PERK pathway helps to reduce hepatic lipid deposition. Interestingly, FDE supplementation reversed the abnormal expression of EIF2α phosphorylation and CHOP in NAFLD mice, indicating that the PERK-EIF2α-CHOP axis may be a primary target through which FDE alleviates NAFLD.

In conclusion, our study provides novel evidence that FDE effectively mitigates ER stress and improves lipid metabolism disorders in the treatment of NAFLD. Additionally, the PERK-EIF2α-CHOP pathway may be the potential mechanism of action for FDE. The experimental evidence also strongly supported the potential of FDE as a promising therapeutic agent for treating ER stress-induced diseases.

Limitations

This study has not yet identified the main bioactive compounds of FDE responsible for its therapeutic effects, and relevant research needs to be strengthened in the future to promote the development of pharmacotherapies targeting NAFLD.

Abbreviations

ATF6	Activating transcription factor 6
CHOP	C/EBP homologous protein
CPT1α	Carnitine palmitoyl transferase 1α
DNL	De novo synthesis
EIF2α	Eukaryotic translation-initiation factor 2α
ER	Endoplasmic reticulum
FDE	*Fagopyrum dibotrys* extract
GRP78	Glucose-regulated protein 78
HFD	High-fat diet
JNK	C-Jun N-terminal kinase
NAFLD	Nonalcoholic fatty liver disease
NF-κB	Nuclear factor kappa B
PERK	Protein kinase RNA–like ER kinas
SCD1	Stearoyl coenzyme a desaturase-1
SREBP-1c	Sterol regulatory element binding protein 1c
TC	Total cholesterol
TG	Triglyceride
VLDL	Very low-density lipoproteins

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Author contributions

DW and DZ performed the experiments and drafted the manuscript. ZYZ and YNZ discussed the results and strategy. YW and HC collected the data. JJL and LQM approved the final version to be published.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Animal Care and Use Committee of Kunming Medical University (Approval no. kmmu20211584). All experiments and methods were conducted in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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