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Review article

Pharmacology of bioactive compounds from plant extracts for improving non-alcoholic fatty liver disease through endoplasmic reticulum stress modulation: A comprehensive review

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition with significant clinical implications. Emerging research indicates endoplasmic reticulum (ER) stress as a critical pathogenic factor governing inflammatory responses, lipid metabolism and insulin signal transduction in patients with NAFLD. ER stress-associated activation of multiple signal transduction pathways, including the unfolded protein response, disrupts lipid homeostasis and substantially contributes to NAFLD development and progression. Targeting ER stress for liver function enhancement presents an innovative therapeutic strategy. Notably, the natural bioactive compounds of plant extracts have shown potential for treating NAFLD by reducing the level of ER stress marker proteins and mitigating inflammation, stress responses, and de novo lipogenesis. However, owing to limited comprehensive reviews, the effectiveness and pharmacology of these bioactive compounds remain uncertain.

Objectives: To address the abovementioned challenges, the current review categorizes the bioactive compounds of plant extracts by chemical structures and properties into flavonoids, phenols, terpenoids, glycosides, lipids and quinones and examines their ameliorative potential for NAFLD under ER stress.

Methods: This review systematically analyses the literature on the interactions of bioactive compounds from plant extracts with molecular targets under ER stress, providing a holistic view of NAFLD therapy.

Results: Bioactive compounds from plant extracts may improve NAFLD by alleviating ER stress; reducing lipid synthesis, inflammation, oxidative stress and apoptosis and enhancing fatty acid metabolism. This provides a multifaceted approach for treating NAFLD.

Conclusion: This review underscores the role of ER stress in NAFLD and the potential of plant bioactive compounds in treating this condition. The molecular mechanisms by which plant bioactive compounds interact with their ER stress targets provide a basis for further exploration in NAFLD management.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver condition characterised by excessive triglyceride (TG) accumulation in hepatocytes, leading to hepatic steatosis [1]. The endoplasmic reticulum (ER) is the primary site of accumulation of lipid metabolism-related enzymes and regulatory proteins [2] that critically influence dynamic lipid balance in hepatocytes. Consequently, the relationship between the ER and NAFLD has garnered substantial attention in metabolic research worldwide. Extensive investigations have revealed that various factors, such as over-nutrition, protein metabolic pathway disorders, redox homeostasis imbalance, inflammation and insulin resistance (IR), disrupt ER homeostasis [3], which may induce the cellular unfolded protein response (UPR) [4], endoplasmic reticulum overload response (EOR) [5,6] and sterol-regulated cascade response (SRCR) [7], leading to ER stress, the 'second strike' in NAFLD development. Notably, excessive ER stress exacerbates steatosis and IR, amplifies inflammatory cascades, induces apoptosis and results in hepatocyte injury [8–10], thereby playing a pivotal role in NAFLD progression. Therefore, ER stress and NAFLD have reciprocal causal relationships, with the former actively regulating hepatic lipid metabolism.

The interaction of ER stress with the abovementioned pathogenic factors is known as the 'cross-talk effect' [11]. Substantial evidence has indicated that ER stress activates the UPR, EOR and SRCR, leading to cross-talk with signal transduction pathways of IR, inflammation and lipid synthesis [11–13] as well as progression of NAFLD to non-alcoholic steatohepatitis (NASH) (Figs. 1 and 2). The specific mechanisms is as follows: the expression of ER stress/UPR marker proteins, including glucose regulatory protein 78 (GRP78), inositol-requiring enzyme 1 (IRE1), protein kinase R-like ER kinase (PERK) and activating transcription factor 6 (ATF6), can over-activate downstream signal transduction pathways [14]. For instance, excessive IRE1 phosphorylation recruits tumour necrosis factor-alpha (TNF-α) receptor-related factor-2 (TRAF2) and activates Jun N-terminal kinase (JNK), which in turn inhibits insulin

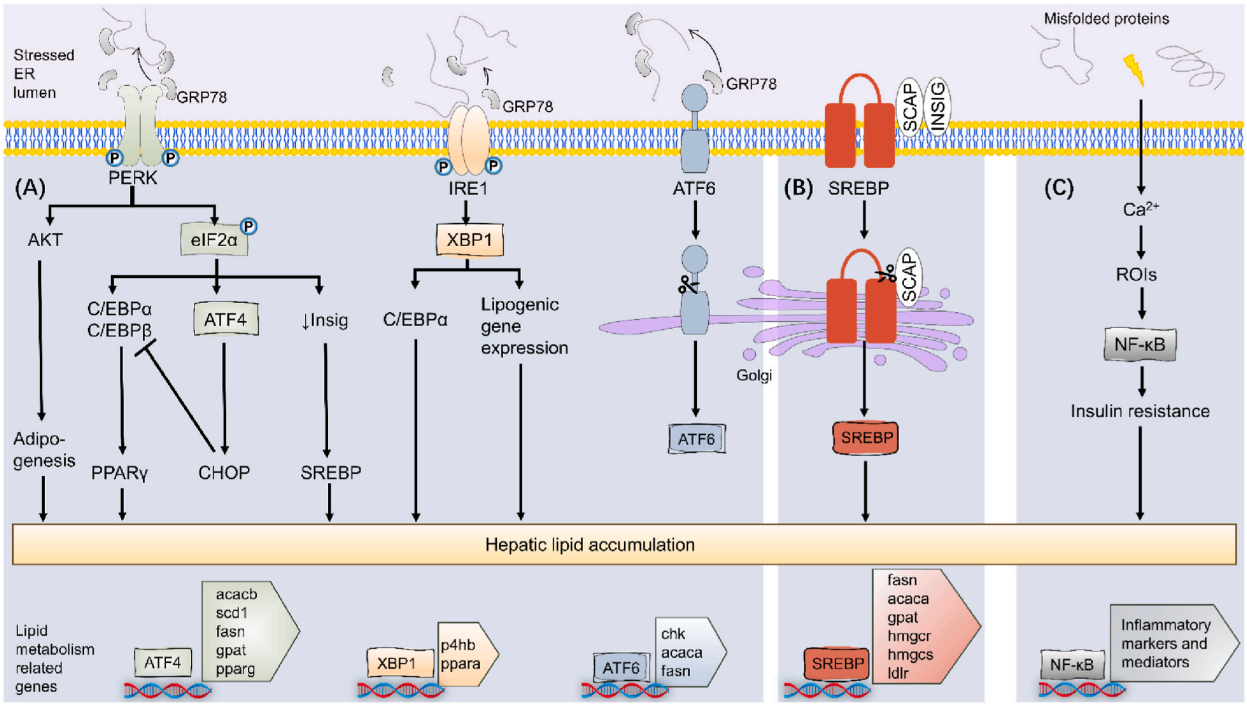


Fig. 1. UPR, SRCR and EOR interact with lipid metabolic pathways. (A) UPR signalling pathways. Protein kinase RNA-like endoplasmic reticulum kinase (PERK) activates protein kinase B (AKT), promoting adipogenesis under ER stress. Simultaneously, PERK stimulates the expression of key adipogenic regulators CCAAT/enhancer binding protein α (C/EBPα), C/EBPβ and peroxisome proliferator-activated receptor γ (PPARγ) and reduces the protein translation of insulin-induced gene 1 (Insig1), thereby enhancing the activation of sterol regulatory element binding protein (SREBP) through the phosphorylation of eukaryotic initiation factor 2α (eIF2α). However, under conditions of severe or prolonged ER stress, the downstream expression of CHOP, regulated by activating transcription factor 4 (ATF4), may disrupt the balance of C/EBPs. In addition, the inositol-requiring enzyme 1α (IRE1α)/X-box binding protein 1 (XBP1) pathway contributes to hepatic lipid accumulation by inducing an increase in the expression of lipogenic genes and augmenting C/EBPα activity. (B) SRCR pathway. Insig and SREBP/SREBP cleavage-activating protein (SCAP) complex dissociates from the ER membrane during ER stress. Subsequently, the SREBP–SCAP complex translocates to the Golgi apparatus, where it undergoes proteolytic cleavage by site 1 and site 2 proteases. The cleaved SREBP fragment enters the nucleus and activates genes responsible for sterol and lipid biosynthesis and uptake. (C) EOR pathway. ER stress, induced by the accumulation of misfolded proteins, prompts the release of Ca^{2+} from the ER into the cytoplasm, inducing the generation of reactive oxygen intermediates (ROIs). Consequently, the EOR pathway is activated, leading to the nuclear translocation of hepatic nuclear factor-kappa B (NF-κB). This, in turn, contributes to insulin resistance (IR) and inflammation, which exerts an influence on lipid accumulation. In summary, Fig. 2 delineates the pivotal role of transcription factors, such as ATF4, XBP1s, ATF6, SREBP and NF-κB, in orchestrating lipid metabolism within the framework of UPR, SRCR and EOR pathways.

receptor signalling by phosphorylating insulin receptor substrate (IRS)-1 via serine, leading to IR [15,16], which is the basis of NAFLD pathology. Moreover, activated PERK phosphorylates eukaryotic initiation factor 2α (eIF2α) under ER stress, promoting adipogenesis and sustaining hepatic steatosis in NAFLD pathogenesis [17].Another ER stress response-related mechanism involves the release of Ca^{2+} via EOR from the ER lumen into the cytosol, inducing the production of reactive oxygen species (ROS) production and activating the expression of nuclear factor-kappa B (NF-κB) [18]. Thus, ER stress can couple with intracellular inflammatory responses, resulting in hepatocellular injury and NASH development. Moreover, ER stress can deplete cholesterol form the ER membrane surface, thereby activating the expression of sterol regulatory element binding proteins (SREBPs), which form a complex with SREBP cleavage activating protein (SCAP) and are enzymatically cleaved into transcription factors. These transcription factors enter the nucleus and enhance the transcription of genes related to cholesterol and fatty acid synthesis and uptake [19]. Additionally, ER stress can inhibit the transcription of insulin-inducible gene 1 via the PERK–eIF2α pathway, enhancing SREBP activity to promote lipid synthesis and aggravate steatosis [20]. These findings reveal the central role of dynamic cross-talk between ER stress and other pathogenic factors in NAFLD development [8,21], implying that novel drugs targeting the UPR, EOR or SREBPs for reducing ER stress may effectively alleviate inflammation, IR and other risk factors in NAFLD treatment.

However, only a few small chemosynthetic molecules have shown positive therapeutic effects in metabolic diseases by inhibiting UPR branches to attenuate ER stress. For example, Simon-Szabo [22] reported that metformin (MET) protects against NAFLD by inhibiting IRE1–X-box binding protein 1 (XBP1) transduction pathway, promoting the proliferation of β-cells and ameliorating IR. Moreover, plant-derived therapeutics exhibit various pharmacological effects, such as insulin-sensitising [23], anti-obesity, hypolipidemic and hepatoprotective effects [24–26]. These multi-pharmacologic bioactive compounds from plant extracts have better safety profiles and lower toxicity and drug resistance than chemically synthesised drugs. Various plant bioactive compounds extracts inhibit ER stress and the associated mitochondrial damage, oxidative stress, inflammatory response and apoptosis, thus inhibiting NAFLD progression [27]. Thus, a comprehensive review of experimental studies on the bioactive compounds from plant extracts targeting ER stress is essential for identifying novel therapeutic agents for NAFLD.

Therefore, the present review discusses the existing literature on plant bioactive extracts, exploring their protective mechanisms against NAFLD through ER stress modulation. Specifically, this review discusses the molecular mechanisms of ER stress regulation associated with flavonoids, phenols, terpenoids, glycosides, lipids and quinones, which were categorised based on their functional groups and chemical structures. Overall, this review provides a valuable reference for clarifying the role of plant bioactive compounds from in NAFLD treatment, which may facilitate the development of botanical drugs targeting the ER, opening new avenues for clinical treatment.

2. Discussion: regulatory effects of bioactive compounds from plant extracts on ER stress

2.1. Flavonoid compounds

Recent studies have established the roles of plant-derived flavonoids in mitigating ER stress, enhancing lipid metabolism, ameliorating IR, attenuating inflammatory responses, and combating oxidative stress, placing them at the forefront of NAFLD research [28]. Notably, the efficacy of flavonoids in modulating the IRE1α/XBP1 signalling pathway has been elucidated through IRE1α

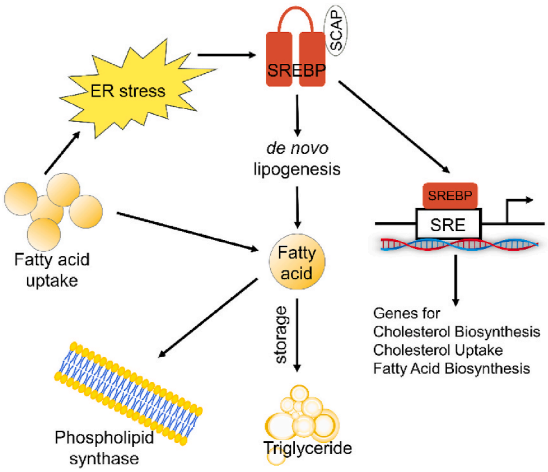


Fig. 2. Cellular function of SRCR in lipidogenesis. Excessive accumulation of fatty acids (FAs) in NAFLD induces ER stress, which activates SRCR, resulting in the generation of phospholipid bilayers by the SREBP/SCAP complex. This augments TG content through the amplification of de novo lipogenesis (DNL). Furthermore, cleaved SREBP undergoes nuclear translocation, where it functions as a transcription factor, binding to sterol response elements (SREs). Notably, SREBP can directly enhance the transcription of genes pivotal for the synthesis and uptake of cholesterol, FA, TG and phospholipids. Despite governing distinct biosynthetic pathways, each isoform of SREBP operates under the regulatory influence of sterols and SCAP.

agonists [29] and targeted experiments using GRP78-specific small interfering RNA (siRNA) [30]. These insights not only enhance our understanding of flavonoid-mediated intervention in NAFLD but also lay a foundation for the advancement of bespoke therapeutic approaches.

2.1.1. Quercetin

Quercetin (Que; 3, 3′,4′,5,7-pentahydroxyflavone) is abundant in onions and tea [31]. Xinhong Zhu et al. [29] established NAFLD models of steatosis using free fatty acid (FFA)-stimulated human hepatocellular carcinoma HepG2 cells and high-fat diet (HFD)-induced male Sprague–Dawley (SD) rats. Compared with the HFD control group, the administration of Que (100 mg/kg.bw) in rats for 8 weeks down-regulated the expression of hepatic ER stress marker proteins GRP78 and XBP1, reduced hepatic TG content by 39 % and increased the content of very low-density lipoprotein (VLDL) by 1.5-fold. Moreover, APY-29 (an IRE1α endonuclease activator) and cells treated with 100 μM Que up-regulated the levels of VLDL. These findings demonstrate that under ER stress conditions, Que promotes hepatic VLDL assembly via the IRE1α/XBP1s pathway, thereby reducing lipid accumulation in the liver and alleviating NAFLD. Consistently, Gnoni et al. [32] demonstrated that incubation with FFAs alone was insufficient to induce XBP-1 expression. They established an NAFLD model by co-incubating HepG2 cells with FFA and glucose. Treatment with 5 μM Que reduced the expression of ER stress marker proteins XBP-1 and *p*-eIF2α and inhibited the expression of SRCR response biomarker SREBP-1 transcription factor along with its downstream fatty acid synthesis enzymes—acetyl-CoA carboxylase (ACC) 1 and diacylglycerol acyltransferase 2 (critical enzymes in TG synthesis)—thereby inhibiting the dysregulation of the de novo lipogenesis (DNL) pathway. Overall, Que exerts a direct anti-adipogenic effect by inhibiting ER stress, regulating the SRCR pathway and reducing intracellular TG accumulation and steatosis. However, none of these experiments examined the dose range and minimal active concentration of Que. Therefore, follow-up experiments should be conducted to detect the optimal therapeutic concentration of Que to improve NAFLD.

2.1.2. Kaempferol

Kaempferol [KP; 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one] is mainly derived from the rhizome of the ginger plant *Kaempferia galanga* L. Ok-Kyung Kim et al. [33] pre-treated HepG2 cells with either 1.5 or 2.5 μg/mL KP, followed by treatment with 100 nM thapsigargin to induce ER stress by releasing Ca^{2+} from the cellular ER. KP treatment reduced the phosphorylation of the ER stress marker eIF2αas well as IRE1α and its downstream factor JNK and inhibited the mRNA expression of ATF4. Additionally, KP inhibited the serine phosphorylation of IRS1. These results indicate that KP partially inhibits ER stress and the ER stress-induced inhibition of IRS signalling, ameliorating IR. However, this study did not directly demonstrate a straightforward ameliorative effect of KP on NAFLD *in vivo*. To further validate the potential of KP, C57BL/6 mouse models of NASH were established and fed with HFD for 24 weeks, and the HFD + KP group was orally administered with 20 mg/kg KP daily during the last 4 weeks of the experiment. HepG2 and AML12 cells were treated *in vitro* with a certain amount of palmitate (PA)/oleic acid (OA) to establish a cell model of steatosis, followed by co-incubation with 20, 40 and 60 μmol/L KP. Xiang et al. [34] conducted *in vitro* and *in vivo* experiments and demonstrated that KP treatment significantly reduces the mRNA and protein expression of various ER stress-related factors, such as PERK, eIF2α, ATF6, ATF4, XBP1, CCAAT-enhancer-binding protein homology protein (CHOP), IRE1α and GRP78, as well as liver X receptor (LXR) and its direct target gene [35,36] lysophosphatidylcholine acyltransferase 3 (*LPCAT3*); these effects were accompanied by reduced contents of TG and lipid droplets. These results suggest that KP dose-dependently modulates the LXRα–LPCAT3–ERS pathway, attenuating hepatocyte ER stress and lipid accumulation, which may exert a therapeutic effect on NASH.

2.1.3. Hesperidin

Hesperidin (HSP; 5,7,3′-trihydroxy-4′-methoxy-flavanone 7-rhamno glucoside; $C_{28}H_{34}O_{15}S$) is predominantly found in the peel and white membranes of citrus fruits. Xie et al. [37] established NAFLD models using HFD-fed SD rats and FFA-stimulated human THP-1 macrophages. They indicated that treatment with 200 mg/kg HSP for 12 weeks significantly inhibited the expression of ER stress markers such as GRP94, ATF6, ATF4, p-PERK and p-IRE1α as well as inflammatory markers such as IL-1β, IL-6 and TNF-α in the rat liver. Similarly, *in vitro* experiments demonstrated that 140 mg/L HSP down-regulated the expression of the abovementioned ER stress- and inflammation-related markers and reduced lipid accumulation in THP-1 cells. Additionally, HSP decreased the protein expression of CCAAT/enhancer binding protein (C/EBP), SREBP-1c and SREBP-2. These results indicate that HSP inhibits HFD/FFA-induced ER stress and inflammatory responses, reduces hepatic lipid synthesis and improves steatosis.

2.1.4. Hesperetin

Hesperetin ($C_{16}H_{14}O_6$), a metabolite of HSP, is widely found in citrus fruits such as *Citrus* × *paradisi* Macfad. and *Citrus* × *limon* (L.) Osbeck. Genga et al. [30] first pre-treated HepG2 cells with 100 μmol/L hesperetin for 30 min and then with 0.5 mmol/L PA to mimic the pathological state of lipid overload in NAFLD. The results showed that hesperetin pre-treatment significantly affected the expression of ER stress marker proteins, increasing the mRNA and protein levels of GRP78 and XBP1 while decreasing the levels of *p*-eIF2α and *p*-JNK levels; furthermore, hesperetin treatment reduced caspase-3/7 activity in HepG2 cells. Moreover, *GRP78* knockdown via siRNA eliminated the protective role of hesperetin in HepG2 cells. Overall, hesperetin exhibits therapeutic potential against NAFLD by activating the GRP78/XBP1 arm of the UPR signalling pathway, augmentation of GRP78 and XBP1 expression, inhibiting of PA-induced ER stress and conferring protection against hepatocyte death.

2.1.5. Procyanidin B2

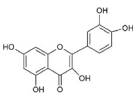
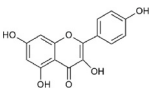
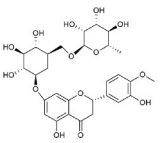
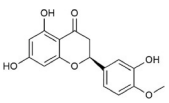
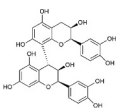
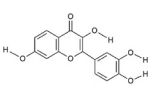
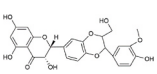
Procyanidin B2 (PCB2) is an active ingredient derived from *Cinnamomum cassia* Siebold. Yi-Ming Li et al. [38] established two HepG2 cell models of NAFLD: one treated with PA alone and the other co-treated with PCB2 (2.5, 5.0 or 10.0 μM) and 125 μM PA for

24 h. They revealed that the protein expression levels of ER stress-related factors such as GRP78, GRP94, PERK, eIF2α, IRE1α, CHOP and ROS were inversely correlated with the PCB2 dose. Additionally, PCB2 treatment in cells was assessed using the ER stress inhibitor 4-phenylbutyric acid and the agonist thapsigargin. Both positive and negative experiments demonstrated that PCB2 treatment attenuated PA-induced ER stress, reduced ER stress-induced oxidative stress and restored anti-oxidant enzyme activity and calcium homeostasis. In summary, PCB2 demonstrates beneficial modulating effects on NAFLD, including the improvement of ER stress.

2.1.6. Fisetin

Fisetin (FisT; 3,3′,4′,7-tetrahydroxyflavone) is mainly found in plants such as *Rhus succedanea* L. Dai et al. [39] treated the hepatocyte lines L-02 and AML12 with 250 μM PA to simulate hepatic lipid deposition. They revealed that 20 μM FisT treatment in both cell lines significantly decreased the mRNA and protein expression levels of ER stress markers such as GRP78 and CHOP as well as mRNA

Table 1
Details regarding flavonoid compounds as potential treatment options for NAFLD.

Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modelling method	Experimental dose of plant bioactive compounds	Mechanism
2.1.1 Quercetin	$C_{15}H_{10}O_7$ 	Male SD rats HepG2 cells	HFD for 8 weeks FFA; co-incubated with FFA and glucose for 24 h	100 mg/kg/d for 8 weeks 100 μM; 5 μM for 24 h	↓UPR: GRP78, IRE1, XBP1 and *p*-eIF2α ↓SRCR: SREBP-1 [29,32] Others: alleviated lipid metabolic dysfunction, regulated synaptic plasticity and balanced the abundance of TREM1 and TREM2 [103].
2.1.2 Kaempferol	$C_{15}H_{10}O_6$ 	Male C57BL/6 mice HepG2 cells; AML12 cells	HFD for 24 weeks 100 nM thapsigargin; 1PA:2OA-stimulated for 24 h	20 mg/kg/d during the last 4 weeks pre-treated with 1.5 or 2.5 μg/mL; treated with 20, 40, and 60 μmol/L for 24 h	↓UPR: GRP78, PERK, eIF2α, ATF4, IRE1α, XBP1 and CHOP [33,34] Others: inhibited the nuclear transcriptional activity of NF-κB and suppressed inflammatory responses [104].
2.1.3 Hesperidin	$C_{28}H_{34}O_{15}$ 	Male SD rats, male C57BL/6 mice Human THP-1 macrophages, HepG2 cells	HFD for 12 weeks 0.5 mmol/L FFA, 1 μM thapsigargin	200 mg/kg/d for 12 weeks 140 mg/L for 24 h	↓UPR: GRP94, p-PERK, ATF4, p-IRE1α and ATF6 ↓SRCR: SREBP-1 and SREBP-2 [37] Others: inhibited NF-κB activation, improving the lipid profile in patients with NAFLD [105]; attenuated lipid accumulation by increasing *p*-AMPK expression [106].
2.1.4 Hesperetin	$C_{16}H_{14}O_6$ 	HepG2 cells	0.5 mmol/L PA for 24 h	pre-treated with 100 μmol/L for 30 min	↑UPR: GRP78, XBP1 ↓UPR: *p*-eIF2α [30] Others: activated the PI3K/AKT-Nrf2 pathway, increasing anti-oxidant expression and inhibiting NF-κB activation and inflammatory cytokine secretion in NAFLD rat models [107].
2.1.5 Procyanidin B2	$C_{30}H_{26}O_{12}$ 	HepG2 cells	125 μM PA for 24 h	2.5, 5.0 and 10.0 μM for 24 h	↓UPR: GRP78, GRP94, PERK, eIF2α, IRE1α and CHOP [38] Others: reduce IR and liver steatosis by remodelling intestinal flora, decreasing endotoxemia and down-regulating SREBP-1c and FASN in NAFLD rabbit models [108].
2.1.6 Fisetin	$C_{15}H_{10}O_6$ 	Male C57BL/6 N mice L-02 and AML12 cells	HFD for 16 weeks 250 μM PA for 24 h	80 mg/kg/d for 8 weeks 20 μM for 24 h	↓UPR: GRP78, CHOP ↓SRCR: FASN, SCD1 and PPARγ [39] Others: increased sirt1 and pAMPKα expression; suppressed SREBP-1c, C/EBPα and PPAR-γ expression; and enhanced β-oxidation to reduce hepatic steatosis [109].
2.1.7 Silybin	$C_{25}H_{22}O_{10}$ 	Male Swiss albino mice; male C57BL/6 mice HepG2 cells	30 % fructose water for 70 d; HFD for 8 weeks 100 μM PA	100 or 200 mg/kg/d for 10 d; 50 or 100 mg/kg/d for 4 weeks pre-treated with 50 μM	↓UPR: GRP78, IRE1, XBP1 and eIF2α [40,41] Others: activated the Nrf2 pathway, inhibited the NF-κB signalling pathway and alleviated hepatic steatosis, fibrosis and inflammation [110].

expression levels of fatty acid synthesis markers (FASN, SCD1 and PPARγ). Additionally, FisT co-incubation reduced the intracellular TG content. *In vivo* experiments demonstrated that treatment with 80 mg/kg FisT reduced the expression of these genes and proteins, mitigated inflammatory cell infiltration and relieved lipid deposition in C57BL/6 N mice with HFD-induced NAFLD after 16 weeks. These findings confirm that FisT inhibits GRP78-mediated ER stress, improves cellular lipid degeneration and alleviates NAFLD pathologies.

2.1.7. Silymarin/Silybin

Silymarin is a natural active ingredient obtained from the dried fruit of *Silybum marianum* (L.) Gaertn., with silybin being one of its main components. Sahin et al. [40] established NAFLD models using male *Swiss albino* mice that were fed with 30 % fructose for 70 days and then treated with 100 or 200 mg/kg silymarin for the next 10 days. They revealed that compared with the NAFLD model group, treatment with 200 mg/kg silymarin effectively reduced the expression of ER stress elements—GRP78 and XBP1—in mouse livers. Additionally, silymarin treatment reduced lipid droplet levels in these livers as well as aspartate aminotransferase, alanine aminotransferase and glucose levels in the serum. These results indicated that silymarin attenuates NAFLD by decreasing the expression levels of the ER stress proteins GRP78 and XBP1. However, further detailed histopathological and biochemical index tests are warranted to determine whether the NAFLD model can be successfully established by feeding mice with normal diet and 30 % fructose water only.

Zhang et al. [41] established NAFLD models using male C57BL/6 mice that were fed with HFD for 8 weeks as well as using HepG2 cells that were treated with PA. Both *in vitro* and *in vivo* experiments revealed that silybin decreased the phosphorylation of ER stress elements IRE1α and eIF2α. Furthermore, silybin almost completely restored the level of NAD+, which is necessary for activating sirtuin 2 (SIRT2). Moreover, the inhibition of NLRP3 inflammasome assembly by silybin was blocked by silencing SIRT2 or treating cells with the SIRT2 inhibitor AGK2. These results indicated that silybin attenuates NAFLD by inhibiting NAD + depletion, relieving ER stress and preventing NLRP3 inflammasome assembly, with SIRT2 being an essential target for silybin to block NLRP3 inflammasome activation.

For an in-depth exploration of flavonoids as potential therapeutic agents in treating NAFLD, refer to Table 1. This table is expected to present a detailed and comprehensive overview, encompassing various aspects, such as experimental models (including *in vitro* cell lines or *in vivo* animal studies), methods of modelling NAFLD, experimental dosage parameters and the specific mechanisms of action of each flavonoid.

2.2. Phenol compounds

Research conducted using cellular and animal models has conclusively shown that phenol compounds markedly diminish the lipid load in the liver, thereby preventing the onset of steatosis and decelerating its progression to NASH through the inhibition of SREBP-1c-mediated DNL [42]. Our study elucidates the mechanisms through which polyphenols regulate ER stress. Specifically, these compounds predominantly mitigate ER stress and the consequent autophagy dysfunction by targeting both PERK–ATF4–CHOP and XBP1 signalling pathways.

2.2.1. Resveratrol

Resveratrol (RSV; 3,5,4′-trihydroxystilbene) is abundant in *Vitis vinifera* L., *Vaccinium corymbosum* L. and red wine [43]. Ding et al. [44] established a male Wistar rat model of NAFLD and treated it with 200 mg/kg RSV for 18 weeks. Compared with the HFD group, RSV treatment reduced the mRNA levels of the ER stress markers such as GRP78, PREK and CHOP while markedly increasing the mRNA level of the autophagy marker SIRT1 in the HFD + RSV group. Additionally, RSV treatment sharply decreased the accumulation of intracellular lipid droplets in rats, decreased the levels of TG and TC in the serum and liver tissue and increased HDL levels in the serum. These results indicate that RSV supplementation protects against HFD-induced NAFLD by reducing ER stress and enhancing the SIRT1–autophagy pathway. However, in this study, RSV was incorporated into HFD (5 g per rat) as the test diet. This approach could result in varying levels of RSV intake in rats with different dietary preferences, potentially introducing issues related to reproducibility and interpretability of results.

Chen et al. [45] improved the dose control by gavaging a unified dose of RSV. They pre-treated male C57BL/6J mice by orally administering 100 mg/kg/day RSV for 2 weeks and then induced ER stress and abnormal lipid metabolism by administering 1 μg/g tunicamycin (TM) intraperitoneally. All mice were sacrificed 24 h post-injection of TM. RSV pre-treatment activated the expression of liver SIRT1 and partially normalised the UPR sensor's activity level in mice. Furthermore, RSV reduced the mRNA expression levels of ER stress markers such as GRP78, GRP94, ATF4 and CHOP and the phosphorylation levels of IRE1α, thereby attenuating ER morphological damage and hepatocyte apoptosis. Therefore, by activating SIRT1 expression, RSV treatment can prevent the over-activation of the UPR sensor and aberrant expression of its downstream targets, alleviate ER stress and potentially prevent the progression of hepatic steatosis to NASH. However, this study employed a prophylactic administration approach, which may not be suitable for replicating the progressive development of NAFLD, which involves multiple stages such as fat accumulation, inflammation, and fibrosis. These processes unfold gradually over time and cannot be accurately simulated within the confines of a prophylactic administration model, with a limited duration of 2 weeks.

Pan et al. [46] established a SD rat model of obesity using HFD and treated rats in the experimental group with 100 mg/kg/day RSV orally for 8 weeks. RSV significantly reduced the protein levels of ER stress markers such as ATF4, CHOP and BiP as well as PERK phosphorylation levels in rat hepatocytes, although PERK remained unaffected by HFD. Additionally, RSV up-regulated the protein levels of PPARδ associated with the oxidative metabolism of fatty acid and cholesterol and down-regulated the protein levels of ATP-citrate lyase related to fatty acid and cholesterol biosynthesis. Compared with the HFD group, liver TG levels and steatosis were

significantly inhibitedin the HFD + RSV group. These results highlight the potential of RSV treatment to improve ER stress, regulate hepatic steatosis-related genes and protect against HFD-induced dyslipidaemia and hepatic steatosis, conferring a protective effect against NAFLD. Notably, in contrast to the current study result suggesting that RSV had no substantial impact on PERK expression, Ding et al. [44] reported a reduction in PERK expression with RSV treatment. These disparities may arise from variations in modelling techniques and treatment protocols. To comprehensively investigate and validate the effect of RSV on the ER stress marker PERK, further efforts are warranted using method optimisation, control variable management, and replication experiments.

2.2.2. Grape seed proanthocyanidins

Grape seed proanthocyanidins (GSPEs), derived from *Vitis vinifera* L., are known to possess high bioavailability for preventing obesity and hyperlipidaemia and targeting liver tissue. Yogalakshmi et al. [47] induced steatosis and ER stress in male albino Wistar rat model of NAFLD by providing a high-calorie diet (HCD) for 45 days. Rats in the HCD + GSPE group received 100 mg/kg/day GSPE via gavage during the last 15 days of the experiment, whereas those in the 50 mg/kg/day MET + HCD group were considered the positive control group. Compared with the HCD model group, GSPE administration reduced the mRNA abundance of ER stress markers such as PERK, IRE1 and ATF6 in rat livers by 0.8-, 1.4- and 0.9-fold, respectively. Additionally, significant decreases were observed in eIF2α and XBP1 protein expression levels by 3.7- and 5.2-fold, respectively, downstream of the ER stress pathway. These findings suggest that the intake of GSPE, MET or both can be a novel therapeutic option for NAFLD involving ER stress.

Sun et al. [48] used HFD for 8 weeks to establish a female SD rat model of obesity. Rats in the HFD + GSPE group received 500 mg/kg/day GSPE via gavage for the next 4 weeks. GSPE supplementation lowered the mRNA expression levels of the ER stress markers ATF6 and CHOP and fat synthesis-related gene *PPARγ*, thus preventing ER stress, apoptosis and fat deposition in rat hepatocytes. Moreover, it reduced steatosis, inflammatory infiltration and lipid droplet levels, with partial restoration of cell morphology observed in hepatocytes of the HFD + GSPE group. Based on these findings, GSPE amay act as a hepatoprotective agent against NAFLD by reducing ER stress, apoptosis and lipid synthesis and reversing liver injury.

2.2.3. Xanthohumol

Xanthohumol (XN) is an anti-oxidant extracted from *Humulus lupulus* L., which accounts for up to 1 % of the hops' dry weight. Miyata et al. [49] used HFD for 10 weeks to induce fatty liver in male C57BL/6J mice, subsequently categorizing all mice into HFD and HFD + XN groups, which were fed for additional 50 days. Adding 0.2 % or 0.4 % XN to the diet reduced the mRNA levels of hepatic SREBP-1 and FA synthesis target genes (*ACC1*, *FAS* and *SCD1*). Additionally, TG and cholesterol accumulation in the plasma and liver were found to be lower in the HFD + XN group. This suggests that XN reduces DNL by inhibiting the activation of SREBP and its downstream target genes in the mouse liver. Cellular experiments demonstrated the specific mechanism of action underlying this process XN maintained the SCAP/SREBP complex anchored to the ER by binding to Sec23/24 on the ER, preventing the complex from entering common coated protein II vesicles and impairing its ER–Golgi translocation. These findings indicate that XN partially alleviates ER stress and SREBP activation, contributing to the improvement of NAFLD induced by HFD.

2.2.4. Sesamol

Sesamol is found in *Sesamum indicum* L. seeds, with the maximum amount found in sesame oil (64.4 mg/100 g) [50]. Yang et al. [51] investigated the protective effect of sesamol in male SD rat models of NASH complicated by atherosclerosis, which were induced by a high-fat, high-carbohydrate and high-cholesterol diet (providing 4.015 kcal/g) along with intraperitoneal injection of 700,000 IU/kg vitamin D3 in weeks 1 and 5. Treatment with 0.05, 0.1 and 0.2 mg/mL sesamol (in drinking water) for 8 weeks inhibited the activation of the ER stress markers BiP and phosphorylated IRE1 as well as the expression of NLRP3 in the rat liver and ERS–IRE1 signalling pathway. In addition, sesamol treatment reduced XO activity, lowering uric acid levels in the liver and serum, and decreased serum and hepatic TG levels. These findings demonstrate that sesamol inhibits the expression of the ERS–IRE1 signalling pathway and NLRP3 in rats with NASH. Additionally, sesamol regulates uric acid metabolism by inhibiting XO activity and expression, alleviating ER stress, weakening steatosis and exerting a strong protective effect on NASH.

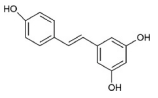
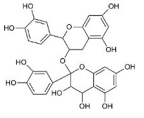
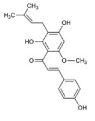
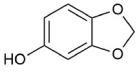
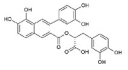
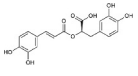
2.2.5. Salvianolic acid A

Salvianolic acid A (Sal A), a water-soluble compound derived from *Salvia miltiorrhiza* Bunge, is widely used in treating acute hepatitis and liver injury. Xiaojing Yan et al. [52] considered normal human hepatocyte line L-02 treated with TNF-α/D-galactosamine acid (D-GalN) as the model group and cells pre-treated with 1, 10 and 100 μmol/L Sal A + TNF-α/D-GalN as the experimental group. They conducted an assay and revealed that the Sal A group showed marked reductions in the levels of ER stress markers such as *p*-eIF2α, ATF4, GRP78, CHOP and caspase-4. Additionally, Sal A down-regulated the levels of cleaved-caspase-9, cleaved-caspase-3 and apoptosis-inducing factor. Moreover, it decreased the Bax/Bcl-2 ratio, calcium release levels and mitochondrial membrane permeability while increasing the mitochondrial membrane potential, a vital apoptosis marker. This study demonstrated that Sal A may attenuate ER stress and mitochondria-dependent apoptosis induced by TNF-α and D-GalN by inhibiting the Bax/Bcl-2 ratio and blocking calcium release in L-02 cells. These findings suggest that Sal A holds promise in treating NAFLD. This study was conducted at the cellular level; however, to extrapolate the potential effectiveness of Sal A to the broader biological system, further validation using animal models is warranted to better replicate the intricate physiological processes of NAFLD.

2.2.6. Rosmarinic acid

Rosmarinic acid (RA) is found in Labiatae or Boraginaceae plants [53], such as *Salvia rosmarinus* Spenn. and *Mentha canadensis* L., and has several biological activities [54], including anti-inflammatory and anti-diabetes effects. Balachander et al. [55] induced

Table 2
Details regarding phenolic compounds with the potential to treat NAFLD.

Biocompounds from Plant Extracts	Chemical and structural formula	Experimental model	Modelling method	Experimental dose of plant bioactive compounds	Mechanism
2.2.1 Resveratrol	$C_{14}H_{12}O_3$ 	Male Wistar rats; Male C57BL/6J mice; Male SD rats	HFD for 18 weeks; i.p. 1 μg/g tunicamycin for 24 h; HFD for 12 weeks	200 mg/kg for 18 weeks; pre-treated with 100 mg/kg/d for 2 weeks; 100 mg/kg/d for 8 weeks	↓UPR: GRP78, GRP94, PREK, ATF4, CHOP and p-IRE1α [44–46] Others: improved hepatic steatosis and induced autophagy by activating the cAMP-PKA-AMPK-SIRT1 signalling pathway [111].
2.2.2 Grape seed proanthocyanidins	$C_{30}H_{26}O_{13}$ 	Male Wistar rats; female SD rats	HCD for 45 d; HFD for 8 weeks	100 mg/kg/d for 45 d; 500 mg/kg/d for 4 weeks	↓UPR: PERK, eIF2α, IRE1, XBP1 and ATF6, as well as CHOP [47, 48] Others: reduced mRNA expression of lipid droplet proteins and SREBP-1c and activated PPAR-α, suppressing lipogenesis and promoting β-oxidation [112].
2.2.3 Xanthohumol	$C_{21}H_{22}O_5$ 	Male C57BL/6J mice	HFD for 10 weeks	0.2 % XN or 0.4 % XN-supplemented HFD for 50 d	↓SRCR: SREBP-1, ACC1, FAS and SCD1 [49] Others: reduced hepatic inflammation and expression of profibrogenic genes by decreasing the expression of TNF and IL-1, MCP-1 mRNA and collagen type I mRNA [113].
2.2.4 Sesamol	$C_7H_6O_3$ 	male SD rats	HF-HCC diet + i.p. 700,000 IU/kg vitamin D3 in weeks 1 and 5 week	0.05, 0.1 and 0.2 mg/mL in drinking water for 8 weeks	↓UPR: BiP/GRP78 and p-IRE1 [51] Others: activated Nrf2, reduced oxidative stress and inflammation and improved hepatic steatosis [114].
2.2.5 Salvianolic acid A	$C_{26}H_{22}O_{10}$ 	L-02 cells	100 ng/mL TNF-α and 44 μg/mL D-galactosamine acid for 24 h	1, 10 and 100 μmol/L for 24 h	↓UPR: GRP78, *p*-eIF2α, ATF4 and CHOP [52] Others: activated AMPK and up-regulated SIRT1, exerting anti-lipotoxic effects [115].
2.2.6 Rosmarinic acid	$C_{18}H_{16}O_8$ 	HepG2 cells	1 mM OA for 24 h	20 μM for 24 h	↓UPR: p-PERK, *p*-eIFα, p-IRE1, ATF6, and CHOP [55] Others: repaired mitochondrial damage, down-regulated YAP1 and TAZand up-regulated PPARγ and PGC-1α [116].
2.2.7 Caffeic acid	$C_9H_{10}FNO_2S$ 	C57BL/6 mice AML12 cells	HFD for 10 weeks 250 μM PA for 24 h	50 mg/kg/d for 10 weeks 50 μM	↓UPR: BiP, eIF2α, ATF4, CHOP and XBP-1 ↓SRCR: SREBP-1c, FasN, HSL, SCD1, C/EBPa and PEPK [56] Others: alleviated endotoxemia and proinflammatory response and attenuated gut microbiota dysbiosis [117].

steatosis in HepG2 cells with 1 mM OA and 20 μM RA. RA treatment decreased the expression of ER stress markers such as p-PERK, p-IRE-1, ATF-6, *p*-eIF-α and CHOP as well as reduced ROS levels while increasing the activity of various enzymes (SOD, CAT and GPx) and antioxidants (GSH and GSSG). Moreover, RA treatment restored the disturbed cellular autophagy by normalising the protein expression of beclin-1, LC3II, autophagy-related protein 7 (ATG7) and ATG5, which was previously inhibited by OA. RA treatment also reduced intracellular TC and TG levels. These findings demonstrate that RA exerts a hepatoprotective effect by inhibiting ER stress, attenuating oxidative stress and restoring disturbed autophagy, thereby abrogating the progression of NAFLD to NASH. However, this study did not explore the underlying molecular mechanisms. Further in-depth molecular studies may offer more compelling evidence.

2.2.7. Caffeic acid

Caffeic acid (CA) is found in high concentrations in *Cynara scolymus* L. and *Solidago decurrens* Lour., and exerts pharmacological effects such as choleretic and anti-oxidant effects. Hong Min Kim et al. [56] administered 50 μM CA to 250 μM PA-treated AML12 hepatocytes with steatosis. *In vitro* experiments revealed that CA treatment decreased the protein expression levels of ER stress markers such as BiP, ATF4, CHOP and XBP-1 but increased the protein expression of ATG7 and microtubule-associated protein 1A/1B-light chain 3. Additionally, CA reduced the mRNA levels of fatty acid synthesis-related genes (*SREBP-1c*, *FasN*, *HSL*, *SCD1*, *C/EBPa* and *PEPCK*) and a lipid transporter gene, thus reducing intracellular lipid accumulation by 60 %. Furthermore, CA restored insulin signalling that was previously inhibited by PA and reduced the levels of inflammatory signalling markers (pIKK and *p*-JNK). Similarly, *in vivo* experiments revealed a decrease in the expression of ATF4, CHOP and eIF2α and an increase in the expression of the hepatic autophagy markers ATG 7 and ATG 5 in C57BL/6 mouse livers in the HFD + CA (50 mg/kg/day) group. Moreover, CA not only lowered lipid accumulation in the liver but also improved glucose intolerance and insulin sensitivity. These results suggest that CA improves NAFLD through multiple pathways, including attenuating ER stress, enhancing autophagy and improving insulin sensitivity.

Moreover, for a comprehensive analysis of the efficacy of phenolic compounds in NAFLD treatment, one is advised to peruse Table 2.

2.3. Terpenoid compounds

Terpenoids, which are active constituents of plant origin with substantial hepatoprotective properties [25], modulate the three principal UPR pathways under ER stress [57]. Our findings indicate that these compounds exert significant preventive and therapeutic effects on NAFLD, predominantly by inhibiting CHOP expression though the modulation of PERK and ATF6 signalling pathways.

2.3.1. Astaxanthin

Astaxanthin (ASX) is a lutein-like carotenoid naturally produced by phytoplanktons, such as *Haemococcus pluvialis* [58,59]. Bhuvaneswari et al. [60] fed adult male *Mus musculus* albino mice with a control diet or high-fructose fat diet (HFFD) for 60 days to induce lipid accumulation. Compared with the HFFD group, treatment from days 16–60, with ASX in 0.3 mL of olive oil (2 mg/kg.bw/day) via gavage reduced the protein expression of ER stress markers such as Ig-binding protein, PERK, phosphorylated eIF2α, spliced XBP-1, ATF6 and apoptotic marker caspase-12 in mouse liver in the HFFD + ASX group. Additionally, ASX treatment decreased the phosphorylation of JNK1 and IκB kinase βwhile reducing the nuclear translocation of NF-κB p65; moreover, it attenuated HFFD-induced lipid droplet deposition in the liver. Thus, ASX may improve steatosis and attenuate NAFLD by reducing ER stress and the associated NF-κB-mediated inflammatory responses. Nevertheless, this study did not exclude the effect of unsaturated fatty acid olive oil on steatosis.

2.3.2. Ursolic acid

Ursolic acid (UA) is found in various plants, including *Prunella vulgaris* L. and *Ilex rotunda* Thunb., and has been shown to affect insulin and lipid metabolism [61]. Jian-Shuang Li et al. [62] used the human hepatic cell line L-02 to simulate NAFLD and revealed that 10–30 μg/mL UA substantially inhibited 400 μM PA-induced increase in the expression of ER stress marker such as IRE1α, p-PERK, *p*-JNK and CHOP; this treatment also decreased intracellular lipid accumulation. These results suggest that UA treatment effectively prevents the development of NAFLD and the associated liver injury by suppressing hepatic ER stress.

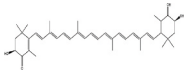
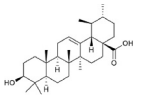
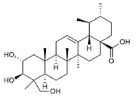
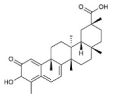
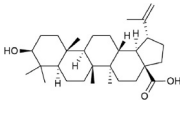
2.3.3. Asiatic acid from Potentilla chinensis

Asiatic acid from *Potentilla chinensis* (AAPC), an active ingredient isolated from *Potentilla chinensis* Ser., is widely used as a traditional botanical drug for treating liver diseases. Dandan Wang et al. [63] established an animal model of NAFLD using SD rats fed with HFD for over 18 weeks. These rats were administered with 4 or 8 mg/kg AAPC from weeks 8–18. Compared with the model group, the expression levels of proteins involved in three UPR pathways, including p-PERK, PERK, *p*-eIF2α, eIF2α, ATF4, CHOP, p-IRE1, XBP-1, caspase-12, *p*-JNK and ATF6, decreased significantly in the liver tissues of treated rats. Additionally, AAPC markedly reduced hepatic steatosis. In HepG2 cells induced with 0.5 mmol/L OA, treatment with 10, 20 or 40 μmol/L AAPC led to a considerable decrease in the expression levels of SREBP-1c, LXRα, FAS and ACC1, whereas *p*-AMPK protein expression levels were up-regulated. These findings demonstrate that AAPC inhibits ER stress-related signalling pathways and lipogenesis-related gene expression, mitigating pathological changes, such as steatosis and lipid accumulation, in NAFLD, both *in vivo* and *in vitro*.

2.3.4. Celastrol

Celastrol is derived from the root bark of *tripterygium wilfordii* Hook.f. Xia et al. [64] used celastrol to treat an NAFLD model established using 0.2 mmol/L PA-induced L-02 cells. Celastrol treatment (0.5 and 1.0 mg/L) significantly reduced the expression levels

Table 3
Details regarding terpenoid compounds with the potential to treat NAFLD.

Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modellingmethod	Experimental dose of plant bioactive compounds	Mechanism
2.3.1 Astaxanthin	$C_{40}H_{52}O_4$ 	Male Mus musculus albino mice	high-fructose fat diet for 60 d	2 mg/kg/d ASX in 0.3 mL olive oil for 44 d	↓UPR: PERK, *p*-eIF2α, spliced XBP-1 and ATF6 [60] Others: alleviated inflammation, cell apoptosis and fibrosis, as well as attenuated mitochondrial dysfunction by up-regulating the FGF21/PGC-1α pathway [118].
2.3.2 Ursolic acid	$C_{30}H_{48}O_3$ 	db/db mice L-02 cells	normal chow vs UA diet 400 μM PA for 24 h	UA diets (0.14 %, w/w) 10–30 μg/mL for 24 h	↓UPR: p-PERK, IRE1α and CHOP [62] Others: up-regulated mRNA and protein levels of PPAR-α and CPT-1 and down-regulated DGAT and FAT/CD36 expression [119].
2.3.3 Asiatic acid	$C_{30}H_{48}O_5$ 	HepG2 cells SD rats	0.5 mmol/L OA for 24 h HFD for 18 weeks	10, 20 or 40 μmol/L for 24 h 4 or 8 mg/kg/d for 10 weeks	↓UPR: p-PERK, PERK, *p*-eIF2α, eIF2α, ATF4, CHOP, p-IRE1, XBP-1 and ATF6. ↓SRCR: SREBP-1c, FAS and ACC1 [63] Others: reduced NF-κB and *p*-JNK expression and lowered plasma insulin secretion and HOMR-IR [120].
2.3.4 Celastrol	$C_{29}H_{38}O_4$ 	L-02 cells	0.2 mmol/L PA for 24 h	0.5 and 1.0 mg/L for 24 h	↓UPR: ATF6, GRP78 and IRE1, ↓SRCR: SREBP-1c and SREBP-2 [64] Others: increased Sirt1 expression, improving the anti-oxidant and anti-inflammatory status [121].
2.3.5 Betulinic acid	$C_{30}H_{48}O_3$ 	female C57BL/6 mice HepG2 cells	MCD and HFD for 12 weeks 2.5 μg/ml TM or 500 μM PA for 24 h	100 mg/kg/d for 6 weeks pre-treatedwith 6, 12, 25 and 50 μM for 12 h	↓UPR: BiP, PERK, eIF2α, *p*-eIF2α, ATF4 and CHOP [66] Others: activated CAMKK and AMPK phosphorylation; reduced SREBP1, mTOR, and S6K protein level; and improved hepatic steatosis in IR cells [122].

(*continued on next page*)

Table 3 (*continued*)

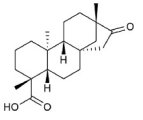
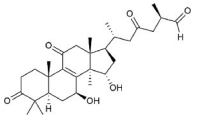
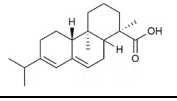
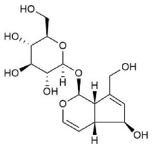
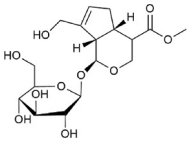
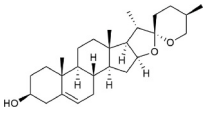
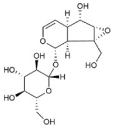
Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modellingmethod	Experimental dose of plant bioactive compounds	Mechanism
2.3.6 Isosteviol	$C_{20}H_{30}O_3$ 	Male SD rats Primary hepatocytes (from SD rats)	HFD for 4 weeks 1 mM PA for 24 h	10 or 20 mg/kg for 4 weeks 1, 3 and 10 μM for 24 h	↓UPR: GRP78, PERK, *p*-eIF2α, ATF4, CHOP, IRE1α, XBP-1s and ATF6 [67] Others: enhanced PPARα mRNA expression and HDL levels, reduced TC and LDL levels as well as the insulin resistance index, and diminished dyslipidemia-induced β-cell damage [123].
2.3.7 Ganoderic acid A	$C_{30}H_{44}O_7$ 	Male C57BL/6J mice	high-fat, high-cholesterol diet for 12 weeks	25 or 50 mg/kg/d for 12 weeks	↓UPR: GRP78, *p*-eIF2α [70] Others: alleviated lipid metabolic disorders and ameliorated the imbalance of gut microflora [124].
2.3.8 Abietic acid	$C_{20}H_{30}O_2$ 	Primary human hepatocytes	250 or 400 μM PA for 24 h	20 and 50 μM for 24 h	↓UPR: eIF2α and CHOP ↓SRCR: SREBP-1 and SCD1 [72]

Table 4
Details regarding glycoside compounds with the potential to treat NAFLD.

Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modellingmethod	Experimental dose of plant bioactive compounds	Mechanism
2.4.1 Aucubin and Geniposide	Aucubin: $C_{15}H_{22}O_9$  Geniposide: $C_{17}H_{24}O_{10}$ 	HepG2 cells	300 μM PA	10 μg/mL aucubin or geniposide for 12 h	↓UPR: PERK, eIF2a and CHOP [74] Others: Aucubin activated Nrf2, PPARα, PPARγ and hemeoxygenase-1 and phosphorylated AMPKα, AMPKβ, ACC and AKT, inhibiting lipid accumulation and oxidative stress [125]. Geniposide promoted ACC, AKT, AMPKα and AMPKβ phosphorylation, and inhibited *p*-mTORC, p-S6K, p-S6 and SREBP-1c expression by up-regulating Nrf2 expression [126].
2.4.2 Diosgenin	$C_{27}H_{42}O_3$ 	Male SD rats	HFD and streptozotocin for 8 weeks	60 mg/kg/d for 4 weeks	↓UPR: BiP and CHOP [75] Others: restored abnormal lipid and amino acid metabolism, improved the disturbance of gut microbiota and alleviated hepatic steatosis [127].
2.4.3 Catalpol	$C_{15}H_{22}O_{10}$ 	Male C57BL/6J mice HepG2 cells	HFD for 12 or 18 weeks 500 μmol/L PA for 24 h; 5 μg/mL TM	100, 200and 400 mg/kg/d for 12 or 18 weeks 100, 200and 400 μmol/L 24 h	↓UPR: GRP78/BiP, p-PERK, *p*-eIF2α, PERK, ATF4, p-IRE1α, IRE1α, ATF6 and CHOP ↓SRCR: SCAP, SREBP-2 and LDLr [76,77] Others: promoted the phosphorylation of AMPK and ACC, repressed SREBP-1c and fatty acid synthase and improved PPARα and ACOX1 expression, enhancing fatty acid β-oxidation in an AMPK-dependent manner [128].

(*continued on next page*)

Table 4 (*continued*)

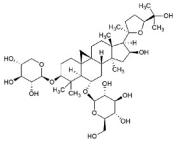
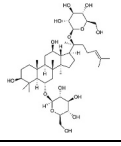
Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modellingmethod	Experimental dose of plant bioactive compounds	Mechanism
2.4.4 Astragaloside IV	$C_{41}H_{68}O_{14}$ 	HepG2 cells; primary hepatocytes (from C57BL/6 mice)	2 oleate:1 palmitate for 24 h	50, 100 and 200 μg/mL for 24 h	↓UPR: GRP78, CHOP and p-PERK ↓SRCR: SREBP-1, ACC1, FAS and SCD1 [78] Others: inhibited TNF-α, IL-6 and IL-8 levels; repressed TLR4, MyD88 and NF-κB expression and attenuated hepatic steatosis and intralobular inflammation [129].
2.4.5 Ginsenoside Rg1	$C_{42}H_{72}O_{14}$ 	female C57BL/6 mice	HFD for 16 weeks	20 and 40 mg/kg for 4 weeks	↓UPR: GRP78 and CHOP [79] Others: inhibited insulin resistance; promoted PPAR-α, CPT1A, CPT2 and CYP-7A expression; inhibited SREBP-1c expression and improved fatty acid oxidation [130].

Table 5
Details regarding lipid compounds with the potential to treat NAFLD by attenuating ER stress.

Bioactive compounds from Plant extracts	Experimental model	Modelling method	Experimental dose of plant bioactive compounds	Mechanism
2.5.1 Omega-3 fatty acids	Male Wistar albino rats pancreatic β-cell (from the RINm5F rat); hepatocyte L8824 cells (from grass carp)	HFD for 8 weeks; 2 μg/mL TM for 3 h; 200 μM PA for 24 h	800 mg/kg ω-3 fatty acids for 4 weeks; pre-treated with 20 μM EPA, DHA or AA for 5 h; 50 or 100 μM DHA for 24 h	↓UPR: GRP78, CHOP, p-PERK, *p*-eIF2, IRE1, sXBP1 and ATF6 ↓SRCR: SREBP-1c, FAS, SCD1 and C/EBPα [80–82]
2.5.2 Oleic acid	Male SD rats HepG2 cells	HFD for 32 weeks 0.4 mM PA for 24 h	Oleic acid in HFD for 16 weeks 0.2 mM OA or combination 0.4 mM PA + 0.2 mM OA (PA/OA) for 24 h	↓UPR: GRP78 and CHOP [84]
2.5.3 Polyenylphosphatidylcholine	HepG2 cells	200 μmol/L PA for 24 h	pre-treated with 100 and 200 μmol/L for 6 h	↓UPR: GRP78 and CHOP [85]
2.5.4 Plant sterol ester of α-linolenic acid	male C57BL/6J mice HepG2 cells	HFD for 16 weeks 0.1 mM OA for 24 h	HFD containing 3.3 % PS-ALA for 16 weeks 0.1 mM for 24 h	Grp78 and CHOP, Ire1α and Xbp1s Srebp-1c and FAS, Srebp-2 and Hmgcr [86,87]

of cellular ER stress-related signalling molecules such as ATF6, GRP78 and IRE1, along with the mRNA and protein levels of the SRCR-related signalling molecules SCAP, SREBP-1c and SREBP-2. Furthermore, celastrol treatment reduced the intracellular contents of TC and TG, lipid particle deposition and degree of steatosis in L-02 cells. These results indicate that celastrol downregulates the transcription and protein expression of key molecules under ER stress as well as the SRCR in hepatic L-02 cells, limiting the disruption of cellular lipid metabolism and improving NAFLD.

2.3.5. Betulinic acid

Betulinic acid (BA) is a pentacyclic lupane-type triterpene found in the medicinal plant *Ziziphus jujuba* var. *spinosa* (Bunge) Hu ex H. F.Chow [65]. Gu et al. [66] used a methionine and choline-deficient L-amino acid diet (MCD) and HFD to induce NAFLD in female C57BL/6 mice for 12 weeks. After treatment for an additional 6 weeks, BA (100 mg/kg/day) inhibited intracellular PERK/EIF2α/ATF4 and CHOP signalling in mice by explicitly activating the farnesoid X receptor. The researchers also revealed that BA improved hepatic steatosis by limiting lipid accumulation in the liver, effectively slowing down the disruption of lipid metabolism in HFD- and MCD-fed mice. This experiment analysed the effect of BA alteration on HFD-induced hepatic steatosis and MCD-induced severe NASH over the same period. Additionally, BA treatment significantly attenuated the intracellular expression of CHOP, ATF4 and BiP as well as PERK-mediated EIF2α phosphorylation in an ER stress model established using PA-induced HepG2 cells. These findings suggest that BA can reduce ER stress and restore ER homeostasis, offering a new potential therapeutic molecule for NAFLD.

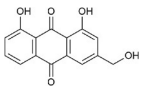
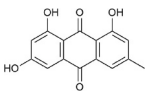
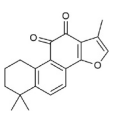
2.3.6. Isosteviol

Isosteviol (ISV), a major component of *Stevia rebaudiana* (Bertoni) Bertoni, is derived from the hydrolysis of stevioside. Yi et al. [67] established SD rat models of NAFLD that were fed with HFD for 4 weeks. After 4 weeks of treatment with 10 or 20 mg/kg ISV via gavage, the protein expression levels of ER stress markers such as PERK, *p*-eIF2α, GRP78, ATF4 and CHOP were appropriately reduced in the rat liver. Adipose vacuolation and steatosis were also found to be mitigated. Furthermore, primary hepatocytes isolated from male SD rats treated with 1 mM PA showed reduced mRNA and protein levels of ER stress markers such as CHOP, XBP-1s, ATF4, IRE1α, PERK and ATF6 in response to ISV treatment (1, 3 and 10 μM) for 24 h. These findings suggest that ISV can prevent FFA-/HFD-induced NAFLD.

2.3.7. Ganoderic acid A

Ganoderic acid (GAA) [68], the main compound of *Ganoderma lucidum* (Curtis) P. Karst., exhibits several biological activities. Studies have shown that GAA ameliorates abnormal lipid accumulation and IR by inhibiting the SREBP signalling pathway [69]. Jing Zhu et al. [70] administered male C57BL/6J mice with 25 or 50 mg/kg/day GAA for 12 weeks to treat lipid metabolism disorders caused by a high-fat, high-cholesterol (HFHC) diet. Compared with the HFHC model group, GAA remarkably down-regulated the mRNA expression of ER stress markers such as GRP78, *p*-eIF2α and *p*-JNK as well as inflammatory factors such as IL-1β, TNF-α and IL-6 in the livers of treated mice. Concurrently, GAA markedly improved visceral fat accumulation and steatosis in mouse modelof NAFLD. Overall, this study suggested that GAA ameliorates liver inflammation and inhibits the progression of NAFLD to NASH by inhibiting HFHC-induced ER stress in the liver.

Table 6
Details regarding quinone compounds with the potential to treat NAFLD by attenuating ER stress.

Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modelling method	Experimental doseof plant bioactive compounds	Mechanism
2.6.1 Aloe emodin	$C_{15}H_{10}O_5$ 	L-02 cells	0.5 mL/L 30 % fat emulsion for 72 h	0.1×10^{-4}, 0.4×10^{-4}, 1.6×10^{-4} mmol/L for 72 h	↓UPR: GRP78 and CHOP [88] Others: inhibited NLRP3 transcription and NLRP3 inflammasome assembly and improved steatosis and liver fibrosis [131].
2.6.2 Emodin	$C_{15}H_{10}O_5$ 	Male SD rats	10 % (w/v) liquid fructose diet for 4 weeks	40, 80 and 160 mg/kg/d for 4 weeks	↓UPR: p-PERK, *p*-eIF2α, ATF4 and XBP1 ↓SRCR: SREBP-1c, FAS and SCD1 [90] Others: upregulated the expression of PI3K, AKT2, AMPKα, PPARα, CPT-1a and ACOX1 and reduced TG levels [132].
2.6.3 Tanshinone IIA	$C_{19}H_{18}O_3$ 	HepG2 cells	500 μM PA for 24 h	Pre-treatment with 10 μM for 30 min	↓UPR: GRP78, eIF2a, ATF6 and CHOP [91, 92] Others: decreased ROS and MDA production, enhanced T-SOD and GSH-PX activity, inhibited apoptosis and ameliorated liver steatosis [93].

2.3.8. Abietic acid

Abietic acid (AA), a major component of *Pinus pinea* L., has been shown to exert positive effects in the treatment of type 2 diabetes mellitus (T2DM) and IR [71]. Jung et al. [72] used an *in vitro* cell model of NAFLD induced by 250 or 400 μM PA and revealed that 20 and 50 μM AA reduced the phosphorylation of ER stress markers such as eIF2α and CHOP as well as the expression of lipid accumulation and adipogenesis-related proteins (SREBP1 and SCD1) in human primary hepatocytes. Additionally, AA treatment increased the expression level of phospho-AMPK and oxygen-regulated protein 150 (ORP150) in hepatocytes. These results indicate that AA inhibits PA-induced ER stress and apoptosis, as well as adipogenesis and lipid deposition in hepatocytes by enhancing AMPK/ORP150 signalling, thereby effectively improving NAFLD.

Additionally, Table 3 delineates the therapeutic prospects of terpenoid molecules in combating NAFLD, providing a systematic and detailed exposition.

2.4. Glycoside compounds

Analogous to terpenoids, the glycoside compounds investigated in this study have demonstrated substantial regulatory effects on the ER stress-associated PERK pathway and the apoptotic transcription factor CHOP [73,74]. Notably, glycoside active substances exhibit high efficacy in modulating CHOP expression, indicating their potential in mitigating ER stress-mediated cellular damage.

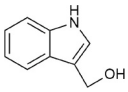
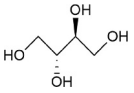
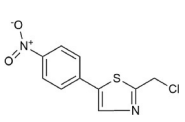
2.4.1. Aucubin and geniposide

Aucubin and geniposide are active ingredients of *Eucommia ulmoides* Oliv. extract and are believed to be effective against hypercholesterolemia and fatty liver [73]. Lee et al. [74] established an NAFLD model by treating HepG2 cells with 300 μM PA. Further, treatment with 10 μg/mL aucubin or geniposide for 12 h inhibited the phosphorylation of ER stress markers such as PERK, eIF2a and CHOP in HepG2 cells. Additionally, oil red O staining revealed that treatment with aucubin and geniposide enhanced apolipoprotein B secretion and reduced intracellular lipid accumulation. Moreover, both glycosides markedly attenuated steatosis by targeting the PERK–eIF2a–CHOP axis. These findings suggest that aucubin and geniposide can modulate PA-induced ER stress and intracellular steatosis, thereby mitigating NAFLD progression.

2.4.2. Diosgenin

Approximately 195.2 ng/mg diosgenin is found in *Trigonella foenum-graecum* L. (Fenugreek) seed extract (FSE) [75]. Mayakrishnan et al. [75] established male SD rat models of T2DM and lipid metabolism disorder by administering HFD and small doses of streptozotocin for 8 weeks. In the treatment group, rats were orally administered with at 60 mg/kgdiosgenin during the last 4 weeks. Diosgenin treatment markedly reduced the levels of ER stress markers such as BiP, CHOP, caspase-12 and caspase-3 in rat livers. Moreover, it reduced serum glucose and hepatic TG levelswhile increasing hepatic glycogen levels. Histological analysis revealed that diosgenin alleviated the extent of hepatic steatosis in rats. These results indicate that diosgenin positively affects hepatic steatosis and ER stress mediated liver damage in rats with T2DM by normalising ER stress and attenuating ER stress-induced hepatocyte apoptosis and steatosis. Although IR is known to be involved in the pathological changes of T2DM and NAFLD by affecting several signalling pathways, which indicates that NAFLD is closely related to T2DM, further experiments are warranted to verify its mechanism of action

Table 7
Details regarding alcohol compounds and carbohydrates potentially used to treat NAFLD by attenuating ER stress.

Bioactive compounds from Plant extracts	Chemical and structural formula	Experimental model	Modellingmethod	Experimental dose of plant bioactive compounds	Mechanism
2.7.1 Indole-3-carbinol	C_9H_9NO 	Male C57BL/6 N mice	HFD for 10 weeks	0.1 % (wt/wt) I3C diet for 10 weeks (100 mg/kg/d)	↓UPR: GRP78, sXBP-1, CHOP and *p*-eIF2α ↓SRCR: SREBP-1c, FAS and LPL [99] Others: increased AhR and CYP1B1 protein expression and reduced lipid droplet accumulation in mature adipocytes [133].
2.7.2 Erythritol	$C_4H_{10}O_4$ 	Male C57BL/6 mice	tylosapol and HFD for 12 weeks	50, 100 and 200 mg/kg/d for 5 weeks	↓UPR: GPR78, p-PERK and CHOP ↓SRCR: SREBP-1c, FAS and ACC [100] Others: increased short-chain fatty acid levels and ILC3 and IL-22 expression and decreased fat deposition [134].
		HepG2 cells	330 μM OA and 660 μM PA for 24 h	250 μM Ery for 24 h	
2.7.3 *Astragalus* polysaccharides	$C_{10}H_7ClN_2O_2S$ 	Female C57BL/6J mice	HFD for 12 weeks	700 mg/kg/d for 8 weeks	↓UPR: GRP78, IRE1 and XBP1 [101,102]
		HepG2 cells	high glucose (30 mmol/L) for 5 h	200 mg/mL for 24 h	Others: increased the expression of AMPK and PPAR-α, decreased SREBP-1 and TNF-α levels and modulated the gut microbiota and SCFA-GPR signalling pathways [135].

in NAFLD.

2.4.3. Catalpol

Catalpol is one of the main components of *Rehmannia glutinosa* (Gaertn.) DC., a common medicine used in China to treat diabetes. Emerging evidence suggests that catalpol can inhibit hepatocyte apoptosis by alleviating HFD-induced persistent ER stress [76], thereby mitigating the onset and progression of NAFLD. Jiting Yan et al. [77] induced NAFLD in male C57BL/6J mice through HFD feeding and treatment with catalpol (100, 200 and 400 mg/kg) via gavage. After 12 weeks, catalpol treatment (400 mg/kg) significantly reversed the HFD-induced increase in the mRNA and protein expression levels of ER stress markers such as GRP78, ATF4 and CHOP in mouse hepatocytes compared with the positive drug atorvastatin calcium (30 mg/kg). Additionally, catalpol treatment substantially decreased the protein expression levels of p-PERK, p-IRE1a, ATF6 and *p*-eIF2a. Moreover, it up-regulated the mRNA and protein expression levels of SCAP, SREBP-2 and LDLr while reducing the mouse body weight and serum TC, TG and FFA levels. Furthermore, catalpol markedly alleviated lipid droplet accumulation in hepatocytes and macrovesicular steatosis. Similar results were obtained in another experiment wherein cellular steatosis was induced via 500 μmol/L PA-stimulation of HepG2 cells for 24 h. Overall, both *in vitro* and *in vivo* experiments revealed that catalpol can improve the pathophysiological process of NAFLD by inhibiting ER stress and regulating the SRCR, thereby reducing steatosis and restoring cholesterol homeostasis.

2.4.4. Astragaloside IV

Astragaloside IV (AS-IV) is the main bioactive component of *Orobanche astragali* Mouterde. Bing Zhou et al. [78] established a cell model of NAFLD by exposing HepG2 cells and primary mouse hepatocytes (isolated from 12-week-old C57BL/6 mice) to FFA medium (1 mmol/L, oleate/palmitate, 2:1 ratio) with and without AS-IV treatment for 24 h. The results showed that AS-IV (100 μg/mL) treatment reduced the protein expression levels of ER stress markers such as GRP78, CHOP and p-PERK in a concentration-dependent manner. Additionally, AS-IV treatment (50, 100 and 200 μg/mL) enhanced the phosphorylation levels of AMPK and its direct target enzyme ACC in a concentration-dependent manner and suppressed mature SREBP-1 accumulation and its movement to the nucleus. Subsequently, it reduced the mRNA levels of adipogenic genes (including *acc1*, *fas* and *scd1*). However, reverse experiments demonstrated that these beneficial effects were attenuated by the AMPK inhibitor compound C (20 μmol/L). These results demonstrated that AS-IV improves NAFLD by reducing FFA-induced ER stress and lipid accumulation in hepatocytes in an AMPK-dependent manner.

2.4.5. Ginsenoside Rg1

Ginsenoside Rg1 is a potent monomer derived from *Panax ginseng* C.A.Mey. Xu et al. [79] established female C57BL/6 mouse models of NAFLD by inducing HFD for 16 weeks, followed by treatment with Rg1 (20 and 40 mg/kg) for 1 month. They revealed that Rg1 treatment inhibited the expression of ER stress markers such as GRP78, CHOP and caspase-12 while promoting the expression of the FFA β-oxidation-related gene *PPARα* and enhancing SOD activity. Furthermore, Rg1 treatment contributed to reducing the liver wet weight and serum TG levels in mice. Additionally, the pathological signs of liver injury, such as diffuse cellular steatosis and inflammation, were relieved. Overall, these findings suggest that Rg1 prevents the development of NAFLD by impairing ER stress and attenuating apoptosis while enhancing fatty acid oxidation, improving anti-oxidant capacity, inhibiting hepatic lipid synthesis and reducing the extent of fatty infiltration and steatosis. However, the study did not elucidate why the treatment time was only one-fourth of the modelling time or why the effect of Rg1 was not significantly better than that of the positive drug metformin. Thus, subsequent experiments are warranted to address these aspects.

Furthermore, an academic exploration into the function of glycoside compounds in NAFLD is extensively presented and critically examined in Table 4.

2.5. Lipid compounds

According to previous studies, the lipid compounds investigated in this study substantially decrease the expression of GRP78 and CHOP, which decelerate apoptosis and alleviate NAFLD [80–87]. These findings suggest that such compounds influence the upstream signalling pathways of ER stress, thereby unveiling a novel research avenue for exploring the molecular mechanisms by which lipid compounds regulate ER stress.

2.5.1. Omega-3 fatty acids

Omega-3 (ω-3) fatty acids, also known as n-3 polyunsaturated fatty acids (n-3 PUFAs), are essential for life. Some examples include docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and alpha-linolenic acid (ALA). Kandeil et al. [80] used male Wistar albino rats fed on a regular diet as the control group and those fed on an HFD for 8 weeks as the NAFLD model group. In these rats, the administration of 800 mg/kg ω-3 fatty acids via oral gavage daily for 4 weeks reduced the expression levels of ER stress genes such as *chop*, *xbp1* and *grp78* as well as the lipogenic gene *chrebp*. Furthermore, plasma biochemical data from rats in the HFD group revealed decreased levels of blood glucose, TG, TC and FFA, and an improvement in liver steatosis. These results confirmed that ω-3 fatty acids effectively modulate ER stress and alleviate NAFLD.

Jie Wang et al. [81] pre-treated the rat pancreatic β-cell line RINm5F with DHA and EPA before exposing the cells to TM, an ER stress inducer, which significantly reduced the expression levels of ER stress markers such as CHOP, p-PERK, *p*-eIF2 and sXBP1 as well as mRNA levels of UPR-related genes such as *EDEM*, *GRP78*, *CHOP* and *ERDJ4*. Moreover, nuclear levels of SREBP-1 and C/EBP were markedly reduced. Additionally, DHA and EPA pre-treatment in RINm5F cells reversed several TM-induced effects, including impaired

cell viability, reduced levels of the anti-apoptotic protein Bcl-2 and increased levels of the pro-apoptotic proteins Bax and cleaved-caspase-3. In summary, ω-3 fatty acids prevent ER stress, protect β-cells from diabetic damage and helpmaintain stable insulin levels, demonstrating potential therapeutic effects on NAFLD.

Huang et al. [82] established an NAFLD model by inducing the grass carp hepatocytecell line L8824 with 200 μM PA. Compared with the control group, treatment with 50 or 100 μM DHA for 24 h significantly reduced the levels of ER stress-related genes such as *GRP78*, *CHOP*, *ATF6* and *IRE1* in a dose-dependent manner. Furthermore, DHA treatment down-regulated the expression of hepatic lipid synthesis-related genes such as *FAS*, *SREBP-1c*, *SCD1* and *C/EBPα*. Additionally, it notably reduced intracellular TG content and improved hepatocyte steatosis. However, the positive effects of DHA were suppressed when the cells were pre-treated with 10 μM CC (an AMPK inhibitor). Furthermore, *in vivo* experiments revealed that 1 % DHA substantially reduced the mRNA expression of CHOP, GRP78, IRE1, ATF6 and PERK and increased that of AMPK in grass carp livers. This study confirms that DHA plays a protective role against hepatic steatosis by activating AMPK to inhibit ER stress in hepatocytes and reducing hepatic lipogenesis.

2.5.2. Oleic acid

Oleic acid, the main component of olive oil (70%–80 %), is an omega-9 PUFA [83]. Zeng et al. [84] used SD rats fed on an HFD for 16 weeks to establish an NAFLD model of hepatic steatosis. During the next 16 weeks, 50 % of the fat content in the HFD was replaced with olive oil, establishing a new dietary pattern of mixed saturated and unsaturated fatty acids. Oleic acid treatment reduced the levels of ER stress markers such as GRP78 and CHOP in the livers of HFD-fed rats and down-regulated the expression of pyroptosis markers such as NLRP3, GSDMD/-N, caspase-1, p20 and IL-1β. In the HFD + oleic acid-fed group, most rats developed grade 1 microvesicular steatosis, with almost complete elimination of inflammatory and necrotic cells. In HepG2 cells, oleic acid treatment attenuated PA-induced cell scorching pyroptosis, a form of ER stress-induced and NLRP3 inflammasome-mediated death, effectively restoring cell viability. In summary, a combined diet of saturated and monounsaturated FFA can effectively slow the progression of NAFLD to NASH, with oleic acid-mediated inhibition of ER stress and downstream pyroptosis potentially playing a key role.

2.5.3. Polyenylphosphatidylcholine

Polyenylphosphatidylcholine (PPC), an essential component of cell and subcellular membranes, is extracted from various plants such as *Glycine* max (L.) Merr. and *Zea mays* L. Gang Zhou et al. [85] established an apoptosis model of NAFLD by inducing HepG2 cells with 200 μmol/L PA for 24 h after pre-treatmentwith 100 and 200 μmol/L PPC. PPC preventively reduced the mRNA and protein expression levels of ER stress-related proteins such as GRP78 and CHOP. Moreover, the PA + PPC group exhibited a lower mRNA expression level of the pro-apoptotic gene *Bax* and a significantly higher mRNA expression level of the anti-apoptotic gene *Bcl-2* than the PA group. These findings indicate that PPC can ameliorate the pathological development of NAFLD by attenuating ER stress-related protein expression and regulating apoptosis to increase cell activity.

2.5.4. Plant sterol ester of α-linolenic acid

Plant sterol ester of α-linolenic acid (PS-ALA), a complex formed via the esterification of ALA and phytosterol, is found in various vegetable oils, including soybean, corn and sunflower oils. Han et al. [86] investigated the effects of PS-ALA using HFD-induced male C57BL/6J mice as a NAFLD model. In the PS-ALA treatment group, mice were fed on the same HFD containing 3.3 % PS-ALA for 16 weeks. At the end of the experiment, compared with the HFD group, the PS-ALA group exhibited substantially lower expression levels of ER stress markers (Grp78 and CHOP) and enzymes that were critical for adipose DNL (Srebp-1c and FAS) and cholesterol synthesis (Srebp-2 and Hmgcr). PS-ALA also blocked NLRP3 inflammasome activation and reduced IL-1β and IL-18 release by inhibiting ER stress-induced sensitisation of UPR sensors (Ire1α and Xbp1s). Moreover, PS-ALA treatment reduced fat accumulation and fat infiltration in liver tissue, lowering serum TC and TG levels, and improved steatosis. It also improved steatosis by blocking IRE1α–XBP1s signalling pathway, activating SREBPS and attenuating ROS overproduction to ameliorate HFD-induced ER stress and lipid disorders. Therefore, PS-ALA may be a novel candidate for the prevention and treatment of NAFLD.

Furthermore, in another study, Hao Han et al. [87] conducted *in vitro* experiments to explore the mechanism of PS-ALA. They used HFD-fed male C57BL/6J mice and 0.1 mM OA-induced HepG2 cells. Supplementing the diet of mice with 3.3 % PS-ALA alleviated HFD-induced ER swelling and down-regulated the expression of ER stress markers such as GRP78 and CHOP. In addition, PS-ALA suppressed the activation of the IR1α/TRAF2/JNK apoptotic signalling pathway and restored the protein expression of its target genes, namely, *Bax* and *Bcl-2*. Furthermore, PS-ALA treatment strongly reinforced the activity of HFD-inhibited AMPK. *In vitro* experiments revealed that 0.1 mM PS-ALA attenuated the protein expression of SREBP-1c and FAS, inhibited OA-induced fatty acid synthesis and effectively reduced lipid droplet accumulation in HepG2 cells. However, pre-treatment of HepG2 cells with the AMPK inhibitor compound C (10 μM) eliminated the anti-apoptotic effect of PS-ALA and failed to reduce lipid droplet accumulation in the presence of OA. Overall, PS-ALA ameliorated NAFLD in both *in vivo* and *in vitro* models by inhibiting the IRE1α/TRAF2/JNK signalling pathway through AMPK activation and attenuating ER stress-induced apoptosis.

Subsequently, Table 5 is a resource for comprehending the therapeutic potential of lipid compounds in the context of NAFLD, encompassing a wide array of pertinent data.

2.6. Quinone compounds

2.6.1. Aloe Emedin

Aloe emodin (AE) is mainly derived from the ingredients of Chinese botanical drugs, including *Rheum officinale* Baill., *Aloe* L. and *Cassia abbreviata* Oliv. Pei et al. [88] used fat emulsion to induce steatosis in human hepatocyte line L-02 to establish a cell model of

NAFLD. They used three experimental groups with different AE concentrations (0.1×10^{-4}, 0.4×10^{-4}, 1.6×10^{-4} mmol/L for 72 h). The AE groups exhibited notably lower protein expression levels of ER stress markers such as GRP78 and CHOP than the model group. Additionally, the number of intracytoplasmic lipid masses, density of lipid droplets and content of hepatocyte TG were inversely correlated with the AE dose. Therefore, AE effectively reduced hepatocyte steatosis by inhibiting ER stress-induced disturbances in lipid metabolism and apoptosis.

2.6.2. Emodin

Emodin (1,3,8-trihydroxy-6-methylanthraquinone; $C_{15}H_{10}O_5$) is an active monomer derived from *Rheum officinale* Baill [89]. Xiaojie Li et al. [90] established SD rat models of NAFLD via liquid fructose feeding and categorised them into intervention groups treated with 40, 80 and 160 mg/kg emodin. Emodin treatment attenuated ER stress in rat hepatocytes by reducing the levels of ER stress marker proteins such as p-PERK, *p*-eIF2α and ATF4 as well as the activity of XBP1 in the liver. In addition, emodin inhibited the mRNA transcription and protein expression of SREBP1c as well as its downstream fat-producing genes FAS and SCD1, attenuating fat DNL through the SRCR. Emodin also diminished various pathological changes, such as hepatocyte vacuolation, severe hepatic steatosis and lipid droplet formation. Thus, the effect of emodin on the ERS–SREBP-1c pathway alleviated lipid accumulation in the fructose-induced NAFLD model.

2.6.3. Tanshinone IIA

Tanshinone IIA (tan IIA) is extracted from *Lamiaceae; Salviae miltiorrhizae radix et rhizome*. Tan IIA has been demonstrated to enhance insulin sensitivity and improve glucose metabolism disorders in various *in vivo* and *in vitro* T2DM models by attenuating ER stress [91]. Wang et al. [92] established an NAFLD model by inducing HepG2 cells with 500 μM PA. Pre-treatment of HepG2 cells with 10 μM tan IIA significantly inhibited intracellular phosphorylation of the ER stress marker eIF2a and reduced the expression of GRP78, ATF6 and CHOP. Tan IIA reduced caspase-3 cleavage and mRNA levels, markedly enhancing PA-mediated impairment of cell viability. These results indicate that tan IIA inhibits excessive ER stress-induced apoptosis and hepatic steatosis in HepG2 cells treated with PA, exerting an ameliorative effect on NAFLD.

Bioactive substances of plant origin, particularly quinones, have demonstrated their unique therapeutic potential in the pathomechanisms of NAFLD. Nevertheless, compared with other plant bioactive extracts, there is limited research on the ER stress-mediated protective effects of quinones against NAFLD. The role of quinones in this stress-related signalling pathway has not yet been elucidated. Numerous studies have substantiated that quinones, including rhodopsin and tanshinone, can significantly mitigate the symptoms of NAFLD through their anti-inflammatory and anti-oxidant properties [93–95]. Consequently, future research should be directed towards detailed exploration of the mechanisms through which these compounds regulate ER stress and their potential therapeutic value in NAFLD.

In a similar vein, Table 6 is instrumental in offering a profound review of the impact of quinone compounds in the therapeutic landscape of NAFLD.

2.7. Other compounds

The impact of alcoholic compounds and carbohydrates on NAFLD remains controversial. A study involving Chinese adults revealed that the intake of alcohol and high-carbohydrate diet was positively associated with NAFLD incidence [96]. However, another study revealed that moderate alcohol consumption might reduce liver fibrosis and mortality due to NAFLD [97]. Combining fructo-oligosaccharide with silybin treatment has been shown to enhance therapeutic effects on NAFLD by modulating the intestinal micro-ecological balance and reducing the mouse body weight [98]. These findings indicate that a moderate intake of alcohol compounds and saccharides has a potential positive impact on NAFLD treatment.

2.7.1. Indole-3-carbinol

Indole-3-carbinol (I3C) is a natural compound found in various *Brassica oleracea* L. vegetables, such as broccoli, cabbage and cauliflower. Choi et al. [99] established 24 male C57BL/6 N mouse models of hepatic steatosis induced by an HFD. Their results showed that providing a diet containing 0.1 % (wt/wt) I3C ad libitum for 10 weeks reduced the mRNA expression levels of ER stress-mediated signalling molecules such as GRP78, sXBP-1 and CHOP along with the phosphorylation level of eIF2α. This diet also decreased the mRNA expression levels of adipogenesis-related genes such as *SREBP-1c*, *LXRα*, *FAS* and *LPL* in mouse livers. Simultaneously, I3C treatment up-regulated the mRNA expression of SIRT1 to a normal level. This treatment also decreased and increased the phosphorylation of S6K1 and AMPK proteins, respectively. Additionally, the I3C group exhibited significantly lower body weight, liver weight and plasma and liver lipid levels (TG and TC) than the HFD-fed mouse group. Overall, this study suggests that I3C activates the SIRT1–AMPK signalling system by reducing the mRNA expression level of SREBP-1c. These findings also indicate that attenuating ER stress is a key mechanism underlying the beneficial effects of I3C on hepatic steatosis.

2.7.2. Erythritol

Erythritol (Ery) is widely found in various fruits, including melons, grapes and pears. Jin et al. [100] established an *in vitro* model of lipid accumulation by inducing HepG2 cells with 330 μM OA and 660 μM PA for 24 h, followed by treatment with 250 μM Ery for 24 h. Ery inhibited the expression of ER stress markers such as GPR78, p-PERK and CHOP; suppressed the activities of various lipid synthesis-related enzymes, including SREBP-1c, FAS and ACC, and reduced the accumulation of lipid droplets in HepG2 cells. The researchers also induced male C57BL/6 mice with tylosapol (hyperlipidemia modeling agent) and HFD to establish an *in vivo* model of

NAFLD. After treatment with 50, 100 and 200 mg/kg Ery, similar results were obtained as the *in vitro* experiment. Interestingly, based on molecular simulation docking experiments of Ery and Nrf2 as well as *Nrf2* knockout experiments, they further confirmed that the potential mechanism underlying Ery's protective effect is the Ery-mediated inhibition of ER stress and lipid accumulation in NAFLD through the activation of the Nrf2 signalling pathway.

2.7.3. Astragalus polysaccharides

Astragalus polysaccharides [APS; 2(chloromethyl)-4-(4-nitrophenyl)-1,3-thiazole], derived from *Astragalus propinquus* Schischk., slow the progression of NAFLD to NASH by regulating the ER stress-associated GRP78–IRE-1–JNK pathway [101]. Mao et al. [102] conducted experiments using female C57BL/6J mice model of steatosis induced by HFD. Further, high glucose treatment (30 mmol/L) for 5 h was used to induce ER stress in HepG2 cell model. Administration of 700 mg/kg/day APS via oral gavage for 8 weeks reduced the mRNA levels of the ER stress marker XBP1 in mouse livers. Furthermore, APS treatment significantly reduced lipid deposition in the liver as well as hepatic TG and blood glucose levels, thus restoring insulin activity in mice. Pre-treatment of HepG2 cells with 200 mg/mL APS for 24 h inhibited the high glucose-induced elevation of XBP1 expression and alleviated ER stress. These results demonstrate that APS exerts beneficial effects by reducing ER stress and improving IR, thereby indirectly slowing the development of hepatic steatosis while exhibiting anti-obesity and hypolipidemic effects.

Lastly, Table 7 articulates a thorough compilation and critical analysis concerning the utilisation of alcohol compounds and carbohydrates in NAFLD treatment modalities.

3. Conclusions

This review provides a comprehensive summary of the beneficial effects of various plant bioactive extracts on NAFLD by targeting ER stress. The studies presented herein illustrate those bioactive compounds from plant extracts modulate key biological processes, including lipid metabolism, inflammatory response and apoptosis, by regulating three major signalling pathways associated with ER stress—UPR, SRCR pathway, and EOR—thus ameliorating NAFLD pathology.

4. Future prospects

It is crucial to acknowledge that these studies have certain limitations. For instance, although bioactive compounds from plant extracts can be categorised into several classes based on functional group classification, such as alkaloids and biogenic amines, existing studies have predominantly foucused on flavonoids, with relatively limited exploration of other classes of compounds. In terms of experimental design, several issues exist regarding the selection of experimental models and standardisation of model establishment methods. Most of the studies incorporated in this review employed male SD rats induced by HFD as an *in vivo* model of NAFLD, or utilised HepG2 cells to induce steatosis through treatment with PA or TM in the *in vitro* experiments. Nevertheless, even for identical bioactive compounds and same types of models, differences were observed in the experimental conditions, including variations in modelling duration. These discrepancies significantly impact the precision of the experimental outcomes and are prone to yield false-positive results.

To understand the impact of bioactive compounds on ER stress and NAFLD, the following enhancements should be considered: 1) Pathway selection: Specific signalling pathways must be prioritised to augment research precision. 2) Model criteria refinement and optimisation: *Ex vivo* and *in vivo* models, with corresponding inducing agents, should be judiciously selected to better simulate the coexisting pathologies of ER stress and steatosis. For instance, the TM-induced NAFLD model may be more suitable for investigating the pathogenesis of non-obese or lean patients with NAFLD. Additional experiments must ascertain optimal modelling duration and dosage of administered compounds. 3) Assay enhancement: The "gold standard" pathological assays must be employed for NAFLD assessment. This encompasses microscopic assessment of lipid accumulation through techniques such as HE staining and oil red O staining, with concurrent evaluation of the associated inflammation, necrosis or otherpathological attributes. Moreover, electron microscopy methods should be utilised to assess changes in ER morphology and structure, thereby elucidating the ameliorative effects of plant bioactive extracts on ER stress and NAFLD. These recommendations may elevate the rigor and comprehensiveness of future investigations in this domain.

Therefore, such efforts may facilitate the development of drugs that regulate ER stress, providing insights into the treatment of chronic diseases, including obesity and NAFLD.

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Liying Huang: Writing – review & editing, Writing – original draft, Investigation. **Liping Tan:** Software. **Zhuo Lv:** Software. **Wenhui Chen:** Conceptualization. **Junzi Wu:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

ATF	activating transcription factor 6
ATG7	autophagy-related protein 7
ASX	Astaxanthin
AAPC	Asiatic acid from Potentilla chinensis
AA	Abietic acid
AS-IV	AstragalosideIV
ALA	alpha-linolenic acid
AE	Aloe emodin
APS	Astragalus polysaccharides
BA	Betulinic acid
C/EBP	CCAAT/enhancer binding protein
CA	Caffeic acid
DNL	de novo lipogenesis; D-GalN
DHA	docosahexaenoic acid
ER	endoplasmic reticulum
EOR	reticulum overload response
eIF2α	eukaryotic initiation factor 2α
EPA	eicosapentaenoic acid
Ery	Erythritol
FFA	free fatty acid
FisT	Fisetin
FSE	(Fenugreek) seed extract
GRP78	glucose regulatory protein 78
GSPEs	Grape seed proanthocyanidins
GAA	Ganoderic acid
HFD	high-fat diet
HSP	Hesperidin
HCD	high-calorie diet
HFFD	high-fructose fat diet
IR	insulin resistance
IRE1	inositol-requiring enzyme 1
IRS-1	insulin receptor substrate-1
ISV	Isosteviol
I3C	Indole-3-carbinol
JNK	Jun N-terminal kinase
KP	Kaempferol
LXR	liver X receptor
LPCAT3	lysophosphatidylcholine acyltransferase 3
MCD	methionine and choline-deficient L-amino acid diet
NAFLD	Non-alcoholic fatty liver disease

NASH	non-alcoholic steatohepatitis
NF-κB	nuclear factor-kappa B
n-3 PUFAs	n-3 polyunsaturated fatty acids
OA	oleic acid
ORP150	oxygen-regulated protein 150
ω-3	Omega-3
PERK	protein kinase R-like ER kinase
PCB2	Procyanidin B2
PPC	Polyenyl phosphatidyl choline
PS-ALA	Plant sterol ester of α-linolenic acid
TRAF2	receptor-related factor-2
ROS	reactive oxygen species
RSV	Resveratrol
RA	Rosmarinic acid
SRCR	sterol-regulated cascade response
SREBPs	sterol regulatory element binding proteins
siRNA	small interfering RNA
SD	Sprague–Dawley
SIRT2	sirtuin 2
Sal A	Salvianolic acid A
TG	triglyceride
TNF-α	tumour necrosis factor-alpha
TM	tunicamycin
T2DM	type 2 diabetes mellitus
tan IIA	Tanshinone IIA
UPR	unfolded protein response
UA	Ursolic acid
VLDL	very low-density lipoprotein
XBP1	X-box binding protein 1
XN	Xanthohumol

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