Current strategies for nonalcoholic fatty liver disease treatment (Review)

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Abstract. Nonalcoholic fatty liver disease (NAFLD), the most common chronic hepatic disease, has become a leading health problem worldwide. The present review summarized the methods and mechanisms to treat NAFLD, including the Mediterranean diet, physical activity and exercise, bariatric surgery and specific therapeutic agents, including statins, peroxisome proliferator-activated receptor agonists, cenicriviroc and farnesoid X receptor agonists. Biologically active substances, such as peptides, alkaloids, polyphenolic compounds, silymarin, antibiotics, fatty acids, vitamins, probiotics, synbiotics and lamiaceae have also demonstrated actions that combat NAFLD. Considering their different mechanisms of action, combining some of them may prove an efficacious treatment for NAFLD. In this light, the present review describes recent progress and future prospects in treating NAFLD.

Contents

1. Introduction

The liver, a central immunological organ, has a significant role in deoxidation, storing glycogen, secreted protein synthesis, body metabolism, secreting and excreting bile, detoxifying, and the maintenance of coagulation and anticoagulation (1). Chronic and acute liver diseases cause irreversible liver damage and, eventually, lead to liver failure (2). Nonalcoholic fatty liver disease (NAFLD), also termed metabolic dysfunction-associated fatty liver disease, is one of the most common chronic liver diseases worldwide (3). The development of NAFLD is fueled by a sedentary lifestyle, low frequency of physical activity, unhealthy diet and excessive calorie intake (4). NAFLD is characterized by fat accumulation in the liver accounting for >5% of hepatic tissue weight (fatty liver), as well as liver inflammation, which is not caused by alcohol abuse (3). NAFLD can range from the simple fatty liver (SFL) to advanced stages of nonalcoholic steatohepatitis (NASH), which may lead to liver fibrosis (LF), liver cirrhosis (LC), liver cancer and liver failure (5). A total of 51% of obese adults worldwide suffer from NAFLD, with higher incidences in men than women (6,7). The prevalence of NAFLD among adults in the general population is 30%, but this is increased to up to 70% in patients with type 2 diabetes mellitus (T2DM) (8,9). Accumulating evidence suggests that NAFLD is tightly associated with insulin resistance, obesity, metabolic syndromes (MetS) and diabetes, and plays a key role in the development of extrahepatic clinical outcomes, such as heart disease and malignancies, which are the most common causes of death in patients with NAFLD (10-13).

NAFLD development involves an aberrant increase in triacylglycerol (TG) levels and a reduction of TG output. Aberrant increases in TGs are caused by hyperglycemia, hyperinsulinemia, obesity and fructose ingestion through the increase of lipogenesis (14,15). Reduction of TG output represents decreasing very low-density lipoprotein (LDL) and decreasing β-oxidation in mitochondria (16). SFL can be induced by aberrant accumulation of TGs. However, SFL is not accompanied by fibrosis, inflammation or hepatocyte injury and can be attenuated by lifestyle modifications. It could develop into NASH after long-term hepatic steatosis, followed by fibrosis, cirrhosis and hepatic carcinoma. In addition, insulin resistance, inflammatory cytokines, oxidative stress, endoplasmic reticulum (ER) stress and lipid peroxidation can also contribute to the development of NAFLD.

At present, there is no approved pharmacological treatment for NAFLD (17). In the present review, the current proposed treatments for NAFLD are summarized under the categories of lifestyle, bioactive compounds and medicines (Fig. 1).

2. Current strategies for NAFLD treatment

Lifestyle

Mediterranean diet. At present, the best treatment to improve NAFLD is lifestyle modification to achieve weight loss (18). It

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is well established that the risk of hepatic steatosis increases after consuming high-calorie, high-sugar and high-fat foods (19). A notable reduction in NAFLD activity score, remission of steatohepatitis and regression of fibrosis were noted in patients with weight loss and diet alteration (20). In addition, patients with NAFLD are advised to consume the Mediterranean diet in the European Association for the Study of the Liver, European Association for the Study of Diabetes and European Association for the Study of Obesity Clinical Practice Guidelines for the management of NAFLD (18). The Mediterranean diet, a nutritional model, began in the regions surrounding the Mediterranean sea and consisted of eating nuts, legumes, fruits, vegetables, fish, white meat and olive oil, which are rich in monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). The diet also recommends drinking red wine in moderation, and eating limited amounts of red meat, processed meats and sweets. Minimizing the intake of processed and high-fructose food is a feature of the Mediterranean diet, which leads to decreased ingestion of advanced glycation end products (AGEs) (21,22). AGEs are associated with diabetes, are increased in patients with NASH and are positively associated with insulin resistance (23,24). Fructose promotes alterations in the gut microbiota, increased intestinal permeability, exacerbated lipid peroxidation and hepatic steatosis, and increased tumor necrosis factor-α (TNF-α) production (25). The risk of NAFLD is negatively associated with omega-3 PUFAs, indicating that patients with NAFLD and NASH consume fewer omega-3 PUFAs (26). Omega-3 PUFA-rich diets reportedly reduce apoptosis, the content and activity of fatty acid synthase and inflammation, and ameliorate glucose homeostasis, thereby decreasing the development of NAFLD (27). Furthermore, they also correct glycemia levels, oxidative stress status and metabolic endotoxemia (28). Individuals who adopted the Mediterranean diet showed a remarkable reduction in circulating oxidized LDL and inflammatory markers (29). It has been demonstrated that the Mediterranean diet reduces the risk of T2DM, obesity, cancer and cardiovascular diseases, all of which are related to NAFLD (30-33). In general, the Mediterranean diet may influence NAFLD via mechanisms including lipidlowering, antioxidant and antiinflammatory effects. However, the Mediterranean diet may not be readily accepted or adapted to by individuals from different countries (34), and may therefore not be a viable therapy for all patients with NAFLD.

Physical activity and exercise. Exercise notably decreases steatosis and the risk of NAFLD developing into NASH (35,36). Hashida *et al* (37) suggested that exercise reduced 20-30% of intrahepatic TG by gathering and analyzing 24 studies. A total of 220 obese patients with NAFLD were randomly divided into the following groups: i) No exercise (control); ii) moderate exercise; and iii) vigorous exercise. The individuals were then evaluated after the 1-year exercise intervention and decreased waist circumference, intrahepatic TG content, blood pressure and hepatic fat accumulation were noted in the two exercise groups compared with the control group (38). A total of 154 patients with NAFLD were assigned to the intervention group or the control group and were assessed after a 12-month regular exercise intervention. Wong *et al* (39) used this method to study the efficacy of exercise intervention in non-obese patients with NAFLD. The results demonstrated that NAFLD could be relieved in 67% of non-obese patients after exercise intervention (39). In a maternal western-style-diet (WSD)-induced obesity mouse model, Kasper *et al* (40) discovered that maternal exercise prevented WSD-induced hepatic steatosis in obese dams by increased hepatic β-oxidation and suppression of lipogenesis through activating the adenosine 5'-monophosphate-activated protein kinase (AMPK) and peroxisome-proliferator-activated-receptor-γ-coactivator-1α (PGC-1α) signaling pathways. In addition, the offspring also displayed increased AMPK-PGC1α activity and were protected against WSD-induced fat accumulation and steatosis of the liver in later life (40). Furthermore, Battista *et al* (41) described a significant reduction of blood pressure, insulin resistance and intrahepatic fat after exercise-training interventions, by analyzing 54 articles. However, the benefits of exercise are only established after relatively long periods of time, which causes the majority of individuals to give up in the process. By contrast, bariatric surgery takes less time to achieve significant weight loss. In addition, bariatric surgery could not only achieve long-term weight loss but also attenuate hypertension, T2DM, insulin resistance, fibrosis and other high-risk factors of NAFLD (18,42,43).

Bariatric surgery

Laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. Laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass are the most common means of bariatric surgery that aim to shrink the stomach. The mechanisms by which they attenuate NAFLD appear to be reduction of oxidative stress and inflammation. Liver histological features, oxidative stress and inflammation in patients with NAFLD were markedly ameliorated 1 year post-laparoscopic sleeve gastrectomy surgery (44). Laparoscopic sleeve gastrectomy led to histologic improvement and later reshaped cellular interactions, thereby reducing liver damage of NAFLD (45).

Roux-en-Y gastric bypass ameliorated hepatic steatosis in diet-induced obese mice that was mediated by mechanistic targeting of the mTOR/AKT2/insulin-induced gene 2 signaling pathway (46). NAFLD was weakened via weight loss and a decrease in steatosis after Roux-en-Y gastric bypass treatment (47). Roux-en-Y gastric bypass relieved diabetes, hypertension and NAFLD. However, it frequently caused diseases related to the lack of nutrients (48).

Duodenal switch and biliopancreatic diversion. Duodenal switch and biliopancreatic diversion lead to notable weight loss, as well as amelioration or resolution in obesity-related diseases (49). Several trials proposed that biliopancreatic diversion reversed whole-body insulin resistance and reduced inflammation, thereby alleviating NASH (50,51). Liver function and inflammation of morbidly obese patients were upgraded by biliopancreatic diversion with duodenal switch (52,53). Furthermore, biliopancreatic diversion altered insulin sensitivity, and accordingly, reducing insulin resistance in men with morbid obesity (54).

In addition, duodenal-jejunal bypass, a key component of bariatric surgery, amended lipid metabolism, inflammatory responses and insulin sensitivity in diet-induced obese rats with NASH (55). Furthermore, bariatric surgery could also

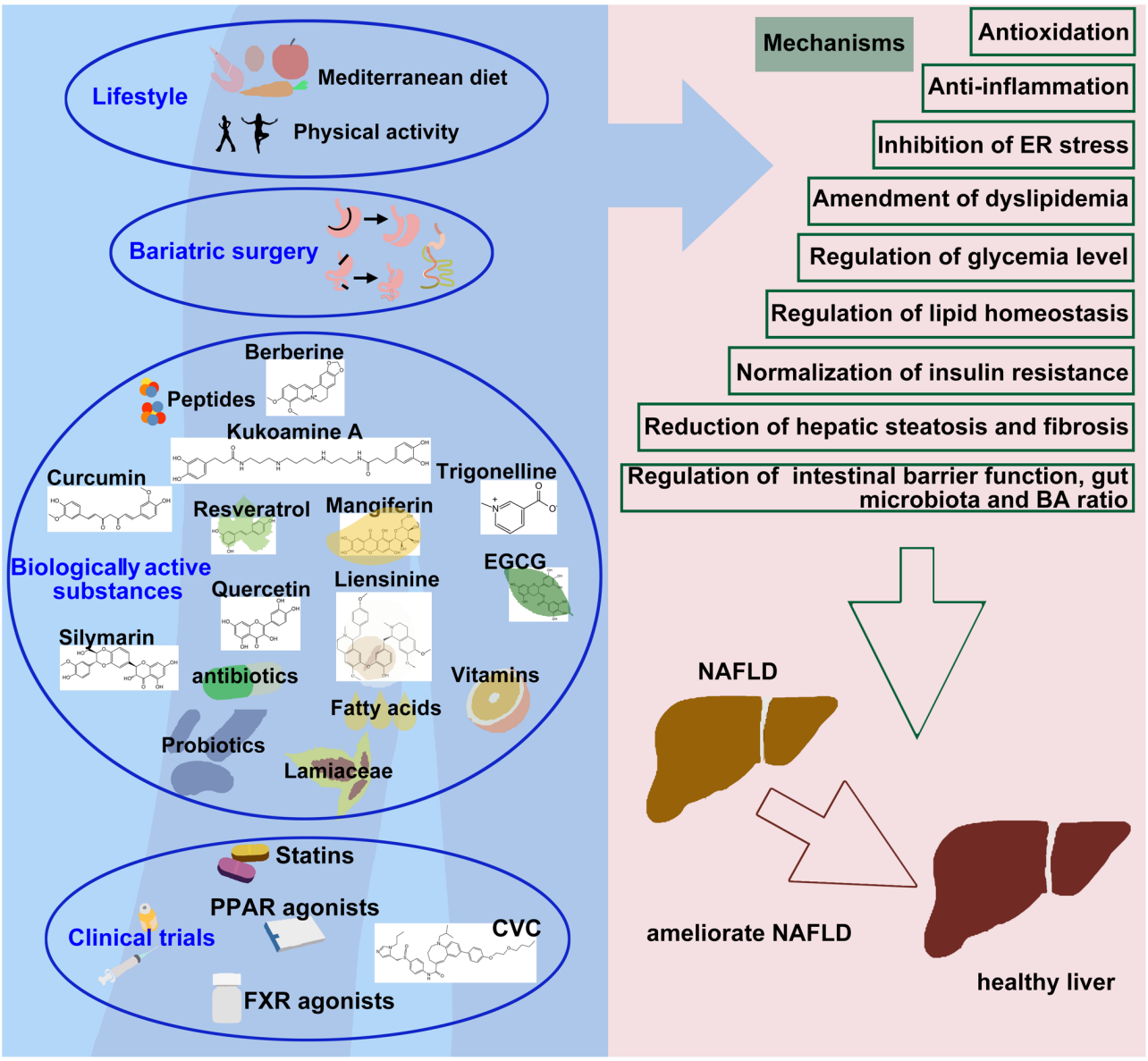

Figure 1. Current strategies for NAFLD treatment. Changes in lifestyle, bariatric surgery, biologically active substances and drugs from clinical trials are methods to weaken NAFLD and have actions through various mechanisms. EGCG, epigallocatechin-3-gallate; PPAR, peroxisome proliferator-activated receptor; CVC, cenicriviroc; FXR, farnesoid X receptor; ER, endoplasmic reticulum; BA, bile acid; NAFLD, nonalcoholic fatty liver disease.

regulate other NAFLD-related factors, such as intraluminal ileal environment, the gut microbiota and the bile acid (BA) ratio (56,57). However, costs, patient acceptability and side effects, including vomiting, diarrhea, infection and even death, limit the implementation of bariatric surgery (43). Biologically active substances, which are cheaper and have fewer side effects, are attractive treatment methods for NAFLD.

Biologically active substances

Peptides. Due to the antioxidant, anti-inflammatory, hormonal and metabolism regulatory functions of peptides, they have attracted increased attention. In a high-fat diet (HFD)-induced rat model of NAFLD, lipid accumulation, insulin resistance and oxidative stress were reduced after treatment with corn peptides (CPs). Yao *et al* (58) found for the first time that CPs could be a potential therapy for NAFLD by regulating anomalous lipid metabolism *in vivo* and *in vitro* by inhibiting ER stress via activating the AMPKα/Sirtuin 1 pathway. Lupin protein hydrolysates decreased lipid accumulation, as well as the hepatic inflammatory and oxidant situation of WSD-induced NAFLD mice (59). In HFD-induced NAFLD mice, intraperitoneally injected peptide that was synthesized from potato protein hydrolysate could reduce hepatic fat deposition and inflammation by activating the AMPK signaling pathway (60). After dyslipidemia was treated with *Ganoderma lucidum* polysaccharide peptide for a month, hepatic dysfunction, steatosis and insulin resistance were ameliorated in NAFLD mice. Zhong *et al* (61) demonstrated that the improvement was achieved by controlling BA synthesis via the farnesoid X receptor-small heterodimer partner/fibroblast growth factor pathway. *In vitro*, *Ganoderma lucidum* polysaccharide peptide also reduced the accumulation of lipid droplets and the TG content (61). Lipid peroxidation, oxidative stress and inflammation were reduced in NAFLD mice with monkfish peptide

treatment. The liver function was repaired by activating the AMPK and nuclear factor erythroid-2-related factor 2 (Nrf2) pathways (62). Furthermore, R-Tf-DLP4 (a mitochondrial voltage-dependent anion channel 1-based peptide) and VHVV (a lipolysis-stimulating peptide) inhibited hepatic apoptosis, hepatic lipid accumulation, inflammation and fibrosis in a mouse model, thereby arresting NASH progression (63,64). However, at present, only a small number of clinical trials is available to support the aforementioned findings.

Glucagon-like peptide 1 (GLP-1) was able to induce insulin secretion, and GLP-1 analogues or receptor agonists have been approved for treating T2DM and obesity. Liraglutide, a GLP-1 analogue, decreased inflammation and fat accumulation, and normalized glycemic parameters and the composition of the gut microbiota in HFD-induced NAFLD mice (65). Liraglutide restored autophagic flux by the GLP-1 receptor-transcription factor EB pathway *in vivo* and *in vitro*, thereby alleviating liver steatosis (66). On the other hand, it targeted the renin-angiotensin system through the PI3K/AKT pathway and ameliorated NAFLD (67). After subcutaneous injections of liraglutide, NAFLD was attenuated in 39% of subjects but diarrhea, constipation and loss of appetite also occurred in the liraglutide treatment group (68). Another GLP-1 receptor agonist, Dulaglutide, reduced lipid accumulation and normalized the liver function of patients with NAFLD in a randomized controlled trial (69). Semaglutide treatment reduced NASH and had a positive impact on NAFLD therapy through decreasing lipid accumulation and inflammation, and regulating blood sugar and liver function (70-72). However, semaglutide led to vomiting and constipation (70). Jin *et al* (73) developed a GLP-1 receptor agonist candidate, AWRK6 (a synthetic peptide), and researched its effect in treating NAFLD. They observed that AWRK6 ameliorated obesity, hepatic steatosis, abnormal lipid and glucose metabolism in high energy diet-induced NAFLD mice. These changes were mediated through the PI3K/AKT/AMPK/acetyl-CoA carboxylase α (ACC) signaling pathway (73). However, another study showed that the GLP-1 analogue did not reduce the risk of NAFLD development compared with insulin treatment (74). Hence, further studies are required to clarify the role of GLP-1 analogues in NAFLD treatment.

Natural compounds. Alkaloids are a class of natural alkaline organic compounds containing nitrogen that are extracted mainly from plants, and have been shown to attenuate NAFLD through various mechanisms, such as lipid lowering, anti-inflammation, autophagy regulation and anti-oxidative stress. Berberine (BBR; $C_{20}H_{18}NO_4$), extracted from the plants *Coptidis chinensis* Franch, *Phellodendron chinense* Schneid or the *berberis* genus, is used for the treatment of cardiovascular disease, hypercholesterolemia, hypertension and diabetes (75,76). The functions of BBR include lipid-lowering, regulation of metabolism disorder and enhancement of insulin sensitivity, indicating that it would be a promising strategy for treating NAFLD (77). A meta-analysis of six random clinical trials showed that BBR was beneficial for liver function and blood lipid improvement in patients with NAFLD (78). Mechanically, in preclinical studies, BBR has been found to exert protective effects through various pathways. It activates the AMPK signaling pathway (79,80), thereby inhibiting the expression of stearoyl CoA desaturase-1, a rate-limiting enzyme involved in *de novo* fatty acid synthesis. In addition, BBR also exhibits anti-inflammatory effects in liver and adipose tissue by blocking NLR family pyrin domain containing 3 (NLRP3) inflammasome assembly (81) and modulating macrophage infiltration and polarization (79). Anti-oxidative stress may also contribute to the hepatic protective effect of BBR. An *in vitro* study demonstrated that BBR activated the Nrf2 signaling pathway and protected against oxidative stress in free fatty acid-exposed Huh7 cells (82). Besides these classic biological pathways, BBR regulated the metabolism in HFD-treated rats or rats with T2DM via the intestinal microflora (83-85), indicating that the compound may modulate lipid metabolism by directly affecting the gut microbiota. Therefore, BBR is a multi-target compound with hepatic protective effects; however, its therapeutic potential on NAFLD is still being elucidated. To date, two clinical trials have been conducted to further observe the effect of BBR on hepatic steatosis markers, the cardiometabolic profile and the gut microbiota profile of NAFLD (clinical trial no. NCT05523024) and evaluate the efficacy and safety of BBR in NASH (clinical trial no. NCT03198572) are in progress. Several other alkaloids have also been reported to exhibit hepatic protective effects. Kukoamine A, a spermine alkaloid extracted from *Lycium chinense* Miller, inhibited the expression of proteins related to the biosynthesis of cholesterol and fatty acids, attenuated inflammation and hepatic oxidative stress, thereby attenuating fatty liver and liver injury in HFD-fed mice (86). Trigonelline, extracted from fenugreek (*Trigonella foenum-graecum* L.) seeds, prevented hepatic steatosis in high-fat and high-cholesterol diet-fed mice via regulating autophagy and ER stress (87). Liensinine, an isoquinoline alkaloid extracted from the seed embryo of *Nelumbo nucifera Gaertn*, reduced lipid accumulation in the liver and improved liver function in HFD-induced NAFLD mice via suppressing oxidative stress and inflammation (88). However, studies onto these alkaloids are still in the preclinical stage and their exact effect on NAFLD and the underlying mechanisms remain to be verified.

Polyphenols, which are mainly derived from plants, have been shown to decrease blood lipids, lower blood pressure, have anti-oxidative effects and inhibit tumor growth (89). Curcumin is extracted from turmeric and has antioxidant and anti-inflammatory activities (90,91). A total of two randomized controlled trials revealed that curcumin reduced blood fat and lipid accumulation, and ameliorated obesity, liver function and insulin metabolism in patients with NAFLD (92,93). Curcumin moderated NAFLD by reducing blood glucose, oxidative stress and inflammation (94). Furthermore, Mahmoudi *et al* (95) demonstrated that curcumin may treat NAFLD via 14 target genes, including cytochrome P450 1A2, NFE2 Like BZIP Transcription Factor 2 and peroxisome proliferator-activated receptor α (PPARα), through analyzing curcumin-interacting proteins and NAFLD-associated genes using a Venn diagram. Resveratrol is widely found in peanuts, mulberries and grapes and ameliorates atherosclerosis, MetS and NAFLD (96-99). The blood fat, hepatic steatosis, hepatic apoptosis, liver function, insulin sensitivity and insulin metabolism of patients with NAFLD were ameliorated after supplementation of resveratrol (98,100). Tejada *et al* (101) proposed that

resveratrol reduces hepatic lipid accumulation and regulates glycaemic and lipid metabolism via sirtuin 1/AMPK/nuclear factor κB (NF-κB) signaling pathways. Resveratrol reduced the HFD-induced methylation of the Nrf2 promoter and attenuated NAFLD by reducing the expression of lipogenesis-related genes and reactive oxygen species production via the Nrf2 signaling pathway (102). Quercetin, a polyphenolic flavonoid, has anti-apoptosis, antioxidant, anti-inflammation and anticancer activities, and may be a potential alternative preventative agent for NAFLD (103). Quercetin activated the farnesoid X receptor 1/Takeda G-protein-coupled receptor 5 signaling pathways, thus inhibiting oxidative stress, reducing inflammation and decreasing lipid accumulation (104). Furthermore, quercetin restored lipid metabolism and the gut microbiota balance through the toll-like receptor 4/NF-κB signaling pathway (105). Quercetin targeted lipid metabolism to ameliorate NAFLD via the inositol-requiring enzyme-1α (IRE1α)/X-box binding protein 1 (XBP1) pathway (106). In addition, regulation of apoptosis and BA metabolism was shown to be associated with the attenuation of NAFLD by quercetin (107). Mangiferin originates from mango leaves and has anti-diabetic, anti-oxidative, anti-inflammatory and anti-cancer activity (108,109). It activated the AMPK signaling pathway, accordingly reducing insulin resistance and inflammation in HFD-induced NAFLD mice (110). By activating the AMPK pathway, epigallocatechin-3-gallate, a main active ingredient of green tea polyphenols, reduced cellular lipid accumulation, thus mitigating NAFLD (111). In addition, polyphenols activated the AMPK pathway and promoted the expression of PPARα, thereby increasing lipid catabolic metabolism. However, in specific cases (high pH and transition metals in the presence of O_2), polyphenols were shown to aggravate oxidative stress (112).

Silymarin is obtained from the seeds of Silybum marianum and was shown to be beneficial in the treatment of liver diseases (113), and it is the active ingredient of the approved drug Legalon®. In an infantile model of NASH, silymarin reduced inflammation and apoptosis, and normalized glycemia, lipid profile, liver function and liver fibrosis (114). In a mouse model of NAFLD, hepatic steatosis was attenuated by silymarin via regulating lipid metabolism and oxidative stress (115). Mechanistically, silymarin enhanced FXR transcriptional activity and inhibited NF-κB signaling, and ameliorated insulin resistance, inflammation and the BA ratio in HFD-fed mice (116). In clinical trials, silymarin reduced liver fibrosis in adult patients with biopsy-proven NASH and was safe and well tolerated (117). However, in another clinical trial, after silymarin treatment, the NAS scores were not reduced (117). Silymarin plus vitamin C, vitamin E, coenzyme Q10 and selenomethionine has been proved to aid the recovery of liver function in patients diagnosed with NAFLD (118). However, allergic skin rashes and gastrointestinal disturbances have been reported as side effects of silymarin (116). As the effective component of silymarin, silibinin has been shown to be beneficial in NAFLD treatment in several studies. In methionine-choline deficiency (MCD)-induced NASH rats, silibinin showed preventive effects in hepatic steatosis, fibrosis and inflammation through upregulating Nrf2 target genes and inhibiting the NF-κB signaling pathway (119). The AMPKα signaling pathway was activated by silibinin, thereby inhibiting lipogenesis and promoting fatty acid consumption in an NAFLD hamster model (120). In NASH models, silibinin regulated the caspase 8 and Fas-associated protein with death domain-like apoptosis regulator/c-Jun N-terminal kinase (JNK) pathway and moderated lipid accumulation and oxidative stress (121). However, currently, clinical trials of silibinin are lacking.

Others. The regulation of gut microbiota via the administration of antibiotics may be a promising approach for NAFLD treatment (122). Rifaximin, a gut-selective antibiotic, mainly has an effect on the gut microflora. Rifaximin improves intestinal permeability by repairing zonula occludens-1 disruption and decreasing portal endotoxin in NASH mice that were induced by a choline-deficient/l-amino acid diet (123). Rifaximin decreased lobular inflammation, hepatic steatosis and fibrogenesis, as well as accumulation of BAs and deoxycholic acid in mice fed an MCD diet, and recovered MCD-induced gut microbiome changes. Therefore, Jian *et al* (124) proposed that rifaximin treatment may be a potential NASH therapy. In an observational study, rifaximin inhibited endotoxin-induced inflammation in patients with NAFLD (125). Rifaximin reduced insulin resistance and inflammation in a randomized controlled trial and rifaximin was reportedly safe and effective in treating NAFLD (126). Solithromycin, a highly potent antibiotic, relieved NASH by recovering liver function and targeting intestinal microbiomes (127,128). In addition, the combination of polymyxin B and neomycin reduced lipid accumulation and ameliorated the intestinal barrier in diet-induced NAFLD mice (129). Numerous studies have shown that antibiotics mainly act to eliminate harmful microbiota and are effective in treating liver disease. However, due to harmful side effects, including increased irreversible peripheral neurotoxicity, long-term clinical use of antibiotics is not recommended (130).

Fatty acids play critical roles in regulating cell proliferation, inflammation, energy and metabolic homeostasis. Caffeic acid reduces blood fat and lipid accumulation through upregulating AMPK/ACC and downregulating sterol-regulatory element binding protein-1 in damaged HepG2 cells (131). MUFAs, particularly oleic acid, have shown a dual role in previous studies. Oleic acid could attenuate apoptosis and activation of stress-related kinases, reduce lipid levels and inflammation but induce hepatic steatosis (132-134). Palmitic acid triggered apoptosis, activation of ER stress and insulin resistance, thereby exacerbating the development of NAFLD (132). Furthermore, MUFAs including myristoleic acid, palmitoleic acid and oleic acid were significantly increased in NAFLD (135). However, the effects of MUFA on NAFLD require further exploration. The beneficial effects of PUFAs have been reported, including regulation of inflammation, steatosis, plasma lipid and obesity (136-140). PUFAs are generally divided into n-3 and n-6, with n-3 PUFAs functioning to limit hepatic TG storage. A low intake of n-3 contributed to hepatic steatosis and insulin resistance, and led to MetS and NAFLD. NAFLD and MetS were ameliorated after adequate n-3 supplementation (141). Diets with a high n-6 to n-3 ratio induced liver function decline, lipid accumulation, oxidative stress and inflammation. This was induced by insufficient n-3 intake and excessive n-6 intake (142). In a cross-sectional study, Da Silva *et al* (143)

found that >80% of individuals (74 patients with NAFLD) did not ingest sufficient n-3. Supplementation with n-3 PUFA (>2 g/d) appeared to be a more effective way to control MetS and NAFDL (144).

Vitamins are necessary for maintaining physical health with an adjustment function. Vitamin E, an effective antioxidant agent, was advised for managing NAFLD in the guidance of the National Institute for Health and Care Excellence and the American Association for the Study of Liver Diseases (42,145). It ameliorated oxidative stress, inflammation and fibrosis in HFD-fed mice, accordingly delaying the progression of NAFLD (146). In addition, hepatic steatosis, hepatocyte apoptosis and inflammation of adults with NAFLD were weakened by vitamin E and vitamin E was well-tolerated (147-149). Vitamin E reduced liver steatosis and lipid accumulation in an NAFLD model via activating the Nrf2/carboxylesterase 1 signaling pathway (150). Furthermore, combination treatment of vitamin E and other drugs, including atorvastatin, decreased the risk of NAFLD (151-153). However, the incidence of bladder cancer and prostate cancer increased after vitamin E administration (154,155). Vitamin D was indicated to have an important role in regulating phosphorus and calcium homeostasis and in the pathogenesis of T1DM, T2DM and MetS (156,157). Low levels of vitamin D were associated with the development of NAFLD and an increased risk for NAFLD (158-160). Liu *et al* (161) demonstrated that NAFLD was exacerbated through Toll-like receptor (TLR) activation under deficiency of vitamin D. Intestinal function was regulated and oxidative stress and lipid accumulation were reduced by vitamin D in HFD-induced NAFLD mice. Liu *et al* (162) demonstrated that the development of NAFLD was prevented by vitamin D through the p53 pathway. Vitamin D enhanced liver function and decreased lipid accumulation, insulin resistance, blood fat and oxidative stress in patients with NAFLD (163). Furthermore, mechanisms by which vitamin D worked on NAFLD included anti-inflammation, antifibrosis and regulating metabolism (164). Xie *et al* (165) summarized that participants with higher serum vitamin C had a lower prevalence of LF, LC and NAFLD. An inverse association existed between serum vitamin C and LF, LC and NAFLD (165). Liver function, insulin sensitivity and intestinal microbiota diversity of patients with NAFLD were increased after daily intake of vitamin C (166). Gu *et al* (167) pointed out that vitamin C attenuated HepG2 cell stresses caused by TNF-α via activating the fibroblast growth factor (FGF)21/FGF receptor 2/adiponectin pathway. This may be a mechanism by which vitamin C treats NAFLD (167). Due to the limited number of trials in humans studying the role of vitamins in NAFLD and the lack of consensus on the optimal level of specific vitamins in the scientific community, the use of vitamins is controversial in NAFLD treatment (164).

Probiotics are active microorganisms that are beneficial to the host by changing the composition of the microbiome in the host, and can improve dysbiosis and prognosis in patients with NAFLD (168). The main mechanisms are regulating intestinal barrier function and gut microbiota (130). In addition, oxidative stress, inflammation, fibrosis and carcinogenesis were reduced by probiotic treatment in a mouse model that imitated the features of human NAFLD (169). Xue *et al* (170) showed that probiotics ameliorated the gut microbiota structure and hepatic pathology and further delayed the progression of NAFLD via downregulating lipopolysaccharide/TLR4 signaling in high-sugar and high-fat diet-fed rats. Clinical trials demonstrated that probiotics ameliorated lipid accumulation, liver function, blood fat, insulin resistance and obesity (171,172). Synbiotics consisting of probiotics and prebiotics could stimulate the growth of probiotics and were effective in treating obesity, T2DM, insulin resistance syndrome and NAFLD (173). After treatment with synbiotics, hepatic fibrosis, inflammation and lipid accumulation were reduced and liver function was ameliorated in patients with NAFLD (174,175). Furthermore, synbiotics are conducive to modifying the gut bacterial flora (176). Further studies are needed to determine the best dose of probiotics and synbiotics (173).

Lamiaceae mostly include shrubs and herbs and have potential in ameliorating diabetes, hyperlipidemia, obesity and NAFLD (177-179). The hepatoprotective and hypolipidemic functions of chia (*Salvia hispanica* L.) were related to its high content of n-3, dietary fiber and phenolics. Prevention of steatohepatitis and reduced lipids were observed in rats that were fed a diet with chia for 4 weeks (180). After eight weeks of a chia-supplemented diet, a study showed that fat accumulation, blood fat and obesity were decreased in patients with NAFLD. Regression was observed in a total of 52% of patients with NAFLD (181). *Thymbra spicata* L. has antioxidant, anti-inflammatory, anti-hypercholesterolaemic and anti-steatohepatitic potential that may be attributed to the richness of phenolic compounds (182). The lipid accumulation, oxidative stress and inflammation were ameliorated by *Thymbra spicata* L. in NAFLD cellular models (183). *Scutellaria baicalensis* and its major component, baicalin, exert antioxidant and anti-inflammatory effects, and regulate lipid metabolism in hepatic diseases (184). Baicalin downregulated the sterol-regulatory element binding protein signaling pathway and upregulated the AMPK signaling pathway, accordingly decreasing hepatocyte lesions, and blood fat and hepatic lipid accumulation in NAFLD rats (182). The mechanisms by which *Scutellaria baicalensis* extracts treat NAFLD include suppression of ER stress and thioredoxin-interacting protein/NLRP3 inflammasome activation, and activating the PGC-1α/PPARα signal pathway (185,186). Due to the small sample size, the short study time and preliminary data, the effectiveness of labiatae plants in treating NAFLD remains to be clarified. Clinical drugs appear to be more effective for urgent treatment. However, currently, these medicines are undergoing clinical trials have not been approved for NAFLD treatment.

Clinical trials

Statins. Statins are mainly used to prevent cardiovascular disease and decrease LDL-cholesterol levels (187). An increasing number of studies suggested that statins were useful to reduce the risk of NAFLD. A systematic review and meta-analysis showed that the liver conditions of patients with NAFLD were ameliorated by treatment with statins, and statin treatment was safe (188). Lee *et al* (189) also summarized that statin use could reduce the chance of getting NAFLD and hepatic fibrosis. Atorvastatin reduced the non-invasive score and fibrosis score, suggesting that atorvastatin weakened

NAFLD progression (190). A combination of resveratrol and atorvastatin attenuated NAFLD by reducing fat accumulation in the liver of mice with fatty liver (191). Reduced inflammatory markers, decreased atherosclerosis and inhibition of cholesterol production in the liver were observed after combined use of ezetimibe and atorvastatin (192). However, these combined uses to abate NAFLD lack the support of clinical trials. Rosuvastatin can improve the histological score and biochemical biomarkers of NAFLD (193). The combined use of rosuvastatin and ezetimibe reduced the liver fat of participants with NAFLD (194). In addition, the combination of rosuvastatin, ursodeoxycholic acid and ezetimibe decreased the fibrosis of NAFLD mice (195). Simvastatin protected mice with a high-fat-high-carbohydrate diet from developing NAFLD by inhibiting oxidative stress, reducing advanced lipoxidation end-product receptors of AGEs and decreasing steatosis, inflammatory parameters and fibrosis (196). However, statin treatment increased the risk for T2DM, which frequently co-occurs with NAFLD, by reducing insulin secretion and impairing insulin signal transduction (197).

PPAR agonists. PPARs, a class of nuclear receptors, have an important role in the treatment of NAFLD due to their function that regulates the transcription of glucose and lipid metabolism. PPAR agonists are traditionally used for treating MetS by lowering TG and glucose levels. PPARα regulated the expression of liver fatty acid binding protein, mitochondrial β-oxidation enzymes and proteins that are related to fatty acid turnover. On the other hand, PPARα regulated inflammation by inhibiting NF-κB via forming inhibitory complexes and increasing the expression of the inhibitory subunit of NF-κB α, which is the NF-κB inhibitory protein (198). Wy-14643, a powerful PPARα agonist, inhibited steatosis and restored insulin sensitivity, as well as blood lipid and adiponectin levels, thereby reducing NAFLD that was driven by PPAR-α dysregulation (199,200). Fenofibrate, a fibrate PPARα agonist, is mainly considered a lipid-lowering drug. Fenofibrate regulated the IRE1α/XBP1/JNK signaling pathway and lessened lipid accumulation, apoptosis, inflammation and ER stress, accordingly attenuating NAFLD in a mouse model (201). In clinical trials, fenofibrate normalized liver enzymes and blood lipids of patients with NAFLD. The body mass index of patients was also lowered after fenofibrate administration (202). PPARδ, an isoform of the PPAR family, regulated mitochondrial metabolism and fatty acid β-oxidation, and has a potential role in fibrosis and inflammation (203). Clinical trials have shown that after GW501516 (a PPARδ agonist) treatment, the incidence of cancer was increased. Therefore, NAFLD treatment with GW501516 was abandoned (204,205). Another PPARδ agonist, GW0742, alleviated ER stress, improved insulin sensitivity, recovered hepatic energy metabolism and tackled hepatic inflammation, accordingly suppressing NAFLD progression in obese mice (206). Elafibranor is an agonist of PPARα and PPARδ. In a clinical trial, fat accumulation and inflammation in patients with NAFLD were reduced after treatment with elafibranor (207). PPARγ has an essential role in regulating adipogenesis and lipid metabolism (208). Pioglitazone, a thiazolidinediones PPARγ agonist, ameliorated liver function by reducing oxidative stress, inflammation and fibrosis in HFD-induced NAFLD mice while preventing obesity via insulin resistance regulation (209). Several clinical trials indicated that liver function and insulin sensitivity were recovered and inflammation and lipid accumulation were reduced in patients with NAFLD after pioglitazone treatment (149,210). However, pioglitazone caused weight gain (149). Saroglitazar, a dual PPARα/γ agonist, ameliorated insulin sensitivity and lipid parameters. In mice with high-fat and choline-deficient diet-induced NAFLD, liver function was recovered and inflammation was decreased after saroglitazar treatment. Mechanistically, saroglitazar reversed mitochondrial dysfunction and NF-κB phosphorylation, thereby blocking the decrease of antioxidant biomarkers and the increase of inflammatory markers. Jain *et al* (211) proposed that among saroglitazar, fenofibrate and pioglitazone, saroglitazar seemed to be the most effective against NAFLD. Lipid accumulation and insulin resistance of patients with NAFLD/NASH were ameliorated after receiving saroglitazar (212). Lanifibranor (IVA337) is a PPAR agonist that activates three isoforms of PPAR (α, δ and γ) and has strong activity in NAFLD models *in vitro* and *in vivo* (213). The results of several preclinical models demonstrated that IVA337 normalized insulin sensitivity and reduced lipid accumulation, inflammation and oxidative stress. Clinical results have suggested that IVA337 improved histology in patients with NASH (214). Side effects of PPAR agonists, including bone loss and increased risk of cancer and cardiovascular complications, are worthy of attention (203).

Cenicriviroc (CVC). Inhibition of C-C motif chemokine receptor 2 (CCR2) reduced the accumulation, migration and infiltration of monocytes and macrophages to the liver, which decreased hepatic damage (215). CCR5 participates in activation of hepatic stellate cells following liver injury, further aggravating hepatic fibrosis (216). CVC is an oral and dual antagonist of CCR2 and CCR5. It exerted anti-inflammatory and antifibrotic effects in a diet-induced NAFLD mouse model and weakened NAFLD (216). In clinical trials, CVC ameliorated fibrosis in subjects with NAFLD (217,218). However, the long-term benefits of CVC are uncertain (219).

Farnesoid X receptor (FXR) agonists. FXR regulated transcription in hepatocytes and maintained BA homeostasis (130). Abenavoli *et al* (220) summarized that the mechanisms of obeticholic acid (OCA, an FXR agonist) to improve NAFLD in a pre-clinical setting included increasing insulin sensitivity, reducing lipid synthesis and hepatic fat accumulation, and ameliorating lipotoxicity, inflammation, oxidative stress and hepatic fibrosis. A total of two randomized controlled trials showed that OCA increased insulin sensitivity, and decreased liver fat, inflammation and fibrosis in patients with NAFLD (221,222). The increase in pruritus and blood fat were shortcomings of OCA treatment (220,221,223). Tropifexor, a novel FXR agonist, reduced lipid accumulation and oxidative stress in preclinical models (224). In a clinical trial, the liver function of patients with NASH was ameliorated, and fat accumulation and inflammation in patients with NASH were reduced in the tropifexor treatment group (225). The side effects of FXR agonists were pruritus and an increase in blood fat (226).

3. Future perspectives

In the present review, the roles of the Mediterranean diet, exercise, bariatric surgery, drugs and biologically active substances in the intervention of NAFLD were summarized, with the aim that this will aid clinical research and disease treatment. However, in order to better restrain the processes of NAFLD, there are various suggestions to be considered.

Personalized treatment plan. The development of NAFLD representatively follows four stages, including liver fat accumulation, early NASH, LF and LC (227). Due to different NAFLD stages and individual patients, treatment approaches in patients with NAFLD should vary.

Determining the optimal dose. Leong and Ko (228) proposed that a long-term, low-dose feed of schisandrin B reduced blood fat levels but a single high-dose intake of schisandrin B increased serum and hepatic lipid levels. Consuming 5 g of omega-3 PUFAs per day had a similar effect in reducing steatosis levels as consuming 2 g per day (229). Although the effects of biologically active substances and medicine to attenuate NAFLD have been demonstrated in animal experiments and clinical trials, the optimal dose needs to be determined and more clinical trials require to be conducted.

Drug combinations. At present, single interventions for the treatment of NAFLD appear to result in various side effects and combined use may be the general trend. For instance, the combined use of bicyclol and BBR was rather safe; they did not influence each other and better ameliorated NAFLD (230).

Exploring new gene targets. After integrating three fibrosis datasets, including NAFLD-induced fibrosis, Zhan *et al* (231) proposed that ATP Binding Cassette Subfamily B Member 1 may be a novel anti-fibrotic target. Upregulated CD36 expression drove lipid accumulation in human hepatocytes and seemed to contribute to hepatic steatosis (232). Exploring new gene targets can help develop new drugs to treat NAFLD.

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Authors' contributions

JS performed the literature search and selection, analysis and writing-original draft preparation. XJ carried out the literature search and selection and analysis. YL performed writing-review and editing. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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