Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 7
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Research Progress and Mechanisms of Traditional Chinese Medicine Lotus Leaf in Treating Non-Alcoholic Fatty Liver Disease

Min Lai [1]†*, Yalu Qin[2]†, Qiongyu Jin[1], Bin Ge[4], Yi Zhou[4], Jia Hu[1], Wenjing Chen[1], Shouquan Zhang [3]

[1]Department of Gastroenterology, Third Affiliated Hospital of Chengdu Medical College / People's Hospital of Pidu District, Chengdu 611730, Sichuan, China;
[2]Department of Cardiology, Third Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (West District) / Traditional Chinese Medicine Hospital of Pidu District, Chengdu 611730, Sichuan , China;
[3]Department of Traditional Chinese Medicine, Third Affiliated Hospital of Chengdu Medical College / People's Hospital of Pidu District, Chengdu, Sichuan, 611730, China;
[4]Department of Laboratory, Third Affiliated Hospital of Chengdu Medical College / People's Hospital of Pidu District, Chengdu, Sichuan, 611730, China
†*These authors contributed equally to this work and share the first authorship.*

**Corresponding author: Min Lai, laimin1128Lm@126.com*

Abstract: Non-alcoholic fatty liver disease (NAFLD) is a globally prevalent chronic liver disease with a complex pathogenesis, driven by an intricate interplay of metabolic disorders, oxidative stress, inflammatory, and gut microbiota imbalance. With changes in lifestyle and dietary habits, in recent years, the incidence of NAFLD has significantly risen, becoming an important public health issue. The traditional Chinese medicine (TCM) diagnostic and therapeutic system has shown unique advantages in the prevention and treatment of NAFLD, especially the use of lotus leaf, which has attracted attention due to its multi-target and multi-pathway regulatory effects. This review examines the pathogenesis of NAFLD, explores the application of TCM in NAFLD, and focuses on the pharmacological effects of lotus leaf and its potential therapeutic value, providing a theoretical basis for the comprehensive prevention and treatment of NAFLD.

Keywords: Lotus leaf; Non-alcoholic fatty liver disease; Metabolic diseases; Gut microbiota

Online publication: August 4, 2025

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasingly becoming a major health burden in China, making it the most common liver disease in the country[1–3]. This poses a significant economic burden on society. Lotus leaf, as a traditional Chinese medicine, offers new directions for the treatment of NAFLD due to its lipid-lowering and anti-

inflammatory properties [4]. Although recent studies have identified the therapeutic effects of lotus leaf in treating NAFLD, the specific mechanisms underlying these effects remain unclear. This article analyzes the current research on the use of lotus leaf in the treatment of NAFLD and explores the mechanisms involved.

NAFLD is a chronic liver disease closely related to metabolic disorders, with its global prevalence increasing annually, posing a significant public health challenge [5–8]. In China, the burden of NAFLD is growing, with a prevalence rate of 15% to 30%, making it the leading liver disease in the country [1]. NAFLD contributes to a considerable economic burden on society. The disease spectrum of NAFLD ranges from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), and may even progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma [9–11]. Although its pathogenesis has not been fully elucidated, insulin resistance, lipid metabolism disorders, oxidative stress, and chronic inflammation are considered core pathophysiological mechanisms. Insulin resistance leads to the excessive accumulation of free fatty acids in the liver, while mitochondrial dysfunction and the accumulation of reactive oxygen species (ROS) further aggravate hepatocyte injury [12–17]. The release of pro-inflammatory cytokines such as TNF-α and IL-6 drives inflammation and fibrosis [18–22].

Traditional Chinese medicine (TCM) categorizes NAFLD as conditions such as “costal pain,” “accumulation,” or “phlegm-dampness,” and considers its pathogenesis to be related to liver Qi stagnation, spleen dysfunction, and the interrelationship of phlegm and blood stasis [23, 24]. TCM diagnostic and therapeutic principles emphasize an overall approach to treatment, regulating metabolic balance by soothing the liver, strengthening the spleen, transforming phlegm, and removing blood stasis. In recent years, lotus leaf (*Nelumbo nucifera*) has attracted attention for its effects in clearing heat, promoting diuresis, activating blood circulation, and lowering lipids [4, 25]. Modern pharmacological studies have shown that active compounds in lotus leaf, such as alkaloids, flavonoids, and polysaccharides, can intervene in NAFLD through multiple pathways, including regulating lipid synthesis and breakdown, improving insulin sensitivity, and inhibiting oxidative stress and inflammation. For example, lotus leaf alkaloids can downregulate the expression of fatty acid synthase (FAS), while flavonoid components can activate the AMPK signaling pathway to promote fatty acid oxidation [26].

This paper systematically reviews the molecular mechanisms of NAFLD and the understanding of its pathogenesis in TCM, with a focus on the potential roles of lotus leaf and its active components in the intervention of NAFLD. The goal is to provide theoretical support and new strategies for integrating Chinese and Western medicine in the prevention and treatment of NAFLD. Future research should further clarify the active constituents and molecular targets of lotus leaf and validate its efficacy and safety through high-quality clinical trials.

2. Review

2.1. Epidemiology and clinical features of non-alcoholic fatty liver disease (NAFLD)

2.1.1. Global trends and risk factors

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease globally, with its prevalence closely mirroring the rising trend of obesity, particularly in developed countries. Epidemiological studies show that the global prevalence of NAFLD is approximately 25%, with non-alcoholic steatohepatitis (NASH) accounting for 15–20% [2, 3]. Major risk factors include obesity, insulin resistance, type 2 diabetes, and metabolic syndrome, all of which contribute to disease progression by promoting hepatic lipid accumulation and inflammation. It is noteworthy that the pathogenesis of NAFLD is multifactorial, involving gut microbiota dysbiosis, abnormal bile acid metabolism, immune cell polarization, and epigenetic regulation disorders [27, 28].

Recent studies have also found that sex differences play an important role in the progression of NAFLD, with men being more prone to developing NASH and liver fibrosis, potentially due to the regulation of lipid metabolism by sex hormones [29–32].

2.1.2. Disease spectrum and clinical classification of NAFLD

The disease spectrum of NAFLD ranges from simple hepatic steatosis (NAFL) to non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC) [33, 34]. NAFL is characterized by lipid accumulation in hepatocytes without significant inflammation or liver injury, while NASH is associated with hepatocellular ballooning, lobular inflammation, and fibrosis, representing a key turning point in disease progression. Histologically, NAFLD can be divided into NAFL and NASH subtypes, with the latter having a higher risk of cirrhosis and HCC [35]. Recent findings have confirmed that extracellular vesicle-mediated intercellular communication and microRNA (miRNA) regulation play roles in the pathogenesis of NASH, providing new insights into the molecular classification of NAFLD [36–38]. Furthermore, the interaction between adipose tissue and the liver significantly affects the clinical phenotype of NAFLD by modulating macrophage function.

2.1.3. Association of NAFLD with other metabolic diseases

NAFLD is bidirectional associated with various metabolic diseases, especially type 2 diabetes and cardiovascular diseases [39–44]. Insulin resistance serves as the central mechanism linking these diseases, accelerating NAFLD progression by promoting hepatic lipid synthesis and oxidative stress. Studies have found that dysfunction of farnesoid X receptor (FXR) in NAFLD patients exacerbates bile acid metabolism disorders and lipid metabolism imbalance, creating a vicious cycle [45-47]. NAFLD is closely related to obesity-related low-grade chronic inflammation, with metabolic reprogramming and polarization of macrophages being key driving factors. Epigenetic studies have also revealed that abnormal DNA methylation and RNA modification play a role in NAFLD pathogenesis and may explain its high comorbidity with metabolic syndrome [48, 49]. These findings suggest that network regulation strategies targeting multi-organ interactions may be important directions for future NAFLD treatment.

2.2. Progress in the pathogenesis of NAFLD

2.2.1. Core role of Insulin Resistance (IR) and lipid metabolism disorders

IR is considered one of the core mechanisms in the development of NAFLD [12]. In an insulin-resistant state, liver sensitivity to insulin is reduced, leading to increased hepatic gluconeogenesis and impaired inhibition of lipolysis, which promotes the excessive delivery of free fatty acids (FFAs) from adipose tissue to the liver [50]. Meanwhile, β-oxidation of fatty acids in the liver decreases, and triglyceride (TG) synthesis increases, resulting in lipid accumulation within hepatocytes [51]. Furthermore, insulin resistance activates transcription factors such as sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP), which further promote the expression of genes involved in lipogenesis, exacerbating lipid deposition in the liver [52]. These metabolic disorders not only directly promote the formation of fatty liver but also lay the foundation for subsequent inflammation and fibrosis.

2.2.2. Role of oxidative stress and mitochondrial dysfunction

Oxidative stress plays a crucial role in the progression of NAFLD. Excessive lipid accumulation within

hepatocytes leads to mitochondrial dysfunction, including reduced efficiency of the electron transport chain and increased production of reactive oxygen species (ROS). The excessive accumulation of ROS induces lipid peroxidation, damaging cell membranes, proteins, and DNA, further aggravating hepatocyte injury. Moreover, oxidative stress activates pro-inflammatory signaling pathways such as nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK), promoting the release of inflammatory factors. Mitochondrial dysfunction also leads to energy metabolism abnormalities, further exacerbating the metabolic stress on hepatocytes, forming a vicious cycle that drives the progression of NAFLD to non-alcoholic steatohepatitis (NASH) and liver fibrosis.

2.2.3. Molecular mechanisms of inflammation and fibrosis

Inflammatory responses are key drivers in the progression of NAFLD to NASH and liver fibrosis [53, 54]. Under the stimulation of hepatocyte injury and oxidative stress, hepatic Kupffer cells and infiltrating immune cells (such as macrophages and neutrophils) are activated, releasing a large number of pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β) [55]. These cytokines amplify the inflammatory response by activating signaling pathways like NF-κB and JNK. At the same time, hepatic stellate cells (HSCs) are activated by inflammatory cytokines and transform into myofibroblasts, secreting large amounts of extracellular matrix (ECM) proteins (such as collagen), leading to liver fibrosis. Additionally, the activation of the TGF-β/Smad signaling pathway plays a critical role in fibrosis [55].

2.2.4. Gut microbiota dysbiosis and the gut-liver axis

In recent years, the relationship between gut microbiota dysbiosis and NAFLD has gained widespread attention [57, 58]. The gut microbiota communicates bidirectionally with the liver through the gut-liver axis. Dysbiosis disrupts the intestinal barrier, increasing intestinal permeability, allowing endotoxins (such as lipopolysaccharides, LPS) and bacterial metabolites (such as short-chain fatty acids and bile acids) to enter the liver via the portal vein. LPS promotes hepatic inflammation and fibrosis by activating Toll-like receptor 4 (TLR4) signaling [59]. Furthermore, short-chain fatty acids (such as acetate, propionate, and butyrate) and secondary bile acids produced by gut microbiota metabolism can influence the progression of NAFLD by regulating host metabolism and immune responses. For example, butyrate has anti-inflammatory effects and protects the intestinal barrier, while certain bile acids can regulate lipid metabolism and inflammation by activating farnesoid X receptor (FXR) and G-protein coupled bile acid receptor (TGR5). Therefore, gut microbiota dysbiosis is considered an important environmental factor in the development and progression of NAFLD.

2.3. Traditional Chinese medicine (TCM) understanding and treatment system for NAFLD

2.3.1. TCM pathogenesis theory: Liver Qi stagnation, spleen deficiency, and phlegm-blood stasis

Clinical practices over the past 30 years have shown that the TCM diagnostic and treatment system for NAFLD has developed a core pathogenesis theory framework of "spleen deficiency as the root and phlegm-blood stasis as the manifestation." Its clinical value is reflected in the following dimensions: First, it has significant advantages in improving clinical symptoms, particularly in regulating gastrointestinal symptoms and physical condition. Second, laboratory indicators show improvements by regulating lipid metabolism and reducing serum transaminase levels, achieving liver protection effects. Furthermore, long-term standardized treatment may promote pathological reversal of liver steatosis. The core competitiveness of TCM treatment lies in its comprehensive adjustment model guided by an overall view, achieving multi-target interventions through multi-dimensional mechanisms, with significant safety advantages of the drugs. TCM emphasizes that "phlegm-blood stasis" is both a pathological

product and a pathogenic factor, which resonates with the modern medical mechanisms of lipotoxicity, oxidative stress, and inflammatory responses that collectively drive disease progression [23, 60].

2.3.2. TCM syndrome differentiation and personalized treatment strategies

TCM syndrome differentiation for NAFLD is primarily based on the characteristic of "deficiency as the root and excess as the manifestation." Common syndromes include liver Qi stagnation and spleen deficiency, phlegm-dampness obstructing the middle, damp-heat accumulation, and Qi stagnation and blood stasis. For liver Qi stagnation and spleen deficiency syndrome, treatment involves soothing the liver and strengthening the spleen, with herbal prescriptions such as Chaihu Shugan Powder combined with Si Jun Zi Tang. For phlegm-dampness obstructing the middle, methods to resolve phlegm and eliminate dampness are used, with formulas like Er Chen Tang and Pingwei San. Modern studies indicate that this individualized treatment strategy may work through multi-target mechanisms, such as regulating the balance of gut microbiota (e.g., increasing short-chain fatty acid-producing bacteria) and improving insulin sensitivity. Notably, for patients with Qi stagnation and blood stasis syndrome who have progressed to the NASH stage, blood-activating and stasis-removing herbs such as Salvia and Panax notoginseng have been confirmed to inhibit hepatic stellate cell activation and reduce liver inflammation and fibrosis.

2.3.3. Application of external TCM therapies in NAFLD (e.g., Acupuncture, Tuina, and Thread-Embedding Therapy)

Acupuncture for NAFLD primarily targeted points like the liver Shu, spleen Shu, and Zusanli, adjusting the autonomic nervous system and hypothalamic-pituitary-adrenal axis to improve hepatic lipid metabolism. Clinical studies have shown that electroacupuncture can significantly reduce serum ALT and AST levels, and its mechanism may involve upregulating PPAR-α expression and promoting fatty acid β-oxidation [61]. Tuina therapy, mainly abdominal massage, improves portal venous blood flow and promotes hepatic microcirculation through mechanical stimulation. Recent studies have found that specific Tuina techniques can regulate the secretion of adipokines (such as reducing leptin resistance), aligning with the "liver-gut axis" and "liver-fat tissue axis" theories proposed by modern medicine [62]. It is important to note that these external therapies, when used in conjunction with internal TCM medicine, can produce a synergistic effect, providing new ideas for the comprehensive management of NAFLD. As representative external TCM therapies, acupuncture and thread-embedding therapy have shown unique clinical value in metabolic disease interventions. Current research shows that these two therapies have accumulated high-level evidence in the treatment of NAFLD, and their mechanisms involve regulating lipid metabolism, improving insulin resistance, and other biological effects. In acupuncture treatment plans, the core point group usually includes Fenglong, Zusanli, and Yanglingquan, where the pairing of Fenglong for resolving phlegm and dampness and Zusanli for strengthening the spleen and stomach embodies the core concept of "treatment from the spleen."

Based on the specific syndrome characteristics of the patient, a dynamic acupuncture point strategy is often implemented: for Qi stagnation and blood stasis syndrome, points like Xuehai and Diji are selected with reducing techniques to enhance liver Qi smoothing, blood activation, and stasis removal; for phlegm-dampness accumulation syndrome, points like Zhongwan and Yinlingquan are used. This "fixed main point + dynamic adjustment of auxiliary points" treatment model fully demonstrates the advantages of individualized TCM therapy. Thread-embedding therapy, as an extension of acupuncture, achieves sustained stimulation of acupuncture points by implanting biodegradable materials. Clinical randomized controlled trials have shown that this therapy alone

can significantly reduce serum ALT and AST levels in NAFLD patients, and when combined with classic formulas like Yinchenhao Decoction, it can produce a synergistic effect [63]. Commonly used thread-embedding points are often focused on liver and spleen-related acupoints, such as liver Shu-spleen Shu, which regulate liver and gallbladder function, and Zhongwan-Tianshu combinations that improve the Qi mechanism of the middle Jiao, while combining Zusanli-Fenglong for systematic regulation of lipid metabolism pathways.

2.4. Pharmacological effects of lotus leaf and its application in NAFLD treatment

2.4.1. Main active ingredients of lotus leaf and their pharmacological properties

Lotus leaf is the dry leaf of the Nymphaeaceae family plant, which mainly grows in Central Asia, Western Asia, North America, and subtropical and temperate regions such as India, China, and Japan. Lotus leaf (*Nelumbo nucifera* Gaertn.) is a traditional Chinese medicine that contains various bioactive compounds, including flavonoids (such as quercetin and kaempferol), alkaloids (such as lotusine), polysaccharides, and polyphenolic substances [64, 65]. These compounds give lotus leaf broad pharmacological activities, such as antioxidant, anti-inflammatory, lipid-lowering, and metabolic regulation effects. Studies have shown that lotus leaf extracts significantly inhibit lipid accumulation in the liver and improve insulin resistance, thus showing potential application value in the treatment of non-alcoholic fatty liver disease (NAFLD) [66]. Additionally, the active ingredients in lotus leaf regulate the expression of lipid metabolism-related genes through various pathways, providing a molecular basis for NAFLD intervention.

2.4.2. Mechanisms of lotus leaf in regulating lipid metabolism

As research on the lipid-lowering and weight-reducing effects of lotus leaf has advanced, it has been found that the main active ingredients responsible for lipid regulation are alkaloids and flavonoids extracted from lotus leaf [67]. Researchers have established a hyperlipidemia rat model and used lotus leaf aqueous decoction to explore the effects on blood lipids, serum total cholesterol (TC), blood rheology, and triglyceride (TG) levels [68]. The results showed that lotus leaf aqueous decoction significantly reduced TC and TG levels in hyperlipidemic rats, and with the reduction of TC and TG, there was a significant decrease in low-density lipoprotein (LDL) components, thereby improving whole blood viscosity, hematocrit, and blood flow resistance, indicating a significant lipid-lowering effect. Other studies using C57 mice found that lotusine could significantly improve hyperlipidemia in mice, possibly related to increased lipase activity, reduced oxidative stress, and regulation of lipid synthesis and oxidative metabolism [69]. Lotusine has been shown to protect against fatty liver, liver injury, visceral fat accumulation, and dyslipidemia in male golden hamsters induced by high-fat diets [70]. Results indicated that high-fat diets significantly upregulated fatty acid synthesis gene expression, increased free fatty acid infiltration, downregulated fat degradation gene expression and LDL-C, while lotusine treatment significantly suppressed the upregulation of these lipid metabolism-related genes. These findings suggest that lotusine can control the expression of lipid metabolism-related genes and reduce blood lipids.

2.4.3. Experimental evidence of lotus leaf's anti-inflammatory and antioxidant effects

Studies have shown that lotus leaf extract has the ability to scavenge various free radicals, demonstrating significant antioxidant activity. The antioxidant capacity of lotus leaf mainly derives from flavonoid compounds, and polyphenols also exhibit strong antioxidant activity [71]. Chemical structure studies of various antioxidants in lotus leaf suggest that phenolic hydroxyl groups may be the key functional groups affecting antioxidant activity [72]. Studies have found that the flavonoid compounds in lotus leaf are one of the key components responsible for its

significant antioxidant effects. Alkaloids regulate oxidative stress markers, effectively reducing malondialdehyde (MDA) levels and significantly enhancing superoxide dismutase (SOD) activity. In terms of anti-inflammatory effects, alkaloids exert their effects through dual regulatory mechanisms: on one hand, they inhibit the gene expression of inflammatory mediators such as IL-6, IL-1β, and TNF-α in adipose tissue; on the other hand, they reduce the concentration of corresponding inflammatory factors in the peripheral blood of obese model mice. Alkaloids activate the Nrf2/HO-1 signaling axis, enhancing antioxidant enzyme activity and alleviating oxidative stress damage.

2.4.4. Regulation of gut microbiota by lotus leaf

Recent studies have shown that lotus leaf can improve lipid metabolism by regulating the gut microbiota. The effect of lotusine on treating obesity may be related to its improvement of gut microbiota, reducing intestinal permeability, and alleviating intestinal inflammation, thus also achieving weight loss effects [73]. One study found that lotus leaf polysaccharides (LLP) can regulate the gut microbiota to improve lipid metabolism disorders [74]. Experiments showed that LLP intervention significantly altered the gut microbiota composition of high-fat diet-induced metabolic abnormality mice, promoting the proliferation of beneficial bacteria, such as *Lactobacillaceae* and *Akkermansia*, inhibiting pro-inflammatory bacteria, such as *Desulfovibrio*, and increasing short-chain fatty acids (SCFAs), especially butyrate, in the gut [75].

2.4.5. Summary of lotus leaf's mechanisms in NAFLD intervention

Recent studies have shown that lotus leaf alkaloids intervene in the pathological progression of NAFLD through multiple pathways: (1) regulating lipid metabolism-related genes (such as PPARα, SREBP-1c), inhibiting hepatic lipid synthesis and promoting fatty acid β-oxidation; (2) inhibiting the NF-κB/NLRP3 pathway, reducing the release of pro-inflammatory factors such as IL-1β and TNF-α; (3) activating the Nrf2/HO-1 signaling axis, enhancing antioxidant enzyme activity, and alleviating oxidative stress damage (**Figure 1**).

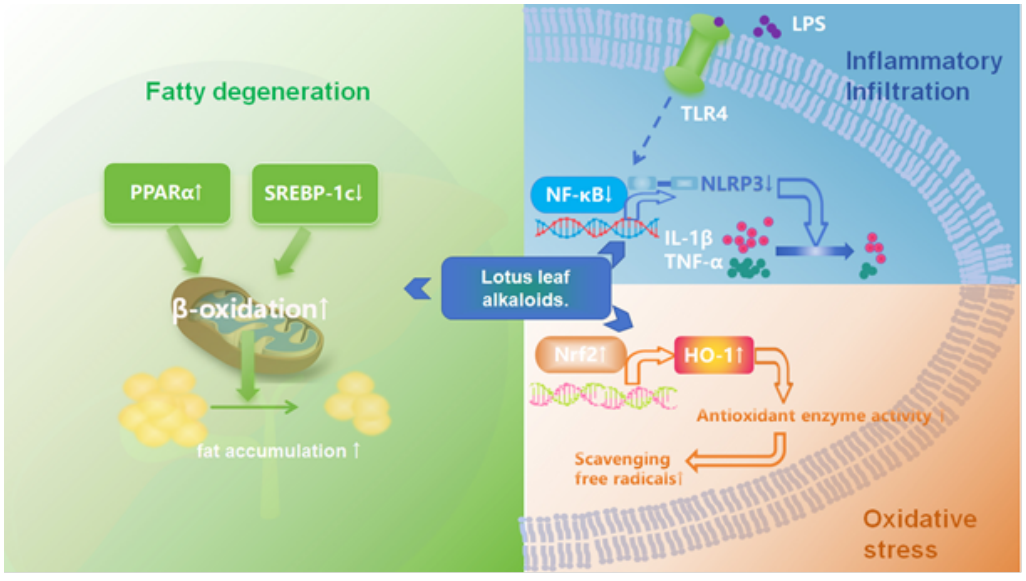

Figure 1. Potential mechanism of lotus leaf in treating NAFLD; Peroxisome Proliferator-Activated Receptor α (PPARα); Sterol Regulatory Element-Binding Protein-1c (SREBP-1c); Nuclear Factor kappa B (NF-κB); Interleukin-1β (IL-1β); Tumor Necrosis Factor-α (TNF-α); Nucleotide-binding Oligomerization Domain-like Receptor Protein 3 (NLRP3); Lipopolysaccharide (LPS); Toll-like Receptor 4 (TLR4)

In various cell and animal models, it has been found that lotus leaf alkaloids effectively reduce the secretion of inflammatory factors and alleviate pathological inflammatory damage in organs such as the liver, lungs, kidneys, and mammary glands. Lotus leaf alkaloids can also lower the levels of serum inflammatory factors such as Interleukin-6 (IL-6), Interleukin-1β (IL-1β), and Tumor Necrosis Factor-α (TNF-α). Through research on NAFLD patients and healthy individuals, it was discovered that serum levels of the fat factor Chemerin were significantly elevated in NAFLD patients, which was closely related to IL-1β and IL-8. Chemerin, IL-1β, and IL-8 may participate in the onset and progression of NAFLD. Further studies on serum from NAFLD patients showed that serum levels of Chemerin, TNF-α, and IL-6 were significantly higher than those in the control group, with positive correlations between Chemerin, TNF-α, and IL-6. This suggests that the abnormal expression of Chemerin, TNF-α, and IL-6 may be associated with the development of NAFLD.

Additionally, lotus leaf alkaloids can activate the NLRP3 inflammasome, as well as the Nrf2/HO-1 pathway, producing anti-inflammatory effects. The peroxisome proliferator-activated receptor (PPAR) signaling pathway is one of the important pathways involved. PPARs control glucose and lipid metabolism to maintain metabolic homeostasis. PPARγ is primarily expressed in adipocytes and can downregulate the levels of genes related to lipid synthesis. PPARα is associated with fat absorption, fat metabolism, fatty acid oxidation, and gluconeogenesis. Therefore, it is speculated that the potential mechanism by which lotus leaf treats non-alcoholic fatty liver disease (NAFLD) is that lotus leaf alkaloids effectively reduce the secretion of inflammatory factors, and the regulation of these inflammatory factors may be related to Chemerin. However, the specific regulation and its correlation with other signaling pathways have not been studied yet.

3. Conclusion

The onset of NAFLD is associated with multiple factors, including environmental factors, obesity, changes in the microbiome, and genetic susceptibility variations, involving various pathological mechanisms, with inflammation playing a key role throughout the entire disease process. Lotus leaf has significant lipid-lowering effects, capable of reducing total cholesterol and triglyceride levels and improving blood rheological parameters. Additionally, lotus leaf possesses antioxidant properties, capable of scavenging free radicals and resisting oxidative stress. Lotus leaf can alleviate fatty liver and non-alcoholic fatty liver disease and has a protective effect against hepatocyte damage. It is speculated that lotus leaf alkaloids may effectively reduce the secretion of inflammatory factors, and the regulation of these inflammatory factors may be associated with Chemerin.

However, there is currently insufficient clinical evidence regarding the role of lotus leaf granules in the treatment of non-alcoholic fatty liver disease, and further research is needed to verify its efficacy. Future studies should focus on multi-center clinical trials to validate the therapeutic effects of lotus leaf preparations and utilize technologies such as metabolomics and single-cell sequencing to further elucidate its molecular mechanisms.

Funding

Sichuan Provincial Administration of Traditional Chinese Medicine Scientific Research Project (Project No.: 2023MS250); Chengdu Medical Research Project (Project No.: 2021077)

Disclosure statement

The authors declare no conflict of interest.

References

[1] Lou T, Yang R, Fan J, 2024, The Global Burden of Fatty Liver Disease: The Major Impact of China. Hepatobiliary Surg Nutr, 13: 119–123.

[2] Zhou F, Zhou J, Wang W, et al., 2019, Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis. Hepatology, 70: 1119–1133.

[3] Zhou J, Zhou F, Wang W, et al., 2020, Epidemiological Features of NAFLD From 1999 to 2018 in China. Hepatology, 71: 1851–1864.

[4] Zheng H, Han L, Shi W, et al., 2022, Research Advances in Lotus Leaf as Chinese Dietary Herbal Medicine. The American Journal of Chinese Medicine, 50: 1423–1445.

[5] Pouwels S, Sakran N, Graham Y, et al., 2022, Non-Alcoholic Fatty Liver Disease (NAFLD): A Review of Pathophysiology, Clinical Management and Effects of Weight Loss. BMC Endocr Disord, 22: 63.

[6] Zarghamravanbakhsh P, Frenkel M, Poretsky L, 2021, Metabolic Causes and Consequences of Nonalcoholic Fatty Liver Disease (NAFLD). Metabolism Open, 12: 100149.

[7] Malnick S, Beergabel M, Knobler H, 2003, Non-Alcoholic Fatty Liver: A Common Manifestation of a Metabolic Disorder. QJM, 96: 699–709.

[8] Cariou B, Byrne C, Loomba R, Sanyal A, 2021, Nonalcoholic Fatty Liver Disease as a Metabolic Disease in Humans: A Literature Review. Diabetes Obes Metab, 23: 1069–1083.

[9] Gabbia D, Cannella L, De Martin S, 2021, The Role of Oxidative Stress in NAFLD–NASH–HCC Transition—Focus on NADPH Oxidases. Biomedicines, 9: 687.

[10] Ioannou G, 2021, Epidemiology and Risk-Stratification of NAFLD-Associated HCC. Journal of Hepatology, 75: 1476–1484.

[11] Longo M, Paolini E, Meroni M, et al., 2021, Remodeling of Mitochondrial Plasticity: The Key Switch From NAFLD/NASH to HCC. International Journal of Molecular Sciences, 22: 4173.

[12] Marušić M, Paić M, Knobloch M, et al., 2021, NAFLD, Insulin Resistance, and Diabetes Mellitus Type 2. Canadian Journal of Gastroenterology and Hepatology, 2021: 6613827.

[13] Palma R, Pronio A, Romeo M, et al., 2022, The Role of Insulin Resistance in Fueling NAFLD Pathogenesis: From Molecular Mechanisms to Clinical Implications. Journal of Clinical Medicine, 11: 3649.

[14] Sakurai Y, Kubota N, Yamauchi T, et al., 2021, Role of Insulin Resistance in MAFLD. International Journal of Molecular Sciences, 22: 4156.

[15] Ramanathan R, Ali A, Ibdah J, 2022, Mitochondrial Dysfunction Plays Central Role in Nonalcoholic Fatty Liver Disease. International Journal of Molecular Sciences, 23: 7280.

[16] Ajaz S, McPhail M, Gnudi L, et al., 2021, Mitochondrial Dysfunction as a Mechanistic Biomarker in Patients With Non-Alcoholic Fatty Liver Disease (NAFLD). Mitochondrion, 57: 119–130.

[17] Clare K, Dillon J, Brennan P, 2022, Reactive Oxygen Species and Oxidative Stress in the Pathogenesis of MAFLD. Journal of Clinical and Translational Hepatology, 10: 939.

[18] Vachliotis ID, Polyzos SA, 2023, The Role of Tumor Necrosis Factor-Alpha in the Pathogenesis and Treatment of Nonalcoholic Fatty Liver Disease. Current Obesity Reports, 12: 191–206.

[19] Potoupni V, Georgiadou M, Chatzigriva E, et al., 2021, Circulating Tumor Necrosis FactorAlpha Levels in NonAlcoholic Fatty Liver Disease: A Systematic Review and a MetaAnalysis. Journal of Gastroenterology and Hepatology, 36: 3002–3014.

[20] Xiong J, Chen X, Zhao Z, et al., 2022, A Potential Link Between Plasma Short-Chain Fatty Acids, TNFAlpha Level and Disease Progression in Non-Alcoholic Fatty Liver Disease: A Retrospective Study. Experimental and Therapeutic Medicine, 24: 598.

[21] Park J, Zhao Y, Zhang F, et al., 2023, IL-6/STAT3 Axis Dictates the PNPLA3-Mediated Susceptibility to Non-Alcoholic Fatty Liver Disease. Journal of Hepatology, 78: 45–56.

[22] Skuratovskaia D, Komar A, Vulf M, et al., 2021, IL-6 Reduces Mitochondrial Replication, and IL-6 Receptors Reduce Chronic Inflammation in NAFLD and Type 2 Diabetes. International Journal of Molecular Sciences, 22: 1774.

[23] Liang Z, Chen X, Shi J, et al., 2021, Efficacy and Safety of Traditional Chinese Medicines for Non-Alcoholic Fatty Liver Disease: A Systematic Literature Review of Randomized Controlled Trials. Chinese Medicine, 16: 1–38.

[24] Ding X, He X, Tang B, et al., 2024, Integrated Traditional Chinese and Western Medicine in the Prevention and Treatment of Non-Alcoholic Fatty Liver Disease: Future Directions and Strategies. Chinese Medicine, 19: 21.

[25] An Y, Hao J, Li J, He W, Wang L, Zhang Y, 2021, The Inhibitory Effect of Lotus Leaf Extract on Hyperuricemia and Its Potential Mechanism. Acupuncture and Herbal Medicine, 1: 122–129.

[26] Xu H, Wang L, Yan K, et al., 2021, Nuciferine Inhibited the Differentiation and Lipid Accumulation of 3T3-L1 Preadipocytes by Regulating the Expression of Lipogenic Genes and Adipokines. Front Pharmacol, 12: 632236.

[27] Arab JP, Arrese M, Trauner M, 2018, Recent Insights into the Pathogenesis of Nonalcoholic Fatty Liver Disease. Annual Review of Pathology: Mechanisms of Disease, 13: 321–350.

[28] Sanyal AJ, 2005, Mechanisms of Disease: Pathogenesis of Nonalcoholic Fatty Liver Disease. Nature Clinical Practice Gastroenterology & Hepatology, 2: 46–53.

[29] Lonardo A, Nascimbeni F, Ballestri S, et al., 2019, Sex Differences in Nonalcoholic Fatty Liver Disease: State of the Art and Identification of Research Gaps. Hepatology, 70: 1457–1469.

[30] Morán-Costoya A, Proenza AM, Gianotti M, Lladó I, Valle A, 2021, Sex Differences in Nonalcoholic Fatty Liver Disease: Estrogen Influence on the Liver–Adipose Tissue Crosstalk. Antioxidants & Redox Signaling, 35: 753–774.

[31] Shaheen M, Schrode KM, Pan D, et al., 2021, Sex-Specific Differences in the Association Between Race/Ethnicity and NAFLD Among US Population. Frontiers in Medicine, 8: 795421.

[32] Yang M, Liu Q, Huang T, et al., 2020, Dysfunction of Estrogen-Related Receptor Alpha-Dependent Hepatic VLDL Secretion Contributes to Sex Disparity in NAFLD/NASH Development. Theranostics, 10: 10874.

[33] Koo SH, 2013, Nonalcoholic Fatty Liver Disease: Molecular Mechanisms for the Hepatic Steatosis. Clinical and Molecular Hepatology, 19: 210.

[34] Sanyal AJ, Castera L, Wong VW-S, 2023, Noninvasive Assessment of Liver Fibrosis in NAFLD. Clinical Gastroenterology and Hepatology, 21: 2026–2039.

[35] Han SK, Baik SK, Kim MY, 2022, Non-Alcoholic Fatty Liver Disease: Definition and Subtypes. Clinical and Molecular Hepatology, 29: S5.

[36] Gjorgjieva M, Sobolewski C, Dolicka D, et al., 2019, miRNAs and NAFLD: From Pathophysiology to Therapy. Gut, 68: 2065–2079.

[37] Szabo G, Csak T, 2016, Role of MicroRNAs in NAFLD/NASH. Digestive Diseases and Sciences, 61: 1314–1324.

[38] Dongiovanni P, Meroni M, Longo M, et al., 2018, miRNA Signature in NAFLD: A Turning Point for a Non-Invasive Diagnosis. International Journal of Molecular Sciences, 19: 3966.

[39] Targher G, Corey KE, Byrne CD, et al., 2021, The Complex Link Between NAFLD and Type 2 Diabetes Mellitus—Mechanisms and Treatments. Nature Reviews Gastroenterology & Hepatology, 18: 599–612.

[40] Ferguson D, Finck BN, 2021, Emerging Therapeutic Approaches for the Treatment of NAFLD and Type 2 Diabetes Mellitus. Nature Reviews Endocrinology, 17: 484–495.

[41] Lattuada G, Ragogna F, Perseghin G, 2011, Why Does NAFLD Predict Type 2 Diabetes? Current Diabetes Reports, 11: 167–172.

[42] Younossi ZM, Golabi P, de Avila L, et al., 2019, The Global Epidemiology of NAFLD and NASH in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Journal of Hepatology, 71: 793–801.

[43] Caussy C, Aubin A, Loomba R, 2021, The Relationship Between Type 2 Diabetes, NAFLD, and Cardiovascular Risk. Current Diabetes Reports, 21: 1–13.

[44] Kasper P, Martin A, Lang S, et al., 2021, NAFLD and Cardiovascular Diseases: A Clinical Review. Clinical Research in Cardiology, 110: 921–937.

[45] Xi Y, Li H, 2020, Role of Farnesoid X Receptor in Hepatic Steatosis in Nonalcoholic Fatty Liver Disease. Biomedicine & Pharmacotherapy, 121: 109609.

[46] Zhou S, You H, Qiu S, et al., 2022, A New Perspective on NAFLD: Focusing on the Crosstalk Between Peroxisome Proliferator-Activated Receptor Alpha (PPARα) and Farnesoid X Receptor (FXR). Biomedicine & Pharmacotherapy, 154: 113577.

[47] Jiang C, Xie C, Li F, et al., 2015, Intestinal Farnesoid X Receptor Signaling Promotes Nonalcoholic Fatty Liver Disease. The Journal of Clinical Investigation, 125: 386–402.

[48] Choudhary NS, Duseja A, 2021, Genetic and Epigenetic Disease Modifiers: Non-Alcoholic Fatty Liver Disease (NAFLD) and Alcoholic Liver Disease (ALD). Translational Gastroenterology and Hepatology, 6: 2.

[49] Theys C, Lauwers D, Perez-Novo C, et al., 2022, PPARα in the Epigenetic Driver Seat of NAFLD: New Therapeutic Opportunities for Epigenetic Drugs? Biomedicines, 10: 3041.

[50] Mocciaro G, Allison M, Jenkins B, et al., 2023, Non-Alcoholic Fatty Liver Disease Is Characterised by a Reduced Polyunsaturated Fatty Acid Transport via Free Fatty Acids and High-Density Lipoproteins (HDL). Molecular Metabolism, 73: 101728.

[51] Nie T, Wang X, Li A, et al., 2024, The Promotion of Fatty Acid β-Oxidation by Hesperidin via Activating SIRT1/PGC1α to Improve NAFLD Induced by a High-Fat Diet. Food & Function, 15: 372–386.

[52] Li N, Li X, Ding Y, et al., 2023, SREBP Regulation of Lipid Metabolism in Liver Disease, and Therapeutic Strategies. Biomedicines, 11: 3280.

[53] Barreby E, Chen P, Aouadi M, 2022, Macrophage Functional Diversity in NAFLD—More Than Inflammation. Nature Reviews Endocrinology, 18: 461–472.

[54] Petrescu M, Vlaicu SI, Ciumărnean L, et al., 2022, Chronic Inflammation—A Link Between Nonalcoholic Fatty Liver Disease (NAFLD) and Dysfunctional Adipose Tissue. Medicina, 58: 641.

[55] Huby T, Gautier EL, 2022, Immune Cell-Mediated Features of Non-Alcoholic Steatohepatitis. Nature Reviews Immunology, 22: 429–443.

[56] Naiki-Ito A, Yeewa R, Xiaochen K, et al., 2024, Hexane Insoluble Fraction from Purple Rice Extract Improves Steatohepatitis and Fibrosis via Inhibition of NF-κB and JNK Signaling. Food & Function, 15: 8562–8571.

[57] Song Q, Zhang X, 2022, The Role of Gut–Liver Axis in Gut Microbiome Dysbiosis Associated NAFLD and NAFLD-HCC. Biomedicines, 10: 524.

[58] Kobayashi T, Iwaki M, Nakajima A, et al., 2022, Current Research on the Pathogenesis of NAFLD/NASH and the Gut–

Liver Axis: Gut Microbiota, Dysbiosis, and Leaky-Gut Syndrome. International Journal of Molecular Sciences, 23: 11689.

[59] Chen S-n, Tan Y, Xiao X-c, et al., 2021, Deletion of TLR4 Attenuates Lipopolysaccharide-Induced Acute Liver Injury by Inhibiting Inflammation and Apoptosis. Acta Pharmacologica Sinica, 42: 1610–1619.

[60] Wu Q, Chen Z, Ding Y, et al., 2022, Protective Effect of Traditional Chinese Medicine on Non-Alcoholic Fatty Liver Disease and Liver Cancer by Targeting Ferroptosis. Front Nutr, 9: 1033129.

[61] Hu XY, Luo Y, Zu F, et al., 2025, Effects of Electroacupuncture at "Fenglong" (ST40) and "Zusanli" (ST36) on the SIRT1/FOXO1 Signaling Pathway in Non-Alcoholic Fatty Liver Disease Model Rats. Zhen Ci Yan Jiu, 50: 150–158.

[62] Duan H, Song S, Li R, et al., 2024, Strategy for Treating MAFLD: Electroacupuncture Alleviates Hepatic Steatosis and Fibrosis by Enhancing AMPK Mediated Glycolipid Metabolism and Autophagy in T2DM Rats. Diabetol Metab Syndr, 16: 218.

[63] Yang R, Jiang D, Xu H, et al., 2024, Network Pharmacology and Molecular Docking Integrated with Molecular Dynamics Simulations Investigate the Pharmacological Mechanism of Yinchenhao Decoction in the Treatment of Non-Alcoholic Fatty Liver Disease. Curr Comput Aided Drug Des, 2024: 721–737.

[64] Ren X, Chen H, Wang H, et al., 2024, Advances in the Pharmacological Effects and Mechanisms of Nelumbo Nucifera Gaertn. Extract Nuciferine. J Ethnopharmacol, 331: 118262.

[65] Sahu B, Sahu M, Sahu M, et al., 2024, An Updated Review on Nelumbo Nucifera Gaertn: Chemical Composition, Nutritional Value and Pharmacological Activities. Chem Biodivers, 21: e202301493.

[66] He Y, Tao Y, Qiu L, et al., 2022, Lotus (Nelumbo nucifera Gaertn.) Leaf-Fermentation Supernatant Inhibits Adipogenesis in 3T3-L1 Preadipocytes and Suppresses Obesity in High-Fat Diet-Induced Obese Rats. Nutrients, 14(20): 4348.

[67] Nguyen ST, Nguyen HTT, Nguyen DCT, et al., 2025, Advancing UPLC-MS/MS for Mapping the Chemical Fingerprint of Bioactive Compounds in Lotus Leaves (Folium nelumbinis). J Pharm Biomed Anal, 261: 116840.

[68] Yanan Z, Lu M, Lu Z, et al., 2023, Effects and Action Mechanisms of Lotus Leaf (Nelumbo nucifera) Ethanol Extract on Gut Microbes and Obesity in High-Fat Diet-Fed Rats. Front Nutr, 10: 1169843.

[69] Kim AR, Jeong SM, Kang MJ, et al., 2013, Lotus Leaf Alleviates Hyperglycemia and Dyslipidemia in Animal Model of Diabetes Mellitus. Nutr Res Pract, 7: 166–171.

[70] Liu QQ, Mi J, Du YY, et al., 2024, Lotusine Ameliorates Propionic Acid-Induced Autism Spectrum Disorder-Like Behavior in Mice by Activating D1 Dopamine Receptor in Medial Prefrontal Cortex. Phytother Res, 38: 1089–1103.

[71] He S, Wang C, Shi W, et al., 2025, Assessment of the Properties and Mechanism of Three Lotus (Nelumbo nucifera Gaertn.) Parts for Sleep Improvement. Chem Biodivers, 22: e202402788.

[72] Zhang Y, Wei Q, Luo Q, et al., 2025, XSBR-Mediated Biomass Polymers: A New Strategy to Solve the Low Toughness and High Hydrophilicity of Sodium Alginate Based Films and Use in Food Packaging. Int J Biol Macromol, 318: 144979.

[73] Liu X, Guan B, Hu Z, et al., 2025, Combined Traditional Chinese Medicine and Probiotics (TCMP) Alleviates Lipid Accumulation and Improves Metabolism in High-Fat Diet Mice via the Microbiota-Gut-Liver Axis. Food Res Int, 207: 116064.

[74] Liu J, Yan P, Li Y, et al., 2024, Gut Microbiota and Serum Metabolome Reveal the Mechanism by Which TCM Polysaccharides Alleviate Salpingitis in Laying Hens Challenged by Bacteria. Poult Sci, 103: 103288.

[75] Su Y, Huang J, Shi P, et al. 2024, Lotus Leaf Extract Alleviates Lipopolysaccharide-Induced Intestinal Injury in Mice by Regulating Oxidative Stress and Inflammation. J Med Food, 27: 428–436.