

# Research Progress of Intestinal Microflora Regulated by Traditional Chinese Medicine in the Treatment of Non-alcoholic Fatty Liver

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**Abstract:** *Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, including fatty liver and nonalcoholic steatohepatitis (NASH), and may develop into more severe liver cirrhosis and even liver cancer. Intestinal barrier can prevent harmful substances such as bacteria and endotoxin from passing through intestinal mucosa and blood circulation, thus affecting the occurrence and development of NAFLD. At present, it has been found that traditional Chinese medicine can regulate the intestinal flora to produce a better effect on NAFLD based on the regulation of intestinal barrier function, and TCM "liver and spleen theory" is closely related to it. By consulting the literature, this paper summarizes the research progress of traditional Chinese medicine based on intestinal barrier in non-alcoholic fatty liver disease in recent years. The regulation of intestinal flora with traditional Chinese medicine has a broad application prospect in the treatment of non-alcoholic fatty liver, which can be used as a reference for doctors.*

**Keywords:** Nonalcoholic fatty liver, Intestinal flora, Intestinal barrier, Intestinal liver axis, Traditional Chinese medicine treatment, Research progress.

## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease with lipid deposition and steatosis of hepatocytes as the main pathological changes, excluding alcohol or other definite causes, including simple fatty liver (NAFLD) and steatohepatitis (NASH), which can develop into liver fibrosis, cirrhosis and even liver cancer. The pathogenesis involves lipotoxicity, changes of intestinal microflora, oxidative stress, insulin resistance and lipid imbalance [1]. At present, with the change of human diet, the incidence of NAFLD is gradually increasing, and it has become one of the most common liver diseases in the world [2].

The intestinal microflora is the microbial community in the human intestinal tract. Under normal physiological conditions, about 50-1000 different kinds of bacteria are colonized in the human intestinal tract in a symbiotic manner, with a total weight of more than 1 inch. Most of them are anaerobes [3] they participate in important physiological functions such as digestion, absorption, metabolism and immune regulation, and maintain the balance of the human body. At the same time, it is also an important link in the pathogenic mechanism of many diseases. Due to the special anatomical and functional relationship between gastrointestinal tract and liver, the imbalance of intestinal flora can cause the destruction of intestinal barrier and metabolic disorder, promote pathogenic bacteria and endotoxin to enter the liver through the portal vein, and aggravate the inflammatory process and lipid accumulation in the pathogenesis of NAFLD [4,5]. The relationship between intestinal flora and NAFLD has been paid more and more attention. The imbalance of intestinal flora may be involved in a variety of attacks on the liver, play a key role in the pathogenesis of NAFLD, and can be used as an important driving factor to promote the occurrence and development of NAFLD and related liver diseases.

In the theory of traditional Chinese medicine, 'liver' and 'spleen' are used for each other, and there is mutual transmission of diseases. 'simultaneous treatment of liver and spleen' is a classic idea for the treatment of liver diseases in traditional Chinese medicine. In traditional Chinese medicine, 'spleen' has the function of transporting water valley, abstractly summarizing the physical body of organs and some physiological functions, but actually includes some organs responsible for digestion and absorption (such as intestine, stomach, etc.), so 'simultaneous treatment of liver and spleen' also takes into account the regulation of intestines and stomach.

The function of spleen and stomach in traditional Chinese medicine is closely related to the intestinal flora in western medicine [6]. Lingshu says: 'large intestine and small intestine belong to stomach'. Intestinal flora is closely related to the digestion and absorption of food, which is the concrete manifestation of the function of 'spleen and stomach' in traditional Chinese medicine. it can belong to the category of spleen and stomach in the theory of viscera in traditional Chinese medicine. The visceral image theory of traditional Chinese medicine holds that the liver and spleen 'use each other and communicate with the meridians and collaterals'. In modern anatomy, the liver is one of the closest organs to the intestinal tract, and the liver is in contact with intestinal flora and its metabolites through the intestinal liver axis. the imbalance of intestinal microenvironment can change the homeostasis of the liver, thus leading to liver-related diseases [7]. Some studies have shown that the 'liver and spleen theory' of traditional Chinese medicine is closely related to the intestinal barrier, and a variety of components and compound prescriptions in traditional Chinese medicine can improve the symptoms of NAFLD based on the intestinal barrier. This article reviews the research progress of traditional Chinese medicine in the treatment of NAFLD by intervening intestinal barrier and regulating intestinal flora, in order to provide a

better strategy for clinical treatment.

## 2. Understanding of Etiology and Pathogenesis of traditional Chinese Medicine

From the point of view of traditional Chinese medicine, liver can be treated from liver and intestine. If the intestinal qi is smooth and the liver qi is sparse, it can ensure the patency of the whole body qi and is conducive to the recovery of liver catharsis function. The disharmony between qi and blood in the large intestine will inevitably lead to abnormal catharsis of the liver, so it is important to soothe the liver. Whether the intestinal function is normal or not is affected by the catharsis of the liver [8]. Liver loss and catharsis, qi obstruction, spleen and stomach disharmony, large intestine qi and blood adverse; on the contrary, if the large intestine qi is disadvantageous, then liver qi stagnation, liver loss of catharsis. The function of storing blood in the liver is normal, and if the blood is regulated to a certain degree, the large intestine can be nourished; if the liver does not store blood, there is disharmony between qi and blood in the large intestine. 'introduction to medicine' said: 'five accumulations and six aggregates belong to the spleen. Long-term diet, overeating fat sweet, spleen loss of health, paste fat accumulation, phlegm and dampness endogenous, stop in the liver, the onset of the disease. Modern doctor Mu Jie and others believe that the pressure of life in modern society is great, which can easily lead to the psychological state of chronic stress, so they think that fatty liver disease begins with liver depression and endogenous phlegm-dampness, and puts forward the treatment method of soothing the liver and resolving phlegm [9]. Based on the theory of 'homology of liver and kidney', Wan Yong and others believed that the disease needed simultaneous treatment of kidney and liver, advocated that the clinical manifestations of qi stagnation, blood stasis and phlegm-dampness all developed from kidney-qi deficiency, and advocated the implementation of NAFLD treatment by tonifying kidney and peiyuan [10]. Although different doctors have different understanding of the disease, its etiology can be divided into internal and external categories: exogenous evil qi and deficiency of vital qi, which are related to improper diet, imbalance of work and rest, emotional injury and physical weakness. The main pathogenesis can be summarized as liver loss and catharsis, spleen failure, phlegm and blood stasis and kidney qi deficiency. The disease is located in liver, spleen and kidney. The pathological factors are qi stagnation, turbid phlegm, dampness-heat and blood stasis.

## 3. Traditional Chinese Medicine Treatment

### 3.1 The Relationship between TCM 'Liver and spleen Theory' and Intestinal Barri

In the theoretical system of traditional Chinese medicine, there are many viewpoints which are similar to the 'intestine-liver' axis theory, among which the theory of 'simultaneous treatment of liver and spleen' is widely used in clinic. The 'spleen' in the theory of traditional Chinese medicine does not only refer to the spleen in anatomy. According to the theory of 'visceral image' in traditional Chinese medicine, 'spleen' is a macroscopic concept and an abstract summary of some physiological and pathological systems in the human body. It includes the organ entity and

the functions of 'main movement', 'main ascending and clearing' and so on. On the other hand, the intestine in anatomy mainly plays the role of digestion, absorption and excretion of waste, which overlaps with the fine transportation and distribution of water valley driven by 'spleen' of traditional Chinese medicine, so the 'spleen' of traditional Chinese medicine contains part of the function of intestine in anatomy. and has the commander-in-chief role of "granary official". The 'liver' in the theory of traditional Chinese medicine is also an abstract macro concept. According to the theories of the five elements, viscera, qi, blood and body fluid, 'liver' belongs to wood and 'spleen' belongs to soil, and wood can control soil. 'spleen' qi is healthy, water grain fine transport is normal, 'liver' can play a normal 'catharsis', smooth qi effect. In addition, the loss of 'liver' can lead to obstruction of qi, which leads to the loss of transportation of 'spleen' and the accumulation of water and dampness, which is 'liver disease spreading spleen'; 'spleen' losing health can lead to 'soil stagnation', which leads to 'liver' qi not sparse, phlegm accumulation, dampness-heat jaundice, this is 'spleen disease transmission of liver'. This pathological transformation between 'liver' and 'spleen' includes the interaction between intestinal barrier function and NAFLD.

### 3.2 Treatment of Monomers and Extracts of Traditional Chinese Medicine

The active components of traditional Chinese medicine are the material basis for the prevention and treatment of diseases, and the pharmacological effects and chemical components are relatively clear, which is helpful to the study of pharmacological effects. Many traditional Chinese medicines with bacteriostatic effect and their extracts are used in the treatment of bacteria-related digestive tract diseases, such as bacillary dysentery and gastroenteritis. Berberine (berberine) is a kind of alkaloid, which mainly exists in *Coptis chinensis*, *Phellodendron Phellodendri* and other medicinal materials. It is cool, has the effect of clearing heat, dryness and dampness, purging fire and detoxification, has a broad spectrum of bacteriostatic effect, and is mainly used in the treatment of intestinal infectious diseases. In recent years, a large number of animal experiments and clinical studies have confirmed that it can regulate intestinal flora in the treatment of NAFLD, activate AMPK and inhibit mitochondrial activity, regulate glucose and lipid metabolism, and improve steatosis. [11] berberine hydrochloride has been widely used in the preparation of drugs for the treatment of NAFLD. In order to verify the bacteriostatic effect of berberine, Li Donghao [12] treated the NAFLD model of male SD rats induced by high-fat diet by intragastric administration of berberine hydrochloride. The body mass and liver index of the treatment group were significantly lower than those of the high-fat diet group, the levels of blood lipid and transaminase in serum were significantly lower, the degree of lipid deposition and steatosis in liver were reduced, and the number of Bacteroides in feces was increased. It is suggested that berberine hydrochloride can improve NAFLD by regulating intestinal flora and improving intestinal permeability.

In addition, [13] some studies have shown that curcumin can improve the imbalance of intestinal flora in rats. It can reduce lipid deposition in the liver of NAFLD mice induced by high-fat diet, and reduce the index of liver inflammation, and

its mechanism may be related to the inhibition of the release of inflammatory factors [14-15]. Mei et al. [16] observed the effect of probiotics combined with semen Cassia on the composition of intestinal flora through animal experiments. The results showed that semen Cassiae could increase the total number of intestinal flora, especially the number of thick-walled bacteria and bacteroides, indicating that semen Cassia can maintain intestinal stability by regulating the total number of intestinal flora, reduce endotoxin and regulate lipid metabolism to treat NAFLD.

### 3.3 Compound Treatment of Traditional Chinese Medicine

With the in-depth study of traditional Chinese medicine compound prescription, at present, scholars at home and abroad are exploring effective treatment methods for NAFLD. Traditional Chinese medicine has accumulated rich clinical experience in the treatment of NAFLD and achieved satisfactory therapeutic effects.

In particular, the compound prescription of traditional Chinese medicine is guided by the basic theory of traditional Chinese medicine, the prescription is scientific and effective, and the pharmacology of various components complement each other. Traditional Chinese medicine plays a role in invigorating the positive and dispelling evil by regulating the partial exuberance of yin and yang in human qi and blood, and has a two-way regulatory effect on intestinal flora. promote the proliferation of beneficial bacteria and inhibit the growth of harmful bacteria. Wang Xingzhang [17] Animal experimental study found that in the feces of NAFLD rats and normal rats induced by high-fat diet, the expression level of *E. coli* gene in feces of NAFLD rats was significantly increased, the expression level of bifidobacterium gene was significantly decreased, the expression of jejunal epithelial tight junction protein Occludin was significantly decreased, and the content of inflammatory factors in liver tissue was increased. After 4 weeks, compared with normal rats, the expression level of *Escherichia coli* gene in feces decreased significantly, the expression level of bifidobacterium gene increased significantly, the expression of Occludin increased significantly, and the content of inflammatory factors in liver tissue decreased. It is suggested that the treatment of NAFLD by Zhongmanfanxiao Pill is realized by regulating the signal pathway of intestinal flora/intestinal permeability increase-metabolic endotoxemia-inflammatory factor-liver steatosis/injury. ect. Fang Jing [18] based on the pathological basis of NAFLD spleen failure and internal obstruction of phlegm, rhubarb Zexie decoction was used to treat NAFLD. The results showed that rhubarb Zexie decoction could improve the structure of intestinal flora, reduce pathogenic bacteria, increase the content of beneficial bacteria and improve the related symptoms of NAFLD in NAFLD rats. Qushi Huayu recipe is widely used in the treatment of NAFLD. Yin Xiaochen [19] applied it to the NAFLD rat model induced by high-fat diet. It was found that Qushi Huayu recipe could not only reduce the body mass and the degree of hepatocyte steatosis in rats, but also reduce the number of bacteria in *Escherichia/Shigella* and increase the number of bacteria in *Collinsella*, indicating that the compound prescription can regulate the structure of intestinal flora in rats. So that the imbalance of flora caused by high-fat

diet can be alleviated to a certain extent. Yin et al. [20] also monitored the composition of intestinal microorganisms and the related manifestations of NAFLD in the NAFLD rat model induced by high-fat diet during the treatment with Qushi Huayu recipe. The weight and NAFLD of rats in the treatment group were reduced, and they also had a regulating effect on intestinal flora. The clinical trial conducted in the later stage of the research group [21] also showed that Qushi Huayu recipe could improve the related blood biochemical indexes and clinical symptoms of NAFLD.

The spleen dominates ascending and clearing, and the liver governs catharsis. Because NAFLD is the pathological basis of the disorder of lipid metabolism due to the loss of spleen and liver, soothing the liver and invigorating the spleen and reducing lipid has become the starting point of TCM treatment. Liu Yue [22] found that Yinchenhao decoction could significantly increase or decrease the number of intestinal bifidobacteria and *Lactobacillus* in patients with NAFLD damp-heat syndrome, and reduce serum ALT and AST. The study of Fang Jing [23] suggested that rhubarb Zexie decoction reduced the level of pathogenic bacteria in the intestinal tract of NAFLD rats, thus reduced the production of LPS, regulated the intestinal mechanical barrier function, and improved liver inflammation and lipid deposition. Cui Xiang [24] believes that Xiaozhi Yigan recipe may reduce liver injury caused by LPS/TLR4 pathway by improving intestinal microbial barrier in NAFLD rats. Liver fibrosis is a serious stage in the course of NAFLD. Chen Bin [25] found that Xiaoyao Powder can improve liver fibrosis and restore part of the structure of intestinal flora, while the drugs with spleen-strengthening effect in the prescription weaken the protective effect of Xiaoyao Powder on liver. Shenling Jianpiwei granule has the effect of invigorating the spleen and soothing the liver, can reduce the expression of UCP-2 and Cytb in the liver of NAFLD mice, improve liver inflammatory response and liver function, and protect the liver [26]. Li Ying et al [27] observed the effects of Yiqi Qinghua recipe (*Radix Astragali*, *Salvia miltiorrhiza*, fried *Atractylodes macrocephala*, dried pericarp, lotus leaf, *Gynostemma pentaphyllum*, *Poria cocos*, corn beard) on intestinal flora of NAFLD model rats. Results after treatment, the blood lipid level in the model group was significantly higher than that in the blank group, and the blood lipid level in the treatment group was significantly lower than that in the model group. Compared with the ERICPCR fingerprints of rats in each group, the structure of intestinal flora in the treatment group was similar to that in the blank group, and the diversity of intestinal flora was increased. Yiqi Qinghua prescription plays a therapeutic role in NAFLD by regulating intestinal flora.

### 3.4 External Treatment of Traditional Chinese Medicine

The external treatment of traditional Chinese medicine is a kind of non-oral drug treatment, which mainly includes acupuncture, moxibustion, massage, ear acupuncture and other methods to stimulate meridians and acupoints, regulate qi to prevent and treat diseases, with the characteristics of simplicity, convenience and cheapness, quick effect and few adverse reactions. it avoids the liver damage caused by drug metabolism through the liver, and is favored by clinicians and patients at home and abroad.

In recent years, external treatment of traditional Chinese medicine, such as acupuncture, catgut embedding, acupoint injection and so on, regulate intestinal flora to regulate lipid metabolism. [28] Related studies have shown that compared with drug treatment, electroacupuncture at Shenshu point can significantly improve the clinical symptoms, B-ultrasound and CT of patients with NAFLD, and regulate the level of blood lipids and liver function. Another study [29] Thirty patients with simple obesity were divided into two groups and treated with acupuncture and moxibustion for 3 courses. After treatment, the body mass, body mass index, waist and hip circumference, TCM symptom score and blood lipid level were improved, and the number of intestinal flora also changed significantly. After treatment, the number of Bacteroides in the treatment group was significantly higher than that before treatment, and enterococci and enterobacteria decreased significantly. There was no significant difference in Bifidobacterium, Lactobacillus and Enterococcus between the two groups and the healthy group before and after treatment. Acupuncture can regulate the intestinal flora and help the maladjusted flora to return to balance, so as to enhance the energy metabolism of the body to achieve the purpose of lowering blood fat. However, there are no related literature reports about acupuncture regulating intestinal flora to treat NAFLD.

#### 4. Summary and Prospect

NAFLD is a disease of abnormal lipid metabolism related to obesity. The regulation of intestinal flora by traditional Chinese medicine provides a new idea and method for the treatment of metabolic diseases. Traditional Chinese medicine treats NAFLD by regulating intestinal flora. In recent years, many compound prescriptions of traditional Chinese medicine for NAFLD have emerged and achieved good clinical results, and there are numerous studies on the therapeutic effect of single traditional Chinese medicine on NAFLD. Under the guidance of the concept of 'treatment based on syndrome differentiation', personalized treatment according to different conditions of patients should be the advantage of traditional Chinese medicine in the treatment of NAFLD in the future. The treatment scheme of traditional Chinese medicine for NAFLD has a broad prospect. However, there is a lack of in-depth and extensive randomized, double-blind, prospective clinical trials. We should further explore the pathogenesis of NAFLD, give full play to the unique advantages of traditional Chinese medicine, combine with TCM syndrome differentiation and treatment, provide personalized diagnosis and treatment measures for different patients, provide scientific and reasonable theoretical basis for scientific research guidance, and formulate more safe, effective and standardized diagnosis and treatment measures.

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