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Review Article

Multi-target modulation of traditional Chinese medicine based on the liver-gut axis: a new therapeutic strategy for NAFLD

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Abstract: As one of the most common liver diseases, non-alcoholic fatty liver disease (NAFLD) has attracted widespread international attention given its rising incidence. The current mainstay of treatment for NAFLD is controlled diet with controlled exercise. Significantly, the development of NAFLD is proposed to be related to the liver-gut axis. The gut barrier function may be disrupted in the case of gut microbial dysbiosis, which may increase the entry of bacteria, lipopolysaccharides and endotoxins into the liver, causing an inflammatory response, increasing the load on the liver, and triggering lipid deposition, thereby advancing the progression of NAFLD. Simultaneously, liver injury can further alter intestinal permeability, inducing systemic inflammatory response, creating a vicious cycle that may subsequently exacerbate the development of NAFLD. Accordingly, the present review focused on the exploration of the relationship between the liver-gut axis and NAFLD, dissection of the biological mechanism of NAFLD induced by liver-gut axis dysfunction, and comprehensive elucidation of the research progress of Chinese medicine on the regulation of the liver-gut axis for treating NAFLD. It is expected that these findings may provide fresh and insightful evidence for the development of suitable preventive and therapeutic strategies of NAFLD.

Keywords: Liver-gut axis, enterohepatic circulation, intestinal microorganisms, non-alcoholic fatty liver disease, traditional Chinese medicine

Introduction

At present, there have been dramatic alterations in people's dietary structure and living habits with the continuous progress of society and the increasing standards of living. Individuals may experience disorders of glucose-lipid metabolism owing to a prolonged high-fat diet (HFD) with excessive alcohol consumption, in turn leading to the advancement of various metabolic-related diseases [1], such as non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus. NAFLD is a metabolic disease that is caused by multiple factors that result in the accumulation of >5% fat in hepatocytes, rather than a history of excessive alcohol consumption. Currently, as a worldwide major chronic liver disease, NAFLD is a serious threat to global public health security. According to the existing epidemiologic surveys, NAFLD has a global prevalence of reaching 38% [2], suggesting that over one quarter of adults suffer from NAFLD [3]. Moreover, given its significant geographic variability, the prevalence of NAFLD is the highest in the Middle East at 31.79 per cent, lowest in Africa at 13.48 per cent, and higher than average in Asia at 27.37 per cent, with continuous increase in its incidence due to rapid urbanization in many parts of Asia [4]. For example, researchers pooled existing publications and revealed through a meta-analysis that the prevalence in Asia was 25.28%, 28.46%, and 33.90% in 1999-2005, 2006-2011, and 2012-2017, respectively [5]. However, the prevalence rate in China is 29.2% [6]. In a Markov model predicting NAFLD burden, in China, the number of NAFLD cases is expected to increase rapidly from 2016 (246.33 million) to 2030

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(314.58 million), with especially higher prevalence in middle-aged and elderly people. In the absence of timely effective treatment, individuals may further develop non-alcoholic fatty hepatitis and liver fibrosis following the gradual expansion of hepatocytes in the body that have undergone steatosis. Through modeling, the number of NAFL cases in China will grow by 102,520 over 24 years [7]. Simultaneously, NAFLD will become a major contributor to cirrhosis and hepatocellular carcinoma (HCC) globally [8]. For example, the incidence of NAFLD-associated HCC in the UK is expected to increase by 88% between 2016 and 2030 [9]. In addition to the negative impact on the liver, NAFLD may cause various extrahepatic complications, such as cardiovascular disease, chronic kidney disease, and type 2 diabetes mellitus. Among them, cardiovascular disease, extrahepatic malignancies, and HCC are the leading causes of death in patients with NAFLD. Moreover, NAFLD-associated HCC is predicted to cause approximately 110,900 deaths in the United States between 2015 and 2030 [9]. Currently, given the aggravation of aging of many countries, the severity of NAFLD increases with age, resulting in a more than doubling of late-stage liver diseases [7]. Therefore, NAFLD has imposed growing health challenges on the healthcare system, highlighting the urgent need for public health interventions and clinical treatments to reduce the significant burden of NAFLD globally.

Furthermore, great concern has been attached to gut microbes in the investigation on metabolism-related diseases. In particular, the gut-liver axis has been a focus of study for metabolism-related diseases. Anatomically, the gut is connected to the liver and the brain through circulation and the nervous system, and the gut-liver axis and gut microbes are regarded as one of the contributors to the onset and progression of NAFLD. In a predictive model of liver fibrosis based on microbial profiling, Tien S Dong et al. found significantly less diverse microbiota in biopsy-proven NAFLD patients [10]. Huaming Mai et al. also revealed a significantly decreased number of firmicutes, with increased number of bacteroidetes in NAFLD patients compared with the healthy controls [11]. Moreover, there was an obvious reduction in the number of *Enterococcus faecalis* in the pre-NAFLD period compared to late stage of NAFLD. Furthermore, there is an alteration in the gut microbial diversity during NAFLD development, and a decrease in its diversity correlates with NAFLD progression. Prior research has revealed that intestinal dysfunction is one of the determinants of impaired liver function [12]. However, clinical treatments for NAFLD are mostly focused on lifestyle changes, food intake control, and energy expenditure improvement, without ideal therapeutic regimens containing clear targeted drugs [13]. Therefore, it is promising to explore the treatment of NAFLD from the perspective of gut microorganisms, which can be a new pathway for NAFLD treatment. Significantly, traditional Chinese medicine (TCM) has been documented to enable an effective regulation of the intestinal flora to treat NAFLD [14]. With multi-target, multi-faceted, multi-system characteristics, it exhibits unique advantages in NAFLD treatment, with better efficacy and fewer adverse reactions in clinical practice. Therefore, it is critical to explore the physiological and pathological relationship between the intestine and the liver from the perspective of TCM, which may open up a new direction for NAFLD treatment.

Pathogenesis of NAFLD

NAFLD mechanism

NAFLD has become the leading cause of chronic liver disease in adults, which occurs when excessive fat accumulates in hepatocytes in people who consume little or no alcohol [15]. Hepatic steatosis has been recognized to be the main feature of NAFLD [16]. The intra-hepatic lipid content is mediated by interactions among various processes involving hepatic uptake, synthesis, oxidation, and secretions, and hepatic steatosis may be developed owing to alterations in any one or more of these processes [15]. Until now, liver biopsy remains the gold standard for clinical diagnosis of NAFLD [17], with the absence of non-invasive and reliable diagnostic and therapeutic tools as well. The liver, as the central metabolic organ of the organism, and its metabolites are inextricably linked with other organs, and the organs are similarly closely related to and influence each other.

As a metabolism-related disease, NAFLD is featured by a complicated pathogenesis with multiple factors involved. So far, there is a poor

understanding of its triggering mechanism. At present, as accepted widely by the academic community, the pathogenesis of NAFLD is related to the "second strike" and "multiple strikes" theories. The "second strike" doctrine, proposed for the first time by Day and James in 1998, is hepatic steatosis caused by insulin resistance (IR). In other words, there is a reduction in the biological effect of the same dose of insulin due to reduced insulin sensitivity in the target organ, leading to excessive accumulation of lipids [e.g., triglyceride (TG)] in hepatocytes and eventually the development of steatosis. The "second strike" is the endogenous damage caused by oxidative stress and lipid peroxidation on top of the hepatic steatosis produced by the "first strike", resulting in fibrosis and liver inflammation, and NAFLD ultimately [18]. However, with advances in the research on NAFLD, the "multiple-strike" doctrine was proposed on the basis of this doctrine [19]. The "multiple strikes" theory suggests the participation of multiple factors in the development of NAFLD, such as IR, endogenous damaging factors, genetic factors, intestinal flora imbalance, oxidative stress, the environment and diet [20], all of which work and interact mutually to induce NAFLD. In particular, IR may promote excessive accumulation of TG, which can further exacerbate the severity of IR and increase the levels of IR-promoting cytokines throughout the body, thus creating a vicious circle between the two factors, and accelerating the pathologic progression of NAFLD [21].

The gut-liver axis

The gut-liver axis, intervened by dietary, genetic and environmental factors, is the feedback pathway between the liver and the intestine. With the portal vein as the link between them, products from the intestine are transported primarily through the portal vein to deliver to the liver [22], which secretes bile through the biliary tree to the intestine, where it is catabolized and metabolized [23]. It is the so-called enterohepatic cycle. Significantly, the enterohepatic circulation (EHC) and intestinal barrier work together to maintain a stable enterohepatic axis. Notably, the EHC stands out as an important part of the gut-liver axis. For instance, bile acids (BAS) are synthesized by the liver and transported to the intestine through the biliary system. Approximately 95% of the bile acids secreted by bile are reabsorbed by the intestine in the form of conjugated bile through ape-dependent bile acid transporters (ASBTs) of the terminal ileum epithelial cells and then re-enter the liver through the portal vein [24]. Furthermore, through the interaction of the gut and liver via the intestinal mucosal and vascular barriers, it may contribute to the prevention of the systemic microorganism and toxin spread, while ensuring efficient nutrient metabolism [25]. Therefore, maintaining a normal function of the gut-liver axis is the keystone for the liver to maintain internal homeostasis. Nevertheless and noticeably, the gut-liver axis is also proposed to exhibit an intimate association with the development of NAFLD and may promote the progression of liver fibrosis [26]. Dysregulation of gut microbial homeostasis has been revealed to advance the development of NAFLD by modulating the gut-liver axis. In addition, alterations in the gut-liver axis can be found in various pathological mechanisms. For example, in the presence of compromised intestinal barrier, there may be an increase in intestinal permeability subsequently, leading to endotoxemia and inflammation, as well as dysregulation of BAs and metabolite levels produced by the intestinal flora, which in turn also destabilizes the gut-liver axis [27]. Pathogen-derived compounds from the gut have been proven to be a key regulator in liver disease [28]. Collectively, maintenance of the health and regulation of the balance of the gut-liver axis depend largely on the integrity of the intestinal epithelium, the immune defenses of the gut and liver, and the composition of the microbiome.

Altogether, the gut-liver axis theory offers fresh insights for the prevention and treatment of NAFLD. It may provide profound evidence on accelerating the design and/or development of probiotics, prebiotics, antibiotics, fecal microbial transplantation, and personalized treatments based on the gut microbiota. Consequently, interpretation on this theory may contribute to the regulation of the balance of gut microorganisms, improvement of the intestinal barrier function, and modulation of metabolic pathways associated with liver health [29].

The gut-liver axis and NAFLD

EHC and NAFLD

EHC is the material circulation formed by the intestine and liver through the portal vein and

bile system, with the core being BA metabolism [30]. The sodium-taurocholate co-transporting polypeptide (NTCP), encoded by Solute Carrier Family 10 Member 1 (SLC10A1) is responsible for transporting BAs from the portal vein to hepatocytes. Loss-of-function mutations in this gene can trigger hypercholacemia [31]. The bile salt export pump (BSEP), encoded by ATP Binding Cassette Subfamily B Member 11 (ABCB11) can transport BAs to the bile ducts, and its genetic defects can cause progressive familial intrahepatic cholestasis [32]. Beyond the regulation of lipid metabolism and cholesterol balance, EHC can also influence pharmacokinetics (e.g., the blood concentration-dependent EHC model of Cabozantinib). In addition, EHC may also interact with the intestinal microbiota [33]. The portal vein system directly transmits intestinal metabolic products to the liver. Microbial imbalance can promote the progression of NAFLD through the alteration of the gut-liver circulation [34].

Gut microbes and NAFLD

The imbalance of intestinal flora may produce a negative impact on the progression of NAFLD through the gut-liver axis. Mechanistically, dysbiosis may disrupt the intestinal barrier, resulting in the entry of endotoxin (lipopolysaccharides, LPS) into the liver through the portal vein, which may further activate inflammatory pathways such as toll-like receptor 4 (TLR4), leading to the aggravation of hepatic steatosis and fibrosis [35, 36]. Abnormal accumulation of metabolic products of the microbiota (e.g., choline and trimethylamine) may be a contributor of hepatic steatosis [25]. Microbiota can mediate the fermentation of dietary fiber, and the produced short-chain fatty acids (SCFAs) can repair the intestinal barrier and regulate lipid metabolism. However, SCFAs, in the context of imbalanced generation, may induce systemic inflammation (elevated Tumour necrosis factor-α (TNF-α) and Interleukin-6 (IL-6)) [36]. In addition, the microbiota can also affect liver lipid and glucose homeostasis by regulating BA metabolism through the farnesoid X receptor (FXR)/Takeda G-protein-coupled receptor 5 (TGR5) [37]. A fat- and glucose-high diet can exacerbate microbiota imbalance, while prebiotics, probiotics or specific diets can alleviate the pathological progression of NAFLD by regulating microbiota balance and barrier function [35, 36].

Understanding of the gut-liver axis from TCM

According to TCM, the gut-liver axis theory reveals a close functional interaction between the gut and the liver. Generally, the liver is responsible for catharsis, while the intestine plays the role of conduction and excretion. Based on the gut-liver axis theory, TCM can be applied for clinical treatment by regulating the gut-liver interaction. For example, in TCM, enema for treating metabolism-associated fatty liver disease (MAFLD) is based on the continuous development and optimization of the gut-liver axis theory. In patients with MAFLD, this herbal enema treatment can effectively improve symptoms and liver function, reduce blood lipids and blood uric acid levels, and enhance the intestinal flora simultaneously, which is applicable for restoring the normal balance of intestinal and liver functions, thus mitigating the condition of the disease [38]. Meanwhile, as evidenced by modern pharmacological studies, many herbal components can play a therapeutic role by regulating NAFLD-related molecular pathways. AMP-activated protein kinase (AMPK) is defined as a cellular energy sensor and pivotal controller of metabolic homeostasis, which is essential in cellular energy balance and metabolic pathways. Usually, AMPK may be activated when intracellular adenosine monophosphate (AMP) levels rise and adenosine triphosphate levels fall, and positively affects NAFLD by promoting fatty acid oxidation, inhibiting fatty acid synthesis, ameliorating IR, as well as exerting anti-inflammatory and antioxidant effects. The AMPK mechanism has been extensively discussed in the ameliorative effects of various herbal ingredients on NAFLD. For example, several active ingredients such as resveratrol, baicalin, and baicalein could ameliorate the pathology of NAFLD by activating the AMPK pathway [39].

In the field of TCM that utilizes multi-targeting properties of herbs and a holistic view to regulate the liver-gut axis, this axis is hence considered an important target for NAFLD treatment. A number of herbal ingredients work to improve the intestinal barrier function and regulate the balance of intestinal microbiota, thereby facilitating the prevention and treatment of NAFLD. Taking rhubarb as an example, it can repair intestinal mechanical barrier function, increase expression of tight junction proteins, decrease intestinal permeability, and reduce the translo-

cation of bacteria and endotoxins. Moreover, it can reduce levels of lipids in the serum and liver, regulate the activity of lipid metabolism-related enzymes, and improve fat deposition in the liver. Moreover, certain components contained in rhubarb can promote BA metabolism and regulate BA levels, in turn affecting bacterial overgrowth in the intestine and the composition of the intestinal flora. In addition, rhubarb can promote the production of more SCFAs within the intestine, thereby exerting anti-inflammatory and intestinal barrier function-promoting effects through diverse mechanisms. Collectively, rhubarb can regulate the gut-liver axis and weaken the effects of harmful substances of intestinal origin on the liver, thus exerting a therapeutic effect on NAFLD [40]. In prior research carried out by Xu Y et al., saponins of *Panax ginseng* exhibited significant anti-adipogenic and anti-fibrotic effects in a mouse model of NAFLD, depending strongly on TLR4-induced hepatic inflammatory signaling pathway. Treatment using saponins of *Panax ginseng* could slow the transport of microbiota-derived SCFAs from the gut to the liver, induce TLR4 inhibition, and restore Claudin-1 and zona occludens-1 (ZO-1) proteins in the gut-liver axis, thereby contributing to the reversal of the increased intestinal permeability. Notably, this trend was further mitigated by suppressing the addition of LPS (agonists of TLR4). In addition, saponins of *Panax ginseng* could ameliorate hepatic steatosis and fibrosis mediated by TLR4-dependent gut-liver axis, thus exhibiting hepatoprotective effects against HFD-induced NAFLD in obese mice [41].

Moreover, other types of herbs have also been documented to reverse the dysbiosis of intestinal flora and maintain the balance of the intestinal micro-ecosystem. For instance, *Radix Bupleuri* is one of the common pungent, cooling and antidepressant herbs that can increase the diversity of intestinal flora and decrease the levels of *Prevotella* and *Ochrobacter*. *Paeoniae Radix Alba*, also known as Chinese peony, is a plant of the buttercup family Paeoniaceae, and is the dried root of *Paeonia lactiflora* of family Mulleinaceae. *Paeoniae Radix Alba* extract can regulate the intestinal mucosal barrier. Meanwhile, *Poria cocos* is a representative water-inducing and dampness-permeating TCM that can be used to strengthen the spleen and tranquilize the heart; while Poria oligosaccharides can improve glucose abnormality and lipid metabolism by regulating the intestinal flora. Glycyrrhizic acid can contribute to the increase of probiotics and decrease of harmful bacteria to stabilize the intestinal flora in chronic liver injury [42]. In view of the above, a great deal of herbal remedies have been proven to alleviate the symptoms of NAFLD by targeting the gut-liver axis, improving gut microbial composition, regulating BA metabolism, and reducing inflammatory responses. In addition to relieving local symptoms, TCM treatment of NAFLD also emphasizes a holistic view and disease prevention, highly consistent with the philosophy of regulating the gut-liver axis in Western medicine. For example, TCM herbal formulas such as Sijunzi Decoction and Jiangpu Decoction are used to improve the condition of NAFLD patients by regulating the gut-liver axis. In summary, the relationship between TCM and the gut-liver axis is reflected in the fact that TCM treatment of NAFLD works mainly by regulating the gut-liver interaction, which is in line with the modern understanding of the function of the gut-liver axis [43].

TCM based on gut-liver axis for the treatment of NAFLD

The treatment of NAFLD via TCM can be explained by multiple mechanisms, such as anti-oxidative stress, lipid metabolism regulation, anti-inflammation, anti-fibrosis, and intestinal flora regulation (**Figure 1**) [44]. Through the elucidation of the impact of the gut-liver axis on NAFLD, it will provide an important theoretical basis for NAFLD prevention and treatment in the clinical setting. This review continues to summarize the research progress of TCM in treating NAFLD by regulating the gut-liver axis, with a view to providing new ideas for clinical treatment.

TCM monomers

Bupleurum, *Salvia miltiorrhiza*, and *Coptis chinensis* are representative drugs applied in the treatment of NAFLD. Bupleurum can sooth the liver and relieve depression, and ascend Yang-Qi. It mainly consists of bupleurum saponins, flavonoids, coumarins, fatty acids and polysaccharides. Saikosaponin D (SSD) has been confirmed to regulate intestinal flora, such as increasing the abundance of *Clostridium viride*, thereby inhibiting the expression level of bile

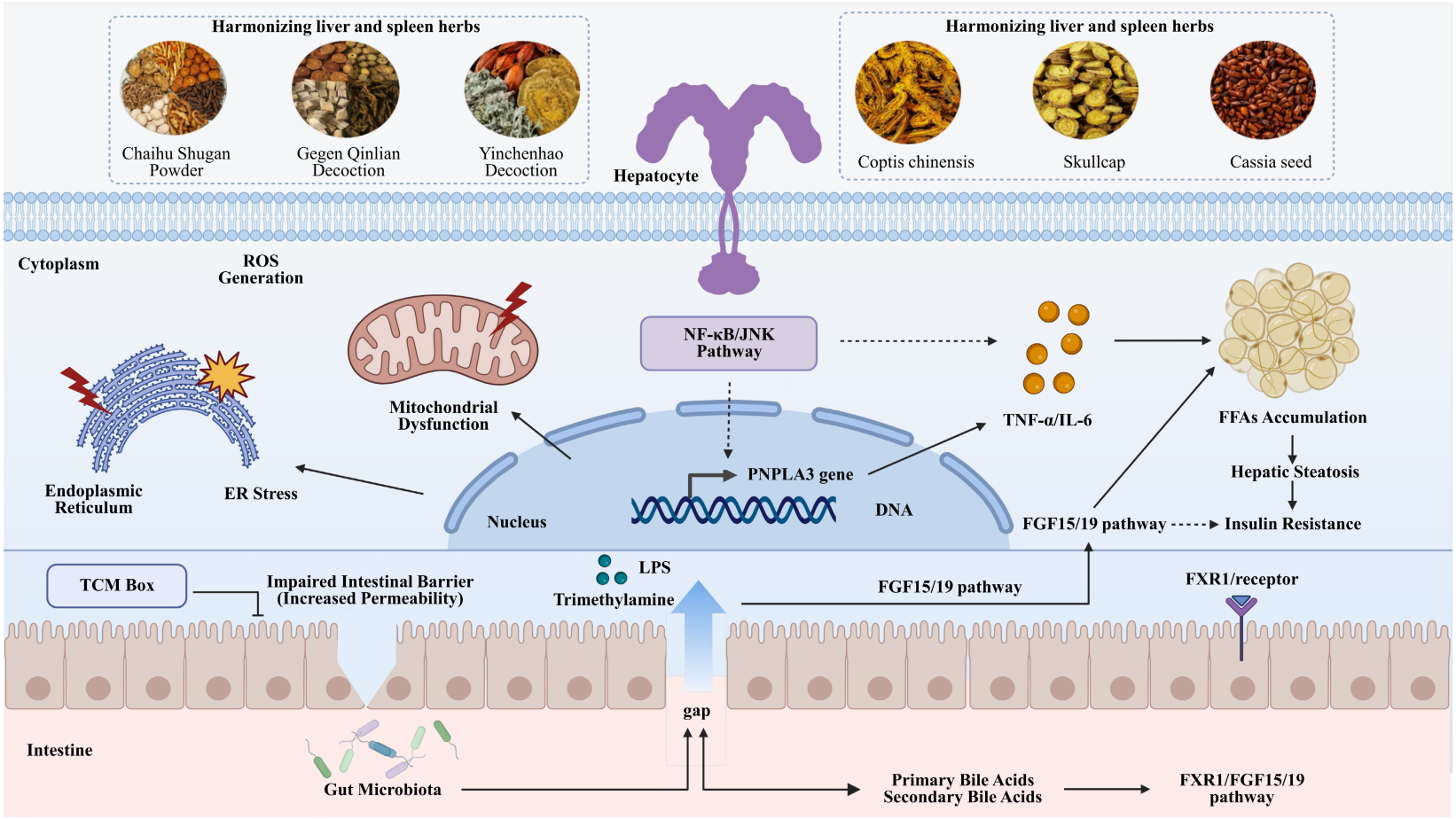

Figure 1. Mechanism of regulating liver and spleen traditional Chinese medicine to improve “gut-liver” axis.

salt hydrolase (BSH). The decrease in BSH expression level, combined with reduced decomposition of conjugated BAs, may lead to increased level of taurine-conjugated BAs, thereby inhibiting the intestinal FXR signaling pathway and improving NAFLD [45]. *Salvia miltiorrhiza* is another common medicinal herb that can promote blood circulation and remove blood stasis. For example, in a mouse model of NAFLD, the consumption of *Salvia miltiorrhiza* increased expression of integration membrane proteins (Claudin and Occludin) and junction complex protein ZO-1 in the jejunum and colon, while decreased LPS concentration in the serum. Therefore, *Salvia miltiorrhiza* polysaccharides may affect the occurrence and development of NAFLD by regulating the intestinal permeability [46]. In addition, the use of *Salvia miltiorrhiza* polysaccharides combined with probiotics could improve IR and exert a therapeutic effect on NAFLD by regulating the structure of intestinal flora [43]. Berberine, as the main active component of *Coptis chinensis*, can improve NAFLD through an intestine-targeted mechanism. For instance, oral administration of berberine in mice resulted in a primary accumulation in the intestinal tract, reduced abundance of Clostridium difficile clusters XIVa and IV in the intestinal flora, and inhibited activity of its BSH. This alteration could affect the metabolism of intestinal BAs, with elevated levels of conjugated BAs such as taurocholic acid, leading to the activation of intestinal FXR signaling pathway that would induce the expression of intestinal fibroblast growth factor 15 (FGF15). Noticeably, FGF15 acts on liver tissue through the gut-liver axis and can down-regulate the mRNA expression of the fatty acid transporter cluster of differentiation 36 (CD36). The reduced expression of CD36 can further weaken the capability of hepatocytes to absorb free fatty acids (FFA), decrease the synthesis and accumulation of TG in the liver, and thereby exerts an anti-NAFLD effect [47, 48].

TCM monomers and active ingredients, such as cassia seed, berberine, ganoderma lucidum, diammonium glycyrrhizinate and total saponins of gypenoside, can produce potential therapeutic effects on NAFLD given their roles in improving the intestinal microecology of patients [49]. Among these, *Cassia tora* is the dried and mature seed of the leguminous genus Cassia, including anthraquinones, flavonoids, terpenoids, and various other bioactive components that confer multiple pharmacological effects on cassia seeds. Specifically, the alcoholic and total sapogenins extracts of *Cassia officinalis* have been discovered to produce certain therapeutic effects on a mouse model of MAFLD. These extracts enhanced the diversity of intestinal flora, increased the relative abundance of beneficial flora, but decreased the relative abundance of harmful flora, and promote the expression of tight junction proteins (Occludin and ZO-1) through the gut-hepatic axis. Consequently, all these changes benefited the improvement of the imbalance of intestinal flora, protection of the intestinal barrier, and reduction of the inflammatory response, thus mitigating subsequent peroxidative accumulation of liver fat. *Ganoderma lucidum* is also a representative medicinal fungus used frequently in TCM, which is a tonic with the same origin as medicine and food. It exhibits various pharmacological functions such as invigorating Qi and calming nerves, relieving cough and asthma, etc. Total naphthoquinone, the main active ingredient from *Ganoderma lucidum* was found to modulate the intestinal flora of mice with HFD-induced MAFLD [50, 51]. This intervention in mice resulted in increased abundance of Firmicutes and decreased abundance of Bacteroidetes, which improved the diversity and abundance of gut microorganisms eventually. By regulating intestinal flora, *Ganoderma lucidum* enabled the enhancement of intestinal microecological structure of the modeled mice, thereby exerting a beneficial effect on this pathological condition. *Scutellaria baicalensis Georgi* is also a common TCM that is frequent applied to enhance effects of clearing heat and drying dampness, as well as clearing fire and detoxifying. Various active ingredients derived from its roots and rhizomes (e.g., baicalin and baicalein) have been used in the treatment of NAFLD to inhibit the release of inflammatory factors and reduce hepatic inflammatory responses. Meanwhile, the antioxidant components of *Scutellaria baicalensis* are functional to scavenge free radicals and protect hepatocytes from oxidative stress-induced damage. *Scutellaria baicalensis* may also promote fatty acid oxidation and inhibit fatty acid synthesis by activating the AMPK pathway to reduce fat content within the liver [52]. Moreover, baicalin has been investigated to ameliorate metabolic

disorders by activating the AMPK pathway, thereby exerting a therapeutic potential in a diet-induced NAFLD mouse model [53]. *Pueraria lobata* is an antipyretic drug in TCM, which can relax muscle, promote fluid to quench thirst, relieve measles, ascend Yang and prevent diarrhea. Puerarin, as a main active component of *Pueraria Mirifica*, has various effects such as antioxidant, anti-inflammatory and anti-apoptotic activities. Puerarin can reduce lipid accumulation by lowering cholesterol levels in the serum and liver to modulate the development of NAFLD. Simultaneously, by activating Peroxisome proliferators-activated receptors (PPAR-α) and AMPK pathways, Puerarin can improve insulin sensitivity in the liver. Puerarin can also reduce the expression of inflammatory cytokines, such as inhibiting the nuclear factor κB (NF-κB) signaling pathway, acting as a decelerator of inflammatory response to the liver to mitigate inflammatory response to the liver. Puerarin also has anti-apoptotic activity and promotes hepatocyte regeneration, which helps to repair NAFLD-induced damage to liver tissues and cells. Puerarin also exert a positive impact on NAFLD through mechanisms such as affecting the gut-liver axis by modulating the gut microbiota [54]. With prebiotic properties, quercetin is also therapeutic for NAFLD by regulating the intestinal flora. Supplementation with quercetin can contribute to the restoration of restore intestinal flora homeostasis by effectively regulating intestinal flora disturbance and reducing the relative abundance percentage of *Firmicute*s and *Proteobacteria*, such as reducing the proportion of *Clostridium* and Phylum *Firmicute*s, *Proteobacteria* triangulata and *Diproteobacteria* (*Proteobacteria*). In addition, quercetin can reduce the activation of hepatic NF-κB signaling pathway and inhibit oxidative stress by inhibiting endotoxemia-mediated TLR4 signaling, in turn affecting the progression of NAFLD. Besides, quercetin can also exert a positive effect on the treatment of NAFLD given its beneficial roles of promoting the production of SCFAs, and enhancing the integrity of intestinal mucosal barrier [55].

Resveratrol has demonstrated significant efficacy in NAFLD through multi-target anti-inflammatory and immunomodulatory mechanisms. In a 12-week randomized, double-blind, placebo-controlled trial for NAFLD, oral administration of 500 mg of resveratrol daily improved the grade of hepatic steatosis and reduced the level of alanine aminotransferase (ALT) by 32.38%±25.63%, significantly better than the 13.54%±45.00% of placebo intervention. In a 3-month randomized, double-blind placebo study on NAFLD, daily consumption of 600 mg of resveratrol led to decreased levels of ALT, aspartate transaminase (AST), total cholesterol (TC), homeostatic model assessment of insulin resistance (HOMA-IR), TNF-α, Cytokeratin 18 (CK-18), and Fibroblast Growth Factor 21 (FGF21) while increased level of APN. Resveratrol has been found to inhibit of the activity of the NF-κB pathway, reduce of the release of inflammatory cytokines (e.g., TNF-α), and suppress of the occurrence of oxidative stress, thereby affecting the progression of NAFLD. In another meta-analysis of *Salvia miltiorrhiza* involving 800 patients from 8 randomized studies, it increased High-density lipoprotein (HDL) levels and the liver-spleen ratio, while reducing ALT, AST, TG and TC levels. Meanwhile, Red ginseng and milk thistle can work synergistically to treat NAFLD. For example, in a randomized, single-blind clinical study incorporating 80 patients with NAFLD, the specific therapeutic regimens included silymarum (450 mg) monotherapy in the control group, and silymarum (450 mg) combined with red ginseng (3000 mg/day, 3×1000 mg) in the experimental group. The experimental group was observed with significantly reduced levels of serum AST, ALT, and Gamma-glutamyl transferase (GGT) following 3 weeks of intervention, accompanied by decreased levels of inflammatory factors such as TNF-α and the liver fibrosis score. Therefore, red ginseng can intervene the occurrence and development of NAFLD by alleviating hepatocyte damage and reducing lipid accumulation. Artichoke leaf extract (ALE) has shown multiple therapeutic effects in improving NAFLD. In an 8-week randomized, double-blind, placebo-controlled trial, 100 patients diagnosed with NAFLD by ultrasound were recruited and randomly divided into the ALE group (600 mg of ALE orally per day) or the placebo group. A total of 90 patients completed the study, including 49 in the ALE group and 41 in the placebo group. Consequently, the ALE group showed significantly improved ultrasound parameters of the liver, manifesting as increased hepatic vein flow, decreased portal vein diameter, and reduced liver volume, sug-

gesting the roles of ALE in improving liver hemodynamics and the degree of steatosis. In addition, the ALE group also exhibited decreased levels of serum ALT, AST and total bilirubin, as well as significantly reduced levels of TC, TG and LDL-C, indicating its effect of mitigating liver lipid accumulation by regulating lipid metabolism (**Table 1**) [56-59].

TCM compounds

Representative TCM compound prescriptions include Chaihushugan Powder and others for treating NAFLD. Bupleurum can soothe the liver, regulate Qi, promote blood circulation and relieve pain, which is mainly suitable for indicators of liver Qi stagnation syndrome. Chaihushugan Powder has been documented to significantly improve the intestinal flora of MAFLD patients, especially by significantly increasing the abundance of *Bifidobacterium* and *Lactobacillus*. Simultaneously, it can obviously reduce the abundance of *Enterobacteriaceae* and *Enterococcus*, thereby increasing the beneficial bacterial community and reducing the harmful bacterial community [60]. As a result, in addition to alleviating the symptoms of liver Qi stagnation, Chaihushugan Powder may also assist in the treatment of MAFLD by improving the balance of intestinal flora.

With the vigorous development of TCM, great concern has been attached by scholars in contemporary medical research to the efficacy and mechanism of TCM compounds in regulating the intestinal flora for NAFLD treatment. With the emergence of a large number of classic TCM formulas, TCM compounds, as effective weapons for NAFLD management, provide valuable insights for the treatment of NAFLD. Dai Zong Fang is derived from the Xiaoxianxiong decoction in the ancient Chinese medicine book "*Treatise on Febrile Diseases*", which consists of *Coptis chinensis*, *Aurantii Fructus Immaturus*, *Pinellia ternata*, *Fructus Trichosanthis*, *Cinnamomum cassia* and red yeast. Zhang et al. found that Dai Zong Fang could improve adverse effects of intestinal barrier damage and endotoxemia on liver metabolism by regulating the structure and function of intestinal microbiota, inhibit lipid absorption, reduce hepatic steatosis, and improve systemic metabolic abnormalities, ultimately mitigating hepatic steatosis and inhibiting the progression of NAFLD [61]. LLKL is a herbal formula containing herbs *Edgeworthia gardneri (Wall.) Meisn.*, *Sibiraea angustata* and *Crocus sativus L.* (saffron). LLKL significantly reduced the expression of TLR4, Myeloid Differentiation Primary Response Protein 88 (MyD88) and Cathepsin K (CTSK) in the liver, and suppressed inflammatory signaling pathways related to the gut flora activation. In terms of glucolipid metabolism, LLKL reduced fat deposition in the liver, increased hepatic glycogen accumulation, and lowered serum FFA, total cholesterol (TC) and TG levels [62]. Yinzhihuang (YZH) could also reduce serum levels of AST, ALT, and blood glucose, as well as hepatic levels of triglyceride (TG), TC, and FFA, while significantly lowering the abundance of harmful bacteria such as *Mucispirillum* and *Desulfovibrionaceae*. YZH could also inactivate TLR4, MyD88, and NF-κB signaling in the liver, pathways associated with intestinal flora imbalance and low-grade liver inflammation, yielding valuable information for developing new therapeutic strategies for NAFLD [63]. TCM compound prescriptions, such as Yin Chaihu Decoction, Huangqin Decoction, Huazhirougan Granules, Qinggan Qushi Huoxue formula and Cangju Qinggan prescription, are able to regulate the intestinal flora [50]. Specifically, Yinchenhao decoction consists of Wormwood, gardenia, and rhubarb mainly, which is suitable for clinical indications of liver-related disorders, such as NAFLD. Yinchenhao decoction can regulate intestinal flora dysbiosis and improve the intestinal flora of rats with HFD-induced NAFLD. Specifically, it can lower the number of *Staphylococcus aureus* and *Streptococcus aureus*, elevate the number of probiotics, regulate the diversity of intestinal microorganisms, improve the intestinal barrier function, and retard the production of intestinal endotoxins, thus exerting a therapeutic effect on NAFLD [64]. Additionally, Yinchenhao decoction can significantly improve body weight, blood lipids and liver function in rats with MAFLD [65]. All these findings suggest the significant potential and effectiveness of Yinchenhao decoction in regulating intestinal flora and treating NAFLD. Gegen-Qinlian Decoction (GGQLD) has been widely used in the treatment of NAFLD, which consists of *Pueraria lobata*, *Scutellaria baicalensis*, *Rhizoma coptidis* and *Glycyrrhiza glabra* in the ratio of 8:3:3:2. Network pharmacology has confirmed

Table 1. TCM monomers and active ingredients for the treatment of NAFLD

Monomer of traditional Chinese medicine	Main ingredients	The mechanism of treating NAFLD	References
Radix Bupleuri	Saikosaponins, flavonoids, coumarins, fatty acids, polysaccharides	Regulate the gut microbiota structure Regulate the gut microbiota structure. Activate the intestinal FXR-FGF15 pathway to improve insulin sensitivity.	[42, 45]
Salvia miltiorrhiza	Polysaccharides from Salvia miltiorrhiza Bunge	Improve gut barrier function. Regulate gut microbiota dysbiosis. Improve insulin resistance.	[46]
Coptis chinensis	Berberine	Improve gut barrier function. Regulate gut microbiota dysbiosis. Improve insulin resistance.	[47, 48]
Cassia seed	Anthraquinones, flavonoids, terpenoids	Improve gut barrier function. Promote the mRNA and protein expression of Occludin and ZO-1. Regulate gut microbiota dysbiosis. Improve insulin resistance.	[49]
Ganoderma lucidum	Total naphthoquinones	Improve gut barrier function. Regulate gut microbiota dysbiosis. Improve insulin resistance.	[50, 51]
Scutellaria baicalensis Georgi	Baicalin	Improve gut barrier function. Regulate gut microbiota dysbiosis. Improve insulin resistance.	[52, 53]
Pueraria Mirifica	Puerarin	Improve gut barrier function. Regulate gut microbiota dysbiosis. Improve insulin resistance. Activate the PPAR-α and AMPK signaling pathways. Inhibit the NF-κB signaling pathway.	[54]
Quercetin	Quercetin	Regulate the disorder of intestinal flora. Reduce the abundance of thick-walled bacteria and Proteobacteria. Inhibit the expression of TLR4 signals. Reduce the occurrence of oxidative stress. Promote the generation of SCFAs.	[55]

the active ingredients of GGQLD, including baicalin, baicalin, puerarin, and glycyrrhetinic acidwhich are active in the treatment of NAFLD [66]. In an animal experiment, experimental mice were randomly divided into a control group (fed standard chow + oral saline); a HFD model group; a glutamine (GLU) group (HFD and oral GLU), and low-, medium-, and high-dose GGQLD groups (HFD at 1.26 kg/day, 2.52 kg/day, and 5.04 kg/day, respectively). Consequently, the low-dose GGQLD group showed promoted growth of *Lactobacillus*, *Bacillus*, etc. Compared with other groups, 7 taxa, 42 taxa, and 17 taxa were increased in the low-dose, medium-dose, and high-dose GGQLD groups, respectively. Therefore, GGQLD can regulate the intestinal flora disorder caused by HFD and restore the balance of intestinal microbiome. In addition, GGQLD can improve the intestinal barrier function and ameliorate the condition of NAFLD by enhancing the expression of closed ZO-1 in the intestine [67]. Hui D et al. [43] carried out a clinical trial to investigate a Chinese herbal formula, Spleen-strengthening Liver-soothing Formula (SLF) which is based on the TCM theory of 'the circumfluence of Qi' for the treatment of NAFLD. SLF is made up of various herbs, such as *Radix bupleurum*, *Radix Glehniae*, *Radix glehniae*, *Atractylodis Macrocephalae Rhizoma*, *Poria cocos*, *Citrus Reticulata and Radix Glycyrrhizae preparate*, *Sedum sarmentosum*, *Carbonized hawthorn*, and *Salvia miltiorrhiza*. SLF has the effect of soothing the liver and promoting Qi, strengthening the spleen and removing turbidity. Treatment using SLF resulted in significant improvements in liver function, control attenuation parameters, liver stiffness measurements, and obvious reductions in patients' lipids and HOMA-IR, demonstrating a better safety profile. Moreover, NAFLD patients also had reduced intestinal flora diversity and altered abundance of specific flora, as revealed by 16S rRNA gene sequencing. SLF treatment resulted in evidently heightened abundance of several NAFLD-associated intestinal flora. It is also documented that SLF, by regulating imbalances in intestinal flora, can remarkably improve liver function and glucose-lipid metabolism, and to some extent, decrease liver fat content in NAFLD patients. Therefore, SLF is an effective adjuvant therapy for NAFLD. In this randomized controlled trial, SLF significantly altered the abundance of intestinal flora. SLF intervention led to a decrease in the relative abundance of the phylum *Thick-walled Bacteria* and the phylum *Mycobacterium*. In addition, SLF modulated the intestinal flora genera, increased the levels of *Butyricicoccus* and *Blautia*, and displayed a tendency towards the restoration of intestinal flora homeostasis. Thus, SLF plays a positive role in restoring intestinal flora disorder and contributes to the treatment of NAFLD (**Table 2**) [43].

Other compounds

Chinese patent medicine: With the development of TCM, increasingly more Chinese patent medicines exhibit their therapeutic potential in the treatment of NAFLD in the clinical setting. For instance, Jiangzhi Granules and Si Miao Formula can delay the onset of NAFLD by regulating the intestinal flora, increasing beneficial bacteria such as *Mycobacterium avium* phylum and *Mycobacterium thicketi* phylum, enhancing the intestinal barrier function, as well as reducing the immune system response and inflammatory cell production caused by harmful bacteria and microorganisms [68]. Fufang Zhenzhu Tiaozhi formula (FTZ) is a common therapeutic option for the treatment of liver diseases. Based on the observational results of Oil-Red-O staining, HE staining and electron microscopy, Wang et al. proposed that FTZ had a positive effect on hepatic fat accumulation and hepatic steatosis. It contributed to the improvement of hepatic function and reduction of TG levels in Non-alcoholic steatohepatitis (NASH) mice. FTZ also resulted in the decreased expression of Hypoxia inducible factor 1α (HIF-1α) and increased phosphorylation of Phosphatidyqinositol-3 kinase (PI3K) - Protein kinase B (AKT), further improving hepatic metabolism and ultimately facilitating the treatment of NAFLD. Meanwhile, FTZ can improve intestinal barrier function, attenuate the intestinal inflammatory response, prevent hepatic inflammatory cell infiltration, and inhibit hepatic fibrosis more effectively. Furthermore, Chinese medicine compound Kangtaizhi granule (KTZG) is also effective in treating NAFLD. Zhang et al. identified the main chemical components of KTZG and the relevant targeting pathways for the treatment of NAFLD using high-performance liquid chromatography (HPLC) and network pharmacological analysis; and through experimental verification, they documented that KTZG could improve hepatic steatosis and lipid

Table 2. TCM compounds and their compositions for the treatment of NAFLD

Traditional Chinese Medicine Compound	Composition	The mechanism of treating NAFLD	References
Chaihushugan Powder	Bupleuri Radix, Paeoniae Radix Alba, Citri Reticulatae Pericarpiu, Chuanxiong Rhizoma, Cyperi Rhizoma, Aurantii Fructus Immaturus, Glycyrrhizae Radix et Rhizoma	Restore the balance of gut microbiota. Increase the abundance of Bifidobacterium and Lactobacillus. Decrease the abundance of Enterobacteriaceae and Enterococcus.	[60]
Herbal formula LLKL	Edgeworthia gardneri (Wall.) Meisn., Sibiraea angustata, Crocus sativus L. (saffron)	Regulate gut microbiota dysbiosis. Reduce intestinal permeability. Reduce the release of endotoxin (LPS) and inflammatory factors (IL-6, TNF-α). Improve glucose and lipid metabolism.	[62]
Yinzhihuang	-	Improve liver function. Inhibit lipid absorption. Reduce the abundance of harmful bacteria. Alleviate liver injury.	[63]
Yinchenhao decoction	Artemisiae Scopariae Herba, Gardeniae Fructus, Rhei Radix et Rhizoma	Regulate the gut microbiota. Improve gut barrier function. Reduce the production of intestinal endotoxins.	[64, 65]
Gegen-Qinlian Decoction	Puerariae Lobatae Radix, Scutellariae Radix, Coptidis Rhizoma, Glycyrrhizae Radix et Rhizoma	Regulate gut microbiota dysbiosis. Improve gut barrier function.	[66]
Spleen-strengthening Liver-soothing Formula	Bupleuri Radix, Paeoniae Radix Alba, Glehniae Radix, Atractylodis Macrocephalae Rhizoma, Poria, Citri Reticulatae Pericarpium, Sedum sarmentosum Bunge, Carbonized hawthorn, Salviae Miltiorrhizae Radix et Rhizoma	Reduce liver injury. Improve insulin resistance. Regulate the gut microbiota and restore microbiota. homeostasis.	[43]
Si Miao Formula	Atractylodis Rhizoma, Phellodendri Chinensis Cortex, Cyathulae Radix, Coicis Semen	Regulate the gut microbiota. Improve gut barrier function. Inhibit harmful bacteria and immune - inflammatory response. Reduce liver injury. Improve glucose and lipid metabolism.	[68]
Fufang Zhenzhu Tiaozhi formula	Ligustri Lucidi Fructus, Citri sarcodactylis Fructus, Eucommiae Cortex, Atractylodis Macrocephalae Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Notoginseng Radix, Coptidis Rhizoma, Cirsii Japonici Herba	Reduce hepatic fat accumulation and fatty degeneration. Improve gut barrier function and inhibit the intestinal inflammatory. response.	[69]
Kangtaizhi granule	Cassiae Semen, Lycii Fructus, Fructus Mori, Carthami Flos, Crataegi Fructus	Improve hepatic steatosis and lipid accumulation	[69]
Ganshuang granules	Cassiae Semen, Lycii Fructus, Fructus Mori, Carthami Flos, Crataegi Fructus	Improve liver function and reduce blood lipid levels. Anti-oxidative stress.	[70]

accumulation in HFD-fed rats and HepG2 cells, thereby preventing the development of NAFLD [69]. As a typical proprietary Chinese medicine for liver disease treatment, Ganshuang granules (GSG) are formulated from the ancient formula of Xiaoyao San, consisting of 13 Chinese medicines including Bupleurum chinense, *Angelica sinensis*, *Poria cocos*, etc. Network pharmacology revealed 159 potential targets of GSG for the treatment of NAFLD, with the PI3K/AKT signaling pathway identified by functional enrichment analysis as a key pathway. Further experiments revealed that GSG intervention increased the protein expression levels of phosphorylated PI3K (p-PI3K) and p-AKT in the liver of modeled mice, and decreased the protein expression level of sterol regulatory element binding protein 1. In addition, GSG treatment also significantly reduced serum ALT, AST, alkaline phosphatase, TC, TG and LDL cholesterol levels, as well as the expression levels of IL-6 and TNF-α in the liver (**Table 2**) [70]. In the therapeutic field of NAFLD, TCM has shown great therapeutic potential by regulating the gut-liver axis and intestinal flora to inhibit the development of the disease. In the future, further in-depth exploration is required to fully unveil the value of TCM, so as to maximize their therapeutic roles in the treatment of NAFLD and bring more benefits to the majority of patients.

Acupuncture and moxibustion: Acupuncture is a time-honored and effective therapeutic technique in China and is effective for a wide range of diseases. Acupuncture can inhibit the progression of NAFLD by attenuating inflammatory factors, alleviating steatosis, etc. [71]. Intestinal flora are important factors in the development of NAFLD. Wang et al. [72] observed and compared the effect of acupuncture treatment on serum lipid levels, inflammatory factors, and hepatic steatosis in HFD-induced rats. It was found that acupuncture led to improvement in steatosis and inflammatory cell infiltration, reduction in inflammatory response, as well as enhancement in dyslipidaemia and hepatic function indexes in the modeled rats. Gut flora analysis also revealed increased abundance of gut microbiota after acupuncture, and correlation analyses suggested intimate associations of changes in lipid levels, inflammatory factors, and other indicators with the gut flora. In addition, Han et al. studied the efficacy and related mechanisms of acupuncture in regulating intestinal absorption to improve lipid metabolism in mice. Compared to mice without acupuncture, acupuncture-treated mice had lighter weight, significantly increased levels of TG, TC and non-esterified fatty acid in small intestinal tissue, while decreased levels of TG and non-esterified fatty acid in serum. As a result, acupuncture treatment may inhibit lipid absorption by down-regulating the expression of apolipoprotein in small intestinal tissue, reduce excess fat intake and cellular steatosis, thereby delaying the occurrence of NAFLD [73].

Conclusions and perspective

NAFLD is a metabolic disease with increasing prevalence due to changes in living habits and dietary factors, and complex pathogenesis that involves multi-organ, multi-system interactions. At present, there are no specific medicinal therapies clinically. The treatment of NAFLD by regulating the gut-liver axis has a broad development prospect. The gut-liver axis is a complex pathway between the intestine and the liver, in which the intestinal flora plays a key role, highlighting the significance of regulating the distribution and homeostatic balance of the intestinal flora in the treatment of NAFLD [74]. We may acquire a new therapeutic strategy for precision intervention in NAFLD by targeting the imbalance of intestinal flora, and based on the unique advantages of TCM's multi-component synergistic regulation of the gut-liver axis. There is still an absence of additional personalized treatments such as through external treatments, and insufficient studies on their specific mechanisms. The chemical structures and pharmacological effects of traditional Chinese medicine monomers are diverse, and it is still difficult to fully understand their specific mechanisms in the regulation of NAFLD. Meanwhile, the occurrence process of NAFLD is extremely complex, involving not only molecular-level changes in the liver but also the interaction of metabolic signals among organs. Moreover, the components of traditional Chinese medicine compound prescriptions are diverse, and the therapeutic effects of different drug combinations vary greatly. It is difficult to clearly identify the active ingredients and dosages, resulting in insufficient homogenization of treatment plans and restricting the research and development of new drugs as well as clinical promotion. Therefore, in subsequent research, we need to

deeply explore the mechanism of action of traditional Chinese medicine monomers and compound prescriptions in improving NAFLD, laying a solid foundation for further optimization of the treatment of this disease. In addition, there is a lack of unified standards for the TCM syndrome differentiation and classification of NAFLD. Most of the studies are single-center and small-sample. The diagnosis and therapeutic effect determination often rely on subjective symptom scores, and there is a lack of internationally recognized biochemical, imaging and histological evaluation standards, which makes it difficult to replicate and promote the results. In terms of research design, most studies are single-center, observational trials, lacking support from large-sample, multicenter randomized controlled trials, and the level of evidence is relatively low. Moreover, some studies have not excluded interfering factors (such as diet and exercise), which affects the reliability of the conclusions. In addition, although acupuncture treatment mentions regulating the gut-liver axis, the selection of acupoints and the standards of treatment courses are not uniform, and the evaluation of therapeutic effects relies on subjective indicators (such as symptom scores), lacking histological or biochemical endpoint data. Therefore, in the future, it is necessary for us to further study the interaction mechanism between traditional Chinese medicine and other influencing factors and NAFLD, and clarify the regulation of the gut-liver axis by traditional Chinese medicine to precisely act on disease targets and achieve the effect of precise treatment.

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Disclosure of conflict of interest

None.

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References

[1] Stefan N, Haring HU and Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol 2019; 7: 313-324.

[2] Golabi P, Owrangi S and Younossi ZM. Global perspective on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis - prevalence, clinical impact, economic implications and management strategies. Aliment Pharmacol Ther 2024; 59 Suppl 1: S1-S9.

[3] Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, Loomba R, Chalasani N, Kowdley K, Hameed B, Wilson LA, Yates KP, Belt P, Lazo M, Kleiner DE, Behling C and Tonascia J; NASH Clinical Research Network (CRN). Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 2021; 385: 1559-1569.

[4] Li D, Zhang M, Wu S, Tan H and Li N. Risk factors and prediction model for nonalcoholic fatty liver disease in northwest China. Sci Rep 2022; 12: 13877.

[5] Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, Fujii H, Wu Y, Kam LY, Ji F, Li X, Chien N, Wei M, Ogawa E, Zhao C, Wu X, Stave CD, Henry L, Barnett S, Takahashi H, Furusyo N, Eguchi Y, Hsu YC, Lee TY, Ren W, Qin C, Jun DW, Toyoda H, Wong VW, Cheung R, Zhu Q and Nguyen MH. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019; 4: 389-398.

[6] Zhou F, Zhou J, Wang W, Zhang XJ, Ji YX, Zhang P, She ZG, Zhu L, Cai J and Li H. Unexpected rapid increase in the burden of NAFLD in China From 2008 to 2018: a systematic review and meta-analysis. Hepatology 2019; 70: 1119-1133.

[7] Estes C, Anstee QM, Arias-Loste MT, Bantel H, Bellentani S, Caballeria J, Colombo M, Craxi A, Crespo J, Day CP, Eguchi Y, Geier A, Kondili LA, Kroy DC, Lazarus JV, Loomba R, Manns MP, Marchesini G, Nakajima A, Negro F, Petta S, Ratziu V, Romero-Gomez M, Sanyal A, Schattenberg JM, Tacke F, Tanaka J, Trautwein C, Wei L, Zeuzem S and Razavi H. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol 2018; 69: 896-904.

[8] Thomas JA, Kendall BJ, El-Serag HB, Thrift AP and Macdonald GA. Hepatocellular and extrahepatic cancer risk in people with non-alcohol-

ic fatty liver disease. Lancet Gastroenterol Hepatol 2024; 9: 159-169.
[9] Huang DQ, El-Serag HB and Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2021; 18: 223-238.
[10] Dong TS, Katzka W, Lagishetty V, Luu K, Hauer M, Pisegna J and Jacobs JP. A microbial signature identifies advanced fibrosis in patients with chronic liver disease mainly due to NAFLD. Sci Rep 2020; 10: 2771.
[11] Mai H, Yang X, Xie Y, Zhou J, Wang Q, Wei Y, Yang Y, Lu D, Ye L, Cui P, Liang H and Huang J. The role of gut microbiota in the occurrence and progression of non-alcoholic fatty liver disease. Front Microbiol 2023; 14: 1257903.
[12] Svegliati-Baroni G, Patricio B, Lioci G, Macedo MP and Gastaldelli A. Gut-pancreas-liver axis as a target for treatment of NAFLD/NASH. Int J Mol Sci 2020; 21: 5820.
[13] Yin X, Guo X, Liu Z and Wang J. Advances in the diagnosis and treatment of non-alcoholic fatty liver disease. Int J Mol Sci 2023; 24: 2844.
[14] Bao Y, Han X, Liu D, Tan Z and Deng Y. Gut microbiota: the key to the treatment of metabolic syndrome in traditional Chinese medicine - a case study of diabetes and nonalcoholic fatty liver disease. Front Immunol 2022; 13: 1072376.
[15] Meex RCR and Watt MJ. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. Nat Rev Endocrinol 2017; 13: 509-520.
[16] Loomba R, Friedman SL and Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell 2021; 184: 2537-2564.
[17] Arab JP, Arrese M and Trauner M. Recent Insights into the pathogenesis of nonalcoholic fatty liver disease. Annu Rev Pathol 2018; 13: 321-350.
[18] Abenavoli L, Milic N, Di Renzo L, Preveden T, Medic-Stojanoska M and De Lorenzo A. Metabolic aspects of adult patients with nonalcoholic fatty liver disease. World J Gastroenterol 2016; 22: 7006-7016.
[19] Kefala G and Tziomalos K. Apoptosis signal-regulating kinase-1 as a therapeutic target in nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol 2019; 13: 189-191.
[20] Smith BW and Adams LA. Nonalcoholic fatty liver disease and diabetes mellitus: pathogenesis and treatment. Nat Rev Endocrinol 2011; 7: 456-465.
[21] Durnik R, Sindlerova L, Babica P and Jurcek O. Bile acids transporters of enterohepatic circulation for targeted drug delivery. Molecules 2022; 27: 2961.
[22] Ohtani N and Hara E. Gut-liver axis-mediated mechanism of liver cancer: a special focus on the role of gut microbiota. Cancer Sci 2021; 112: 4433-4443.
[23] Tilg H, Adolph TE and Trauner M. Gut-liver axis: pathophysiological concepts and clinical implications. Cell Metab 2022; 34: 1700-1718.
[24] Wahlstrom A, Sayin SI, Marschall HU and Backhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab 2016; 24: 41-50.
[25] Albillos A, de Gottardi A and Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol 2020; 72: 558-577.
[26] Frasinariu OE, Ceccarelli S, Alisi A, Moraru E and Nobili V. Gut-liver axis and fibrosis in nonalcoholic fatty liver disease: an input for novel therapies. Dig Liver Dis 2013; 45: 543-551.
[27] Pezzino S, Sofia M, Faletra G, Mazzone C, Litrico G, La Greca G and Latteri S. Gut-liver axis and non-alcoholic fatty liver disease: a vicious circle of dysfunctions orchestrated by the gut microbiome. Biology (Basel) 2022; 11: 1622.
[28] Szabo G, Bala S, Petrasek J and Gattu A. Gut-liver axis and sensing microbes. Dig Dis 2010; 28: 737-744.
[29] Song Q and Zhang X. The role of gut-liver axis in gut microbiome dysbiosis associated NAFLD and NAFLD-HCC. Biomedicines 2022; 10: 524.
[30] Talevi A. The ADME Encyclopedia: a comprehensive guide on biopharmacy and pharmacokinetics. Cham: Springer International Publishing: Imprint: Springer, 2022.
[31] Roberts MS, Magnusson BM, Burczynski FJ and Weiss M. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. Clin Pharmacokinet 2002; 41: 751-790.
[32] Gerner B and Scherf-Clavel O. Physiologically based pharmacokinetic modelling of cabozantinib to simulate enterohepatic recirculation, drug-drug interaction with rifampin and liver impairment. Pharmaceutics 2021; 13: 778.
[33] Liu S and Yang X. Intestinal flora plays a role in the progression of hepatitis-cirrhosis-liver cancer. Front Cell Infect Microbiol 2023; 13: 1140126.
[34] Bashiardes S, Shapiro H, Rozin S, Shibolet O and Elinav E. Non-alcoholic fatty liver and the gut microbiota. Mol Metab 2016; 5: 782-794.
[35] Bauer KC, Littlejohn PT, Ayala V, Creus-Cuadros A and Finlay BB. Nonalcoholic fatty liver disease and the gut-liver axis: exploring an undernutrition perspective. Gastroenterology 2022; 162: 1858-1875, e1852.
[36] Ohtani N, Kamiya T and Kawada N. Recent updates on the role of the gut-liver axis in the pathogenesis of NAFLD/NASH, HCC, and beyond. Hepatol Commun 2023; 7: e0241.

[37] Mavilia-Scranton MG, Wu GY and Dharan M. Impact of helicobacter pylori infection on the pathogenesis and management of nonalcoholic fatty liver disease. J Clin Transl Hepatol 2023; 11: 670-674.
[38] Xie Y and Hao J. Treatment of metabolic associated fatty liver disease with traditional Chinese medicine colon dialysis based on "gut-liver axis". Academic Journal of Medicine & Health Sciences 2023; 4.
[39] Zhou Z, Zhang J, You L, Wang T, Wang K, Wang L, Kong X, Gao Y and Sun X. Application of herbs and active ingredients ameliorate nonalcoholic fatty liver disease under the guidance of traditional Chinese medicine. Front Endocrinol (Lausanne) 2022; 13: 1000727.
[40] Guo K, Xu S and Zeng Z. "Liver-gut" axis: a target of traditional Chinese medicine for the treatment of non-alcoholic fatty liver disease. Front Endocrinol (Lausanne) 2022; 13: 1050709.
[41] Xu Y, Wang N, Tan HY, Li S, Zhang C and Feng Y. Gut-liver axis modulation of Panax notoginseng saponins in nonalcoholic fatty liver disease. Hepatol Int 2021; 15: 350-365.
[42] Hui D, Liu L, Azami NLB, Song J, Huang Y, Xu W, Wu C, Xie D, Jiang Y, Bian Y and Sun M. The spleen-strengthening and liver-draining herbal formula treatment of non-alcoholic fatty liver disease by regulation of intestinal flora in clinical trial. Front Endocrinol (Lausanne) 2022; 13: 1107071.
[43] Zhang S, Wong YT, Tang KY, Kwan HY and Su T. Chinese medicinal herbs targeting the gut-liver axis and adipose tissue-liver axis for non-alcoholic fatty liver disease treatments: the ancient wisdom and modern science. Front Endocrinol (Lausanne) 2020; 11: 572729.
[44] Dai X, Feng J, Chen Y, Huang S, Shi X, Liu X and Sun Y. Traditional Chinese medicine in nonalcoholic fatty liver disease: molecular insights and therapeutic perspectives. Chin Med 2021; 16: 68.
[45] Li L, Yang S, Liang X, Liu Y, Xu H, Guo X, Xie C and Xu X. Saikosaponin D improves nonalcoholic fatty liver disease via gut microbiota-bile acid metabolism pathway. Food Science and Human Wellness 2024; 13: 2703-2717.
[46] Li L, Lan X, Peng X, Shi S, Zhao Y, Liu W, Luo Q, Jia L, Feng B, Chen Z, Zou Y and Huang C. Polysaccharide from Salviae miltiorrhizae Radix et Rhizoma Attenuates the progress of obesity-induced non-alcoholic fatty liver disease through modulating intestinal microbiota-related gut-liver axis. Int J Mol Sci 2022; 23: 10620.
[47] Wang Y, Shou JW, Li XY, Zhao ZX, Fu J, He CY, Feng R, Ma C, Wen BY, Guo F, Yang XY, Han YX, Wang LL, Tong Q, You XF, Lin Y, Kong WJ, Si SY and Jiang JD. Berberine-induced bioactive metabolites of the gut microbiota improve energy metabolism. Metabolism 2017; 70: 72-84.
[48] Bieghs V, Wouters K, van Gorp PJ, Gijbels MJ, de Winther MP, Binder CJ, Lutjohann D, Febbraio M, Moore KJ, van Bilsen M, Hofker MH and Shiri-Sverdlov R. Role of scavenger receptor A and CD36 in diet-induced nonalcoholic steatohepatitis in hyperlipidemic mice. Gastroenterology 2010; 138: 2477-2486, 2486.e1-3.
[49] Xie Y and Hao J. Research progress on the regulation of intestinal flora by traditional chinese medicine in the treatment of metabolic associated fatty liver disease. MEDS Chinese Medicine 2023; 5: 48-55.
[50] Ren F, Meng C, Chen W, Chen H and Chen W. Ganoderma amboinense polysaccharide prevents obesity by regulating gut microbiota in high-fat-diet mice. Food Bioscience 2021; 42.
[51] Zhang J, Wang W, Cui X, Zhu P, Li S, Yuan S, Peng D and Peng C. Ganoderma lucidum ethanol extracts ameliorate hepatic fibrosis and promote the communication between metabolites and gut microbiota g_Ruminococcus through the NF-kappaB and TGF-beta1/Smads pathways. J Ethnopharmacol 2024; 322: 117656.
[52] Xi Y, Wu M, Li H, Dong S, Luo E, Gu M, Shen X, Jiang Y, Liu Y and Liu H. Baicalin attenuates high fat diet-induced obesity and liver dysfunction: dose-response and potential role of CaMKKbeta/AMPK/ACC pathway. Cell Physiol Biochem 2015; 35: 2349-2359.
[53] Pu P, Wang XA, Salim M, Zhu LH, Wang L, Chen KJ, Xiao JF, Deng W, Shi HW, Jiang H and Li HL. Baicalein, a natural product, selectively activating AMPKalpha(2) and ameliorates metabolic disorder in diet-induced mice. Mol Cell Endocrinol 2012; 362: 128-138.
[54] Liu Q, Zhu L, Cheng C, Hu YY and Feng Q. Natural active compounds from plant food and chinese herbal medicine for nonalcoholic fatty liver disease. Curr Pharm Des 2017; 23: 5136-5162.
[55] Porras D, Nistal E, Martinez-Florez S, Pisonero-Vaquero S, Olcoz JL, Jover R, Gonzalez-Gallego J, Garcia-Mediavilla MV and Sanchez-Campos S. Protective effect of quercetin on high-fat diet-induced non-alcoholic fatty liver disease in mice is mediated by modulating intestinal microbiota imbalance and related gut-liver axis activation. Free Radic Biol Med 2017; 102: 188-202.
[56] Mancak M, Altintas D, Balaban Y and Caliskan UK. Evidence-based herbal treatments in liver diseases. Hepatol Forum 2024; 5: 50-60.
[57] Panahi Y, Kianpour P, Mohtashami R, Atkin SL, Butler AE, Jafari R, Badeli R and Sahebkar A. Efficacy of artichoke leaf extract in non-alcoholic fatty liver disease: a pilot double-blind

randomized controlled trial. Phytother Res 2018; 32: 1382-1387.
[58] Bose Mazumdar Ghosh A, Banerjee A and Chattopadhyay S. An insight into the potent medicinal plant Phyllanthus amarus Schum. and Thonn. Nucleus (Calcutta) 2022; 65: 437-472.
[59] Zhao CQ, Zhou Y, Ping J and Xu LM. Traditional Chinese medicine for treatment of liver diseases: progress, challenges and opportunities. J Integr Med 2014; 12: 401-408.
[60] Liang Y, Zhang Y, Deng Y, Liang S, He Y, Chen Y, Liu C, Lin C, Han L, Tu G and Yang Q. Chaihu-Shugan-San decoction modulates intestinal microbe dysbiosis and alleviates chronic metabolic inflammation in NAFLD rats via the NLRP3 inflammasome pathway. Evid Based Complement Alternat Med 2018; 2018: 9390786.
[61] Zhang LW, Zhu LL, Zhu XY, Fu SQ and Liu XM. Traditional Chinese medicine formula Dai-Zong-Fang alleviating hepatic steatosis in db/db mice via gut microbiota modulation. Front Pharmacol 2024; 15: 1337057.
[62] Li M, Ding L, Hu YL, Qin LL, Wu Y, Liu W, Wu LL and Liu TH. Herbal formula LLKL ameliorates hyperglycaemia, modulates the gut microbiota and regulates the gut-liver axis in Zucker diabetic fatty rats. J Cell Mol Med 2021; 25: 367-382.
[63] Li S, Chen F, Zou Y, Ning L, Zhang G, Zhang S and Yao Q. Yinzhihuang oral liquid protects against non-alcoholic steatohepatitis via modulation of the gut-liver axis in mice. Ann Transl Med 2022; 10: 631.
[64] Li ZH, Zhang N, Wang Y, Pang M and Liu SM. Mechanism of Yinchenhao Decoction in treating non-alcoholic fatty liver based on 16S rRNA technique and metabonomics. China Journal of Traditional Chinese Medicine and Pharmacy 2019; 34: 1908-1913.
[65] Chen SD, Fan Y and Xu WJ. Effects of yinchenhao decoction (see text) for non-alcoholic steatohepatitis in rats and study of the mechanism. J Tradit Chin Med 2011; 31: 220-223.
[66] Lu JZ, Ye D and Ma BL. Constituents, pharmacokinetics, and pharmacology of Gegen-Qinlian decoction. Front Pharmacol 2021; 12: 668418.
[67] Guo Y, Ding PH, Liu LJ, Shi L, Mao TY, Li JX and Wang YL. Gegen Qinlian decoction attenuates high-fat diet-induced steatohepatitis in rats via gut microbiota. Evid Based Complement Alternat Med 2018; 2018: 7370891.
[68] Zhu LR, Li SS, Zheng WQ, Ni WJ, Cai M and Liu HP. Targeted modulation of gut microbiota by traditional Chinese medicine and natural products for liver disease therapy. Front Immunol 2023; 14: 1086078.
[69] Wang H, Tan H, Zhan W, Song L, Zhang D, Chen X, Lin Z, Wang W, Yang Y, Wang L, Bei W and Guo J. Molecular mechanism of Fufang Zhenzhu Tiaozhi capsule in the treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease based on network pharmacology and validation in minipigs. J Ethnopharmacol 2021; 274: 114056.
[70] Guoguo Z, Bingjie S, Tianyan Z, Shaoxiu JI, Jingwei LI, Yanni D, Feng L and Dong W. Efficacy of Ganshuang granules on non-alcoholic fatty liver and underlying mechanism: a network pharmacology and experimental verification. J Tradit Chin Med 2024; 44: 122-130.
[71] Li B and Fang L. Research progress on the mechanism of acupuncture treatment for non-alcoholic fatty liver disease. Gastroenterol Res Pract 2022; 2022: 5259088.
[72] Wang H, Wang Q, Liang C, Pan L, Hu H and Fang H. Acupuncture improved hepatic steatosis in HFD-induced NAFLD rats by regulating intestinal microbiota. Front Microbiol 2023; 14: 1131092.
[73] Han J, Guo X, Meng XJ, Zhang J, Yamaguchi R, Motoo Y and Yamada S. Acupuncture improved lipid metabolism by regulating intestinal absorption in mice. World J Gastroenterol 2020; 26: 5118-5129.
[74] He LH, Yao DH, Wang LY, Zhang L and Bai XL. Gut microbiome-mediated alteration of immunity, inflammation, and metabolism involved in the regulation of non-alcoholic fatty liver disease. Front Microbiol 2021; 12: 761836.