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# Therapeutic Strategies for Non-alcoholic Fatty Liver Disease from the Gut Microbiota Perspective (Postprint)

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide, with a disease spectrum encompassing non-alcoholic hepatic steatosis (NHS), non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). Recent studies have revealed the involvement of the gut-liver axis in the pathogenesis and progression of NAFLD, suggesting that modulation of gut microbiota may represent a novel therapeutic target for NAFLD. Current research has demonstrated that various interventions, including exercise, dietary modifications, microecological agents, antibiotics, fecal microbiota transplantation, and bacteriophages, can ameliorate NAFLD by altering gut microbiota. This article reviews the relationship between gut microbiota and NAFLD, as well as research advances in targeting gut microbiota as a therapeutic strategy for NAFLD, aiming to provide insights and references for the clinical prevention and management of NAFLD.

## Full Text

## Treatment Strategies for Non-alcoholic Fatty Liver Disease from the Perspective of Gut Microbiota

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide, with a disease spectrum that primarily includes non-alcoholic hepatic steatosis (NHS), non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). Recent studies have revealed that the gut-liver axis is intimately involved in the pathogenesis and progression of NAFLD, suggesting that modulating intestinal microorganisms may represent a novel therapeutic target. Current research indicates that interventions including exercise, dietary modification, microecological preparations, antibiotics, fecal microbiota transplantation, and bacteriophages can alleviate NAFLD by altering the gut microbiota. This article reviews the relationship between gut microbiota and NAFLD and summarizes research progress on gut microbiota modulation as a therapeutic target for NAFLD, aiming to provide insights and references for clinical prevention and treatment of this condition.

**Keywords:** Intestinal flora; Non-alcoholic fatty liver disease; Treatment; Metabolic syndrome; Microecological preparation; Fecal microbiota transplantation

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) refers to a clinical syndrome characterized by hepatic fat deposition exceeding 5%, excluding alcohol and other definitive hepatotoxic factors. Its disease spectrum primarily includes non-alcoholic hepatic steatosis (NHS), non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC) [1]. NAFLD is closely associated with obesity, insulin resistance, type 2 diabetes, and cardiovascular disease, and is considered the hepatic manifestation of metabolic syndrome [2]. Based on this understanding, recent expert consensus has proposed renaming NAFLD as metabolic-associated fatty liver disease (MAFLD). Globally, NAFLD currently affects approximately 25% of adults, making it the most common chronic liver disease, with NASH incidence projected to increase by 56% over the next decade [3]. Regional prevalence varies significantly: 30% in South America, 24% in North America/Europe, 13% in Africa, and 5–51% in Asia [2]. In China, the prevalence ranges from 6% to 27%, surpassing chronic hepatitis B as the leading chronic liver disease and posing serious consequences including cirrhosis and hepatocellular carcinoma that substantially impact national health and economic development.

NAFLD involves a series of pathological processes including hepatic fat deposition, inflammatory response, hepatocellular degeneration and necrosis, and fibrosis [4]. Current therapeutic research primarily focuses on ameliorating hepatic inflammation and fibrosis, with no approved drugs currently available [5]. Recent studies have revealed that the gut-liver axis is intimately involved in NAFLD pathogenesis, suggesting that modulating intestinal microorganisms may become a novel therapeutic target [6, 7]. Interventions such as exercise, dietary modification, microecological preparations, antibiotics, fecal microbiota transplantation, and bacteriophages can alleviate NAFLD by altering gut microbiota composition. This article reviews the relationship between gut microbiota and NAFLD and summarizes research progress on gut microbiota modulation as a therapeutic target, aiming to provide insights and references for clinical prevention and treatment.

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## 1. Gut Microbiota and Health

The human intestine harbors a dynamic microbial community comprising millions of microorganisms, with over 500 different species and containing 100 times more genes than the human genome [8]. More than 99% of these are obligate anaerobes, with the remainder including aerobic bacteria, facultative anaerobes, and other microorganisms [9]. Under normal conditions, despite influences from age, lifestyle, and emotional factors, these intestinal flora maintain dynamic equilibrium, establishing long-term mutualistic symbiosis with the host and playing active roles in maintaining intestinal microecological balance and overall health [10, 11]. Once this balance is disrupted, it may lead to various diseases [8]. Indeed, studies have demonstrated a direct relationship between colorectal cancer development and gut microbiota dysbiosis [12].

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## 2. Gut Microbiota and NAFLD

Research confirms that NAFLD patients exhibit reduced gut microbiota diversity and altered proportions of dominant bacterial groups compared to healthy individuals, with decreased *Ruminococcaceae*, *Bacteroides*, and *Prevotella*, and significantly increased *Proteobacteria*, *Escherichia coli*, *Ruminococcus*, and *Firmicutes* [13, 14]. However, other studies have found increased *Bacteroides* and decreased *Firmicutes* in pediatric NASH patients. Additionally, one study [15] discovered that approximately 60% of NAFLD patients harbor *Klebsiella pneumoniae* capable of producing high concentrations of alcohol in the gut, compared to only 6% of healthy individuals. These discrepancies may be related to heterogeneity in dietary structure, living environment, age, and genetics between populations, as the intestinal environment in some individuals may be more suitable for *K. pneumoniae* growth and colonization. Numerous cross-sectional studies have also demonstrated associations between gut microbiota perturba-

tions and NAFLD severity, with increased abundance of *Bacteroides* and *E. coli* correlating closely with advanced fibrosis, while *Firmicutes* are more abundant in mild-to-moderate NAFLD patients, suggesting disease stage-specific patterns [16]. Although gut microbiota dysbiosis is evident in NAFLD patients, whether these microbial changes are a cause or consequence of the disease remains to be clarified. Nevertheless, modulating gut microbiota to improve NAFLD has emerged as a promising therapeutic target.

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## 3. Mechanisms of Gut Microbiota-Mediated NAFLD Pathogenesis

The intestine and liver are bidirectionally connected through the gut-liver axis. The liver secretes bile acids and other bioactive substances into the intestine, where they are metabolized by gut microbiota and subsequently reabsorbed into the portal circulation to return to the liver. Mechanisms by which gut microbiota mediate NAFLD development include: (1) **Increased intestinal permeability**: Dysbiosis in NAFLD patients compromises intestinal barrier integrity, facilitating translocation of bacteria and their metabolites from the intestinal lumen to the lamina propria, with toxins entering the liver via the portal vein to trigger inflammatory responses [17]. (2) **Enhanced endogenous ethanol production**: Excessive endogenous ethanol production by gut microbiota increases intestinal permeability, promotes entry of harmful intestinal substances into the liver, impairs lipid metabolism, generates oxygen free radicals, and accelerates hepatic steatosis and inflammatory processes [15]. (3) **Modulation of bile acid metabolism**: Bile acids reduce hepatic inflammation and fibrosis through farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 5 (TGR5) signaling pathways. When gut microbiota are disturbed, altered bile acid metabolism downregulates FXR signaling, enhances lipogenesis, and inhibits fatty acid $\beta$-oxidation, thereby promoting NAFLD progression [18]. (4) **Involvement in choline metabolism**: Choline is a component of cell membranes. Altered gut microbiota diversity increases bacterial choline synthesis requirements, reducing hepatic choline availability for very low-density lipoprotein (VLDL) production and impairing triglyceride (TG) export from hepatocytes, leading to intrahepatic lipid deposition and NAFLD development [19]. (5) **Short-chain fatty acids (SCFAs)**: SCFAs activate intestinal L cells to release glucagon-like peptide 1 (GLP-1) and peptide tyrosine-tyrosine (PYY) to regulate metabolism, while directly inhibiting histone deacetylases to upregulate lipid oxidation gene expression and promote hepatic lipid oxidation [20].

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## 4. Therapeutic Strategies Targeting Gut Microbiota

**4.1 Exercise** Current research demonstrates that exercise not only directly influences metabolic responses but also affects gut microbiome structure and

function, which may represent a key mechanism for exercise-induced NAFLD improvement [21]. Compared to sedentary individuals, actively training athletes exhibit significantly increased abundance of *Akkermansia* and *Faecalibacterium*, a pattern also observed in obese patients and non-obese individuals who exercise regularly. These bacterial groups promote hepatic lipid metabolism and exert positive health effects [22, 23]. In animal studies, Carbajo-Pescador et al. [24] established a high-fat diet-induced NAFLD rat model, dividing animals into control and experimental groups. The control group remained sedentary, while the experimental group underwent five weeks of combined aerobic and resistance training to evaluate exercise benefits on gut microbial composition and functional balance, as well as subsequent effects on early obesity and NAFLD development. The trained rats exhibited lower final body weight, increased relative abundance of *Bacteroides* and *Proteobacteria*, and decreased abundance of *Bacillus*, *Verrucomicrobia*, and *Firmicutes*, significantly correcting the microbial imbalance induced by high-fat diet. Further analysis revealed that control rats showed micro- and macrovesicular hepatic steatosis with significantly increased NAFLD activity scores, whereas trained rats demonstrated reduced hepatic lipid droplets and improved fasting insulin and insulin sensitivity. These results confirm that exercise can ameliorate NAFLD metabolic disorders through gut microbiota modulation. A recent randomized controlled trial [25] showed that NAFLD patients undergoing 8.6 months of aerobic exercise exhibited significant changes in gut microbiota composition, with increased abundance of *Ruminococcus* and *Bacteroides* members. Notably, *Ruminococcaceae* correlated negatively with fibrosis severity, and hepatic fat content decreased by 24.4%, indicating that exercise intervention substantially altered microbiome abundance and function. However, current research on NAFLD patients' gut microbiota has focused primarily on taxonomic composition rather than functional capacity, and the specific mechanisms by which exercise modulates gut microbiota to improve NAFLD remain unclear and require further investigation. Nevertheless, existing studies affirm the positive impact of appropriate exercise on NAFLD development and progression, recommending regular aerobic exercise for NAFLD patients with long-term maintenance.

**4.2 Dietary Modification** Dietary adjustment and physical exercise remain the cornerstone of NAFLD management, with dietary modification being one of the simplest and most effective methods for regulating gut microbiota [26]. High-fat diets have been confirmed to associate with hepatic steatosis, inflammation, and fibrosis [27]. Animal studies demonstrate that long-term high-fat feeding reduces gut microbial diversity, decreases *Bifidobacterium* and *Bacteroides* populations, affects bile acid metabolism, downregulates FXR signaling, increases lipogenesis, and inhibits fatty acid $\beta$-oxidation, thereby promoting NAFLD progression [18]. High-sugar diets reduce insulin sensitivity and enhance hepatic lipogenesis, facilitating NAFLD development. Therefore, NAFLD dietary management recommends low-fat, low-carbohydrate diets with restricted daily caloric intake [28]. A cross-sectional study [29] showed that long-term adherence to the

Mediterranean diet serves as an independent protective factor against hepatic fibrosis and non-alcoholic steatohepatitis in overweight participants. Calabrese et al. investigated the combined effects of Mediterranean diet and aerobic exercise on NAFLD patients' gut microbiota, finding increased $\alpha$-diversity and relative abundance of *Ruminococcus*, *Firmicutes*, and *Bacteroides* in the Mediterranean diet group. *Ruminococcus* protects the liver by improving gastrointestinal barrier integrity and regulating intestinal microecology. Furthermore, the beneficial effects of Mediterranean diet were amplified when combined with aerobic exercise [18, 30]. However, individual responses vary even under identical dietary patterns, necessitating personalized dietary therapy and identification of predictive diet-responsive gut microbiota signatures to guide NAFLD interventions.

**4.3 Microecological Preparations** Given the intimate relationship between gut microbiota and NAFLD pathogenesis, microecological preparations that directly modulate gut microbiota have been investigated for NAFLD prevention and treatment. These preparations primarily include probiotics, prebiotics, synbiotics, and postbiotics, with probiotics being the most common and clinically applied.

**4.3.1 Probiotics** Defined by the WHO as live microorganisms that confer health benefits when administered in adequate amounts [31], probiotics have been studied primarily in animal experiments, with limited clinical trials. Research demonstrates that probiotics increase gut microbiota diversity and beneficial bacterial abundance, improve mucosal permeability, inhibit lipid synthesis, promote lipid oxidative metabolism, and reduce hepatic inflammation and fibrosis [32-34]. Ahn et al. [35] found that obese NAFLD patients receiving probiotic formulations showed increased relative abundance of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Pseudomonas pentosacea*, and *Bifidobacterium lactis*, with significant reductions in intrahepatic fat fraction and body weight compared to placebo. Duseja et al. [36] conducted a randomized, double-blind, placebo-controlled trial evaluating probiotic efficacy in adult NAFLD patients. After one-year follow-up, the probiotic group showed decreased biochemical markers including alanine aminotransferase (ALT), aspartate aminotransferase (AST), leptin, tumor necrosis factor-$\alpha$ (TNF-$\alpha$), and endotoxin levels. Liver biopsy revealed significant improvements in hepatocellular ballooning ($p=0.036$), lobular inflammation ($p=0.003$), and NAFLD Activity Score (NAS) ($p=0.007$) compared to baseline, with more pronounced improvements than placebo. Meta-analyses [37] similarly confirmed that probiotic use significantly reduced body mass index (BMI), ALT, AST, insulin resistance, and ultrasonographic grades of fatty liver in NAFLD patients. However, improvement magnitudes varied across studies due to differences in probiotic strains, dosing regimens, and treatment durations. Future research must establish consensus on probiotic types, doses, and treatment durations, and conduct more comprehensive large-sample, multicenter prospective studies to validate efficacy.

**4.3.2 Prebiotics** Prebiotics are non-digestible food components that selectively stimulate the growth and activity of beneficial bacteria to improve host health, primarily including various fructo-oligosaccharides or galacto-oligosaccharides [38]. Numerous trials support prebiotic efficacy in NAFLD treatment. Animal studies demonstrate that prebiotics induce compositional changes in rodent gut microbiota, increase *Bifidobacterium* and *Lactobacillus* abundance, and stimulate GLP-2 production to modulate endotoxin translocation and improve intestinal barrier function [39]. Additionally, GLP-2 influences plasma lipopolysaccharide levels, reduces hepatic inflammation and oxidative stress, and alleviates hepatic lipid accumulation and steatohepatitis [40]. In clinical trials, Bomhof et al. [41] showed that prebiotics increased fecal *Faecalibacterium* and *Bifidobacterium* abundance in NASH patients while reducing serum AST and ALT levels and improving histologically confirmed hepatic steatosis. Chong et al. [42] similarly supported prebiotic efficacy in modulating gut microbiota and improving steatosis.

**4.3.3 Synbiotics** Synbiotics combine probiotics and prebiotics to replace dysfunctional gut microbiota, improve insulin resistance, reduce pro-inflammatory factors and endotoxin levels, and ameliorate liver histology [43, 44]. Eleonora et al. [45] found that synbiotic supplementation altered the gut microbiota of NAFLD patients, increasing *Actinobacteria* and *Bifidobacterium* relative abundance while decreasing *Oscillospira* levels. Ferolla et al. [46] conducted a randomized double-blind trial of synbiotics in NAFLD patients, observing significant reductions in pro-inflammatory cytokines IL-6 and TNF-$\alpha$, improved serum AST, ALT, and alkaline phosphatase (ALP) levels, and decreased proportions of moderate/severe steatosis patients from 40.7% to 18.5% while increasing mild steatosis patients from 59.2% to 81.5%, significantly improving hepatic fibrosis in steatohepatitis patients. Meta-analyses [47] similarly confirmed that synbiotic supplementation induced gut microbiota changes, effectively reduced BMI and liver enzyme levels, and improved hepatic steatosis.

**4.3.4 Postbiotics** Postbiotics are a recently proposed concept encompassing bacterial metabolites and cellular components with potential biological activity in the host, including certain vitamins, short-chain fatty acids, polyamines, branched-chain amino acids, or bacterial cell wall components that influence intestinal mucosal barrier integrity by stimulating the immune system [48, 49]. Current data on postbiotic efficacy in NAFLD remain limited, primarily confined to preclinical studies. In aged mice, lipoteichoic acid from heat-killed *Lactobacillus paracasei* D3-5 increased *Akkermansia* abundance and mucin expression, enhanced mucosal barrier function, and prevented metabolic dysfunction induced by high-fat diet feeding [50]. Ma et al. [51] found that polyamine spermidine administration altered gut microbiota composition and function in obese mice, particularly increasing butyrate-producing *Lachnospira* abundance, significantly improving intestinal barrier function and metabolic phenotype.

**4.4 Fecal Microbiota Transplantation** Fecal microbiota transplantation (FMT) involves transplanting functional microbiota from donor feces into patients' intestines to improve dysbiosis, reconstruct normal intestinal microecology, and achieve disease treatment [52]. In animal studies, high-fat diet-fed mice receiving FMT showed reduced *Bacteroidetes*, increased *Firmicutes*, improved intestinal barrier function and endotoxemia, decreased hepatic lipid accumulation and pro-inflammatory cytokine levels, and attenuated steatohepatitis [53]. A study in metabolic syndrome patients [54] demonstrated that FMT from lean donors improved insulin sensitivity and intrahepatic lipid metabolism, associated with increased butyrate-producing strains. Witjes et al. [55] conducted a randomized double-blind controlled trial comparing eight-week FMT from lean vegetarian donors versus autologous FMT in NAFLD patients. FMT induced significant gut microbiota changes converging toward donor microbial profiles, particularly evident in *Bacteroides* and *Firmicutes*. However, overall NAFLD activity scores and fibrosis scores showed no statistically significant differences, although necrotizing inflammatory scores (including lobular inflammation and hepatocellular ballooning) demonstrated improvement trends. Another trial in 21 NAFLD subjects [56] showed that FMT improved intestinal permeability but did not increase insulin sensitivity or reduce intrahepatic lipid content after six months of follow-up. FMT efficacy is closely related to donor characteristics, particularly fecal microbial richness, diversity, and compatibility. Therefore, whether FMT can be clinically applied for NAFLD treatment requires extensive clinical trials to provide evidence.

**4.5 Antibiotics** Rifaximin is a non-systemic antibiotic derived from rifamycin that is poorly absorbed in the gastrointestinal tract and does not significantly affect overall gut microbiome diversity [57]. In NAFLD mouse models, oral rifaximin reduced intestinal permeability and endotoxin levels, decreased intrahepatic lipid deposition, lowered AST and ALT levels in NASH mice, and attenuated hepatic inflammation and fibrosis. Additionally, rifaximin altered gut microbiota and reduced secondary bile acid levels in the terminal ileum, reversed Fxr-Fgf15 signaling activation, and promoted hepatic Cyp7a1 and Cyp7b1 expression, which may represent mechanisms for NASH amelioration [58]. These findings align with Fujinaga et al. [59]. However, studies evaluating rifaximin efficacy in human NASH have yielded conflicting conclusions. Gangarapu et al. [60] enrolled 42 biopsy-confirmed NAFLD patients and found that short-term rifaximin administration (1200 mg/day) for 28 days significantly reduced endotoxin levels, AST, ALT, pro-inflammatory cytokines, and NAFLD activity scores, with improvements attributed to altered gut microbiota and bile acid metabolism and downregulated FXR signaling. Conversely, Cobbold et al. [61] reported that six weeks of rifaximin treatment (400 mg twice daily) increased serum ALT levels and insulin resistance, suggesting no benefit for NASH, with no consistent differences in fecal microbial relative abundance post-treatment. These discrepancies may relate to different treatment doses and durations. Another study [62] found that triclosan increased beneficial bacterial

abundance in NAFLD mouse models, including *Lactobacillus*, *Bifidobacterium*, and *Lachnospiraceae*, while increasing the *Bacteroidetes*/*Firmicutes* ratio and significantly improving hepatic steatosis, suggesting triclosan may target gut microbiota for NAFLD treatment. However, antibiotics may have divergent effects. Mahana et al. [63] found that antibiotic-treated mice developed severe insulin resistance and increased incidence and severity of NAFLD histological lesions, associated with antibiotic-induced perturbations in *Bifidobacterium* and *Prevotella*. Therefore, antibiotics represent a double-edged sword: while they can alleviate or treat disease by inactivating harmful bacteria and modulating dysbiosis, long-term use may promote bacterial resistance and affect beneficial bacterial growth, creating new microbial imbalances. Caution is warranted in using antibiotics for NAFLD treatment, and future development of antibiotics targeting specific bacterial populations may resolve this dilemma.

**4.6 Bacteriophages** Bacteriophages exhibit bacterial specificity and can targetedly edit gut microbial community structure. This approach has not yet been evaluated in NAFLD, but preclinical studies support its efficacy in alcohol-associated liver disease [64, 65]. Duan et al. [66] colonized germ-free mice with feces from alcoholic liver disease patients and investigated phages targeting cytolytic *Enterococcus faecalis*, finding that these phages eliminated ethanol-induced liver injury and steatosis without affecting overall gut microbiota composition. The presence of cytolytic *E. faecalis* correlates with alcohol-associated liver disease severity and mortality. However, phage therapy for liver disease has only been studied in mouse models, and clinical trials are needed to evaluate its effectiveness and efficacy in NAFLD patients.

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## 5. Conclusions and Challenges

Gut microbiota play crucial roles in maintaining intestinal homeostasis and NAFLD pathogenesis. Interventions targeting gut microbiota modulation—including exercise, dietary modification, probiotic preparations, FMT, and antibiotics—can effectively alleviate NAFLD, while bacteriophage efficacy requires further clarification. However, current trials exhibit heterogeneity attributable to multiple factors. First, although exercise, diet, probiotic preparations, and FMT can temporarily alter gut microbiota structure, these changes are not sustained long-term after intervention cessation, limiting therapeutic efficacy. Second, consensus has not been reached regarding specific protocols, including dietary patterns, exercise intensity and duration, microbial species selection, dosing, and frequency for microecological preparations. Additionally, using serological biomarkers rather than liver biopsy (the gold standard) to assess efficacy may influence trial outcomes. Furthermore, despite correlational evidence from cross-sectional studies, establishing causal relationships between gut microbiota and NAFLD remains challenging. The specific bacterial strains that may drive key NAFLD features—including steatosis, inflammation, insulin resistance, or

fibrosis progression—require further elucidation. In summary, despite current limitations, gut microbiota modulation as a therapeutic target for NAFLD remains promising and warrants extensive future animal and clinical trials. Once causal relationships between gut microbiota and NAFLD pathogenesis are firmly established, they will provide novel insights and targets for NAFLD prevention and treatment through microbiota modulation.

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### Author Contributions

Fu Weiqiang was responsible for conceptualization, literature organization, and manuscript writing; Zhou Jianbo conducted literature collection; Wu Xiongjian performed manuscript revision; Huang Caibing was responsible for quality control and final approval, with overall accountability and supervision.

### Conflict of Interest

The authors declare no conflict of interest.

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### Figure 1

[Figure 1: see original paper] The mechanism of action of NAFLD treatment based on intestinal flora

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### Literature Search Strategy

English databases (PubMed, Medline, Web of Science) were searched using keywords: "Intestinal flora, metabolic syndrome, probiotics, prebiotics, synbiotics, postbiotics, antibiotics, exercise, diet, microecological preparation, FMT, bacteriophage, NAFLD" . Chinese databases (CNKI, Wanfang Data, SinoMed) were searched using keywords: "肠道菌群，代谢综合征，微生态制剂，益生菌，益生元，合生元，后生元，抗生素，运动，饮食，粪菌移植，噬菌体，非酒精性脂肪性肝病" . Search period: database inception to June 15, 2022. Inclusion criteria: clinical, basic, and literature studies on NAFLD prevention and treatment based on gut microbiota. Exclusion criteria: studies not involving gut microbiota, weak relevance to NAFLD prevention/treatment, incomplete data, overlapping viewpoints, or poor methodological quality.

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### Data Availability Statement

The scientific data supporting this study have been publicly released in the Science Data Bank of the Chinese Academy of Sciences, accessible at

http://cstr.cn/31253.11.sciencedb.02919 or http://doi.org/10.57760/sciencedb.02919.

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