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MINIREVIEWS

Therapeutic advances in non-alcoholic fatty liver disease: A microbiota-centered view

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a highly prevalent metabolic disorder with steadily increasing incidence rates worldwide, especially in the West. There are no drugs available at present to treat NAFLD, and the primary therapeutic options include weight loss and the combination of healthy diet and exercise. Therefore, novel interventions are required that can target the underlying risk factors. Gut microbiota is an "invisible organ" of the human body and vital for normal metabolism and immuno-modulation. The number and diversity of microbes differ across the gastrointestinal tract from the mouth to the anus, and is most abundant in the intestine. Since dysregulated gut microbiota is an underlying pathological factor of NAFLD, it is a viable therapeutic target that can be modulated by antibiotics, probiotics, prebiotics, synbiotics, fecal microbiota transplantation, and microbial metabolites. In this review, we summarize the most recent advances in gut microbiota-targeted therapies against NAFLD in clinical and experimental studies, and critically evaluate novel targets and strategies for treating NAFLD.

Key words: Non-alcoholic fatty liver disease; Gut microbiota; Probiotics; Prebiotics; Fecal microbiota transplantation; Metabolites

Core tip: Non-alcoholic fatty liver disease is a highly prevalent metabolic disease worldwide. In this review, we summarize the most recent advances in gut microbiota-targeted therapies against non-alcoholic fatty liver disease, including antibiotics, probiotics, prebiotics, synbiotics, fecal microbiota transplantation, and the gut

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INTRODUCTION

The liver is the largest organ in our body, with vital functions in digestion, energy storage, and detoxification. Fatty liver disease is the most common hepato-pathological condition characterized by excessive fat accumulation in the liver. Based on the etiology, fatty liver disease can be classified into the alcoholic and non-alcoholic types. As the name indicates, alcoholic fatty liver disease is the result of alcohol overconsumption. Ethanol metabolism in the liver produces fatty acids which steadily accumulate within the liver cells, along with acetaldehyde and free radicals that also have deleterious effects on the liver and other organs[1]. Non-alcoholic fatty liver disease (NAFLD) is caused by multiple factors including poor diet, insulin resistance, and other metabolic disturbances[2]. In addition, lifestyle-related factors like sleep shortage, irregular food intake, sedentary habits, and excessive weight gain are also risk factors for NAFLD[3]. It can be further sub-divided into the fatty liver without inflammation and nonalcoholic steatohepatitis (NASH) types. The latter frequently progresses to fibrosis, advanced cirrhosis, hepatocellular carcinoma (HCC), and even death[4]. NAFLD is in fact the most rapidly increasing underlying condition requiring liver transplantation[5], and can be considered a hepatic manifestation of the metabolic syndrome. Several clinical trials are underway to develop novel therapies against NAFLD[6], since the current treatments focusing on lifestyle modifications have been largely approved. Mediterranean diet and physical activity for instance have been shown to prevent the onset of NAFLD[7,8]. The ultimate goal of NAFLD treatment is to inhibit fibrotic development that can eventually lead to cirrhosis and HCC[6]. However, there are no Food and Drug Administration approved drugs at present for treating this condition[9].

The gut microbiota is considered by many as a "metabolic organ" that plays a vital role in host metabolism and liver function[10]. In addition to the classic "two-hit" theory or the updated "multiple hit" model[11], intestinal dysbiosis is also a causative factor of NAFLD, and promotes its progression by modulating host energy metabolism, insulin sensitivity, immune response, and inflammation[12]. The pathophysiological relationship between the gut microbiota and NAFLD is complex and involves diverse immunological and metabolic pathways. For instance, impaired intestinal permeability in mice lacking the junctional adhesion molecule A protein (Jam1) or Muc2 increases the risk of liver inflammation when the animals are fed a high-fat diet (HFD)[13,14]. Furthermore, the microbiota from adult NAFLD patients exhibits differences in carbon and amino acid metabolism[15]. NAFLD is also associated with increased serum TMAO levels and hepatic bile acid (BA) synthesis[16] and less production of phosphatidylcholine[17]. The pathological roles of various bacterial metabolites and microbiota-generated secondary BA in NAFLD have been unearthed in recent years[18]. These metabolites can trigger metabolic dysfunction and contribute to NAFLD development and progression by targeting relevant pathways. The gut microbiota also diversifies the repertoire of host BAs by modulating its metabolism, thereby regulating pathways mediated by BA receptors such as farnesoid X receptor (FXR) and TGR5[19,20].

Therefore, researchers are increasingly focusing on the gut microbiota as a new therapeutic target for NAFLD, and have developed various treatment modalities including antibiotics, probiotics, prebiotics, synbiotics, fecal microbiota transplantation (FMT), gut microbiota-derived components, and metabolites (Figure 1). In this review, we summarize the most recent advances in gut microbiota-targeted therapies against NAFLD in clinical and experimental studies, and critically evaluate novel targets and strategies for treating NAFLD.

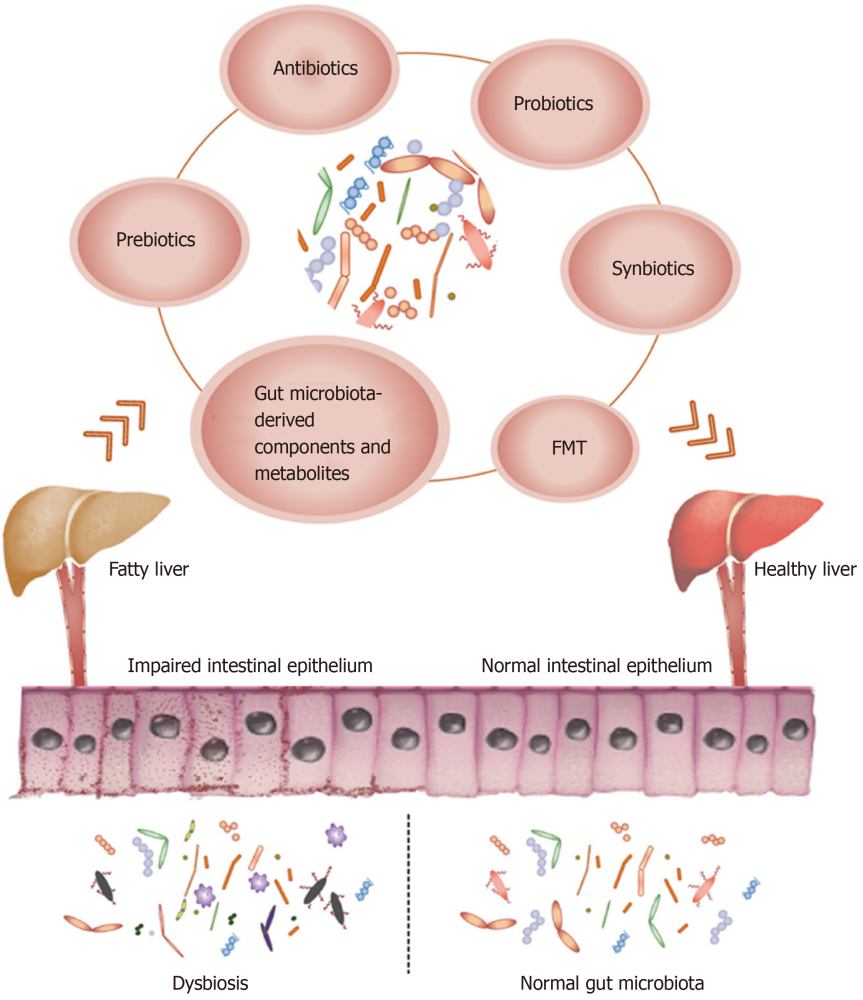

Figure 1 Microbiota-centered therapies against non-alcoholic fatty liver disease. Gut microbiota dysbiosis and impaired intestinal barrier have been elucidated as pathogenic factors in non-alcoholic fatty liver disease. Antibiotics, probiotics, prebiotics, synbiotics, fecal microbiota transplantation, and gut microbiota-derived components and metabolites are important treatments targeting the gut microbiota. FMT: Fecal microbiota transplantation.

ANTIBIOTICS

Antibiotics can eliminate harmful microbiota, and their efficacy has been confirmed in various liver diseases[21-27]. Since the 1950s[28,29], neomycin, metronidazole, rifaximin, and polymyxin B have been used extensively for treating cirrhosis and hepatic encephalopathy. In addition, concurrent polymyxin B and neomycin use prevented lipid accumulation in the liver by altering the gut microbiota[30]. Gangarapu *et al*[31] found that short-term administration of antibiotics improved the clinical symptoms in NAFLD/NASH patients by lowering circulating endotoxins as well as serum transaminases. Consistent with this, another study[32] reported a significant reduction in the levels of transaminase and NAFLD-liver fat score after rifaximin treatment. However, in a recent clinical trial conducted by Ponziani *et al*[33], rifaximin showed little therapeutic effects against NASH. This discrepancy could be the result of low drug dose, short duration of the treatment, and small sample size. Antibiotic-induced changes in the gut microbiota can provide valuable insights into its therapeutic utility in various diseases. Specific antibiotics can positively affect the gut microbiota by promoting the growth of beneficial gut bacteria like *Bifidobacteria* and *Lactobacilli*. While short-term antibiotic treatment may have a therapeutic effect, long-term application can lead to the emergence of bacterial resistance, thereby limiting the efficacy of the drug and increasing the risk of secondary infections. Therefore, chronic antibiotic use is not encouraged since they can affect the beneficial gut bacteria and cause intestinal dysbiosis[34].

PROBIOTICS

Probiotics are non-pathogenic microbes that alleviate gut disorders by restoring the normal microbiota, and provide overall health benefits to the host[35]. These beneficial bacteria can reduce lipid deposition, endotoxemia, oxidative stress, and inflammation by regulating the expression levels of TNF-α, NF-κB, and collagen[35]. Probiotic strains for therapeutic applications are selected on the basis of safety, functionality, and technical requirements[36]. For instance, some *Streptococcus*, *Lactobacillus*, and *Bifidobacteria* strains can regulate the mucosa-motivated immune system and gastrointestinal inflammation, and promote the growth and survival of gut epithelial cells[37].

Probiotics have shown significant therapeutic effects on the murine fatty liver model as well. Administrating probiotics to mice fed an HFD significantly slowed the progression of hepatic steatosis and fibrosis[35]. However, most studies on NAFLD rodent models have been aimed at preventing, rather than treating, diet-induced liver disease[38]. Clinical trials on NAFLD patients have shown that *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* strains play an ameliorative role by restoring the levels of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[35]. For instance, the intra-hepatic levels of AST and ALT increased significantly in NAFLD patients following 3 mo of treatment with *Lactobacillus bulgaricus (L. bulgaricus)* and *Streptococcus thermophilus (S. thermophiles)*[39]. MIYAIRI 588, a probiotic *Clostridium butyricum* strain originally from Japan and used widely in Asia, prevented fatty degeneration from progressing to liver cancer in a rat NAFLD model[40,41]. In addition, co-administration of several probiotic strains, such as the VSL3 formulation including eight probiotic bacterial strains [*S. thermophiles*, *Bifidobacterium breve*, *Bifidobacterium longum (B. longum)*, *Bifidobacterium infantis*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *L. bulgaricus*] resulted in greater therapeutic effects compared to any single strain[42-44]. A randomized controlled trial conducted on overweight children with NAFLD showed significant improvement in the fatty liver condition and BMI following treatment with VSL3. Subsequent studies indicated that the increase in total and active GLP-1 as well as decrease in the plasma levels of S-nitrosothiols, malondialdehyde, and 4-hydroxynonenal was the potential mechanisms underlying the therapeutic effects of VSL3[45,46]. Furthermore, VSL3 can alleviate chronic liver diseases by protecting the intestinal barrier and reducing endotoxemia and oxidative/nitrosative stress[46,47].

However, probiotics are primarily derived from bacteria, which raises concerns of biosafety. A few probiotics derived from yeast (*e.g.*, *Saccharomyces boulardii*) have shown encouraging effects, especially when combined with traditional bacterial probiotics[48]. Further research is needed to optimize the efficacy, safety, and sustainability of probiotics for treating NAFLD.

PREBIOTICS

The International Scientific Association for Probiotics and Prebiotics defines prebiotics as substrates that are broken down by host microorganisms into metabolites[22] that promote the growth of beneficial bacteria[49]. Prebiotic feeding is an effective adjuvant therapy for liver diseases, which improves the symptoms by restoring gut microbiota[10,50]. Oligofructose, a mixture of nondigestible fermentable dietary fiber[51], reduced liver oxidative stress and inflammation by improving intestinal permeability and tight junction integrity. Prebiotics stimulated the growth of *Bifidobacteria* and normalized plasma endotoxin levels, which improved glucose tolerance and subsequently resulted in weight loss in obese individuals[52]. Lactulose is another prebiotic that promotes the growth of *Bifidobacteria*, *Lactobacillus*, and Gram-positive bacteria and inhibits the endotoxemic Gram-negative bacteria[53]. HFD-fed obese mice that were administered lactulose for 6 wk showed reduced inflammation and liver damage, which correlated to decreased circulating levels of lipopolysaccharides[54]. In addition, the fungal prebiotic chitin-glucan can also limit weight gain, glucose intolerance, liver triglyceride accumulation, and fasting hyperglycemia by modulating the gut microbiota[55].

The beneficial effects of prebiotics on NAFLD can be attributed to reduced *de novo* lipogenesis, weight and fat loss, improved blood glucose control, restored gut microbiota, and lower inflammation[56]. Clinical trials have also demonstrated therapeutic effects of prebiotics on NAFLD/NASH progression *via* modulation of glucose homeostasis and lipid metabolism[57]. In conclusion, prebiotics are a highly suitable therapeutic tool against NAFLD.

SYNBIOTICS

Synbiotics are the combination of probiotics and prebiotics. NASH patients treated with *Bifidobacterium* and fructo-oligosaccharides (FOS) for 6 mo showed significantly lower serum ALT and AST levels compared to the placebo group[58], indicating the potential advantage of using synbiotics against liver diseases. Another study showed that synbiotic supplementation with seven probiotic strains (*Lactobacillus casei, L. bulgaricus, Lactobacillus rhamnosus, Lactobacillus acidophilus, Bifidobacterium breve*, *B. longum*, and *S. thermophilus*) and FOS for 28 wk, along with healthy lifestyle modifications, was more beneficial (in terms of reduced inflammation and BMI) to NAFLD patients compared to lifestyle changes alone[59]. Malaguarnera *et al*[60] reported that co-administering *B. longum* and FOS for 24 wk combined with a healthy lifestyle significantly decreased NASH activity index and hepatic fat accumulation. Likewise, Safavi *et al*[61] found that long-term synbiotic treatment significantly decreased serum lipid levels in obese children. A meta-analysis of 15 randomized controlled trials including a total of 782 NAFLD patients showed that synbiotics markedly attenuated liver steatosis, ALT, AST, high-density lipoprotein, low-density lipoprotein, triglyceride and cholesterol levels, TNF-α expression, the degree of liver stiffness, and homeostasis model assessment-insulin resistance[62].

FECAL MICROBIOTA TRANSPLANTATION

FMT involves transferring functional microbiomes from the feces of healthy individuals to the gastrointestinal tract of patients with intestinal dysbiosis. It was introduced by Chinese medical and herbal practitioners for treating severe diarrhea and food poisoning[63]. FMT is an effective therapeutic option for recurrent *Clostridium difficile* infection, as well as liver and metabolic diseases associated with intestinal microbiota dysbiosis. The clinical studies conducted so far on microbiota-targeting strategies, including FMT, in NAFLD patients are summarized in Table 1.

Studies show[64,65] that transplanting the gut microbiota from lean or obese mice induced phenotypes similar to that of the host, with the microbiota of lean donors significantly reducing adiposity in the obese mice. However, Fischer *et al*[66] observed no improvement in the BMI of *Clostridium difficile* infection patients within 12 mo of a single FMT, regardless of the donor BMI. In contrast, overweight patients with metabolic syndrome showed a significant improvement in hepatic (119%) and peripheral (176%) insulin sensitivity 6 wk after receiving microbiota from lean healthy controls compared to the autologous microbiota[67]. Several studies have demonstrated the therapeutic effects of FMT on type 2 diabetes and ulcerative colitis patients[68-72], which were associated with restored healthy microbiota, normalized blood lipid levels, and improved insulin resistance.

Based on these reports, we can surmise that FMT is a potential therapeutic option for NAFLD and NASH as well. To determine the role of the gut microbiota in NAFLD development, Le Roy *et al*[73] transplanted the feces from HFD responder and non-responder mice into germ-free recipients. The mice that received microbiota from the responder group developed steatosis and showed a high abundance of *Barnesiella* and *Roseburia* in the intestine, whereas microbiota from the non-responder mice markedly increased the abundance of *Allobaculum* in the recipients. Furthermore, an 8-wk FMT intervention[74] significantly restored the disordered gut microbiota in HFD-induced NASH mouse models by increasing the abundance of beneficial bacteria such as *Christensen* and *Lactobacillus*. It also alleviated endotoxemia, liver steatosis, necrosis, and intra-hepatic inflammation compared to the untreated controls. Consistent with this, metabolic syndrome patients transplanted with the gut microbes of healthy individuals showed increased butyrate production and improved insulin sensitivity[75], which could be attributed to the higher abundance of beneficial bacteria in the lower gut.

Fecal matter can be implanted through nasogastric tubes, nasojejunostomy tubes, upper gastrointestinal endoscopy (gastroduodenoscopy), colonoscopy, or retention enema, and the outcomes of these methods differ significantly. In addition, the heterogeneity of donor fecal matter also influences the therapeutic effect. FMT is also associated with the risk of unpredictable infections from the transplanted microorganisms under certain circumstances. Finally, the stability of foreign bacteria into the host gut is limited, which can reduce their long-term survival and therapeutic effects[76]. Therefore, further clinical trials are warranted to confirm the therapeutic benefit of this strategy.

Table 1 Clinical trials (centered on phase 2 or phase 3) that target the gut microbiota involved in non-alcoholic fatty liver disease

NCT number	Condition(s)	Intervention	Phase	Status	Country
NCT01355575	NAFLD	Antibiotics	Phase 4	Terminated	United Kingdom
NCT02329405	NAFLD	Antibiotics	Phase 4	Completed	Finland
NCT01759628	NAFLD	Antibiotics	Phase 2	Completed	Iran
NCT01712711	NAFLD	Antibiotics	Phase 2	Completed	Iran
NCT01654549	NAFLD	Antibiotics	Phase 2	Completed	Iran
NCT01876108	Fatty liver	Antibiotics	Phase 2	Completed	Iran
NCT02510599	NASH	Antibiotics	Phase 2	Completed	United States
NCT00068094	Fatty liver	Probiotics	Phase 1/Phase 2	Terminated	United States
NCT02972567	Metabolic syndrome/NAFLD	Probiotics	Phase 2	Unknown status[1]	Spain
NCT03511365	NAFLD	Probiotics	Phase 1/Phase 2	Terminated	United States
NCT03585413	Obesity/NAFLD	Probiotics	Phase 3	Recruiting	Germany
NCT04175392	Fatty liver disease	Probiotics	Phase 1/Phase 2	Not yet recruiting	United States
NCT02530138	NASH	Synbiotics	Phase 2/Phase 3	Unknown status[1]	Iran
NCT01791959	NASH	Synbiotics	Phase 2/Phase 3	Completed	Iran
NCT02496390	Diabetes mellitus/NAFLD	FMT	Phase 1/Phase 2	Completed	Canada
NCT02530385	Obesity/NAFLD	FMT	Phase 1/Phase 2	Completed	United States
NCT02741518	Obesity/NAFLD	FMT	Phase 1/Phase 2	Active, not recruiting	United States
NCT02970877	Obesity/NAFLD	FMT	Phase 2	Recruiting	Canada
NCT02050607	Metabolic syndrome/NAFLD	FMT	Phase 3	Unknown status[1]	Italy
NCT02862249	Cirrhosis	FMT	Phase 3	Recruiting	United Kingdom
NCT03014505	Cirrhosis	FMT	Phase 1/Phase 2	Unknown status[1]	China

[1]Study has passed its completion date and status has not been verified in more than two years. Data from https://clinicaltrials.gov/. FMT: Fecal microbiota transplantation; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis.

GUT MICROBIOTA-DERIVED COMPONENTS AND METABOLITES

Studies[77-84] show that the interaction between gut microbiota and their hosts is mediated by various metabolites that are secreted, degraded, or modified by the former, such as short-chain and long-chain fatty acids, amino acids, bile acids, vitamins, and polysaccharides. These metabolites form an intricate signaling network that affects host metabolism and prevents the growth of pathogenic bacteria, and therefore can be utilized to restore the gut microbiota and supplement the effects of FMT or probiotics[85].

Short chain fatty acids (SCFA) supplementation have shown ameliorative effects in cancer[86,87], metabolic diseases[88-90], and other diseases. SCFA is produced during the fermentation of dietary fiber in the gut, and can activate G protein coupled receptor and lower histone deacetylase activity. It is also a fuel for gut epithelial cells and regulates multiple metabolic pathways in the intestine[91]. SCFA administration in metabolic diseases modulates immune homeostasis, gut hormone secretion, inflammatory response, gut barrier, and other functions[92-95].

Bile acid (BA) is a cholesterol derivative that is synthesized and conjugated in the liver. It plays a central role in digestion by emulsifying dietary fats and promoting the absorption of lipids and vitamins in the small intestine (mainly the ileum), which affects hepatic lipid accumulation and inflammation. Thus, BA is a critical signaling molecule that functionally connects the intestine and liver. The BA receptor (BAR), also known as FXR, is highly expressed in the liver and intestine and regulates the synthesis of bile acids through a feedback mechanism. A recent study identified TGR5 as another major BAR in the liver[96]. The underlying mechanisms remain to be elucidated in order to determine whether FXR agonistic or antagonistic effects are beneficial to NAFLD. Amino acid catabolites play a regulatory role in NAFLD by influencing intestinal epithelial barrier and have therapeutic effects on liver function[96]. Indole propionic acid and other indole-like molecules maintain the integrity of intestinal epithelial barrier[97] and control inflammation, and can directly act on hepatocytes and liver immune cells[98].

Gut microbiota-derived metabolites can overcome the major disadvantage of colonization resistance associated with probiotics and FMT. However, metabolite

therapy also has several limitations that ought to be considered[85]. First, the endogenous gut microbiota and the exogenous metabolites may interact unpredictably, which can aggravate the intestinal dysbiosis or even alter the gut microbiota to produce harmful metabolites. Second, the sudden change in the intestinal levels of the supplemented metabolites may also disrupt the feedback loops of the endogenous metabolites. Long-term supplementation of metabolites can even lead to the emergence of host or bacterial resistance, and thus alter the therapeutic target. Third, the low level of some metabolites in the feces may not truly reflect the status in the intestine, and the suboptimal absorption of oral metabolites in the proximal gastrointestinal tract would decrease their effects on the distal small intestine and colon. In addition, the long-term and systemic effects of these metabolites are unknown and need to be elucidated through detailed pharmacokinetics and pharmacodynamics studies. Finally, bacterial metabolites have very complex chemical structures and some are even volatile, which makes laboratory synthesis technically challenging[85]. Taken together, the clinical application of bacterial metabolites will have to be supported by strong experimental foundations.

CONCLUSION

NAFLD is a common chronic liver disease that can progress to cirrhosis and HCC, and the prevalence of NAFLD/NASH is increasing globally. The advent of 16S high-throughput sequencing has increased the potential for microbiota-targeted NAFLD/NASH treatment. Apart from bacteria, the intestinal microbiome includes fungi, viruses, and archaeabacteria, which are associated with various liver diseases. Therefore, it is logical to target the gut–liver axis, especially the microbiota, in order to alleviate the symptoms of NAFLD. Although conventional antibiotics can modulate NAFLD symptoms, their clinical use is largely limited due to their side effects and the emergence and prevalence of bacterial resistance. Probiotics, prebiotics, and synbiotics are safe and effective alternatives to conventional antibiotics for treating NAFLD. In addition, FMT is also a promising strategy that can reverse the intestinal dysbiosis associated with NAFLD. Novel therapies involving gut microbiota-derived components and metabolites are increasingly being developed for their unique advantages. The next generation microbiota-targeted therapies against NAFLD include genetically engineered microbiota and recombinant metabolites. Furthermore, the genomes of NAFLD patients and possible genetic determinants of therapeutic responses should also be explored to develop more personalized therapies.

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