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REVIEW

Antioxidant and anti-inflammatory agents in chronic liver diseases: Molecular mechanisms and therapy

Chun-Ye Zhang, Shuai Liu, Ming Yang

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Abstract

Chronic liver disease (CLD) is a continuous process that causes a reduction of liver function lasting more than six months. CLD includes alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), chronic viral infection, and autoimmune hepatitis, which can lead to liver fibrosis, cirrhosis, and cancer. Liver inflammation and oxidative stress are commonly associated with the development and progression of CLD. Molecular signaling pathways such as AMP-activated protein kinase (AMPK), C-Jun N-terminal kinase, and peroxisome proliferator-activated receptors (PPARs) are implicated in the pathogenesis of CLD. Therefore, antioxidant and anti-inflammatory agents from natural products are new potent therapies for ALD, NAFLD, and hepatocellular carcinoma (HCC). In this review, we summarize some powerful products that can be potential applied in all the stages of CLD, from ALD/NAFLD to HCC. The selected agents such as β-sitosterol, curcumin, genistein, and silymarin can regulate the activation of several important molecules, including AMPK, Farnesoid X receptor, nuclear factor erythroid 2-related factor-2, PPARs, phosphatidylinositol-3-kinase, and lysyl oxidase-like proteins. In addition, clinical trials are undergoing to evaluate their efficacy and safety.

Key Words: Chronic liver disease; Alcoholic liver disease; Non-alcoholic fatty liver disease; Hepatocellular carcinoma; Natural products; Inflammation; Oxidative stress; Treatment; Clinical trials

Core Tip: Chronic liver disease (CLD) is a continuous process that causes a reduction of liver function lasting more than six months. CLD can be subclassified into alcoholic liver disease, non-alcoholic fatty liver disease, chronic viral infection, and autoimmune hepatitis, which can lead to liver fibrosis, cirrhosis, and cancer. Liver inflammation and oxidative stress are commonly associated with the development and progression of CLD. Therefore, anti-inflammatory and antioxidant agents are promising drugs for CLD treatment. Clinical trials are undergoing to evaluate their efficacy and safety.

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INTRODUCTION

Chronic liver disease (CLD) is a continuous process of inflammation, destruction, and regeneration of liver parenchyma, with a reduction of liver function that lasts more than six months[1]. According to the spectrum of etiologies of CLD, it can be subclassified into alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), chronic viral infection, and autoimmune hepatitis, which can lead to liver fibrosis, cirrhosis, and cancer[2-4].

The spectrum of ALD includes alcoholic fatty liver, alcoholic hepatitis, fibrosis, and cirrhosis[5]. Alcohol drinking history and volume are direct causing factors for ALD, which can progress into hepatocellular carcinoma (HCC, Figure 1), the most common type of primary liver cancer[3]. In addition, factors such as age, gender, genetic variants, chronic virus infection, and smoking contribute to the development and progression of ALD[6,7]. Development of transgenic mouse models of ALD has provided a powerful tool to understand the disease pathogenesis[8]. Cellular and molecular mechanism studies have advanced our knowledge of the pathogenesis of ALD[8,9]. Multiple processes including excessive accumulation of lipids, reactive oxygen species (ROS) production, mitochondrial dysfunction, and cell inflammation and death are involved in ALD pathogenesis[10]. Despite all these efforts, there are no Food and Drug Administration-approved therapies for ALD[11].

NAFLD is the most common CLD with a broad spectrum, ranging from non-alcohol fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) with the progression of liver inflammation and different degrees of fibrosis[12]. NASH also can progression to HCC (Figure 1)[13]. The global prevalence of NAFLD was estimated to be 29.8% [95% confidence interval (CI): 28.6%-31.1%] in 2019[14], and the prevalence is estimated to be 32.4% (95%CI: 29.9-34.9) in 2022[15]. It affects more than 30% of people in the United States[16]. NAFLD is closely associated with other metabolic disorders, including obesity, diabetes, chronic kidney disease, and cardiovascular disease[17,18]. A new nomenclature for NAFLD has been suggested by a group of experts, namely metabolic dysfunction-associated fatty liver disease (MAFLD), which is based on the evidence of hepatic steatosis plus one of the following three criteria, including the presence of overweight or obesity, or presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation[19,20]. However, there are no currently approved medicines for NAFLD or MAFLD treatment[12].

Oxidative stress and inflammation are commonly associated with CLD independent of disease types [21,22]. For example, ethanol consumption can induce alcohol liver steatosis, inflammation, and production of ROS, resulting in the development of ALD with liver inflammation and oxidative stress [23]. In addition to hepatocyte injury, both innate and adaptive immune cells including macrophages, dendritic cells, neutrophils, and lymphocytes are involved in the development of CLD[24,25]. Production of ROS and inflammatory cytokines produced by immune cells under the stimuli of alcohol and diet metabolites, such as cholesterol and acetaldehyde, can further trigger liver oxidative stress, inflammation, and cell apoptosis or death to cause the progression of CLD[26,27].

Treatments, such as lifestyle intervention[28,29], gene editing[30,31], and pharmaceutical therapies [32], can ameliorate or cure CLD at the early stages. However, server condition of CLD requires liver transplantation, which lacks donor availability. Here, the roles of antioxidants and anti-inflammatory agents in CLD treatment, especially for ALD, NAFLD, and HCC, are reviewed. Examples of clinical trials for evaluating the potential efficacies of potential treatment agents are summarized.

DATABASE SEARCHING

The databases of PubMed, Cochrane Library (Wiley), Embase, Web of Science, and Google Scholar from the last five years (from July 2020) were searched for studies by keywords of CLD, ALD, NAFLD, or HCC, and their treatments with anti-oxidative and anti-inflammatory agents. Papers written in English

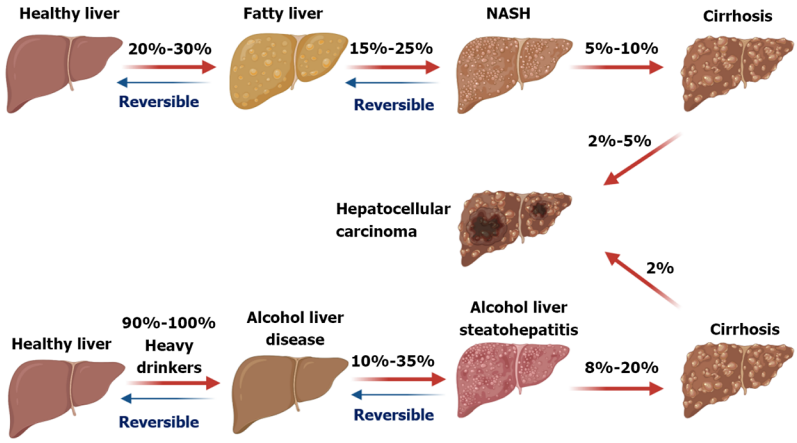

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Figure 1 The development of hepatocellular carcinoma from non-alcoholic fatty liver disease and alcoholic fatty liver disease. The prevalence (20%-30%) of non-alcoholic fatty liver (NAFL) in the world population and the following percentages of NAFL into non-alcoholic steatohepatitis (NASH) (15%-25%), NASH into cirrhosis (5%-10%), and cirrhosis into hepatocellular carcinoma (HCC) (2%-5%) are labeled. Around 90%-100% of heavy drinkers can develop alcoholic liver disease (ALD), then the percentages of progression from simple ALD into alcohol liver steatohepatitis (10%-35%), cirrhosis (8%-20%), and HCC (2%) are shown in the graphic. This cartoon was created using Biorender online tools (https://biorender.com). NASH: Non-alcoholic steatohepatitis.

were studied. When reviewing oxidative stress and/or inflammation-related molecules in CLD, the time restriction of the published data was removed.

INFLAMMATION AND OXIDATIVE STRESS IN CLD AND UNDERLYING MOLECULAR MECHANISMS

Inflammation and oxidative stress are commonly associated with each other in the pathogenesis of CLD [33], including ALD, NAFLD, and HCC. Several common signaling pathways are involved in liver inflammation and oxidative stress, such as Toll-like receptor (TLR)/nuclear factor kappa B (NF-κB) and heme oxygenase-1 (HO-1) signaling pathways[34,35]. Dysregulation of lipid metabolism contributes to the pathogenesis of CLD[36,37], which is commonly associated with liver oxidative stress and inflammation. Molecules such as peroxisome proliferator-activated receptors (PPARs) are involved in alcohol or non-alcohol factors-induced lipid metabolism dysregulation and hepatic steatosis[38,39]. In this section, we review some important signaling pathways involved in liver inflammation and oxidative stress during CLD.

AMP-activated protein kinase

AMP-activated protein kinase (AMPK) as a crucial energy sensor plays an important role in energy metabolism in multiple tissues, including the liver[40]. Activation of AMPK by metformin can reduce induced triglyceride accumulation in the livers of mice treated with ethanol compared to control groups [41]. Activation of sirtuin 1 (SIRT1)/Liver kinase B1/AMPK signaling with botulin (a triterpene) treatment reduces serum aminotransferase and triglyceride levels in mice with chronic-binge ethanol [42]. Activation of the AMPK signaling pathway with plant sterol ester of α-linolenic acid can also attenuate endoplasmic reticulum (ER) stress-induced hepatocyte apoptosis in mice with NAFLD[43]. Similarly, stimulating the activation of AMPK by an activator PXL770 reduces *de novo* lipogenesis in primary mice and human hepatocytes, which can result in the suppression of hepatic steatosis, inflammation, and fibrogenesis in mice with NASH. In addition, PXL770 has a direct inhibitory effect on the production of proinflammatory cytokines and activation of hepatic stellate cells[44].

C-Jun N-terminal kinase

Activation of C-Jun N-terminal kinase (JNK) signaling pathway is involved in lipotoxicity, inflammation, ER stress, and mitochondrial dysfunction. Palmitic acid (PA)-induced activation of JNK/Sab (SH3 domain-binding protein 5) signaling contributes to NASH progression, which is associated with mitochondrial dysfunction, oxidative stress, hepatic steatosis, and inflammation[45].

Deficiency of hypoxia-induced gene domain protein-1α (Higd-1α), a mitochondrial inner membrane protein, promotes free fatty acids (FFAs)-induced apoptosis and oxidative stress in hepatocytes[46]. In this process, the production of cytosolic oxidized mitochondrial DNA (ox-mtDNA) is increased, which induces activation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes and JNK signaling but decreases fatty acid oxidation (FAO). In contrast, exercise can increase the expression

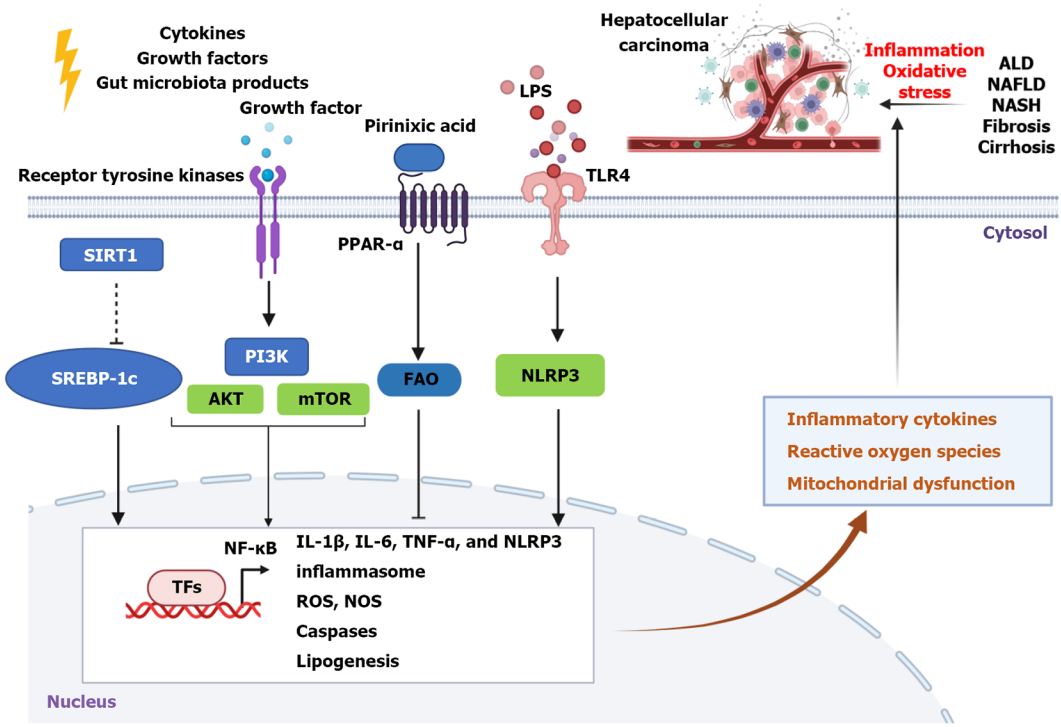

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Figure 2 Molecular signaling pathway in liver inflammation and oxidative stress. Inflammation and oxidative stress are involved in the development of chronic liver diseases such as alcoholic liver disease, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, fibrosis, and cirrhosis into hepatocellular carcinoma. Many factors including cytokines, growth factors, and gut microbiota-derived products such as lipopolysaccharide can activate their receptors such as peroxisome proliferator-activated receptor-α and toll-like receptor 4, resulting in upregulation or inhibition of downstream genes to induce or prevent inflammatory cytokines and production of reactive oxygen species. This cartoon was created using Biorender online tools (https://biorender.com). LPS: Lipopolysaccharide; TLR4: Toll-like receptor 4; ALD: Alcoholic liver disease; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; PPAR-α: Peroxisome proliferator-activated receptor-α; SIRT1: Sirtuin 1; SREBP-1c: Sterol regulatory element binding protein 1c; PI3K: Phosphatidylinositol-3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; FAO: Fatty acid oxidation; NLRP3: NOD-like receptor family pyrin domain containing 3; NF-κB: Nuclear factor kappa B; IL: Interleukin; TNF-α: Tumor necrosis factor-α; NLRP3: NOD-like receptor family pyrin domain containing 3; ROS: Reactive oxygen species; NOS: Nitric oxide synthase.

of Higd-1α in the liver to ameliorate hepatic steatosis and inflammation by suppressing ox-mtDNA/NLRP3/JNK pathway[46].

Farnesoid X receptor

Farnesoid X receptor (FXR) is a nuclear receptor that metabolically regulates glucose, bile acid, and lipid metabolism[47,48]. Treatment of Lactobacillus reuteri can ameliorate lipid accumulation in mice with ALD by upregulating FXR expression, which is associated with the upregulation of carbohydrate response element binding protein and downregulation of sterol regulatory element binding transcription factor 1 and cluster of differentiation (CD36)[49]. In addition, the FXR/fibroblast growth factors (FGFs) axis (FGF-15 and FGF-19) also plays a key in the regulation of hepatic inflammation, lipid metabolism, and fibrosis[50,51]. Clinically, treatment of FXR agonist vonafexor also shows anti-fibrotic effects in patients with NASH[52].

Nuclear factor erythroid 2-related factor-2/HO-1

Nuclear factor erythroid 2-related factor-2 (Nrf2) is a key transcription factor that plays a critical role in oxidative stress and inflammatory responses. For example, Nrf2 expression is positively associated with oyster peptide-mediated suppression of inflammation mediated by upregulation of NF-κB signaling and upregulation of antioxidant response in mice with ALD[53]. Activation of Nrf2 is involved in the protective effect of diallyl disulfide against chemical (CCl_4)-induced liver injury and oxidative stress [54]. HO-1, an inducible form of antioxidant zyme HO isoforms that regulates heme group degradation, plays an essential role in liver inflammation and oxidative stress[55]. Nrf2 can regulate HO-1 to suppress liver oxidative stress, ER stress, and inflammation[56].

Nrf2 also plays an important role in the pathogenesis of NASH. Activation of Nrf2 can ameliorate liver inflammation, ER stress, iron overload, and lipotoxicity to suppress NASH and oxidative stress, which can be suppressed by transforming growth factor-beta (TGF-β)[57]. Activation of Nrf2 can suppress the expression of ROS and NLRP3 and inhibit Caspase 1/interleukin (IL)-1β and IL-18-mediated inflammation[58]. In addition, pharmacologic activation of Nrf2 by TBE-31, acetylenic tricyclic bis(cyano enone), decreases insulin resistance and liver fat accumulation, inflammation, fibrosis, and

oxidative stress in mice with a high-fat plus fructose diet. However, the TBR-31-mediated effect was abolished in Nrf2-null mice[59].

PPARs

PPARs are a group of nuclear receptor proteins that function as ligand-activated receptors to regulate genes in energy metabolism and inflammation. PPARs comprise three subtypes, PPAR-α, PPAR-β/δ, and PPAR-γ, which are pharmaceutical targets for disease treatments[60,61]. These PPARs play important roles in ALD[62], NAFLD[63], hepatitis virus-mediated liver injury[64], and HCC[65].

Activation of PPAR-α by agonist WY-14643 (Pirinixic Acid, Figure 2) ameliorates ethanol-induced liver fat accumulation by increasing FAO[66]. Sustained activation of PPAR-α can decrease obesity and improve insulin resistance to rebuild glucose homeostasis. However, it increases the risk of HCC development due to liver ER stress[67]. Treatment with GW9662, an antagonist of PPAR-γ, significantly decreased lipopolysaccharide (LPS)/TLR4-mediated expression of IL-1β, IL-6, inducible nitric oxide synthase, and nitrite (NO_2^-) concentration[68].

Treatment with a dual PPAR-α/γ agonist Saroglitazar is able to reduce serum transaminases and 63% of overweight patients with NALFD reduced bodyweight (> 5%)[69]. In addition, many clinical trials have been performed to evaluate the effects of PPARs in ALD. For example, pemafibrate can improve liver function and glucose metabolism in patients with hypertriglyceridemia[70] and decrease liver stiffness in patients with NAFLD measured by magnetic resonance elastography (ClinicalTrials.gov, number: NCT03350165)[71]. Treatments that target PPAR-α such as pemafibrate[71], PPAR-β/δ such as seladelpar[72], and PPAR-γ such as pioglitazone[73,74] show promising efficacy in the clinic for CLD treatment (Figure 3). Meanwhile, a dual PPAR-α/δ agonist elafibranor and a pan-PPAR regulator lanifibranor show promising efficacy for CLD treatment in the clinic[75,76]. For example, a phase 2b clinical trial reveals that treatment of lanifibranor (1200 mg) compared with the placebo can decrease at least 2 points of steatosis, activity, and fibrosis score that incorporates scores for ballooning and inflammation[76].

Phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin

The phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB or AKT)/mammalian target of rapamycin (mTOR) signaling pathway is implicated in the pathogenesis of liver disease and therapy[77,78]. For example, this signaling pathway is involved in the anti-steatosis effect of D-mannose in ALD [79]. Activation of PI3K/AKT/mTOR signaling pathway by arecoline (2.5 μM), an alkaloid ester found in the betel nut palm seeds, promotes the proliferation and migration of HepG2 cells[80]. Acid-sensitive ion channel 1α can upregulate the activation of PI3K/AKT/mTOR signaling pathway to enhance the expression of matrix metalloproteinase (MMP)2 and MMP9 to promote liver cancer cell (HepG2 and SK-Hep1 cells) migration and invasion[81]. One human study also indicates that PI3K is more strongly expressed in tumors than that in cirrhotic livers but not AKT and mTOR, and the expression of PI3K in tumor tissues is independent of etiology[82]. In addition, activation of growth factor receptor protein tyrosine kinases (Figure 2) can result in autophosphorylation on tyrosine residues and subsequent binding and activation of PI3K[83], playing an important role in cancer development. Inhibition or blockade of this signaling pathway can suppress liver fibrosis[84,85] and cancer progression[86,87].

Furthermore, lysyl oxidase family members (LOX) and LOX-like proteins (LOXL1-4) play important roles in liver fibrosis and cancer[88]. Insulin resistance can promote extracellular matrix stabilization by upregulating hepatic production of LOXL2 through upregulation of the expression of Forkhead box protein O1 in NAFLD[89]. In addition, galectins such as galectin-3 also play an essential role in CLD[90-92], including liver fibrosis and cancer. Overall, these molecular signaling pathways are involved in liver inflammation and oxidative stress to promote the development of CLD to HCC (Figure 2).

ANTIOXIDANT AND ANTI-INFLAMMATORY AGENTS IN ALD

Many ingredients from natural products or plants have both antioxidant and anti-inflammatory functions, which are good candidates for CLD treatment. Some of these products may have preventive effects on hepatic steatosis in ALD and NAFLD. For example, diallyl trisulfide (DATS) is a bioactive compound isolated from garlic and can reduce serum levels of aspartate transaminase (AST) and alanine aminotransferase (ALT) and decrease alcohol-induced liver injury[93]. DATS can upregulate PPAR-α expression and down-regulate sterol regulatory element binding protein 1c (SREBP-1c) expression to inhibit hepatic steatosis. Meanwhile, it can reduce liver oxidative stress by increasing antioxidant products and reducing ROS and malondialdehyde (MDA) production in the fatty liver[93]. In this section, we review some promising agents in ALD treatments either in animal models or clinical trials.

β-sitosterol

β-sitosterol is isolated from the roots of *Panax ginseng*[94]. As a plant sterol, β-sitosterol can reduce alcohol-induced liver injury and oxidative stress *via* restoration of erythrocyte membrane fluidity,

upregulation of glutathione (GSH) activity, and reduction of MDA production. In addition, β-sitosterol can suppress apoptosis-related gene expression by increasing the phosphorylation of PI3K and AKT[95].

Curcumin

Curcumin is an orange-yellow component of turmeric or curry powder isolated from the rhizome of *Curcuma longa*[96,97]. Supplementation of curcumin can significantly increase the activities of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) to reduce swimming-induced oxidative stress in mice, by activating Nrf2 signaling pathway[98]. Treatment of curcumin significantly decreases serum levels of ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transferase, Arginase I, and blood urea nitrogen, while it increases serum levels of Albumin and total protein in ethanol-treated rats compared to the control group[99]. Development of self-assembled micelles of curcumin can be administered by oral delivery to enhance its anti-oxidative stress ability to prevent ALD and gastric mucosa damage[100]. Encapsulation enables to improve the adsorption of curcumin in intestinal epithelial cells and enhance its hepatoprotective effects in rats, *via* increasing the activity of GPx and decreasing high levels of MDA in the liver[101]. Furthermore, a combined treatment of curcumin and bacicalin shows more protective effects on ALD in rats by reducing liver oxidative damage through activation of the Nrf2/HO-1 signaling pathway[102].

Empagliflozin

Empagliflozin (EMPA) has benefits in cardiovascular, renal, and cerebral diseases, which is potentially mediated through its antioxidant and anti-inflammatory activities. Treatment with EMPA can decrease serum levels of ALT, AST, and ALP. It also increases the activities of GSH and SOD in the liver homogenates and decreases the liver content of MDA and nitric oxide (NO)[103]. Moreover, EMPA can downregulate NF-κB signaling to suppress the expression of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, which is associated with the upregulation of PPAR-γ, Nrf2, and their target gene HO-1[103].

Gastrodin

Gastrodin is the main bioactive component of *Gastrodia elata Blume* and displays anti-inflammatory and antioxidant properties. For example, administration of gastrodin (50 or 100 mg/kg) in mice significantly inhibits concanavalin A (ConA)-induced acute hepatitis, partly by suppressing IL-6/Janus Kinase 2/signal transducer and activator of transcription 3 signaling pathway[104]. In addition, treatment with gastrodin ameliorated acetaminophen-induced liver injury in mice. The anti-inflammatory and anti-oxidative stress functions of gastrodin are mediated through the inhibition of signal-regulated kinase/JNK/mitogen-activated protein kinase signaling pathways and hepatic MDA activity, as well as activation of Nrf2 expression and SOD activity[105].

Genistein

Genistein is an isoflavone first isolated from the brooming plant Dyer's *Genista tinctoria*, which is widely distributed in the Fabaceae family[106-109]. Treatment of genistein at a dose of 0.3 mmol/kg of bodyweight can ameliorate liver fibrosis and apoptosis in mice by suppressing the expression of proinflammatory cytokines such as TNF-α, IL-6, profibrotic cytokines such as TGF-β1, and cell caspase 3 [110]. In contrast, another study shows that supplementation of soy proteins significantly decreases serum ALT concentrations and hepatic TNF-α and CD-14 expression and decreases NF-κB protein in casein-based 35% high-fat ethanol liquid diet (EtOH)-treated mice by inhibiting β-catenin signaling [111]. More functional studies of genistein have been performed in NAFLD models, which are discussed in the following section.

Lactoferrin

Lactoferrin (LF) is an iron-binding protein found at relatively high concentrations in mammalian milk [112]. LF displays multiple functions, including antioxidant, anti-cancer, and anti-inflammatory activities. For example, LF treatment can decrease the levels of liver superoxide and suppress liver inflammation in male mice with alcoholic-induced liver injury (ALI) by upregulating the expression of aldehyde dehydrogenase-2 and suppressing overexpression of cytochrome P450 2E1 (CYP2E1)[113]. LF treatment also displays a protective effect in female mice with acute ALI by regulating redox-stress response capacity[114]. The protective effect of LF on ALI is associated with the manipulation of gut microbiota and the modulation of hepatic alcohol metabolism[113].

Selenium

Selenium plays an essential role against oxidation, which is part of the catalytic center of different antioxidant selenoproteins including GPxs and selenoprotein P[115]. The serum levels of selenium are decreased in adult patients with acute and chronic alcoholic-related diseases, accompanied by liver damage and the severity of oxidation[115,116].

Silymarin

Silymarin is an active compound from the extracts of milk thistle (*Silybum marianum*)[117]. Silymarin displays antioxidant, antifibrotic, anti-inflammatory, and hepatoprotective properties in different types of CLD[118,119], such as ALD. Simultaneous supplementation of silymarin with alcohol treatment can reduce the ethanol-induced increase of serum ALT levels and hepatic microvesicular steatosis and TNF-α expression[120]. Another study on non-human primates also shows that silymarin can prevent the development of alcohol-induced liver fibrosis by decreasing the production of type I collagens[121].

Taraxasterol

Taraxasterol (TAS) is an active ingredient of *Taraxacum officinale*, which has protective effects on the liver and kidneys by reducing serum levels of ALT and AST, increasing serum and liver SOD and GPx, and maintaining the balance of ion homeostasis[122]. TAS also displays anti-inflammatory function in cultured mouse primary lymphocytes stimulated with Con A and in mice with Con A-induced acute hepatitis[123]. Mechanism studies reveal that TAS inhibits T cell activation and proliferation by suppressing IL-2/IL-2 receptor-mediated downstream signaling pathways[123].

Telmisartan

Telmisartan (TEL) exhibits similar effects with EMPA on ALD. Treatment of TEL (10 mg/kg/day) decreased serum levels of ALT, AST, and ALP in mice with ALD[124]. In addition, TEL displays anti-inflammatory and antioxidant properties in mice with ALD by increasing the activity of SOD and GPx to reduce liver contents of NO and MDA, upregulating the expression of Nrf-2, PPAR-γ, and Hmox-1, and downregulating NF-κB expression[124].

ANTIOXIDANT AND ANTI-INFLAMMATORY AGENTS IN NAFLD

Hepatic inflammation and oxidative stress are also associated with NAFLD pathogenesis[125]. Therefore, many above-discussed products also display similar bioactive functions against NAFLD.

β-sitosterol

Treatment with β-sitosterol can prevent high-fructose diet-induced macrovesicular hepatic steatosis and inhibit the progression of NAFL to NASH in male rats[126]. Meanwhile, it is also able to inhibit high-fructose diet-induced visceral obesity, hypertriglyceridemia, plasma insulin concentration, and homeostatic model assessment of insulin resistance (HOMA-IR) but increase plasma levels of adiponectin in female rats[127]. Another study shows that in combination with stigmasterol, a dietary phytosterol, β-sitosterol can alleviate a high-fat western-style diet-induced NAFLD in mice post-17-wk treatment, by decreasing hepatic di- and tri-acylglycerols and circulating ceramide levels[128].

Curcumin

Curcumin is a natural polyphenol, which shows anti-inflammatory and antioxidant activities. It can improve insulin resistance and reduce hepatic fat accumulation in dietary obese rat models[129]. Accumulating evidence identifies that curcumin can attenuate hepatic steatosis by suppressing hepatic expression of CD36, PPAR-γ, SREBP-1c, and fatty acid synthase (FAS) in NAFLD mice, through upregulation of Nrf2 and FXR expression and downregulation of liver X receptor α expression[130,131]. In addition, curcumin can induce activation of AMPK and upregulation of PPAR-α, and suppress the high-fat diet (HFD)-induced increase in the expression of SREBP-1, acetyl-CoA carboxylase 1, FAS, and CD36 [132]. Meanwhile, curcumin is able to prevent intestinal permeability and suppress LPS/TLR4/NF-κB-mediated inflammatory response to protect against diet-induced hepatic steatosis and inflammation [133]. In addition, curcumin can also suppress NLRP3 inflammasome (Figure 2) and pro–IL-1β synthesis by suppressing LPS-mediated activation of NF-κB signaling pathway[134].

Ex vivo studies also show that treatment of curcumin decreases linoleic acid-induced ROS production and leptin-induced TNF-α expression in human peripheral blood mononuclear cells[135]. A randomized controlled trial in Iran demonstrates that supplementation with curcumin in a phytosomal form (1000 mg/day) significantly reduces body mass index (BMI), waist circumference, and serum levels of AST and ALT[136]. This dose was safe and well tolerated in NAFLD patients[136]. Another double-blind, randomized, placebo-controlled trial displays that daily supplementation of low-dose phospholipid curcumin (250 mg) for 2 mo can significantly decrease hepatic steatosis and serum AST levels in NAFLD patients compared to placebo[137]. In addition, a combined therapy of curcumin (500 mg/day) with piperine, an alkaloid in black pepper with many pharmacological effects on chronic diseases[138], also decreases the severity of NAFLD and serum ALP levels[139]. Large clinical trials are needed for further evaluation of the efficacy of curcumin and its synergistic treatments.

EMPA

EMPA is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), which plays an important role in

NAFLD. EMPA treatment can inhibit PA-induced lipid deposition in hepatocytes (HepG2 cells) and HFD-induced hepatic lipid accumulation and inflammation in mice by upregulating the expression of a stress-inducible protein Sestrin2 and activating AMPK-mTOR signaling pathway[140]. Another study demonstrates that EMPA can upregulate the expression of medium-chain acyl-CoA dehydrogenase in NASH liver and PA and glucose-treated hepatocytes by activating AMPK/forkhead box A2 signaling pathway, resulting in a reduction of hepatic lipid deposition *in vivo* and *in vitro*[141]. A meta-analysis shows that EMPA can significantly reduce BMI, HOMA-IR, AST, and liver fibrosis in patients with NAFLD[142].

In addition, other SGLT2 inhibitors or gliflozins, such as licogliflozin[143,144] and dapagliflozin[145, 146], also can control glycemic production and bodyweight, normalize serum ALT levels, and reduce Fibrosis-4 NAFLD patients with T2DM.

Gastrodin

Gastrodin has been shown to significantly decrease lipid accumulation and inflammatory response in primary mice and human hepatocytes treated with 0.5 mmol/L PA along with 1.0 mmol/L oleic acid. In addition, it ameliorates diet-induced hepatic steatosis and inflammation in mice by activating the AMPK signaling pathway[147]. Gastrodin can also regulate lipid metabolism and display antioxidant effects in larval zebrafish with high-cholesterol diet-induced NAFLD[148].

Genistein

Genistein has been shown to play an important role in NAFLD and NASH treatment. Treatment of genistein reduces the levels of TNF-α and reduces TLR4 mRNA and protein expression and inflammation in the livers of rats with NASH[149]. A combination of genistein with metformin (0.2% + 0.23%) for 3 mo shows a synergistic effect on the reduction of AST, ALT, and TG, liver TG and number of macrophages, and NAFLD activity score (NAS) in HFD-fed mice[150]. The reduction of hepatic steatosis is associated with decreased mRNA levels of lipogenic-related genes *SREBP-1c* and *FAS* and upregulated mRNA expression of FAO-related gene *carnitine palmitoyl transferase 1*[150]. Genistein treatment (16 mg/kg BW/day) for 5 wk can significantly decrease hepatic steatosis, inflammation, and hepatocyte ballooning in ovariectomized rats with high-fat and high-fructose diet-induced NASH[151].

Consumption of dietary isoflavones including genistein is reversely associated with NAFLD, hypertension, and hyperlipidemia in a study on Chinese adults[152]. Molecular mechanism studies show that genistein can suppress the activation of SREBP-1c in FFA-induced fat accumulation in primary human hepatocytes, whereas genistein-mediated upregulation of PPAR-α proteins in normal hepatocytes is abolished in steatotic hepatocytes[153].

LF

LF is an iron-binding protein in mammalian milk and displays multiple functions, including antioxidant, anti-cancer, and anti-inflammatory activities. During NASH progression, LF treatment can inhibit NF-κB activation to downregulate a high-fat diet and chemical dimethylnitrosamine-induced liver injury, inflammation, and fibrosis[154]. Treatment with LF improves insulin sensitivity and reduces hepatic steatosis in ob/ob mice by downregulating SREBP-2. It also regulates hepatocellular iron transport by controlling the hepcidin-ferroportin axis to maintain liver oxidative balance and suppress hepatocyte death[155].

Mastiha

Mastiha is a natural and aromatic resin isolated from the trunk and brunches of mastic trees with antioxidant and anti-inflammatory properties[156]. Mice with diet-induced NASH fed with 0.2% (w/w) Mastiha supplementation for 8 wk can reduce the circulating ALT levels, NAS, hepatic steatosis, and liver collagen production[157]. This study also identifies that Mastiha supplementation changes NASH-induced gut microbiota profile to the diversity and composition of healthy mice. A randomized clinical trial (NCT03135873, www.clinicaltrials.gov) shows that supplementation of Mastiha improves the total antioxidant status (TAS) levels in NAFLD patients with severe obesity compared to that in the corresponding placebo group[158]. The anti-inflammatory function of Mastiha is associated with the expression of microRNA-155 in the plasma of NAFLD patients, which may regulate the differentiation and function of T helper-17 cells[159].

Selenium

Treatment with selenium-enriched green tea extract (200 mg/kg body weight) for 15 wk can significantly reduce body weight gain and visceral fat accumulation in mice with obesity and NAFLD [160]. Reduced serum levels of selenium are independently associated with hepatic fibrosis in NAFLD patients[161]. Another study reveals that selenium deficiency induces hepatic inflammation in pigs by activating the NF-κB signaling pathway, decreasing antioxidant capacity, and increasing ROS levels [162]. Selenium-enriched *Lactobacillus acidophilus* SNZ 86 (probiotic) can decrease western-style diet-induced hepatic steatosis in mice with NAFLD, by activating autophagy through the upregulation of AMPK/SIRT1 signaling pathway[163]. Co-supplementation of selenium with vitamin B6 can reduce

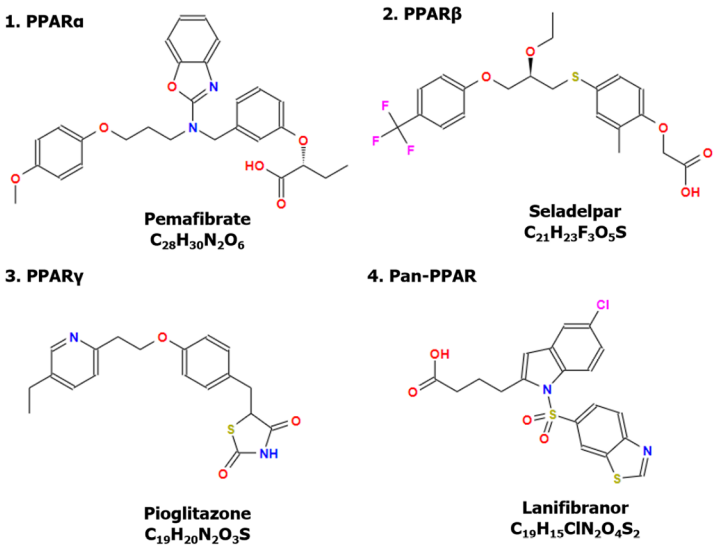

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Figure 3 Structures of peroxisome proliferator-activated receptor agonists or modulators applied for the treatment of chronic liver disease. Many peroxisome proliferator-activated receptor regulators have been evaluated in the clinic, showing promising effects in patients with chronic liver disease. All the chemical structures were collected online from the Chemical Book (https://www.chemicalbook.com, accessed on August 10, 2022). PPAR: Peroxisome proliferator-activated receptor.

liver lipid synthesis and deposition by increasing the expression of SIRT1 to downregulate SREBP-1c expression (Figure 2) and upregulate PPAR-α expression in HFD-fed rats[164].

Silymarin

The major active compound of silymarin is silybin. Treatment with silybin can significantly decrease lipid accumulation in mice with NAFLD by activating PPAR-α[165]. Since it can partially inhibit the effect of PPAR-α agonist fenofibrate, it is not suggested to be simultaneously applied with PPAR-α agonists. Silymarin also displays a synergistic effect with quercetin on the reduction of lipid accumulation in rat hepatocytes[166]. Silymarin treatment significantly ameliorates high fructose-induced oxidative stress and hepatic steatosis in rats[167]. Silymarin supplementation (560 mg daily) for 8 wk significantly improves serum AST/ALT ratio, ultrasound fatty liver grading, and BMI in patients with morbid obesity and NAFLD[168].

TEL

Treatment with TEL significantly improves fibrosis scores and reduces the levels of serum leptin and its expression in liver tissue[169]. As an angiotensin receptor blocker, it significantly decreases fasting serum-FFA levels and triglyceride-glucose index in patients with NAFLD[170]. TEL displays a similar effect as vitamin E on the reduction of NAS, and improvement of hepatic steatosis, but it has a better effect on the reduction of liver lobular inflammation and hepatocyte ballooning[171]. It can function as a PPAR-γ/α dual agonist to simultaneously improve insulin-sensitivity *via* activating PPAR-γ and improve lipid metabolism by activating PPAR-α[172].

Delta-tocotrienol

Tocotrienols are natural compounds that belong to one part of two vitamin E components (Tocopherols as another part), including α, β, γ, and δ tocotrienols[173]. Among them, δ-tocotrienol shows strongly anti-inflammatory activity, which can decrease insulin resistance, hepatic steatosis, and serum triglyceride concentrations in rats with diet-induced obesity[174]. Recent studies also show that δ-tocotrienol has anti-cancer properties by regulating angiogenesis and cell proliferation and apoptosis[175].

A human study indicates that oral supplementation of δ-tocotrienol (300 mg, twice daily) for 12 wk significantly decreases serum aminotransferases, high sensitivity C-reactive protein (hs-CRP), and MDA, and fatty liver index (FLI) score compared to placebo[176]. Clinical trials reveal that δ-tocotrienol supplementation results in a significant reduction in plasma glucose, insulin, glycosylated hemoglobin, MDA, high sensitive C-reactive protein, and proinflammatory cytokines (TNF-α and IL-6), and HOMA-IR in pre-diabetic and diabetic patients[177,178]. Another trial also demonstrates that treatment of δ-tocotrienol (300 mg, twice daily) for 24 wk further significantly reduces FLI score, HOMA-IR, and hepatic steatosis than placebo, except decreased serum levels of hs-CRP, MDA, ALT, and AST, without causing adverse events[179].

ANTIOXIDANT AND ANTI-INFLAMMATORY AGENTS IN LIVER CANCER

Both ALD and NAFLD are major contributors to HCC initiation and progression. Therefore, the above-discussed biomolecules may also exhibit anti-HCC effects. For example, treatment of β-sitosterol niosomes, a form of β-sitosterol with polyethylene glycol modification, shows cytotoxicity to HepG2 cells due to increased cellular uptake and displays *in vivo* anti-HCC ability in *Wistar albino* rats[180]. Treatment of β-sitosterol-assisted silver nanoparticles (BSS-SNPs) significantly inhibits the proliferation of HepG2 cells and their production of ROS and Nrf2, resulting in the regulation of pro-apoptotic genes such as Bcl-2 Associated X-protein and caspases 3 and 9[181]. Similarly, compounds including curcumin [182], EMPA[183], gastrodin[184], genistein[185], LF[186], selenium[187], silymarin[188], TAS[189], TEL [190], and delta-tocotrienol[191] display anti-HCC effects either *in vitro* or *in vivo*, or both (Table 1).

CLINICAL TRIALS

Clinical trials have been started to evaluate the efficacy of these molecules in CLD (Table 2), such as EMPA[192] and silymarin[193,194]. For example, treatment with EMPA can improve liver steatosis in patients with NAFLD without T2DM[192]. Another trial shows that oral supplementation of genistein (250 mg) for 8 wk can decrease insulin resistance, oxidative stress, and inflammation and improve lipid metabolism in patients with NAFLD[195].

CONCLUSION

CLD is a continuous process that causes a reduction of liver function that lasts more than six months. CLD has a broad spectrum with complex cellular and molecular mechanisms. It can be subclassified into ALD, NAFLD or MAFLD, chronic viral infection, and autoimmune hepatitis, which can lead to liver fibrosis, cirrhosis, and cancer. However, there are no currently available treatments for ALD, NAFLD, and liver fibrosis, except the preventive strategies, such as changes in exercise, diet, and alcohol use. Early preventive strategies predict good outcomes. Patients with advanced ALD and NAFLD require liver transplantation, but without enough donor organs. Liver inflammation and oxidative stress are ubiquitously associated with the development and progression of CLD. Molecular signaling pathways such as AMPK, JNK, and PPAR-mediated signaling pathways are implicated in liver inflammation, oxidative stress, and lipid metabolism. Accumulating studies have demonstrated that natural products with antioxidant and anti-inflammatory functions display therapeutic effects against inflammation, fibrosis, and metabolic disorders, including ALD and NAFLD. These products such as β-sitosterol, curcumin, EMPA, gastrodin, and genistein have shown potential application at all the stages of CLD, from ALD/NAFLD to HCC. In addition, clinical trials that are undergoing to evaluate their efficacy and safety are reviewed. Overall, pre-clinical studies in cell and animal models reveal the protective effects of these agents in CLD. However, more clinical trials are required to evaluate their efficacy and safety.

Natural products, especially antioxidant and anti-inflammatory products, show potent therapeutic alternatives for CLD treatment with their efficacy and low side effects. Remarkably, these products also display anti-HCC functions. However, many pharmaceutical dynamic assays have not been tested, and the potential adverse effects of long-term use of these products are not available. In the future, the synergistic effects of different drugs should be evaluated to treat CLD, due to its complex pathogenic factors.

Table 1 Antioxidant and anti-inflammatory agents for the treatment of hepatocellular carcinoma

Molecules	Model	Function	Ref.
β-sitosterol	HepG2 cells; Rat HCC	Treatment of β-sitosterol niosomes displays direct cytotoxicity to HepG2 cells in vitro and anti-HCC ability in rats	[182]
Curcumin	HepG2 and SK-Hep-1 cells. A nude mouse xenograft model bearing HepG2 cells	It can inhibit cell proliferation and increase cell apoptosis and cell cycle arrest at the G0/G1 phase of cancer cells by downregulating the expression of BCLAF1 and inhibiting the activation of the PI3K/AKT/GSK-3β pathway	[183]
Empagliflozin	DENA-induced HCC in mice	It shows a synergistic effect on the control of angiogenesis, invasion, and metastasis of tumor cells in mice with DENA-induced HCC by inhibiting the expression of MAPKs and reducing liver injury enzymes	[184]
Gastrodin	Subcutaneous H22 cells-induced tumor	It can specifically increase the expression of NF-κB	[185]

	in mice	downstream genes such as Bcl-xL, Bcl-2, and IL-2 in CD4 but not CD8 T cells	
Genistein	TAA-induced HCC in rats	It displays antioxidant and anti-HCC effects by suppressing the versican/PDGF bidirectional axis and protein expression of PKC and ERK-1	[186]
Lactoferrin	DEN-induced HCC in rats	It shows a chemopreventive effect against DEN-induced HCC in rats in a dose-dependent manner by suppressing the expression and activation of AKT	[187]
Selenium	TAA-induced HCC in rats	Selenium nanoparticles improve the tumor suppressive effect of sorafenib and overcome drug resistance in rat HCC by inducing apoptosis and targeting AKT/mTOR and NF-κB signaling pathways, as well as epigenetic regulation	[188]
Silymarin	DEN/AAF/CCl_4 induced HCC in rats	It suppresses cancer cell growth in rats with DEN/AAF/CCl_4-induced tumors by inhibiting the expression of Ki-67 and HGF/c-Met, Wnt/β-catenin, and PI3K/Akt/mTOR signaling pathways	[189]
Taraxasterol	HepG2 and Huh7H22 bearing mice	It can suppress tumor cell growth by suppressing Ki67 expression and inducing cell apoptosis *via* suppressing IL-6/STAT3 signaling pathway, as well as promoting T cell infiltration in tumor tissue	[190]
Telmisartan	NDEA-induced HCC in mice	It exerts an anti-HCC effect and increases tumor cell sensitivity to sorafenib treatment by suppressing phosphorylation-induced activation of TAK1 and the ERK1/2 and NF-κB signaling pathways	[191]
Delta-tocotrienol	HCC cell lines SK Hep-1 and Huh7	It promotes the anti-HCC cell activity of IFN-α by increasing ROS and increasing cell apoptosis together with an increased Bax/Bcl-xL ratio. In addition, it can activate Notch1 signaling pathway	[192]

AKT: Protein kinase B; Bax: Bcl-2-like protein 4; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma extra-large; BCLAF1: BCL-2-associated transcription factor 1; CD4: Cluster of differentiation 4; c-Met: Tyrosine-protein kinase Met; ERK-1/2: Extracellular signal-regulated kinases 1/2; GSK-3β: Glycogen synthase kinase-3β; HCC: Hepatocellular carcinoma; HGF: Hepatocyte growth factor; IL-2: Interleukin 2; Ki-67: Marker of proliferation Ki-67; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor κB; PI3K: Phosphatidylinositol-3-kinase; PDGF: Platelet-derived growth factor; SIRT1: Sirtuin 1; SREBP-1c: Sterol regulatory element binding protein 1c; STAT3: Signal transducer and activator of transcription 3; DENA Diethylnitrosamine; TAA: Thioacetamide; ROS: Reactive oxygen species; NDEA: N-Nitrosodiethylamine; AAF: 2-acetylaminofluorene; CCl_4: Carbon tetrachloride.

Table 2 Clinical trials for evaluating the efficacy of compounds in liver disease

Treatment	Trial number	Phase	Aims or results
Curcumin	NCT02908152	2-3	To investigate the effects of curcumin supplements on metabolic factors and hepatic fibrosis in NAFLD patients with T2DM
	NCT04109742	2	To test the effect of curcumin in pediatric patients with NAFLD
Empagliflozin	NCT03867487	2	To evaluate the preliminary feasibility, initial efficacy, and safety of empagliflozin as a SGLT2 inhibitor for treating NAFLD in adolescents with obesity
	NCT04642261	4	To test the effects of empagliflozin on reducing hepatic fat content as measured by MRI-PDFF in NAFLD patients without DM
Gastrodin	NCT04035824	4	To treat hypertension together with Uncaria
Genistein	IRCT201312132480N5	3	Oral supplementation of genistein (250 mg) for 8 wk can decrease insulin resistance, oxidative stress, and inflammation and improve lipid metabolism in patients with NAFLD
Lactoferrin	NCT04335058	None	To test the effect of lactoferrin with iron versus iron alone in the treatment of anemia in CLD
Selenium	NCT00271245	None	To test the effect of selenium in patients with cirrhosis
	NCT01650181	4	To test the impacts using siliphos-selenium-methionine-alpha lipoic acid plus metformin versus metformin in patients with fatty liver and NASH
Silymarin	NCT00389376	1	An increase in silymarin is observed in NAFLD patients, compared to that in patients with HCV
	NCT00680407	2	The effect of silymarin on NASH patients remains inconclusive due to the lack of a

			substantial number of patients
Telmisartan	NCT02213224	4	To evaluate the therapeutic effects of telmisartan and perindopril for NAFLD patients with hypertension

T2DM: Type 2 diabetes mellitus; NAFLD: Non-alcoholic fatty liver disease; SGLT2: Sodium-glucose cotransporter-2; MRI-PDFF: Magnetic resonance imaging-derived proton density fat fraction; CLD: Chronic liver disease; NASH: Non-alcoholic steatohepatitis; HCV: Hepatitis C virus.

FOOTNOTES

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