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# Advances in the Study of Intestinal Flora and Its Metabolites in Nonalcoholic Fatty Liver Disease

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**Abstract:** ***Non alcoholic fatty liver disease (NAFLD), as an increasingly serious global public health problem, has become the largest chronic liver disease in China, with a global incidence rate of about 25%, and is increasing year by year. disease in China, with a global incidence rate of about 25%, and is increasing year by year. As an important disease in the liver, an increasing number of studies have confirmed the significant role of gut microbiota and its metabolites in the progression of non-alcoholic fatty liver disease. There is a close structural and functional relationship between the gut microbiota and its metabolites in the liver. There is a close structural and functional relationship between the gut and liver due to the "gut liver axis". The gut microbiota and its metabolites, such as abnormal metabolism of bile acids (TBA), trimethylamine oxide (TMAO), lipopolysaccharides (LPS), short chain fatty acids (SCFAs), and other metabolites in the progression of non-alcoholic fatty liver disease. short chain fatty acids (SCFAs), tryptophan (Trp), etc., can restrict and regulate the use of host cells by binding to corresponding receptor activated signaling pathways, thereby participating in the occurrence and development of NAFLD and affecting the process of non-alcoholic fatty liver disease. Studies have shown that probiotics can be used to regulate the gut microbiota to promote the treatment of NAFLD. This article mainly studies the relationship and mechanism between gut microbiota and NAFLD. relationship and mechanism between gut microbiota and related metabolites and the pathogenesis of NAFLD, providing new ideas for the prevention, delay NAFLD, providing new ideas for the prevention, delay, and treatment of NAFLD.***

**Keywords:** Intestinal microbiota and its metabolites, Non-alcoholic fatty liver disease, Enterohepatic axis, Signaling pathways**.**

## 1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has today become the most common chronic liver disease in the world, with a prevalence of about 20.09%-25.24% in the global and Asian populations according to domestic and international statistics in 2016 [1]. Some experts predict that by 2030, the number of domestic NAFLD patients will be as high as 314 million [2,3]. It is a metabolic pathology disease manifested by excessive accumulation of liver fat, with the rise of obesity and metabolic syndrome year by year, NAFLD has also gradually become the No.1 leading cause of chronic liver disease in China [4], and more and more patients with chronic hepatitis B virus (Hepatitis B virus (HBV) infection are co-infected with NAFLD, and such diseases often metabolic stress liver injury closely related to insulin resistance (IR) or genetic susceptibility, which seriously jeopardizes people's lives and health. The spectrum of the disease includes non-alcoholic simple hepatic steatosis, non-alcoholic Steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC) etc. [5]. The pathogenesis of NAFLD still lacks a unified understanding, and the literature has elaborated that it may be closely related to a variety of factors, such as abnormalities of hepatic metabolism, oxidative stress, and inflammatory response [6]. The intestinal flora plays an important role in the development of hepatic steatosis, in which tryptophan, as a biosynthetic precursor of many microbial and host metabolites, has also been shown to be involved in lipid metabolism and its metabolites also in hepatic steatosis as well as the development of steatohepatitis [7]. This review on the effect of gut flora and its metabolites on NAFLD aims to provide some new therapeutic ideas for the treatment of NAFLD.

## 2. Impact of Gut Microbial Dysbiosis on NAFLD

Intestinal flora, as an important "special organ" of the human body, plays an important role in human health. It is involved in the entire metabolism of our body and has been shown to be inextricably linked to the development of NAFLD [8]. The two are mainly regulated through the "gut-liver axis" [9]. Approximately 70% of the blood supply in our body is supplied to the liver from the portal vein, and this blood supply via the portal vein is derived from nutrients in the gut. A normal intestinal barrier prevents the leakage of microorganisms or metabolites from the intestinal lumen. If the barrier is compromised, this may lead to translocation of microorganisms and their metabolites within the intestinal lumen, which may affect the intestinal morphology and immune response, abnormally activating the immune system, releasing inflammatory products and vasoactive substances, and forming intestinal endotoxemia, which may trigger or contribute to the development of liver injury and dysfunction [10]. Thus, intestinal flora and metabolite imbalances can influence the development and progression of NAFLD, and we will now provide an overview of how intestinal flora and metabolite imbalances affect NAFLD through possible mechanisms of action.

### 2.1 Intestinal Flora and Bile Acid Metabolism

Bile acid (TBA) is mainly evolved from cholesterol, which is synthesized in the liver and combined with glycine or taurine to form bound bile acid, which is then secreted into bile by hepatocytes, and then hydrolyzed into free bile acid under the

action of intestinal bacteria after entering into intestines with

the bile, the primary bile acid in the intestines is transformed into free bile acid through the above process, and the research also proves that the abundance and structure composition of intestinal bacteria can also affect the metabolism of bile acid. Research has also demonstrated that the abundance and structural composition of the intestinal flora can also affect bile acid metabolism, and similarly, bile acid can also reverse the abundance and composition of the intestinal flora [11]. Bile acids activate signaling pathways through farnesol X receptor (FXR) and G protein-coupled bile acid receptor 5 (TGR5, also known as GPBAR1) regulation, which play critical roles in the maintenance of hepatic glucose, intestinal flora, immunity, and the regulation of lipid-energy metabolism [12].

It acts as a signaling pathway activating two major classes of receptors, nuclear receptors (NRs) and G protein-coupled receptors (GPCRs), in order to regulate the metabolic functions of the body [13]. On the one hand, farnesol X receptor induces the production of fibroblast growth factor 19 (FGF-19) and fibroblast growth factor 15 (FGF-15) through the activation of peroxisome proliferator-activated receptor alpha (PPARα) expression, reduces cholesterol 7α-hydroxylase (CYP7A1), and thus decreases macrophage accumulation and attenuates hepatic steatosis [14]. DY Z et al. [6] also concluded that FXR induces the expression of mouse ileocyte fibroblast growth factor 15 (FGF15) in enterocytes, which activates hepatic FGF receptor 4/β-Klotho signaling and binds to hepatocyte fibroblast growth factor receptor 4 (FGFR4) to ultimately modulate the homeostasis of TBA in the entero-hepatic circulation to ameliorate liver injury. On the other hand, TGR5 is a receptor located on the cell membrane and has seven G protein couplings, which is mainly distributed in a variety of tissues both inside and outside the intestine, and is widely expressed in Kupffer cells (also known as hepatic macrophages) in human liver tissues, which inhibits the production of pro-inflammatory cytokines from NF-κB signaling in hepatic macrophages and inhibits hepatic steatosis and inflammatory responses, thus delaying the progression of NAFLD and has therapeutic potential for NALFD [15]. TGR5 has also been shown to regulate the specific gravity of the bile acid pool and enhance hepatic lipid metabolism through oxidative effects, and also inhibit inflammatory vesicle-induced apoptosis of hepatic cells through mitochondrial autophagy, and accelerate glucagon like-1 (GLP-1) secretion to achieve amelioration of hepatic and vascular injury to regulate the NALFD progression [16,17]. In summary, the imbalance of intestinal flora can affect bile acid metabolism, and the body's liver tissue in turn can ameliorate the inflammatory response and injury of liver cells through TBA metabolism.

### 2.2 Intestinal Flora and Oxidized Trimethylamine Metabolism

Trimethylamine-N-oxide (TMAO) is an intestinal-derived colony-associated metabolite and N-oxide of trimethylamine, which is a small amine compound widely found in aquatic products in nature, as well as in mammals, plants, and fungi. When its metabolism is derived from dietary red meat or high-fat dairy beverages, choline or its choline compounds in food will be generated in the intestinal lumen through the enterohepatic cycle to produce trimethylamine (TMA) in the liver, where it is oxidized to TMAO by enzymes such as flavin-containing monooxygenases 3 (FMO3), and other enzymes. In the liver, TMAO is oxidized to TMAO by enzymes such as flavin-containing monooxygenases 3 (FMO3) [18], and finally metabolized by the kidney and excreted in the urine. Currently, there are different views on the mechanism of action of TMAO in NAFLD. Some studies have shown that TMAO and its TMA have been demonstrated to be a potential risk factor for a variety of chronic diseases including cardiovascular disease and liver disease [19]. In a clinical study, we found a significant correlation between the relevant percentage of TMAO in the blood and the occurrence of NAFLD [20]. With elevated levels of TMAO in the blood of the organism and overexpression of pro-inflammatory factors (IL-10, IL-6) in the cells [21], there is also a certain increase in hepatic fat damage in NAFLD.

TMAO can also accelerate hepatic steatosis by modulating bile acid metabolism-mediated hepatic Farnesoid X Receptor (FXR) signaling [22]. In animal experiments, two groups of mice were fed with normal diet and fed with TMAO, respectively. It was observed that the mice in the TMAO-fed group had significant disorders of lipid metabolism, and a small number of hepatocytes showed necrosis and enlarged capillaries, as well as extensive intracellular lipid deposition in the hepatocytes, and the serum of mice showed significantly elevated levels of hepatic free fatty acids and malondialdehyde (MDA), and the levels of liver fatty acids and MDA were significantly elevated. MDA levels were significantly elevated, while antioxidant serum superoxide dismutase (SOD) activity was reduced, concluding that TMAO levels in the organism are inextricably linked to oxidative stress in the liver [23]. On the contrary, it has been suggested that the regulation of intestinal flora by oral administration of TMAO to mice inhibits intestinal cholesterol absorption and relieves hepatic endoplasmic reticulum stress, thus inhibiting and protecting against steatohepatitis caused by high-fat and high cholesterol food in mice [24]. Therefore, the trend of detecting TMAO and TMAO-related metabolites within the intestinal flora may provide certain therapeutic ideas for the prevention and diagnosis of NALFD-associated diseases, and this type of research has received more and more attention from scholars.

### 2.3 Intestinal Flora and Lipopolysaccharide Metabolism

Lipopolysaccharide (LPS), also known as endotoxin, is a metabolite of intestinal flora, derived from a major component of the outer membrane of Gram-negative bacteria, where the external lipid component of the outer membrane of the cell wall consists of endotoxin molecules, which are released for transport to the liver after cell death or catabolism, resulting in an adaptive immune response and a cascading inflammatory response [25]. Overseas studies have shown that long-term high-fat and high-sugar diets can easily lead to intestinal flora disorders, and plasma LPS concentration increases, the intestinal barrier function is impaired, and intestinal permeability increases, resulting in leakage of intestinal LPS into the bloodstream, and then transported to the liver through the intestinal-hepatic axis, which activates an inflammatory response resulting in hepatic injury and

accelerates the progression of NAFLD [26, 27]. HEGAZY [28] et al. also demonstrated that there is a relationship between serum LPS concentration and the grade of hepatic steatosis and the degree of hepatic inflammation in patients with NAFLD. toll-like receptor 4 (TLR4), an important member of the LPS family, acts as an agonist of LPS, which is activated by myeloid differentiation factor 88 (MDF 88), a key factor in liver inflammation, and is also involved in the development and progression of NAFLD. As an agonist of LPS, TLR4 activates nuclear factor kappa-B (NF-κB) and TRIF/IRF-3 signaling pathways through the myeloid differentiation factor 88 (MyD88)-dependent and MyD88-independent pathways, and induces hepatic macrophages to secrete a series of chemokines and inflammatory cytokines after entering the liver, such as pro-inflammatory factor interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), etc., resulting in hepatic tissue damage, inflammatory response and hepatocyte apoptosis [29]. An animal experiment [30] showed that deficiencies in Toll-like receptor 4 gene expression in high-fat-fed mice significantly attenuated hepatic steatosis, inflammation, and fibrosis, demonstrating that TLR4 is involved in the development of NAFLD. Conversely, the livers of NAFLD patients also result in high expression of TLR4 [31] through activation of TLR4-mediated inflammatory signaling pathways. Therefore, when TLR4 overexpression is present in liver cells, it can induce a cascading immune response in hepatocytes, leading to liver injury or NAFLD-like disease. When the metabolism of intestinal flora-associated LPS is abnormal, we can regulate the intestinal ecological flora and inhibit TLR4-induced liver injury in LPS through the gut-hepatic axis, which can provide a new therapeutic approach for NAFLD.

**2.4 Intestinal Flora and Short-chain Fatty Acids**

Short-chain fatty acids (SCFAs), also known as volatile fatty acids (VFAs), are indigestible compounds that are fermented by intestinal microorganisms in the colon to produce intestinal flora metabolites [32]. The types and amounts of SCFAs are mainly dependent on intestinal flora composition, digestion time (time spent in the gut), host-microbe metabolic flux, and fiber content of the host food [33]. Of these, acetic acid, propionic acid and butyric acid are the three main short-chain fatty acids produced by intestinal fermentation, accounting for well over 95% of the total in the gut [34]. It has been shown that acetic acid can modulate adipocyte differentiation [35]. It can also reduce blood lipids, alleviate the level of liver damage and delay liver fibrosis by activating FXR [36]. In an in vitro observation, it was found that the application of propionic acid co-incubated with human adipose tissue explants reduced the secretion of pro-inflammatory cytokines IL-4, TNF and chemokines [37]. In animal experiments, butyrate supplementation in NASH model mice fed a high-fat diet prevented obesity, and it was hypothesized that butyrate could reduce intracellular lipid accumulation and oxidative stress by enhancing fatty acid oxidation, thereby decreasing the release of inflammatory factors such as TNFα, IL-2, etc., and ultimately alleviating inflammation and hepatocyte lipid deposition in mice [38,39]. ZHOU et al. [40] also found that butyrate can also inhibit the progression of NAFLD by activating AMPK signaling, which mainly inhibits lipogenesis and suppresses hepatic inflammatory responses by regulating fatty acid oxidative metabolism.

Short-chain fatty acids (SCFAs) can enter the liver directly through the portal vein and regulate the energy metabolism of hepatic adipocytes. HONG et al. [41] experimentally demonstrated that, by feeding two groups of mice with normal and high-fat diets respectively, the adipocytes of mice in the high-fat diet group showed a significantly higher expression of antibodies against G Protein-Coupled Receptor 43 (GPCR43) as compared with that of mice in the normal diet group. As a receptor for SCFAs, G Protein-Coupled Receptor (GPCR) plays a crucial role in the regulation of metabolism, inflammation and liver diseases, and G Protein-Coupled Receptor 109A antibody (GPCR109A) can even activate macrophages in adipose tissue and inhibit lipid aggregation [42]. On the other hand, SCFAs may also regulate hepatic lipid metabolism mediated by GLP-1 signaling. TOLHURST et al. [43] reported that there was a low expression of GLP-1 receptor in hepatocytes of rats fed a high-fat diet and patients with nonalcoholic steatohepatitis (NASH), and a low expression of Glucagon-like peptide 1 receptor, GLP-1 receptor, GPCR109A, in hepatocytes. peptide 1 receptor (GLP-1r) in hepatocytes activates fatty acid β-oxidation. Animal experiments have also shown that GLP-1 receptor activation also attenuates high-fat diet-induced hepatic lipid deposition in NAFLD mice [44]. Overall, gut flora metabolites SCFAs play a positive role in the organism. We can improve the intestinal barrier function to prevent NAFLD by regulating SCFAs in the intestinal flora [45]. Therefore, when the intestinal microbiota is dysbiotic, decreasing the production of harmful SCFAs and elevating the level of beneficial SCFAs will ultimately lead to the treatment of NAFLD.

**2.5 Intestinal Flora and Tryptophan**

Tryptophan (Tryptophan, Trp), also known as α-amino-β-indolepropionic acid, is an aromatic amino acid that occupies a major position among the essential amino acids in humans and animals, and serves as a biosynthetic precursor for the energy metabolism of most intestinal microorganisms and their hosts.It is metabolized by the tryptophan-5-hydroxytryptamine (5-HT), indole, and kynurenine metabolic pathways in the intestinal chromaffin cells It is converted to biogenic amines through the induction of tryptophan hydroxylase (TPH) to generate derivatives to exert biological effects [46]. It has been speculated that it may be due to the association with 5 -hydroxytryptamine receptor 2A (HTR2A) and 5 -hydroxytryptamine transporter (SERT) mutually directing hepatic tissue steatosis and hepatic oxidative stress [47]. In addition to this, it has also been suggested that the tryptophan metabolites indoles and kynurenine also play an important role in the hepatic metabolism of the organism.

Researchers at Tufts University [48] found that three key metabolites were missing in mice on a high-fat diet, tryptophan, indole-3-acetate (I3A), and xanthuric acid, concluding that I3A may attenuate pro-inflammatory cytokine secretion by acting on hepatic macrophages and inducing hepatic synthesis of free fatty acids to radicalize macrophages. In 2014, some scholars [49] also confirmed through melatonin that it can improve metabolic parameters in NAFLD patients,

while among them tryptophan significantly attenuated the blood levels of pro-inflammatory cytokines IL-1, IL-6, and TNF-alpha, and lipid metabolism indexes of triglycerides and lipoproteins were also improved. Indole-3-propionic acid blocked NF-κB signaling to attenuate inflammatory cytokine levels, inhibited liver tissue injury and inflammation, and alleviated NAFLD progression [50]. These suggest that tryptophan has antioxidant and anti-inflammatory properties in NAFLD patients. Recently, a research team from Sun Yat-sen University [51] found that theaflavin may exert preventive and therapeutic effects on NAFLD by modulating 5-HT-related signaling. In addition, it was also observed that the beneficial regulation of 5-HT and hepatocyte target of rapamycin (mTOR)-related target proteins in the liver by teffilin was dependent on the involvement of intestinal flora. High duodenal 5-HT levels are also recognized as a risk factor for pathological progression of NASH, and may be a novel target for prevention of NAFLD/NASH by blocking 5-HT receptor synthesis [47]. The tryptophan-kynurenine pathway, as another pathway of tryptophan metabolism, is mainly synthesized under the action of indoleamine 2,3-dioxygenase 1 and then degraded to flavourour uric acid, which is mainly involved in the development of metabolic syndrome-like disorders [52], and has also been guided in the treatment of NAFLD.

## 3. Probiotics for the Treatment of NAFLD

Probiotics, as one of the most widely used microecological agents for regulating the intestinal flora of NAFLD patients, are also known as living microorganism symbionts, which can improve the damage of liver tissues in NAFLD patients by regulating hepatic oxidative stress and modulating lipid metabolism, etc. [53]. In addition, it can also be used for the treatment of NAFLD by regulating the intestinal microbiota and the production of antimicrobial factors, thereby altering the barrier permeability of intestinal epithelial cells, alleviating the infiltration of endotoxins into the bloodstream to inhibit the inflammatory response, and regulating the immune system [54]. A Meta-analysis showed that oral probiotics can improve hepatic steatosis in NAFLD patients [55]. Some scholars have concluded from a double-blind controlled trial that giving short-term probiotic supplementation to children with NAFLD can significantly reduce their fatty liver levels and BMI [56]. In conclusion, we can conclude that probiotic preparations can improve lipid metabolism abnormality and inflammatory response during the development of NAFLD, which proves the positive value of probiotics in the treatment of NAFLD patients [56].

## 4. Prospects and Shortcomings

The alteration of intestinal microbiota and the development of NAFLD affect each other and are inseparable. In summary, by studying the mechanism of action of intestinal flora and its related metabolites in NAFLD patients, it can be a combination of immune homeostasis and improvement of metabolism level of the disease, which can provide a new target for the treatment of NAFLD. However, with the mechanism of continuous in-depth study, the shortcoming is that the current intestinal flora and its metabolites and NAFLD-related clinical research is still relatively small, many new drugs have also been in the clinical trial stage, the safety of which has to be monitored, therefore, in the future research, we still need a large number of clinical studies to support the unified mechanism of action of NAFLD and its intestinal flora metabolites, and to consider whether it is possible for a variety of target and consider whether it is possible to target multiple targets with different drug interventions.

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