

Research Progress on the Treatment of Non-Alcoholic Fatty Liver Disease with Traditional Chinese Medicine Based on the Gut-Liver Axis

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Abstract: *The pathogenesis of non-alcoholic fatty liver disease (NAFLD) remains unclear. Existing treatment strategies primarily focus on lifestyle interventions and the management of metabolic syndrome, with notable limitations in their efficacy and sustainability. The TCM concept that “the liver is connected with the large intestine” succinctly captures the close relationship between the liver and the intestines, aligning with the modern medical theory of the “gut-liver axis.” This paper analyzes the theoretical basis of the gut-liver axis from both TCM and Western medicine perspectives. It elucidates the physiological connections between the liver and intestines in Western medicine and the pathological evolution mechanisms in TCM. By reviewing recent research progress on the prevention and treatment of NAFLD with TCM based on the gut-liver axis theory, this analysis provides a solid theoretical foundation and an in-depth research perspective for developing TCM strategies for NAFLD from the gut-liver axis viewpoint.*

Keywords: Non-alcoholic fatty liver disease, Gut-liver axis, Bile acid metabolism, Intestinal immune barrier, Metabolic syndrome.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a liver condition closely associated with insulin resistance and represents the hepatic manifestation of metabolic syndrome. It is characterized by excessive fat accumulation in liver cells not caused by alcohol consumption, though its pathogenesis remains incompletely understood [1]. Risk factors include male gender, age, and obesity. Although NAFLD is generally stable, its long-term progression can lead to non-alcoholic steatohepatitis (NASH) [2], a significant risk factor for cirrhosis and hepatocellular carcinoma [3]. With advancing medical research, the anatomical and physiological connections between the liver and intestines have become increasingly evident. Gut microbiota and their metabolites can enter the liver through the enterohepatic circulation, triggering immune-inflammatory responses and contributing to the progression of NAFLD. Studies indicate a close relationship between the development of NAFLD and disruptions in the intestinal biological, chemical, and immune barriers [4]. Traditional Chinese Medicine (TCM) posits that the liver and spleen interact dynamically. Liver depression can impair the spleen's transformative and transport functions, leading to internal dampness accumulation and deficiency in nutrient production. Conversely, spleen deficiency can hinder the smooth flow of liver qi, resulting in concurrent liver-spleen disorders. As stated in the Jingui Yaolue: “When observing liver disease, recognize that it can affect the spleen; thus, tonify the spleen first.” Clinically, liver disorders are often treated by addressing the spleen. Therefore, exploring TCM approaches for the prevention and treatment of NAFLD from the perspective of the gut-liver axis not only provides a modern interpretation of traditional theories but also serves as a crucial starting point for academic innovation.

2. The Gut-Liver Axis Theory

In 1998, Marshall proposed the “gut-liver axis” theory [5],

which describes a bidirectional regulatory system formed by close communication between the intestines and the liver through pathways such as the portal vein, bile acid metabolism, and the immune system. This system involves the direct transport of gut-derived products to the liver via the portal vein, influencing hepatic metabolism, while the liver secretes bile and antibodies into the intestines [6]. Impairment of the intestinal barrier function, dysbiosis, and the resulting endotoxemia and chronic inflammation play critical roles in the development and progression of NAFLD. Central to this interaction is the gut microbiota-bile acid axis, which emphasizes the continuous bidirectional communication between the liver and intestines via the portal vein and bile ducts. It also highlights the close association between various liver diseases and disorders of the intestinal barrier function and microbiota [7].

2.1 Anatomical Structure

The intestines and the liver both originate from the foregut endoderm during the embryonic period and establish a close anatomical and functional connection through the portal vein system and the biliary system. The liver delivers bile acids, immunoglobulins, and other bioactive substances to the intestines via the biliary system, while gut microbiota and their metabolites enter the liver through the portal vein system [8], forming the basis for bidirectional material exchange. In terms of blood supply, the liver receives its blood primarily from the portal vein and the hepatic artery, with the portal vein contributing approximately 70% of the total hepatic blood flow. The portal vein's blood mainly comes from the superior mesenteric vein and the inferior mesenteric vein, which typically contain metabolites and microbial products from the digestive tract. When the intestinal barrier is impaired, substances such as endotoxins in the portal vein increase, persistently activating hepatic Kupffer cells and triggering chronic low-grade inflammation. This process serves as a critical mechanism leading to hepatocellular steatosis, inflammation, and fibrosis—key features of non-alcoholic

steatohepatitis (NASH).

2.2 Relationship between the Gut-Liver Axis and NAFLD

The involvement of the gut-liver axis in the pathogenesis of NAFLD has become a key research focus. Regulating the gut-liver axis is recognized as an important approach for the prevention and treatment of NAFLD [9]. As core components of the gut-liver axis, gut microbiota, intestinal barrier integrity, and bile acids play crucial roles in the onset and progression of NAFLD.

2.2.1 Gut Microbiota

Changes in the structure of gut microbiota influence the onset and progression of NAFLD. When dysbiosis occurs, harmful bacteria and their metabolites accumulate in the intestines, damaging the intestinal epithelial barrier. This disruption allows excessive microbiota and endotoxins to enter the liver via the portal circulation, stimulating hepatic macrophages to produce pro-inflammatory factors and promoting inflammatory liver injury [10]. Dysbiosis also accelerates NAFLD progression by promoting endogenous ethanol production, increasing short-chain fatty acids, participating in choline metabolism, and modulating bile acid synthesis and metabolism [11][12]. Clinical evidence indicates that patients with NAFLD exhibit reduced levels of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, alongside increased levels of *Enterococcus* and *Enterobacter*. Furthermore, indicators of gut microbiota colonization resistance are negatively correlated with insulin resistance indices and serum inflammatory cytokine levels [13].

2.2.2 Intestinal Immune Barrier

The specific pathogenesis of NAFLD is not yet fully understood. Among various theories, the “multiple-hit hypothesis” has garnered significant attention. Within this hypothesis, research on intestinal barrier function has increasingly become a focus for scholars. The immune, chemical, mechanical, and biological barriers of the intestine are functionally interconnected and closely associated with the onset and progression of NAFLD [14]. Among these, the intestinal mucosal immune barrier is particularly important, as it is closely linked to the production of liver-derived inflammatory factors. Due to the anatomical proximity of the liver’s blood supply system to the digestive tract, the liver is frequently exposed to bacterial products and metabolites originating from the intestines [15]. Conversely, liver-derived products influence the composition of the gut microbiota and the integrity of the intestinal barrier, while intestinal factors can regulate hepatic bile acid synthesis and glucose-lipid metabolism. If the intestinal mucosal barrier is impaired, gut bacteria can enter the liver via the portal vein, abnormally activating the immune system and triggering inflammatory liver injury. Liver-derived inflammatory factors can then travel to the intestines via the bile ducts, further damaging the intestinal mucosal barrier and creating a vicious cycle between the liver and intestines [16].

2.2.3 Bile Acid Metabolism

Bile acids are signaling molecules and metabolic integrators

that regulate glucose, lipid, and energy metabolism primarily by activating the farnesoid X receptor (FXR), playing a crucial role in NAFLD [17]. Bile acids mainly circulate within the enterohepatic system, and the interplay among gut microbiota, bile acids, and intestinal mucosal barrier function is likely a key factor in the development of NAFLD. Normal bile acid metabolism effectively maintains a healthy intestinal mucosal barrier. Additionally, bile acids can activate FXR to induce the expression of nitric oxide synthase and antimicrobial peptide genes, thereby exerting indirect antibacterial effects [18]. Bile acids are synthesized in the liver. Upon entering the intestines, they undergo modifications such as deconjugation and dehydroxylation by gut microbiota, forming secondary bile acids. This process not only affects fat absorption but, more importantly, as key signaling molecules, bile acids regulate their own synthesis, glucose-lipid metabolism, and inflammatory responses in the liver through the activation of receptors such as FXR and Takeda G protein-coupled receptor 5. In the intestines, they promote the secretion of antimicrobial peptides by intestinal mucosal cells to maintain microbial balance and stimulate enteroendocrine cells to secrete glucagon-like peptide-1, thereby improving insulin resistance. Patients with NAFLD often exhibit disturbances in bile acid metabolism and gut microbiota dysbiosis, which interact in a mutually reinforcing manner, creating a vicious cycle.

3. Theoretical Basis of Traditional Chinese Medicine

In ancient TCM texts, there is no direct record of the disease name “non-alcoholic fatty liver disease.” Based on its clinical manifestations and signs, it should be categorized under terms such as “Gan Pi”, “Tan Zhuo”, or “Fei Qi”. The core pathogenesis involves dysfunction of the liver, spleen, and kidneys, leading to the accumulation of pathological products such as phlegm, dampness, and stasis in the liver collaterals. Its development begins with liver qi stagnation, which impairs the free flow of qi and affects the circulation of body fluids and blood. This is followed by spleen dysfunction in transportation and transformation, resulting in internal production of phlegm-dampness, which forms the pathological basis for lipid turbidity accumulation. Over time, kidney deficiency may occur, disrupting water metabolism and exacerbating phlegm-dampness. Prolonged stagnation of phlegm-dampness can transform into heat, leading to damp-heat in the liver and gallbladder. If the condition persists, phlegm-turbidity and blood stasis may intertwine, obstructing the liver collaterals and potentially progressing to “Zheng Ji” (concretions and accumulations, referring to fibrosis and cirrhosis). The entire pathological process demonstrates a dynamic evolution: “liver depression and spleen deficiency, damp stagnation producing phlegm, prolonged transformation into heat, and phlegm congealing with blood stasis.” This aligns closely with modern medical mechanisms such as insulin resistance, lipid metabolism disorders, inflammatory oxidative stress, and gut-liver axis dysfunction (intestinal turbidity affecting the liver). TCM prevention and treatment emphasize simultaneous management of the liver and intestines, addressing both the root cause and symptoms. The treatment principles focus on soothing the liver, strengthening the spleen, and tonifying the kidney to treat the root, while resolving phlegm, dispelling

dampness, activating blood circulation, and eliminating turbidity to manage the symptoms.

3.1 The Liver Governs Free Flow of Qi and the Large Intestine Governs Transportation and Transformation

The liver, associated with the wood element, favors free flow and governs the free coursing of qi. The large intestine, associated with the metal element, is responsible for transporting and transforming waste. When liver qi flows freely, the ascent and descent of qi remain orderly, allowing the large intestine to properly transport and transform waste. This reflects the principle that “when qi flows, the fu organs remain unobstructed.” Conversely, smooth and orderly transportation by the large intestine, ensuring fu-organ qi remains free-flowing, aids in maintaining the harmonious regulation of liver qi. Additionally, the liver stores blood and regulates blood volume and distribution. Since body fluids and blood share a common source, the large intestine requires the lubrication of fluids for its transport function. Ample liver blood ensures normal distribution of body fluids, thereby keeping the intestines moist and preventing waste retention. The Liver Meridian of Foot-Jueyin and the Large Intestine Meridian of Hand-Yangming are interconnected through the meridian system, forming the physiological basis of the “liver-intestine axis” and establishing a close functional relationship between the liver and the intestines. If a patient experiences emotional distress, leading to liver qi stagnation and disrupted flow of qi, the large intestine’s transportation function may be impaired. This results in obstruction of fu-organ qi, prolonged retention of waste, stagnation of qi, blood, and fluids, and the internal generation of turbid toxins. This further leads to the retention of phlegm-turbidity, stasis, and toxins in the middle jiao, thereby contributing to the formation of liver accumulation.

3.2 The Liver and Kidney Share a Common Source, and the Kidney Governs the Two Lower Orifices

The formation of liver accumulation originates from liver qi stagnation, leading to impaired free flow of qi and dysfunction of the body’s pivot mechanism. The pouring of phlegm-dampness into the liver collaterals marks the beginning of liver accumulation. As phlegm-dampness lingers and the disease progresses deeper over time, it inevitably involves the kidneys. However, the essence and blood of the liver and kidneys transform into each other. Prolonged liver depression can lead to the “child organ” stealing qi from the “mother organ”, depleting kidney essence. Additionally, the yin and yang of the liver and kidneys nourish and restrain each other, jointly hosting ministerial fire. When liver yang is constrained and fails to warm and nourish kidney yang, it results in kidney yang deficiency. The kidney, as the water zang-organ, governs the two lower orifices (urination and defecation). Insufficient kidney yang leads to impaired qi transformation and dysfunction in the opening and closing of the two lower orifices. The normal peristalsis of the large intestine relies on the warming function of kidney yang. When kidney yang is weak, intestinal propulsion becomes insufficient, exacerbating the accumulation of turbid waste. Similarly, impaired qi transformation in the urinary bladder hinders the proper distribution of water-dampness, leading to further internal retention of damp-turbidity. This state of kidney

deficiency fails to support the liver in its free-flowing function or assist the spleen in transforming dampness. Instead, it causes phlegm-dampness and turbid pathogenic factors to become entrenched in the liver collaterals, gradually forming a stubborn accumulation.

3.3 The Relationship Between the Liver-Intestine Axis and the Pivotal Mechanism of Qi Movement

The formation of liver accumulation hinges on the dysfunction of the body’s pivotal mechanism, primarily due to the obstruction and disharmony in the qi transformation pathway between the liver and intestines. The liver governs free flow and regulates qi movement, serving as the key pivot for qi transformation in the triple energizer. When liver qi flows freely, intestinal transportation proceeds in an orderly manner, with ascent and descent in proper sequence: clear qi ascends while turbid yin descends and is eliminated. This represents the normal state of “harmonious interaction between the liver and intestines, with qi transformation circulating smoothly.” Conversely, if liver qi becomes stagnant, wood depression may over-restrict earth, impairing the spleen’s transportation and transformation functions. This leads to the failure of food and water to transform into essence, instead congealing into damp-turbidity. The downward pouring of damp-turbidity into the intestines obstructs fu-organ qi, causing congestion and stagnation in the large intestine’s transportation. This marks the beginning of “liver depression with intestinal stagnation.” When the qi movement of both the liver and intestines becomes mutually obstructed, the pivotal mechanism malfunctions. With the pivot obstructed, the waterways of the triple energizer become impaired, and the mechanism of qi transformation becomes sluggish. If qi transformation in the middle energizer fails, damp-turbidity accumulates further and condenses into phlegm. If qi transformation in the lower energizer is insufficient, water retention occurs and combines with phlegm. These phlegm-dampness and turbid pathogenic factors, driven by congested qi movement, ascend to invade the liver collaterals. Trapped by phlegm-dampness, the liver collaterals experience tangled qi movement and sluggish blood flow, giving rise to phlegm-stasis. The phlegm-stasis adheres stubbornly within the membranes, interstices, and cou li of the liver. Over time, accumulating day by day, it consolidates and forms an accumulation.

4. Related Treatments in Traditional Chinese Medicine

4.1 Internal Therapies of Chinese Medicine

The etiology and pathogenesis of NAFLD are diverse, and its development is complex. Currently, there is no unified pattern differentiation for this disease. Therefore, many practitioners combine TCM theory with clinical experience in the diagnostic and treatment process. Based on herbal compatibility, formulation principles, and considering the patient’s clinical manifestations alongside foundational TCM theory, they have analyzed and summarized pattern differentiations and corresponding treatment methods for NAFLD. Chen Xu [19] classifies NAFLD into five patterns: Liver Depression and Spleen Deficiency, Phlegm-Dampness Obstructing the Middle Jiao, Damp-Heat in the Liver and

Gallbladder, Blood Stasis Obstructing the Collaterals, and Liver-Kidney Yin Deficiency. Corresponding treatments involve formulas to soothe the liver and strengthen the spleen, dry dampness and resolve phlegm, clear the gallbladder and drain dampness, invigorate blood and unblock collaterals, or nourish yin and soften the liver. Professor Luo Lingjie [20] emphasizes stage-based pattern differentiation and treatment, combining disease patterns with medication. The early stage often corresponds to the Liver Depression and Spleen Deficiency pattern, for which the foundation formula is Manqian Gan Fang (containing herbs such as Bupleurum root, Chinese Angelica root, White Peony root, White Atractylodes rhizome, Poria, Salvia root, Medicated Leaven, etc.) to promote liver regulation and spleen function. The middle stage often aligns with the Phlegm-Dampness Retention pattern, using Pingwei San combined with Manqian Gan Fang as the main formula (containing herbs such as Magnolia bark, Tangerine peel, Bupleurum root, Chinese Angelica root, White Peony root, Salvia root, White Atractylodes rhizome, Poria, Fresh Ginger, Medicated Leaven, etc.) to soothe liver qi and regulate spleen qi, as smooth qi movement naturally eliminates damp-turbidity. The later stage often corresponds to the Blood Stasis Obstructing the Collaterals pattern, for which the self-formulated Kangxian Gan Fang is selected (containing herbs such as Chinese Angelica root, Salvia root, Curcuma root, Astragalus root, White Atractylodes rhizome, Turtle shell, Tree peony bark, Pseudoginseng, etc.) aiming to unblock collaterals and resolve stasis on the basis of soothing the liver, strengthening the spleen, and boosting qi.

4.2 External Therapies of Chinese Medicine

External treatment methods include acupuncture, tuina (therapeutic massage), acupoint catgut embedding, and others. Due to their minimal side effects, these methods are increasingly chosen by patients for the clinical treatment of NAFLD. Zhang Qiuling [21] selected 110 NAFLD patients meeting diagnostic criteria. The observation group received acupuncture treatment at acupoints including Zusanli (ST36), Guanyuan (CV4), Zhongwan (CV12), Hegu (LI4), Taichong (LR3), and Neiguan (PC6). The control group received oral Livzonjia (a hepatoprotective agent). The total effective rate in the observation group was 96.4%, higher than the 72.7% in the control group. Wang Hailong et al. [22] applied abdominal pushing manipulation to treat 40 NAFLD patients once every other day, with 10 sessions constituting one course. A comparison of fatty liver scores before and after treatment showed a statistically significant difference, with a total effective rate of 92.5%, indicating satisfactory therapeutic effects. Li Yongfeng et al. [23] conducted acupoint catgut embedding treatment on 50 NAFLD patients using acupoints such as Tianshu (ST25), Zhongwan (CV12), Ganshu (BL18), and Zusanli (ST36). Another 50 patients in the control group received oral Legalon (silymarin) capsules. After 28 days, a statistical analysis of the efficacy of the two treatment methods revealed a total effective rate of 91.8% in the catgut embedding group, significantly higher than the 76% in the control group. Furthermore, the catgut embedding group demonstrated more significant relief of clinical symptoms, hepatoprotective effects, and lipid-lowering benefits.

4.3 Integrated Traditional Chinese and Western Medicine Treatment

Chang Ying et al. [24] divided 97 NAFLD patients into two groups. Group A received oral polyene phosphatidylcholine, while Group B additionally received oral Shugan Granules. Liver function, blood lipid levels, and total effective rates were compared before and after treatment. The results showed that liver function and lipid indicators improved in both groups after treatment, with a greater improvement observed in Group B compared to Group A. The total effective rate in Group B was 93.62%, higher than the 78.72% in Group A. Song Yingjing [25] observed the therapeutic effect of Compound Shugan Jiangzhi Decoction combined with ursodeoxycholic acid capsules on NAFLD, using ursodeoxycholic acid capsules alone as the control. After a 3-month treatment course, the results indicated that the total effective rate for the combined treatment was 87.8%, higher than that of ursodeoxycholic acid capsules alone. Furthermore, the combined therapy demonstrated more significant effects in restoring liver function and reducing blood lipid levels.

5. Conclusion and Outlook

This article, based on the gut-liver axis theory, systematically reviews the pathological mechanisms of non-alcoholic fatty liver disease (NAFLD, categorized as “Gan Pi” in Traditional Chinese Medicine) and the TCM approach to its prevention and treatment from both TCM and Western medicine perspectives. It establishes a shared theoretical foundation for the gut-liver axis, elucidating the close physiological interaction between the liver and intestines and the role of their dysfunction in promoting NAFLD development. From the TCM theoretical standpoint, the article identifies the core pathogenesis of NAFLD as dysfunction of the liver, spleen, and kidneys, with pathological products being phlegm, dampness, and stasis. Dysfunction of the gut-liver axis—manifested as liver depression with intestinal stagnation and intestinal turbidity affecting the liver—is identified as a key link throughout the onset and progression of the disease. Grounded in this understanding of the pathogenesis, TCM prevention and treatment emphasize the principle of “simultaneously treating the liver and intestines, addressing both the root cause and symptoms.” The treatment strategy focuses on soothing the liver, strengthening the spleen, and tonifying the kidney to address the root, while unblocking the fu organs, resolving phlegm, dispelling dampness, and activating blood circulation to manage the symptoms. Future efforts should employ modern technological methods to further explore the scientific rationale underlying TCM’s therapeutic effects on NAFLD through improving gut-liver axis function. Research on the gut-liver axis characteristics and gut microbiota profile differences among NAFLD patients with different TCM patterns will provide new insights for achieving precise and individualized TCM treatments based on the principle of “treating the same disease with different methods.”

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