



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

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Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide. The pathogenesis of NAFLD is complex. Frontline western medicines only ameliorate the symptoms of NAFLD. On the contrary, the uniqueness of Chinese medicine in its interpretation of NAFLD and the holistic therapeutic approach lead to a promising therapeutic efficacy. Recent studies reveal that the gut–liver axis and adipose tissue–liver axis play important roles in the development of NAFLD. Interestingly, with advanced technology, many herbal formulae are found to target the gut–liver axis and adipose tissue–liver axis and resolve the inflammation in NAFLD. This is the first review summarizes the current findings on the Chinese herbal formulae that target the two axes in NAFLD treatment. This review not only demonstrates how the ancient wisdom of Chinese medicine is being interpreted by modern pharmacological studies, but also provides valuable information for the further development of the herbal-based treatment for NAFLD.

Keywords: non-alcoholic fatty liver disease, pathogenesis, Chinese medicinal herbs, gut–liver axis, adipose tissue–liver axis

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease. It develops from hepatic fatty infiltration known as non-alcoholic fatty liver (NAFL), to the stage of nonalcoholic steatohepatitis (NASH) with inflammatory cell infiltration accompanied with various degrees of fibrosis (1). NAFLD may eventually develop into hepatocellular carcinoma (HCC) (2, 3) (**Figure 1**).

Around 17–51% of adults in countries like China, France, Germany, Italy, Japan, Spain, UK, and US have developed NAFLD (4). The number of NAFLD cases with end-stage disease is expected to increase in these countries. Among them, China will have the highest incidence of NAFLD that may reach 314.58 million cases in 2030 (5); and the NASH population will also increase by 48% to 48.26 million cases or 15% of all the NAFLD cases (5). People with NAFLD have increased mortality. In particular, the liver-related mortality such as cirrhosis and HCC are markedly increased in the NASH population (6). Liver-related deaths in 2016 ranged from 2,490 in France to 30,240 in the US; it is

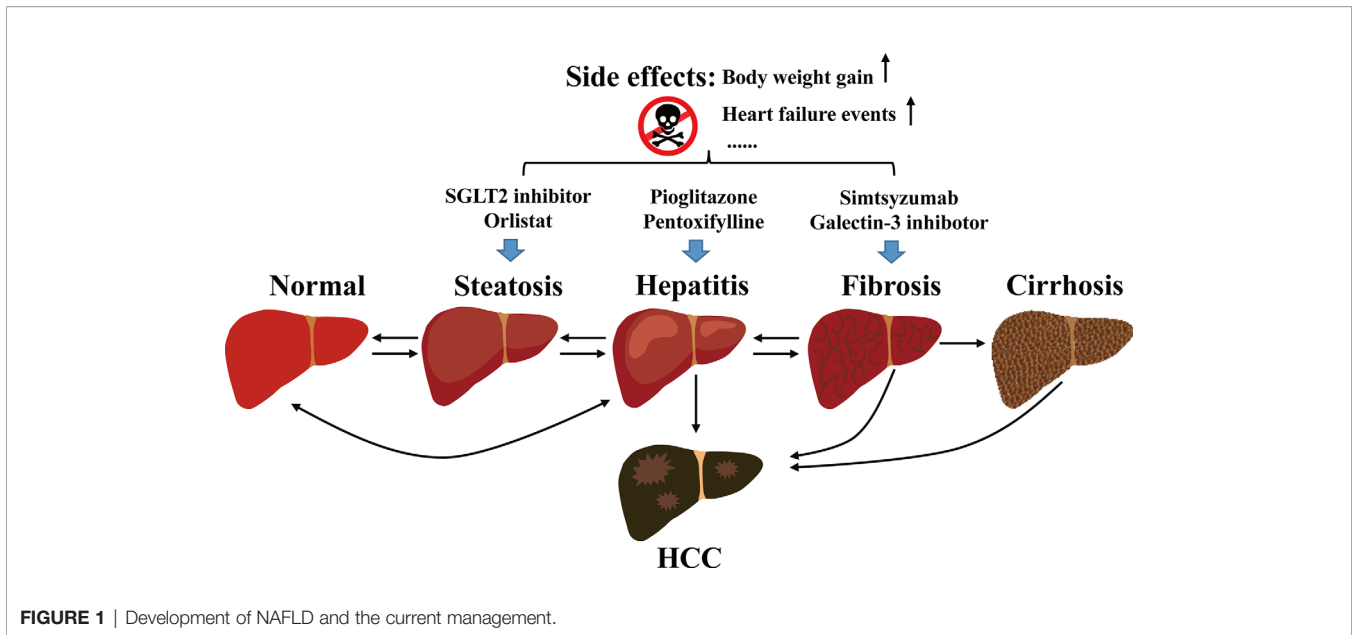


FIGURE 1 | Development of NAFLD and the current management.

predicted that China will surpass these countries and will have the largest number of liver-related deaths by 2030 (5). Hence, a better understanding of the pathogenesis of NAFLD is essential for the design of new and effective therapeutic interventions.

THE PATHOGENESIS OF NAFLD IS COMPLEX

The pathogenesis of NAFLD involves a complex interaction between obesity, environmental factors, and the gut microbiota (7). It is generally believed that changes in lifestyle and the global pandemic of obesity account for the rapid increase in the NAFLD prevalence in these countries (8). In particular, the western style dietary habit, such as high consumption of high-energy and processed foods (9). These foods are often referred as “junk food”, which are rich in monosaccharide, saturated fats and trans fats, and lack of nutrients (9, 10). Studies have demonstrated that the experimental animals exposed to “junk foods” could develop NAFLD within 10 weeks (11–13).

Many clinical and experimental studies have already revealed that NAFLD and NASH patients have elevated oxidative DNA damage in the liver (14, 15), which is due to the enhanced production of reactive oxygen species (ROS). ROS are the by-products of metabolism in the hepatocytes. Hepatic fatty acid accumulation promotes ROS generation because mitochondrial respiratory chain activity cannot couple with the enhanced mitochondrial fatty acid oxidation. Besides, liver specimens from NAFLD patients are also characterized by the elevated phosphorylation of endoplasmic reticulum (ER) stress marker such as eukaryotic initiation factor 2 (eIF2) (16), suggesting ER stress also contributes to the pathogenesis of NAFLD. These pathways can participate in the adaptive response of lipid accumulation and promote the production of ROS and oxidative stress (17). It is noteworthy that CYP2E1 and CYP4A have been

considered as major sources of oxidative stress (18). Subsequently, oxidative stress leads to DNA damage, phospholipid membrane disruption by lipid peroxidation, and secretion of proinflammatory cytokines (19). Autophagy, which is an important degradative cellular pathway of the autodigestion of cellular proteins and organelles to obtain energy, has been suggested to have critical functions in both hepatocytes and nonparenchymal cells (i.e., macrophages and hepatic stellate cells) influencing insulin sensitivity, lipid accumulation, hepatocellular injury, and the innate immune response (20). In addition, insulin resistance can be acquired *via* multiple mechanisms, and may affect various steps in the insulin signaling cascade which finally suppresses important metabolic pathways causing overproduction of glucose, and ultimately result in liver cell damage and death, and hence accelerates NAFLD progression (21). Kupffer cells in the liver are capable to release large amounts of tumor necrosis factor (TNF) and interleukin-6 (IL-6), which directly induce hepatic inflammation and fibrogenesis, releasing several proinflammatory cytokines that are pathogenetic in NAFLD (22). Hence, understanding the pathogenesis of NAFLD is necessary for the identification of biomarkers for the prevention and treatment of the disease.

THE GUT-LIVER AXIS IN NAFLD

Recent studies discover that alteration in the gut-liver axis is closely associated with the progression of NAFLD in the patients (23). Changes in the gut microbiome promote NAFLD development. In NAFLD patients, bacterial families Prevotellaceae and Enterobacteriaceae Proteobacteria, Enterobacteriaceae, and Escherichia are increased (24); while Oscillobacter, Bacteroidetes and Clostridium leptum (family Clostridiaceae) are reduced (25, 26). Patients with NASH have increased Ruminococcus, Blautia, and Dorea abundance, but a lower rate of Bacteroidetes compared

to steatosis and healthy controls (27). These data imply an association between the presence of these bacterial families and NASH development. Indeed, the Bacteroides abundance is directly correlated with NASH severity (28).

The gut flora modifies bile acid metabolism (29). The gut microbes produce enzymes that convert primary bile acids into secondary bile acids in the intestines. NAFLD or NASH patients have moderate elevations of total bile acid, besides, the bile acid compositions in these patients are also changed (30). Disturbance of the gut microbiota decreases the synthesis of secondary bile acids, which in turn decreases activation of nuclear receptors such as farnesoid X receptor (FXR), pregnane X receptor, Takeda G-protein-coupled bile acid protein 5 and vitamin D receptor. Dysregulation of these receptor can lead to the development of NAFLD (31–33). For example, activation of FXR represses hepatic *de novo* lipogenesis, stimulates fatty acid β -oxidation, and hence reduces hepatic lipid accumulation (34–36); whereas reduced FXR activity promotes NAFLD development. The gut microbiota also regulates the immune balance in the gut *via* different pathways. For example, the abundance of *Faecalibacterium prausnitzii* is reduced in the patients. *F. prausnitzii* is an anti-inflammatory commensal, its reduced abundance increases interleukin-10 (IL-10) secretion and reduces IL-12 and interferon- γ expressions (37). Besides, the thinned intestinal mucus layer and increased gut permeability will increase the leakage of bacterial components that could activate Toll-like receptors (TLRs) or NOD-like receptors (38). TLRs recognize the microbial molecules “pathogen-associated molecular patterns” such as lipopolysaccharide (LPS) or the damage-associated molecular pattern. Activation of TLRs increases the production of tumor necrosis factor- α (TNF- α), IL-6, IL-8, and IL-12. In TLR-4 null mice, hepatic fat deposition is reduced, and NASH development is slowed down (39–41). The intestinal permeability is controlled by several multiprotein adhesive complexes including tight junctions, subjacent adherens junctions and desmosomes (42, 43). Studies have demonstrated that NAFLD is associated with increased gut permeability and the increased permeability appears to be caused by disruption of intercellular tight junctions (44). The increased gut permeability in these patients further promotes the inflammatory responses (45). Experimental study shows that in high-fat diet-fed mice, the gut becomes more permeable to the translocation of LPS; therefore, LPS can reach the liver through the portal vein and exacerbate liver inflammation and fibrosis (23, 46).

All these clinical and experimental studies suggest that the gut–liver axis will trigger the proinflammatory and profibrogenetic pathways in the liver and promote NAFLD development (23, 46) (Figure 2).

THE ADIPOSE TISSUE–LIVER AXIS IN NAFLD

The adipose tissue–liver axis also contributes to the NAFLD pathogenesis. Adipose tissues in NAFLD patients have elevated

expressions of inflammatory mediators (47). Besides, the adipose tissues may have enhanced infiltrate of macrophages. Clinical studies show that the severity of macrophage infiltration in the adipose tissue in the patients is directly correlated with the degree of hepatic steatosis, inflammation and fibrosis (48, 49). Besides, adipocyte hypertrophy leads to adipocyte cell death (50, 51), which alters the pro-inflammatory cytokine production and secretion (52). For example, the increased secretion of TNF- α (53) will induces hepatocyte death and modulates hepatic immune function. Clinical studies also suggest that TNF- α is a predictor of NASH and its level is directly related to the disease stages (54–57).

Adipose tissues are a source of lipids. However, dysfunctional adipose tissues will have limited fat storage capacity thus promoting the deposition of ectopic fat in liver and muscle (58), which is known as lipotoxicity. Lipotoxicity induces hepatic mitochondrial oxidative stress (59), which further accelerates the progression of NAFLD.

The dysfunctional adipose tissues will also alter adipokine production (60). Adiponectin and leptin are the two common adipokines. Adiponectin has anti-fibrotic effect in the liver (61), mediated by AMPK activity (62). Adiponectin also has anti-inflammatory effect, it blocks the activation of NF- κ B, increases secretion of anti-inflammatory cytokines, and reduces the release of pro-inflammatory cytokines such as TNF- α and IL-6 (63). Therefore, decreased adiponectin level is associated with the advanced stage of the disease, it is considered as a predictor of the necro-inflammatory grade and fibrosis in NAFLD (64–66). Clinical studies have reported that reduced adiponectin and increased leptin levels result in hepatic steatosis and activation of inflammation and fibrogenesis (29). In mouse model, delivery of adiponectin improves steatohepatitis in the mouse models (67).

Experimental study shows that removal of inflamed white adipose tissue indeed attenuates the development of NASH in the mice (68). Clinical studies have shown that the expression of adipocytokines in NAFLD patients is different from that in healthy people (56, 69, 70). Compared to the healthy, levels of leptin, TNF- α and IL-6 are significantly elevated in NAFLD patients, whereas the adiponectin level is significantly reduced. Therefore, adipocyte hypertrophy, adipocytes dysfunction and the subsequent inflammation in the adipose tissue–liver axis contribute to the development of NAFLD (Figure 3).

CLINICAL CHALLENGES IN NAFLD TREATMENT

Current managements of NAFLD or NASH include diet regimen, aerobic exercise, and interventions that target the associated metabolic abnormalities (71, 72). For example, diabetic drug pioglitazone reduces NASH and the mean fibrosis score in patients with biopsy-proven NASH, regardless of the diabetes status (1). However, pioglitazone causes weight gain (73) and increases heart failure events (74), it is not an ideal medication for NAFLD patients. Furthermore, given the

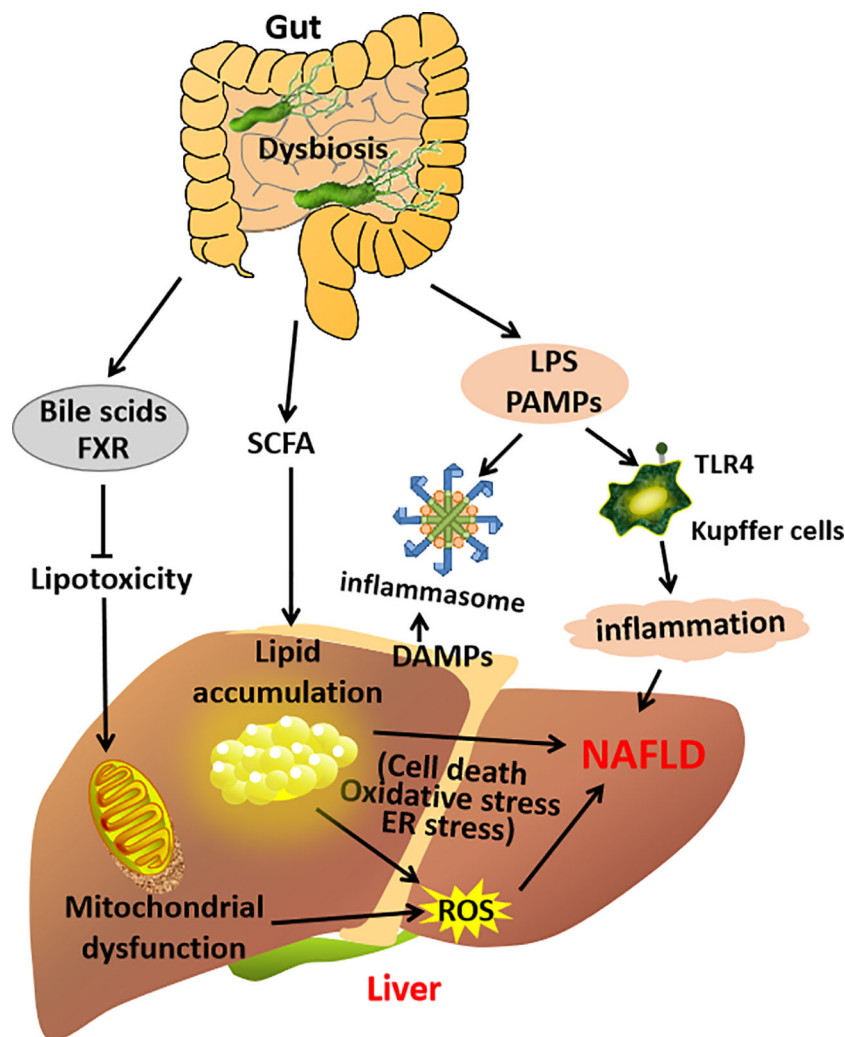


FIGURE 2 | A schematic diagram demonstrating the contribution of the gut-liver axis in NAFLD pathogenesis.

complicated pathogenesis, modifying lifestyle and dietary intervention may not always be effective to alleviate or ameliorate the NAFLD conditions. The current management of NAFLD is illustrated in **Figure 1**.

Studies also try to explore the beneficial effects of various dietary supplements. A clinical study shows that vitamin E, an anti-inflammatory medication, improves the NASH condition when compared with placebo in a randomized study of non-diabetic NAFLD individuals (75). Similar result is also demonstrated in a meta-analysis study which suggests vitamin E improves the histologic features of NASH, but not fibrosis (76). Besides, polyunsaturated fatty acids (PUFAs) have also been postulated to mitigate NAFLD and NASH. Experimental studies suggest that PUFAs activates hepatic peroxisome proliferator-activated receptor alpha and promotes fatty acid oxidation (77); downregulates sterol regulatory element binding protein-1 and reduces lipogenesis (78). PUFAs also reduces the production of pro-inflammatory mediators such as interleukin-6 (IL-6) and

tumor necrosis factor (79). A meta-analysis study suggests that omega-3 PUFA supplementation significantly reduces hepatic lipid contents (80–82). However, the supplementation does not improve the NASH condition (82). All these studies suggest that taking dietary supplement is not an effective approach to reverse the NAFLD or NASH conditions.

COMBINING ANCIENT WISDOM AND MODERN SCIENCE TO EXPLORE HERBAL-BASED THERAPEUTICS FOR NAFLD TREATMENT

Nowadays, modern pharmacological and experimental studies have elucidated the mechanisms of action of Chinese herbal medicine in the treatment of NAFLD. In a meta-analysis study, twenty herbs that are commonly used for treating NAFLD have

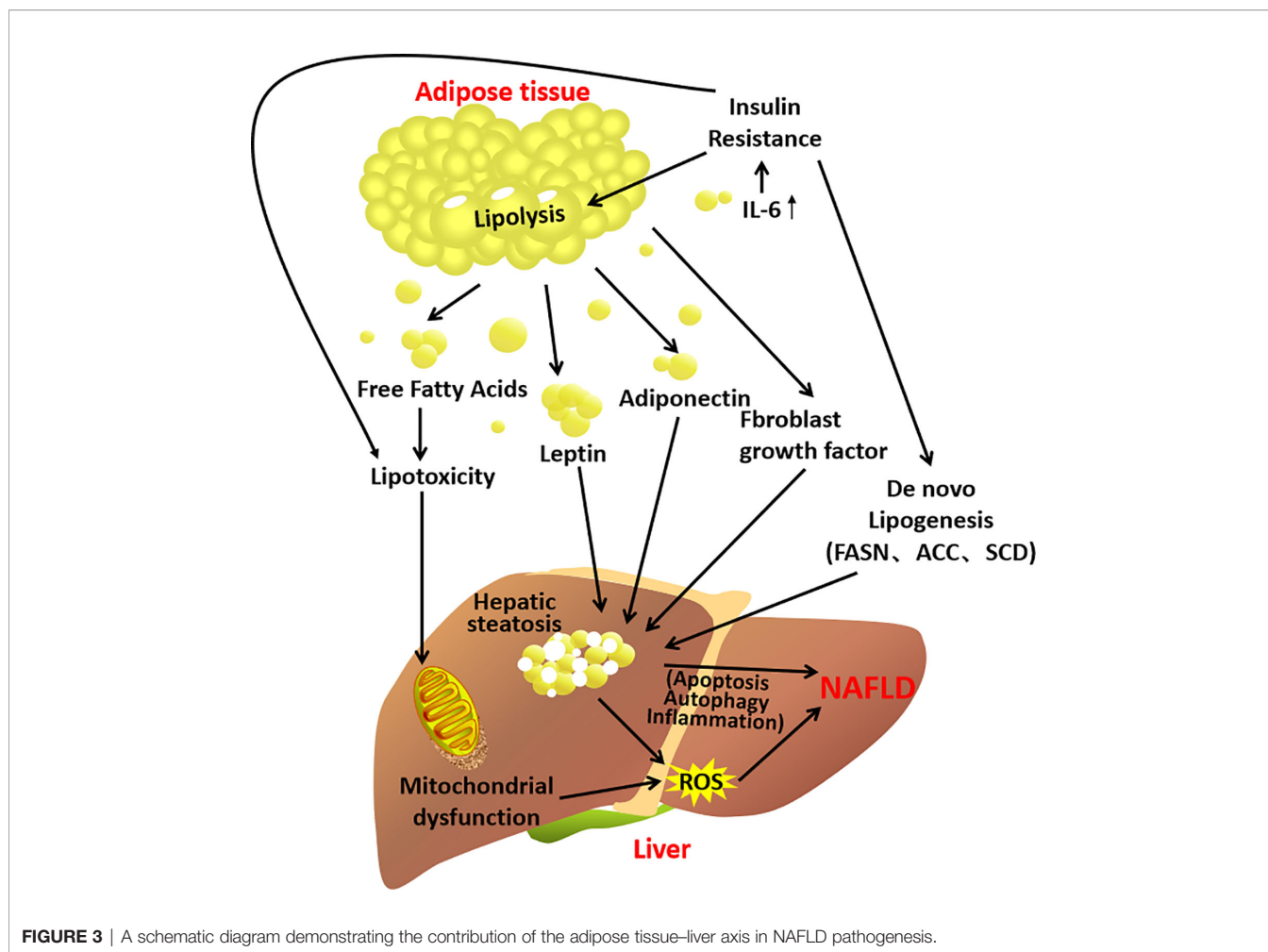


FIGURE 3 | A schematic diagram demonstrating the contribution of the adipose tissue–liver axis in NAFLD pathogenesis.

been identified (83). Among them, the top eight frequently used herbs and their constituting anti-NAFLD active compounds are summarized in **Table 1**.

The diagnosis and interpretation for NAFLD in Chinese medicine is different from Western medicine. In Chinese medicine, NAFLD is further subdivided into syndromes (**Figure 4**), and a holistic therapeutic approach is employed to treat the patients. For example, the therapies include spleen tonification and qi regulation, phlegm elimination and dehumidification, blood activation and phlegm emission and liver clearance (110).

Many clinical studies show that Chinese herbal formulae are effective for NAFLD treatment as assessed by the clinical outcomes such as the NAFLD activity score (NAS) and hepatic or serum lipid levels. For example, a clinical trial has been done to study the effectiveness of Qu Yu Hua Tan Tong Luo (QYHTTL) in NAFLD treatment. QYHTTL comprises of Bupleuri Radix, Scutellariae Radix, Pinelliae Rhizoma, Codonopsis Radix, Glycyrrhizae Radix et Rhizoma, Jujubae Fructus, RJ, Morindae Officinalis Radix, and Oldenlandia Diffusa. The study demonstrates that QYHTTL significantly lowers the levels of hepatic aminotransferases and improves lipid profiles (111). Besides, a meta-analysis including 13 studies involving 1429

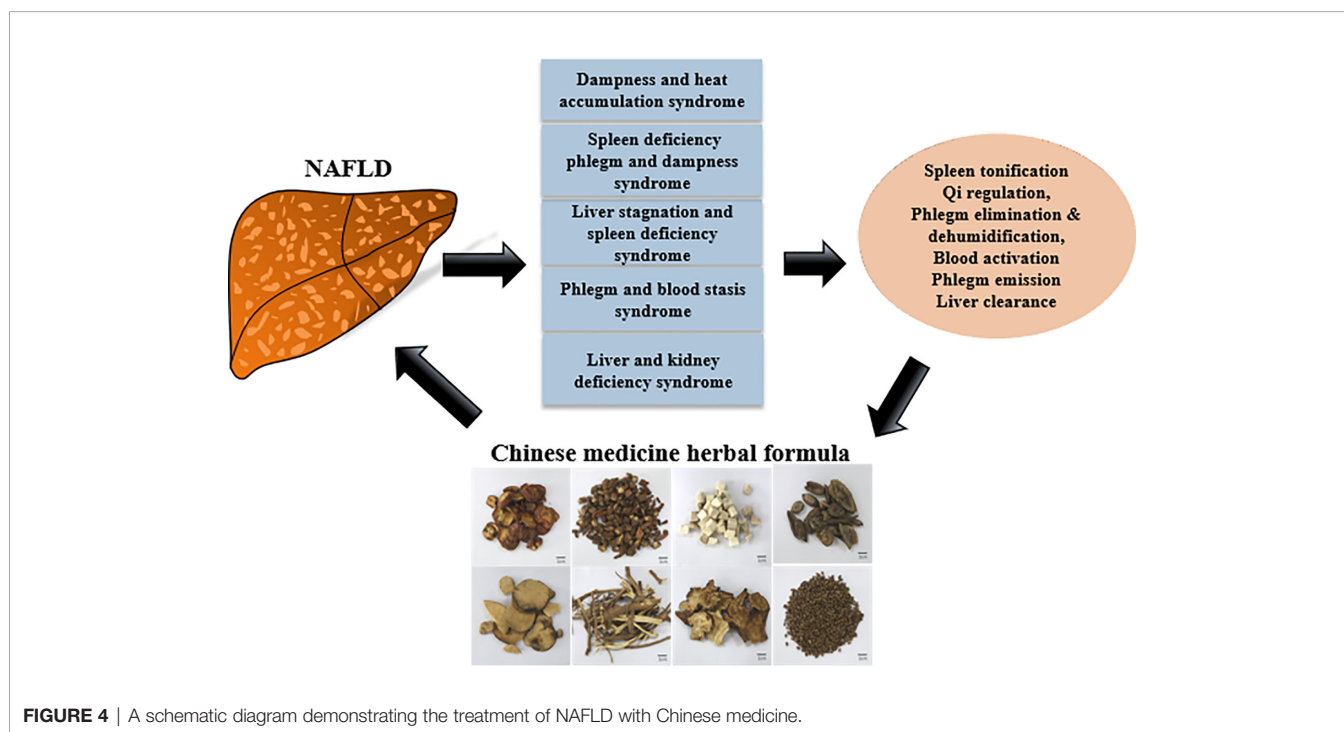
patients shows that another herbal formula, Huo Xue Hua Yu (HXHY) significantly reduces total cholesterol and triglyceride levels when compared to conventional treatment. HXHY also has a greater beneficial effect on liver function in reducing alanine transaminase (ALT) and aspartate transaminase (AST) (112). The main constituent herbs in HXHY are *Salviae Miltiorrhizae radix et Rhizoma*, *Chuanxiong Rhizoma*, *Crataegi Fructus*, *Curcuma Longae Rhizoma*, *Curcuma Radix*, *Notoginseng Radix et Rhizoma*, *Persicae Semen*, *Sparganii Rhizoma*, *Curcuma zedoaria Rhizoma*, *Carthami Flos*, *Eupatorii Herba*, *Corydalis Rhizoma* and *Vaccariae Semen*. However, the mechanisms of action underlying the therapeutic effects of these herbal formula are less studied.

Experimental Studies Reveal That Many of the Herbal Formulae Regulate Hepatic Lipid Metabolism to Alleviate the NAFLD Condition

Since NAFLD has been described in 1980s, lots of experimental studies and clinical trials in China have been done to study the efficacies of TCMs for treating NAFLD. A Chinese herbal formula, Jiang Zhi Granule (JZG), is composed of *Gynostematis Herba*, *Nelumbinis Folium*, *Salviae Miltiorrhizae radix et Rhizoma*,

TABLE 1 | The top eight commonly used herbs and their constituting anti-NAFLD active compounds.

Herbs	Active compounds	Mechanisms underlying the anti-NAFLD effects	References
Crataegi Fructus (Shanzha)	Chlorogenic acid	Improve the adiponectin level; ameliorate liver injury and insulin resistance	(84–86)
	Hyperoside	Improve the adiponectin level	(84)
	Oleanolic acid	Stimulate AMPK phosphorylation and inhibit lipogenesis; improve insulin sensitivity	(87, 88)
Salviae Miltiorrhizae radix et Rhizoma (Danshen)	Salvianolic acid A	Decrease the hepatotoxic levels of cytokines and inhibit the excessive production of ROS	(89)
	Salvia miltiorrhiza polysaccharide	Decrease the expression levels of proinflammatory factors (eg. TNF- α , IL-6)	(90)
	Tanshinone IIA	Inhibit the TLR4/NF- κ B signaling pathway	(91, 92)
Poria (Fuling)	Salvianolic acid B	Increase the expression levels of tight junction protein occludin and ZO-1	(93)
	Polysaccharide	Increase butyrate-producing bacteria Lachnospiracea and improve the gut mucosal integrity	(94)
	Poricoic acid	Ameliorate liver steatosis through the activation of AMPK phosphorylation	(95)
Alismatis rhizoma (Zexie)	Alisol B 23-acetate	Reduce hepatic triglyceride accumulation via FXR activation	(96, 97)
	Alisol A 24-acetate	Inhibit inflammatory cytokines (eg. TNF α , IL-6 levels); inhibit oxidative stress and induce autophagy	(98, 99)
Bupleuri Radix (Chaihu)	Saikosaponin A	Induce autophagy	(100, 101)
	Atractylodes macrocephala	Activate the AMPK signaling pathway	(102)
	Koidz. (Baizhu)		
Cassiae Semen (Juemingzi)	Atractylenolide III	Increase the phosphorylation of AMPK	(103)
	Obtusin	Increase the expression of intestinal tight-junction protein occludin and ZO-1; improve the intestinal mucosal barrier function	(104, 105)
Curcumae Radix (Yujin)	Emodin	Inhibit the expression levels of proinflammatory cytokines	(106, 107)
	Curcumin	Attenuate the hepatic steatosis via the Nrf2-FXR-LXR pathway; improve intestinal barrier function; decrease the expression levels of proinflammatory cytokines	(108, 109)

**FIGURE 4** | A schematic diagram demonstrating the treatment of NAFLD with Chinese medicine.

Polygoni Cuspidati Rhizoma et Radix and Artemisiae Scopariae Herba (113). It is clinically safe, no adverse effect has been reported (114). In a clinical trial of 220 NAFLD patients, prescription of JZG significantly reduces body weight and improves hepatic steatosis (114). As the effectiveness of Chinese herbal formulas depends on the synergistic effects between multiple compounds and their targets, systems pharmacology approach has been used to explore the pharmacological mechanisms of JZG. Systems

pharmacology is a novel strategy that can clarify the synergistic effects and the mechanisms of multi-component and multi-targeted agents (115). It can predict the active compounds within the herbal formula JZG and their corresponding therapeutic targets and synergistic effects. The analysis has highlighted a number of signaling pathways that may be involved in therapeutic effects of JZG, they are ER-phagosome pathway, proteasomal ubiquitin-dependent protein catabolic process, TRAF6-mediated induction

of pro-inflammatory cytokines, MAPK cascade, regulation of lipid metabolism including steroid biosynthesis, cholesterol transport and fatty acid metabolism (116). Indeed, mechanistic study also shows that JZG regulates lipid metabolism. JZG significantly inhibits sterol regulatory element binding protein-1c (SREBP-1c) activity by inhibiting the liver X receptor- α (LXR α)-mediated SREBP-1c transcription and LXR α -independent SREBP-1c maturation (117, 118). It is well-known that LXR α trans-activates SREBP-1c (119), and SREBP-1c is involved in the pathogenesis of NAFL and NASH. Indeed, SREBP-1c is a critical transcription factor in lipogenesis, it initiates the transcription of lipogenic genes which enzymes cause lipid deposition. SREBP-1c also plays a role in ER stress. Study shows that AMP-activated protein kinase (AMPK)-mediated down-regulation of SREBP-1c alleviates the ER stress response in hepatocytes by suppressing the mechanistic target of rapamycin complex 1 signaling (120). Other experimental study demonstrates that JZG activates autophagy progression by inducing autophagosomes or co-localization of autophagosomes and lysosomes (121). Degradation of autolysosomes protects the hepatocytes against palmitic acid-induced injury. JZG also protects mitochondrial integrity against oxidative stress in the hepatocyte model (121). In the mouse model of NAFLD, JZG reduces hepatic lipid content and ameliorates inflammation, improves metabolic disorder and reduces liver injury (116, 118, 121). In CCl₄-induced liver injury in NAFLD rat, JZG also significantly reduces hepatic inflammation, ER stress, hepatic necrosis, hepatic lipid, blood transaminases and blood lipids (122). Further delineation suggests that protopanaxadiol, tanshinone IIA, and emodin in the JZG formula significantly reduce hepatic lipid content while protopanaxadiol reduces the oxidative stress in the steatotic liver cell models (113). All these studies strongly suggest that JZG can be developed as herbal-based therapeutics as an adjunct treatment for NAFLD, by regulating the lipid metabolism, inducing autophagy and reducing hepatic inflammation.

Besides, experimental studies have revealed many other herbal formulae that can directly regulate hepatic lipid metabolism in the NAFLD subjects to alleviate the conditions. For example, Jiangzhi Capsule has been clinically used for the management of lipid abnormalities. It is composed of Astragali Radix, Poria, Nelumbinis Folium, Alismatis Rhizoma, Crataegi Fructus, Chaenomelis Fructus, Salviae Miltiorrhizae Radix et Rhizoma, Notoginseng Radix et Rhizoma, Typhae Pollen, Polygoni Cuspidati Rhizoma et Radix, Taraxaci Herba, Polygoni Multiflori Radix and Ligustri Lucidi Fructus. A recent study in NAFLD rat model shows that Jiangzhi Capsule downregulates fructose-stimulated hepatic overexpression of SREBP-1a and 1c, and hence the hepatic expressions of acetyl-CoA carboxylase-1, stearoyl-CoA desaturase-1 and acyl-coenzyme A: diacylglycerol acyltransferase (DGAT)-2, suggesting that Jiangzhi capsule possesses therapeutic effect on NAFLD treatment by modulating the lipid metabolism (123). A classical traditional Chinese medicine formula known as Da Chai Hu Decoction (DCHD) is shown to reduce the levels of total cholesterol and triglyceride in the NAFLD rat models (124). Besides, DCHD also reduces the expressions of proinflammatory mediators such as transforming growth factor- β 1 (TGF- β 1), TLR4,

TNF- α and nuclear factor-kappa B (NF- κ B), suggesting DCHD is a potential therapeutics for the treatment of NAFLD by reducing hepatic lipids and resolving the hepatic inflammation (124). Another study shows that a Chinese herbal formula Chai Hu Li Zhong Tang (CHLZT) significantly reduces serum levels of total cholesterol and triglyceride in the NAFLD rat models, the treatment also significantly reduces the numbers of lipid droplets in the liver tissues and also in HepG2 liver cell models (125). Further mechanistic study suggests that CHLZT increases the levels of p-AMPK α and PPAR γ in the NAFLD liver tissues and HepG2 cells, while decreasing the expressions and activities of ACC, SREBP-2 and 3-hydroxyl-3-methylglutaryl-coenzyme A reductase (125), suggesting that CHLZT improves the NAFLD condition by regulating the hepatic lipid metabolism.

Herbal Formulae Modulate the Gut–Liver Axis in NAFLD Treatment

Other formulae can modulate the gut–liver axis for the NAFLD treatment. Si Ni San (SNS) is first recorded by Zhong-Jing Zhang during the Eastern Han Dynasty. In Chinese medicine theory, SNS coordinates the functions of liver and spleen, and has been used for thousands of years. SNS consists of Bupleuri Radix, Paeoniae Alba Radix, Aurantii Immaturus Fructus, and honey-fried Glycyrrhizae Radix et Rhizoma in equal proportions. In Chinese medicine, SNS is used to “dispel cold and cause restoration upon collapse”, it eliminates interior heat and relieves stagnation. Although SNS has not been used to treat NAFLD patient, it has been tested for its therapeutic effect on NAFLD in animal models. In NAFLD rat models, SNS treatment significantly reduces hepatic total cholesterol, triglyceride and free fatty acid levels (126). The treatment also has limited toxicity to the mice as it does not elevate the serum levels of aspartate aminotransferase and alanine aminotransferase (126). Similar results are observed in the NAFLD mouse models, SNS significantly reduces body weight, liver index, liver triglyceride level, visceral fat index, serum ALT and liver TNF- α levels (127). In the clinical cases, high systemic level of TNF- α is associated with the severity of NAFLD in morbidly obese patients (128). Indeed, TNF- α plays a pivotal role in the development and progression of NAFLD. In mouse model, TNF- α increases the expression of monocyte chemoattractant protein-1 (Mcp1), TGF- β 1, and tissue inhibitor of metalloproteinase-1 (Timp1) in hepatocytes (129). MCP1, TGF β 1 and TIMP1 are all involved in the development of hepatic fibrogenesis. Knockout of TNF in mice improves glucose tolerance and significantly reduces the prevalence of hepatic steatosis (20% vs. 100%, $p < 0.0001$) and fibrosis (15% vs. 65%, $p = 0.0057$) (129). Furthermore, SNS may also control the development of NAFLD *via* the gut–liver axis. A study with NAFLD mouse model has been done to examine the changes in the gut microbiota after SNS treatment. The data show that gut bacterial composition and functions in the NAFLD mice are changed after SNS treatment. PICRUST (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) reveals that the abundance of Oscillospira (genus level), Ruminococcaceae (family level), Clostridiales (order level), and Clostridia (class level) are higher in the SNS treatment group

compared to control group (127). LEfSe (Linear discriminant analysis Effect Size) method is then used to determine the features (organisms, clades, operational taxonomic units, genes, or functions) that most likely to explain differences between classes by coupling standard tests for statistical significance with additional tests encoding biological consistency and effect relevance. The LEfSe analysis suggests that carbohydrate metabolism is changed after SNS treatment (127), which may due to the changes in the abundance of Clostridia (130). High carbohydrate consumption is known to contribute to NAFLD (131). Fructose and sugar are the major mediators of NAFLD (132). Manipulating the carbohydrate metabolism or lipogenesis may help to alleviate the NAFLD conditions. Indeed, SNS treatment significantly reduces the liver triglyceride contents in the NAFLD mouse models (127), which may due to reduced lipogenesis. However, further investigation is needed to validate the involvement of Clostridia in the SNS-mediated effects on NAFLD.

Besides, Shen Ling Bai Zhu powder (SLBZP) is also found to ameliorate NAFLD condition by manipulating the gut–liver axis. In NAFLD rat models, SLBZP reduces the serum level of total cholesterol and alleviates hepatic steatosis (133). Microbiome analysis reveals that SLBZP changes the intestinal microbiota. SLBZP-treated rats have increased abundance of short-chain fatty acid-producing bacteria such as Bifidobacterium and Anaerostipes when compared to control rats (133). During the development of NAFLD, SCFAs can bind to the G-protein-coupled receptor GPR43, which helps to maintain normal intestinal permeability and reduce mucosal inflammation. Interestingly, a clinical study suggests that Bifidobacterium spp abundance is inversely associated with NAFLD severity, and Bifidobacteria may have a protective role against the development of NAFLD and obesity (134).

Hu Gan Qing Zhi tablet (HGQZT) has been used to alleviate NAFLD condition in clinical practice. Experimental studies also confirm that the HGQZT has lipid-lowering and anti-inflammatory effects in NAFLD subjects (135, 136). Recently, an experimental study suggests that HGQZT ameliorates the NAFLD condition by manipulating the gut microbiota. 16s rRNA gene sequencing analysis shows that abundance of 39 genera is significantly different after HGQZT treatment in the NAFLD rat models. HGQZT reduces the abundance of the Firmicutes/Bacteroidetes ratio and increases those that have been reported to relieve the NAFLD condition. For example, Ruminococcaceae, Bacteroidales_S24-7_group, Bifidobacteria, Alistipes, and Anaeroplasmata. Besides HGQZT also reduces the abundance of those that promote NAFLD progression, such as Enterobacteriaceae, Streptococcus, Holdemanella, Allobaculum, and Blautia. By changing the intestinal microbial abundance, the function of mucosal barrier could be improved, hence, the inflammatory responses in the NAFLD subjects can be alleviated (137).

Another Chinese herbal formula, Hong-qi Jiang-zhi Fang (HJF) is found to improve the hepatic steatosis and alleviate HFD-induced endotoxemia, inhibit NLRP3 inflammasome activation and reduce cytokine release such as IL-1 β and IL-18 (138). Interestingly it also improves intestinal barrier integrity

and gut microbiota structure in these rats. After HJF treatment, 15 families, including Helicobacteraceae, Verrucomicrobiaceae and Enterobacteriaceae are significantly decreased in the NAFLD rat models (138). These bacterial families have been shown to promote the development of NAFLD by increasing liver fat deposition and inflammation.

Herbal Formula Modulates the Adipose Tissue–Liver Axis in NAFLD Treatment

Given the adipose tissue–liver axis contributes to the development of NAFLD, targeting this axis may help to improve the NAFLD condition and slow down its progression. However, Chinese herbal formula that target at the adipose tissue–liver axis in NAFLD are less studied.

Qing Gan Zi Shen Tang (QGZST) is a famous Chinese herbal formula. It is clinically used for the treatment of hypertension, obesity, hyperlipidemia and insulin resistance. Experimental study shows that QGZST significantly decreases adipocyte size of the high-fat diet-fed rat, it also remarkably reduces the serum levels of cholesterol and triglyceride (139). Furthermore, QGZST also dramatically attenuates the production of proinflammatory cytokines and adiponectin from the adipocytes by stimulating the activities of Sirtuin-1 and Forkhead box protein-O1, while reducing the expression of PPAR- γ , C/EBP- α , fatty acid binding protein-4, acetylated nuclear factor- κ B-p65 and protein-tyrosine phosphatase-1B (139). These results strongly suggest that QGZST can be used to treat adipocyte hyperplasia and the inflammation. Study with NAFLD animal model will further suggest the potential of QGZST in ameliorating the NAFLD condition by reducing adipocyte hyperplasia and resolving the associated inflammation. Sobokchuko-Tang (ST) is a well-known formula that is used to treat primary dysmenorrhea caused by blood stasis syndrome in China and Korea. It comprises Foeniculi Fructus, Zingiberis Rhizoma, Carthami Flos, Myrrha, Angelicae Sinensis Radix, Cnidii Fructus, Cinnammomi Cortex, Paeoniae Rubra Radix, Typhae Pollen and Trogopterori Faeces. An experimental study shows that ST inhibits 3T3-L1 pre-adipocyte differentiation by reducing the expressions of peroxisome proliferator-activated receptor- γ (PPAR- γ) and CCAAT-enhancer-binding proteins- α (C/EBP- α), it also reduces triglyceride and leptin levels in the adipocytes, suggesting ST possesses anti-adipogenesis effect. Besides, ST also significantly inhibits TNF- α and IL-6 production in the LPS-treated macrophages compared with LPS stimulation alone, suggesting ST has anti-inflammatory effect in the macrophages (140). Inhibiting adipogenesis and resolving inflammation in the infiltrate macrophage can help to slow down the progression of NAFLD. A modified Sijunzi decoction CHF03 comprises Scutellariae Barbatae Herba, Rehmanniae Radix, and Smilacis Glabrae Rhizoma shows protective effect against NAFLD by reducing oxidative stress that arisen from lipotoxicity. The accumulation of lipids induces oxidative stress and apoptosis (141), which are crucial to the pathogenesis of lipotoxic injury in the liver and accelerates NAFLD progression. In the palmitic acid-treated liver cell models that mimic the condition under lipotoxicity, CHF03 significantly alleviates oxidative stress as indicated by the reduced expressions of

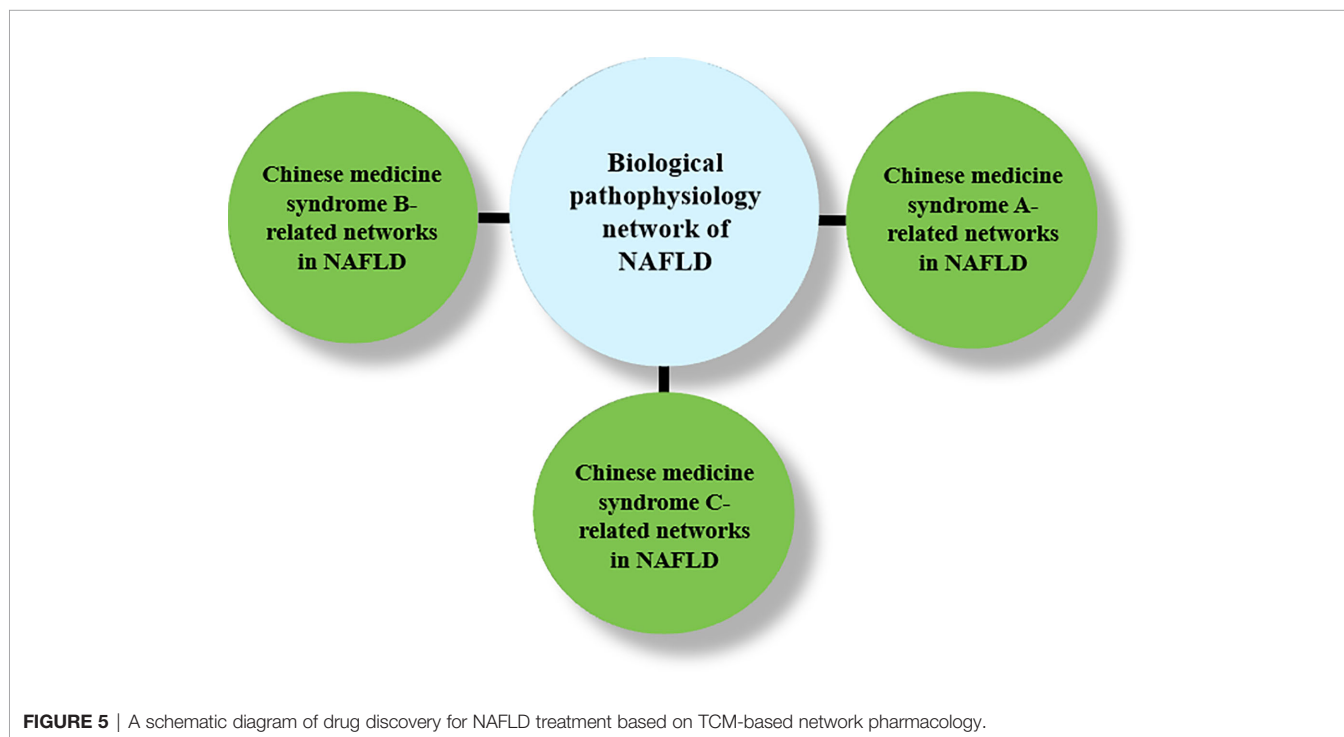
GSH, GSH-px, MDA, SOD, and CAT, it also reduces the abundance of NF- κ B proteins in the cell models, indicating CHF03 reduces inflammation and oxidative stress in the livers. Besides, hepatic expressions of SERBP-1 and fatty acid synthase are also reduced after the treatment. These data suggest that CHF03 might have a beneficial role in the prevention of hepatic steatosis by attenuating lipotoxicity-associated oxidative stress and reducing lipogenesis (142). Similarly, another herbal formula, Liuwei Dihuang (LWDH) also reduces oxidative stress in the obese rat model. The study demonstrates that LWDH lowers serum levels of C-reactive protein, GSH and TNF- α , suggesting LWDH can reduce the oxidative stress in the rats (143). However, studies with NAFLD rat model can better suggest whether LWDH can be used to treat NAFLD by reducing the lipotoxicity-associated oxidative stress. Other formula may regulate the release and production of adipokines and hence improve the NAFLD condition. Visfatin is an adipokine. Many clinical studies show that serum visfatin concentration in the NAFLD subjects is significantly higher than in controls (144, 145), suggesting a pathogenic role of visfatin in NAFLD development. A Chinese herbal formula Zhi Yi Xiao (ZYX) is found to reduce the expression of visfatin in the liver of NAFLD rat models (106). Further studies are needed to further suggest the therapeutic role of ZYX in treating NAFLD.

PERSPECTIVE

Chinese medicine employs a holistic approach as its therapeutic strategy, and the formulation usually comprises herbs that are

classified into four catalogues, they are the “emperor drug” that acts on the main cause in pathophysiology, “minister drug” that acts on the main or the second causes in the pathophysiology, “assistant drug” that strengthens the effects of emperor drug and reduces any toxic effect of the emperor and minister drugs, “messenger drug” that boosts the action of the herbs in the formulation. Due to the complexity, Chinese medicine theory is usually difficult to be comprehended. Therefore, analysis of the underlying mechanisms of action of the herbal formulae becomes difficult. Furthermore, the synergies between the herbs and the herbal compounds in the decoction may further enhance the therapeutic effects, which will not be known without experimental studies.

Modern technologies have been developed to elucidate the molecular mechanism and to identify the effective components of the Chinese herbal formulae. Computational systems biology such as connectivity map or multilayer map that consists of phenotype network, biological network and herbal network have been applied to study the therapeutic mechanisms of the herbal formulas (146–148). Metabolomics-based phenomics and the network construction can highlight the metabolic pathways that lead to the therapeutic effects of the herbal treatment. Ligand-based pharmacophore and molecular docking models can further suggest the therapeutic targets of the herbal formula. In addition, with the development of bioinformatics, the combination of traditional Chinese medicine and intestinal microbiology is of great significance for maintaining the health status of host–microorganism. Beside the gut microbiota, by comparing the differences of the microflora of the tongue coating between gastritis and healthy people, the tongue coating



microbiome is also considered as potential biomarkers for diseases like gastritis including precancerous cascade (149).

The state-of-the-art technologies can also bring about the discovery of novel herbal-based therapeutics for the treatment. For example, computer-aid drug design (CADD) can be used to design novel herbal formula or to modify the existing formula (150). The Chinese medicine-based network pharmacology that comprises the Chinese medicine-syndrome network and the biological network of the disease is a new strategy of multiple-compound drug discoveries (147) (**Figure 5**). The combination of the Chinese medicine syndrome and the western pathophysiological understanding of NAFLD also demonstrates the integration of the ancient wisdom and the modern technology for the discovery of new drugs.

CONCLUSION

The NAFLD pandemic implies an increase number of patients diagnosed with NAFL, NASH, liver fibrosis and HCC in the near future. Although the interpretation and diagnosis of NAFLD in Chinese medicine are different from those in western medicine, many clinical and experimental studies suggest that Chinese herbal formula are effective in reducing hepatic steatosis, and revolving inflammation *via* many mechanistic pathways. Some Chinese herbal formulae also target at the gut–liver axis in NAFLD, while the adipose tissue–liver axis emerges to be a

therapeutic approach for the treatment of NAFLD. More clinical and in-depth mechanistic investigations may help to validate the roles of these Chinese herbal formulae for the treatment of NAFLD. Application of the modern technology can also help to discover novel herbal-based therapeutics for the treatment.

AUTHOR CONTRIBUTIONS

H-YK and TS wrote and edited the manuscript. SZ, Y-TW, and K-YT participated in writing process. TS revised and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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