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REVIEW

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The gut-liver nexus: exploring gut microbiota dysbiosis in non-alcoholic fatty liver disease and its therapeutic implications

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Abstract

Background The human gut microbiota (GM) is a diverse ecosystem crucial for health, impacting physiological processes across the host's body. This review highlights the GM's involvement in Non-Alcoholic Fatty Liver Disease (NAFLD) and explores its diagnosis, treatment, and management.

Main Text The GM influences gut functionality, digestion, immunity, and more. Short-chain fatty acids (SCFAs), produced by microbial fermentation, regulate metabolism, inflammation, and immune responses. Bile acids (BAs) modulate the microbiome and liver functions, affecting NAFLD progression. Dysbiosis and increased gut permeability contribute to NAFLD through bacterial components and metabolites reaching the liver, causing inflammation and oxidative stress. The microbiome's impact on immune cells further exacerbates liver damage. Symptoms of NAFLD can be subtle or absent, making diagnosis challenging. Imaging techniques assist in diagnosing and staging NAFLD, but liver biopsy remains vital for accurate assessment. Promising treatments include FXR agonists, GLP-1 agonists, and FGF19 and FGF21 mimetics, targeting various pathways associated with NAFLD pathogenesis. Fecal Microbiota Transplantation (FMT) emerges as a potential therapeutic avenue to restore gut microbiota diversity and alleviate NAFLD. Lifestyle interventions, such as dietary modifications, exercise, and probiotics, also play a pivotal role in managing NAFLD and restoring gut health.

Conclusion Despite significant progress, the complex interplay between the gut microbiome, NAFLD, and potential treatments necessitates further research to unravel underlying mechanisms and develop effective therapeutic strategies.

Keywords Gut Microbiota, Non-Alcoholic Fatty Liver Disease, Short-Chain Fatty Acids, Bile Acids, Dysbiosis, Fecal Microbiota Transplantation

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Introduction

The human gut microbiota (GM) is a complex and diverse ecosystem essential to human health and overall well-being. It comprises an immense number of microorganisms, including bacteria, fungi, archaea, viruses, and helminths [1]. Collectively, these microorganisms are referred to as the gut microbiota, and their combined genetic material is termed the gut microbiome [2]. These microorganisms consist of up to 5000 different species and weigh approximately 1% of an adult human's body mass [3]. Indeed, the GM plays a vital role in supporting various physiological processes of the host. Its most significant contribution lies in supporting the intestine, which ensures optimal gut functionality across multiple aspects. These include aiding in digestion, harvesting energy from nutrients, enhancing mucosal immunity, maintaining the integrity of the intestinal barrier, defending against pathogens, and producing essential vitamins, neurotransmitters (NT), and potentially beneficial bioactive compounds, such as short-chain fatty acids (SCFAs), which are valuable molecules for the host [4–8]. The human gut microbiome closely interacts with different organs within the host body, such as the gut responsible for food digestion, the liver for processing after absorption, and adipose tissue for storage. This significant level of integration has led numerous researchers to assume the human GM to a microbial organ of human body [9]. The gut microbiota consists mainly of four primary categories of microorganisms: *Firmicutes*, *Bacteroides, Actinomycetes, Verrucomicrobia*, and *Proteus* [10] Among these, the ratio of *Firmicutes* to *Bacteroidetes* is commonly used as a critical parameter in identifying potential gut health disorders [11]. In recent years, the field of gut microbiota research has experienced significant progress, driven by advancements in molecular biology, genomics, bioinformatics analysis technology, and high-throughput sequencing technology. This review elaborates on the involvement of the gut microbiome in chronic diseases like non-alcoholic fatty liver disease (NAFLD) and explores how it can be diagnosed, treated, and managed for prevention.

Gut microbiota dysbiosis in non-alcoholic fatty liver disease

In gut, the microbiota community plays a crucial role in various physiological processes within the human digestive system. Importantly, this community significantly contributes to functions like digestion, metabolism, and protective mechanisms. Several studies illustrate that different pathway of the gut microbiome are involved in the progression of NAFLD [12, 13]. The gut microbiota's utilization of enzymes is vital for the efficient conversion of undigested polysaccharides into monosaccharides and the conversion of dietary fibers into short-chain fatty acids (SCFAs). This process is crucial as it provides essential energy support to the host cells. These SCFAs form a group of organic acids produced through bacterial fermentation of dietary fibers within the colon (Fig. 1). They have attracted considerable interest due to their potential health benefits, particularly in regulating metabolism, immune responses, the absorption of electrolytes and nutrients, as well as exhibiting anti-inflammatory and antitumor characteristics [14]. The daily production of SCFAs in the colon varies based on the intake of dietary fiber, usually falling within the range of 500 to 600 mmol. Among these SCFAs, acetate, propionate, and butyrate are notable for being the most abundant within the intestinal tract [15].

Acetic acid plays a significant role as a vital energy source for the body, contributing roughly 10% of the daily energy requirement. In contrast, butyric acid assumes a crucial function in providing energy to support epithelial cells, thereby playing a vital role in upholding the integrity of the intestinal barrier. Furthermore, it acts as the primary metabolic substance for the gastrointestinal microbiota, meeting at least 60–70% of their energy demands for growth and differentiation [16]. Moreover, butyric acid has the ability to hinder the activation of Carbohydrate response element binding protein (ChREBP) and sterol regulatory element binding protein 1 (SREBP-1), then, suppress the process of lipogenesis [17]. Propionic acid primarily undergoes catabolism within the liver, participating in the conversion of pyruvate to glucose. Furthermore, it has demonstrated the capacity to diminish lipid buildup in individuals dealing with excess weight and adiposity [18]. Unlike butyric and acetic acids, which serve as energy sources for host cells, propionic acid serves as a precursor for adipogenesis and gluconeogenesis. These latter processes hold greater significance in the development of NAFLD [19]. Dietary fiber has gained recognition for its multitude of health advantages, especially in enhancing digestive well-being and overall vitality. The consumption of dietary fiber, irrespective of its origin, can exert favorable impacts on the intestinal tract, particularly benefiting individuals with insufficient dietary fiber intake [20].

The SCFAs trigger the activation of G protein-coupled receptors, namely GPR41 and GPR43, located within the intestinal and adipose tissues [21]. The stimulation of GPR41 leads to enhance the secretion of glucagon-like peptide 1 and peptide YY (PYY) from enteroendocrine cells. This process, in turn, causes a reduction in intestinal motility while concurrently enhancing the absorption of nutrients. On the other hand, the activation of GPR43 hinders the differentiation of adipocytes and amplifies hepatic lipogenesis, thus fostering the

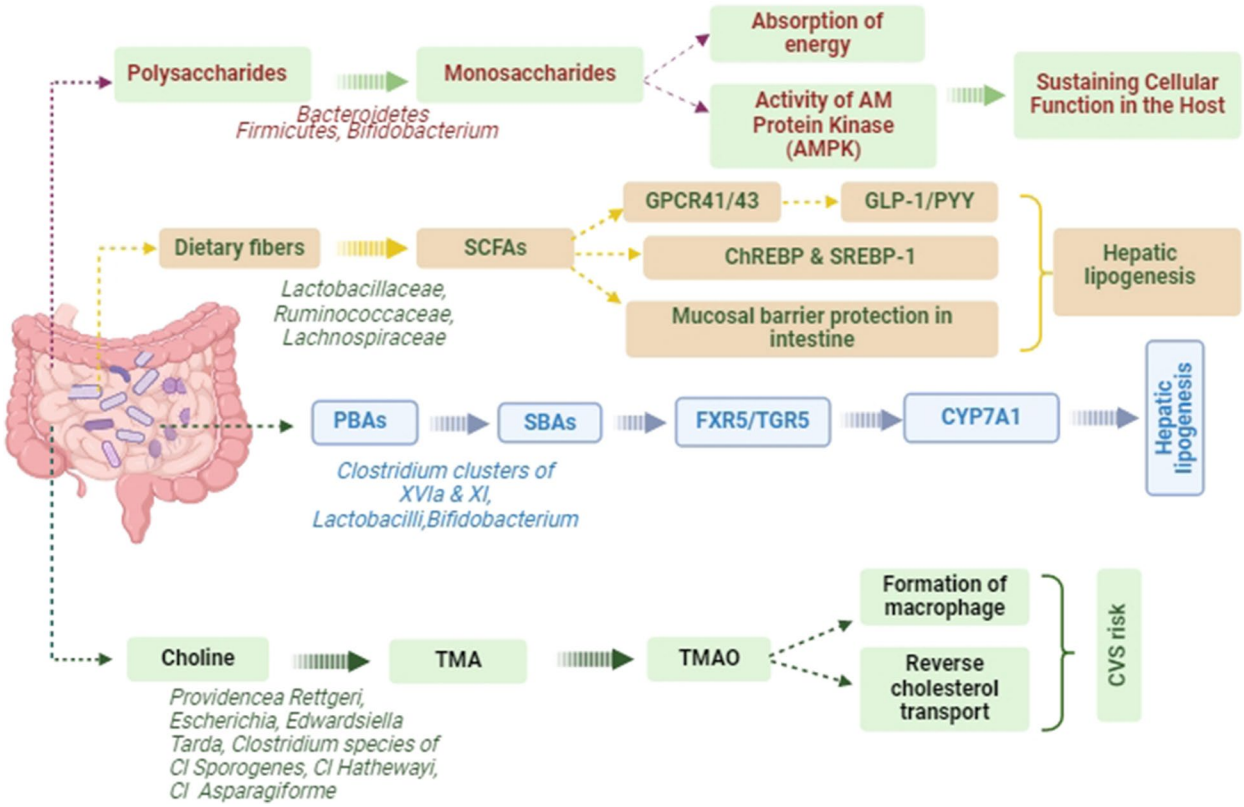

Fig. 1 The involvement of gut microbiota and their resulting substances in the progression of NAFLD. The products generated by gut microorganisms, encompassing monosaccharides, short-chain fatty acids (SCFAs), bile acids (BAs), and trimethylamine oxide (TMAO), assume crucial roles not only in the liver's energy metabolism and the cellular lining of the intestines but also exert a direct influence on the production of liver fat and overall systemic inflammation. A range of molecular elements come into play, including adenosine monophosphate-dependent protein kinase (AMPK), carbohydrate-responsive element-binding protein (ChREBP), Cytochrome P450 7A1 (CYP7A1), farnesoid X receptor (FXR), glucagon-like peptide-1 (GLP-1), G protein-coupled receptor 41/43 (GPCR41/43), peptide YY (PYY), sterol regulatory element-binding protein 1 (SREBP-1), and Takeda G protein receptor 5 (TGR5). Collectively, these elements contribute to these effects

progression of NAFLD [22]. Bile acids constitute the principal elements of bile and can be categorized into primary and secondary forms. Hepatocytes manufacture primary bile acids (PBAs), which encompass cholic acid (CA) and chenodeoxycholic acid (CDCA), through the conversion of cholesterol. Subsequently, these PBAs are secreted into the bile duct. Bacteria located in the small intestine then facilitate the conversion of primary bile acids into secondary bile acids (SBAs), which comprise lithocholic acid (LCA), deoxycholic acid (DCA), ursodeoxycholic acid (UDCA), and corresponding isoforms like isolithocholic acid. Primarily, bile acids play a significant role in regulating the balance of intestinal microbiota by directly preventing the proliferation of harmful bacteria, but they also function as natural activators of the intestinal farnesoid X receptor receptor (FXR). This activation sequence, prioritized as CDCA, DCA, LCA, and CA, triggers the activation of protective genes in the mucosal lining of the ileum. As a result, this helps safeguard the intestinal epithelial cells from the corrosive effects of bacteria and other microorganisms, contributing to overall gut health [23]. Furthermore, FXR decreases the expression of liver X receptor (LXR) and sterol regulatory element binding protein-1c (SREBP-1c), leading to a reduction in the synthesis of fatty acids and triglycerides within the liver. This, in turn, mitigates the processes of steatogenesis and gluconeogenesis. Additionally, FXR enhances hepatic glycogen synthesis by activating fibroblast growth factor (FGF) 15/19, PPARg, GLUT-4, and GLP-1, thereby enhancing insulin sensitivity [24].

The bile acid G-protein-coupled membrane receptor-5 (TGR5) represents another conventional BA receptor, primarily triggered by SBAs (TGR5 activation sequence: LCA > DCA > CDCA > CA). Insufficient SBAs result in decreased FXR activity but heightened inflammation within the body, whereas excessive SBAs have the potential to induce harm to cellular DNA through the generation of reactive oxygen species (ROS), subsequently leading to the emergence of hepatocellular carcinoma (HCC). Research has demonstrated that the activation

of TGR5 through SBAs initiates the transcription of the type 2 iodothyronine deiodinase (Dio2) gene. This, in turn, facilitates the conversion of thyroid hormone (T4) to the more potent triiodothyronine (T3), consequently elevating basal metabolism and fostering energy utilization in the brown adipose tissue and muscle of mice fed a high-fat diet (HFD) [25]. Stimulation of TGR5 within cells responsible for intestinal secretion through SBAs triggers the upregulation of GLP1 expression. This, in turn, enhances insulin production and release, leading to safeguarding against apoptosis of islet b-cells and enhancement of blood glucose regulation. Nevertheless, changes in gut microbiota and liver function directly impact the eventual compositions and quantities of BAs. As a result, distinct expression patterns of BA receptors (such as FXR and TGR5) emerge at various stages of the NAFLD progression. In any case, both FXR and TGR5, the two BA receptors, have emerged as potential targets for addressing obesity and NAFLD. Trimethylamine (TMA) and trimethylamine N-oxide (TMAO) are metabolites of choline and its derivatives synthesized by gut microbiota. These compounds not only contribute to the onset of atherosclerosis, but also have a significant effect on the metabolism of cholesterol and triglycerides [26]. Clinical trials have demonstrated that a decrease in choline levels can result in the accumulation of lipids in the liver. This occurs due to a reduction in the production and release of very low-density lipoproteins (VLDL) in liver cells, which ultimately leads to the development of steatohepatitis. This outcome is commonly observed in rodents that are fed a diet deficient in methionine and choline (MCD). It has been established that foods containing dietary methylamine, choline, phosphatidylcholine, and carnitine undergo breakdown into various metabolites, including trimethylamine (TMA), through the degradation of trimethylamine lytic enzymes in bacteria of the *Proteobacteria* and *Firmicutes* phyla. TMA is transported to the liver through the portal vein. Within the liver, it undergoes conversion by flavin-containing monooxygenases, resulting in the formation of TMAO. This compound plays a pivotal role in fostering the buildup of activated leukocytes within human endothelial cells. Consequently, this process leads to impaired functioning of endothelial cells, thereby substantially amplifying the susceptibility to atherosclerosis and cardiovascular diseases [27, 28].

Influence of gut microbiota on intestinal and hepatic immune function

Research indicates that the advancement of NAFLD is associated with the decline in the integrity of the intestinal barrier [29, 30]. During the development and advancement of NAFLD, significant amounts of metabolites originating from gut bacteria, along with bacterial components and other potential hazards, enter the liver through the portal vein. This occurs due to the disruption of the intestinal mucosal barrier caused by various factors, leading to an increased permeability of the intestines (Fig. 2). These intrusions have the capability to accelerate liver damage and fibrosis by amplifying inflammation, oxidative stress, and the accumulation of lipids [31]. The investigation through in situ hybridization discovered the presence of bacterial metabolites and DNA fragments from the gut in the livers of mice fed a high-fat diet (HFD). However, it remains unclear whether bacteria are present in the livers of patients with non-alcoholic steatohepatitis (NASH). In comparison to individuals with normal health, individuals with obesity or non-alcoholic fatty liver disease (NAFLD) exhibited a significant increase in the number of enteric bacteria, particularly Gram-negative types, which led to noticeable endotoxemia [32].

Abundant of lipopolysaccharides (LPS) trigger the activation of adenylate cyclase in the intestinal mucosa, which subsequently harms mitochondria and lysosomes within epithelial cells. This harmful cascade ultimately results in the necrosis of apical cells on intestinal villi and the autolysis of epithelial cells. Additionally, the inflammation of the liver and its ongoing damage are primarily driven by gut-derived LPS. These LPS molecules play a crucial role in initiating signaling through LPS-dependent pattern recognition receptors, contributing to the inflammatory process [33]. LPS triggers the activation of TLR4 within endothelial cells and TLR9 within dendritic cells. This activation leads to the secretion of a significant array of pro-inflammatory cytokines like TNF-a, IL-1b, and IL-6 and chemokines such as CCL2, CXCL2, CXCL10, and CXCL16. These molecules collectively drive inflammation and pathological harm to the liver [34, 35]. Consequently, LPS initiates inflammation and substantial metabolic alterations in the body, including increased fat utilization, enhanced circulation of free fatty acids (FFA), and elevated triglyceride (TG) levels. This accumulation of FFA in the liver could also incite inflammation and insulin resistance (IR), thereby further promoting the progression of NAFLD [36, 37]. Conversely, the gut microbiota has the capacity to modify the equilibrium between proinflammatory and anti-inflammatory cytokines produced by M1 and M2 macrophages. This modulation occurs through the influence on the metabolism of short-chain fatty acids (SBAs), ultimately impacting the immune function of the liver [38]. Small amounts of SBAs produced by the gut microbiota can have the capability to decrease FXR activity and enhance inflammation in the body. On the other hand, high levels of SBAs can result in the production of a considerable

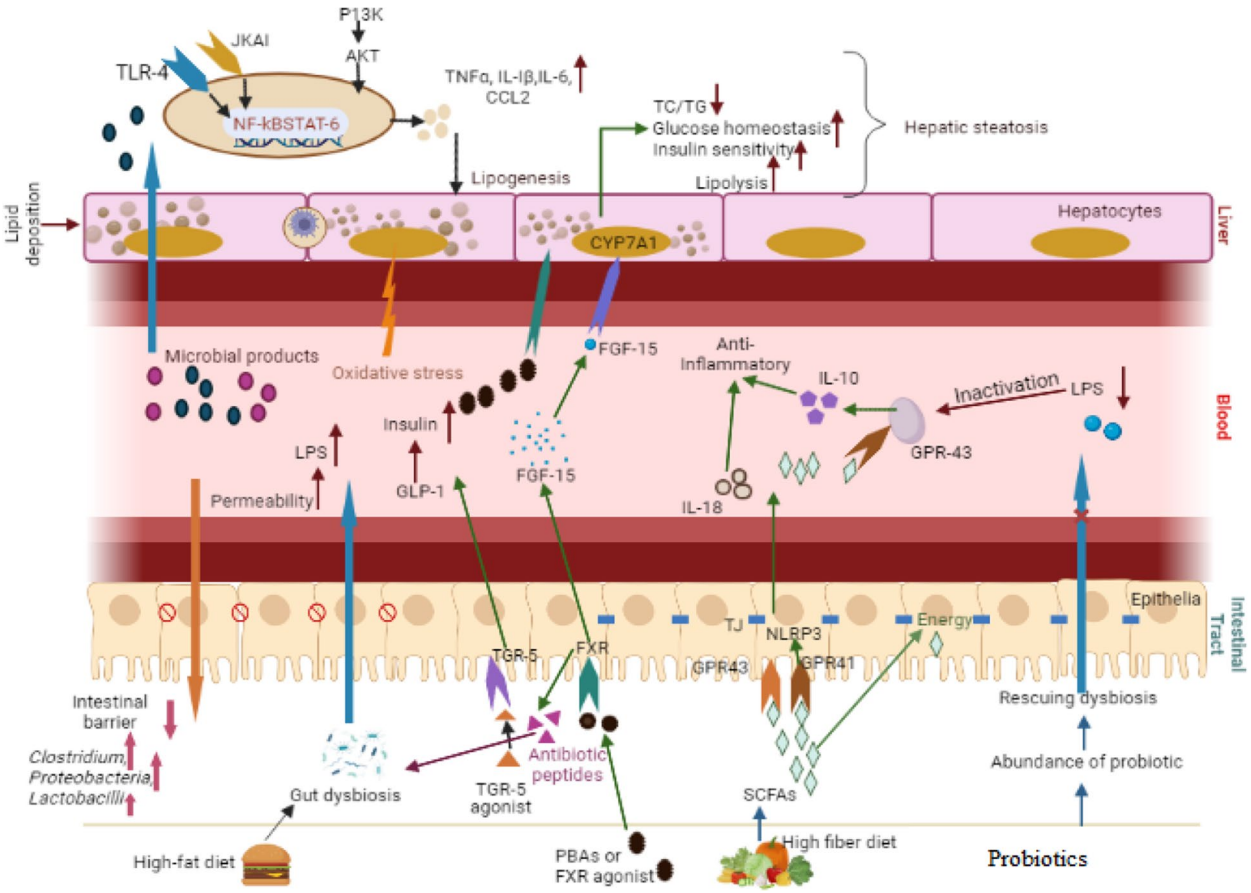

Fig. 2 Gut dysbiosis disrupts the integrity of the intestinal barrier, enabling the passage of bacterial endotoxins into the liver. This, in turn, amplifies the inflammatory processes and the accumulation of fat, contributing to the development of NAFLD. Unhealthy lifestyle choices, such as a high-fat, low-fiber diet, alter the composition of the gut microbiota. This alteration increases the permeability of the gut, leading to the production of various proinflammatory molecules, including LPS, TMAO, SBAs, and bacterial 16sDNA. These proinflammatory molecules further exacerbate liver inflammation and fibrosis, potentially accelerating the progression of NAFLD. Various interventions, such as treatment with FXR/TGR5 agonists, and probiotics play a crucial role in strengthening the tight junctions within the intestinal barrier. They also regulate glucose and lipid metabolism by activating FXR and TGR5 signaling pathways, while simultaneously inhibiting the TLR4/NF-kB and JAK1/STAT6 pathways

number of ROS, leading to damage to the DNA of cells and promoting the development of HCC [39]. Additionally, PBAs can prompt an increased expression of CXCL16 in hepatic vascular endothelial cells. Subsequently, this process triggers the attraction of NKT cells, which are capable of eliminating tumor cells in a manner that relies on CD1d [40].

Symptoms of NAFLD

NAFLD often presents either mild or vague symptoms during its initial stages [41]. Some individuals may not perceive any noticeable symptoms at all. This lack of prominent indicators can create difficulties in identifying the condition without specific medical assessments. Certain individuals might not show any observable signs. The absence of notable symptoms can hinder the detection of the condition without particular medical examinations. Fatigue, discomfort in the upper right abdomen, enlarged liver (hepatomegaly), a skin condition with dark and thickened patches, (acanthosis nigricans), and accumulation of excess fat (lipomatosis) might be experienced by some individuals. In certain cases, NAFLD can progress to more severe liver disorders, ultimately leading to cirrhosis. Patients with cirrhosis may exhibit symptoms that are characteristic of end-stage liver disease.

Diagnosis of NAFLD

Different imaging techniques can be used in NAFLD to support the diagnosis. However, these imaging modalities are not routinely employed to differentiate between the histological subtypes of NAFLD. Following are some diagnostic tools utilized for detecting hepatic steatosis.

Ultrasound

Ultrasound emerges as the primary imaging modality for evaluating patients diagnosed or suspected with NAFLD. B-Mode ultrasound images show the potential to improve diagnostic accuracy for detecting and grading hepatic steatosis. It proves to be an exceptional tool for identifying moderate to severe steatosis among NAFLD patients [42].

Computed tomography (CT)

Clinical CT shows significant promise in detecting incidental steatosis and aiding in understanding the typical course of NAFLD. Dual-energy CT (DECT), utilizing different energy levels, offers potential to distinguish diverse tissue compositions, such as fat, thereby providing improved diagnostic accuracy for hepatic steatosis compared to traditional single-energy CT [43].

Magnetic resonance imaging

MRI technology, particularly multiparametric methods like PDFF, T2 and T1 mapping, and MR elastography, is continuously being integrated into clinical practice. This comprehensive approach to liver imaging shows potential in managing NAFLD by accurately measuring fat content, iron levels, and fibrosis, essential features of the disease [44].

Transient elastography (FibroScan)

assist in diagnosing liver diseases and provide information about the fat presence and liver stiffness, they cannot substitute for a liver biopsy when it comes to accurately determining the histological subtypes and to guide appropriate clinical management and monitoring [45].

Vibration-controlled transient elastography (VCTE)

VCTE is a non-invasive medical imaging technique used to assess the stiffness or elasticity of the liver [46, 47]. This quick and painless procedure offers valuable information on liver fibrosis and cirrhosis. VCTE also aids in guiding treatment decisions and monitoring disease progression. However, it does not identify the underlying cause of liver disease.

Liver biopsy

Liver biopsy plays an important role as a diagnostic tool in differentiating between simple fatty liver and NASH and in assessing the state of fibrosis in NAFLD patients. This enables assessment of the degree of fibrosis, which provides valuable prognostic information and improves the clinical management of NAFLD [48–50]. However, it carries some risks and discomfort for the patient. Therefore, non-invasive methods are also employed to assess liver health and fibrosis in NAFLD patients. These non-invasive techniques include imaging studies such as transient elastography and blood tests (Fibrosis-4 Index and enhanced liver fibrosis tests) [51]. These methods offer valuable information about liver stiffness and fibrosis levels without the need for a liver biopsy, and they play a significant role in the clinical evaluation of NAFLD patients, providing an alternative or complementary approach to liver biopsy when appropriate.

Loomba etal. investigated the potential correlation between the gut microbiome and liver disease associated with obesity [52]. To explore this connection, Loomba analyzed two distinct sets of patients. The initial group encompassed 86 patients who were diagnosed with non-alcoholic fatty liver disease (NAFLD) via biopsy. Among them, 72 had mild to moderate NAFLD, while 14 had advanced-stage disease. The team employed sequencing techniques to scrutinize the microbial genes derived from stool samples provided by each participant. This allowed them to pinpoint the species present and their relative proportions. Noteworthy findings emerged, as they identified 37 bacterial species that could differentiate between mild/moderate NAFLD and advanced-stage disease. Remarkably, this differentiation accurately predicted advanced-stage disease in patients with an impressive 93.6% accuracy. To validate this discovery, a subsequent study involving 16 patients with advanced NAFLD and 33 healthy individuals as a control group was conducted. This phase revealed nine bacterial species that set apart NAFLD patients from the healthy volunteers, achieving an accuracy rate of 88%. Notably, seven of these bacterial species aligned with the previously discovered 37. The study demonstrated that patients with advanced NAFLD exhibited a higher prevalence of *Proteobacteria* and a lower presence of *Firmicutes* in their stool compared to those with early-stage NAFLD. At a more specific level, the abundance of E. coli was notably three times higher in patients with advanced NAFLD compared to those in the early stages of the disease.

Treatment

In recent years, a multitude of trials have investigated diverse medications with varying mechanisms of action in the context of NAFLD/NASH, yielding encouraging results. Within this specific context, we aim to provide a comprehensive overview of key clinical findings, alongside stratified pharmacological mechanisms designed to specifically target NAFLD. Effective drugs like vitamin E and Pioglitazone exist for treating and preventing NAFLD [53]. Pioglitazone has shown efficacy in cases involving advanced NASH patients with type 2 diabetes; However, this underscores the lack of reliable clinical

Table 1 The current clinical scenario involving the use of agents that focus on the gut microbiota for the treatment of NAFLD

Target	Drug	Clinical Status	Disease	Impact
FXR-agonist	Obeticholic acid (OCA)	Approved	NAFLD	It regulates glucose, lipid metabolism, oxidative stress, and inflammation [54, 55]
	PX-104	Phase IIa	Non-diabetic NAFLD	Improve insulin sensitivity, a key regulator of bile acid glucose and lipid homeostasis [56]
	Nidufexor (LMB-763)	Phase II	NASH and diabetic nephropathy	Diminish NAFLD activity scores, lower triglyceride levels, and mitigate liver fibrosis [57]
	Cilofexor (GS-9674)	Phase III	NAFLD, NASH, and primary sclerosing cholangitis [58–60]	Reduce levels of serum g-glutamyl transferase, C4, and primary bile acids [61]
	Tropifexor	Phase II	Cholestatic liver diseases and NASH	Inhibits bile acid synthesis and increases bile acid conjugation, transport, and excretion [62]
	EDP-305	Phase II	NASH, cholangiopathies, renal fibrosis	Reduce alanine aminotransferase ALT levels and liver fat content [63]
	Chenodeoxycholic acid (CDCA)	Approved	NAFLD	Enhance liver functionality while reducing the synthesis of endogenous bile acids [64]
FXR-antagonist	Ursodeoxycholic Acid (UDCA)	Approved	NASH	Reduce serum levels of ALT and GGT in patients with NASH [65]
	Glycine-β-muricholic Acid (Gly-MCA)	Approved	NAFLD	Reduction of plasma ceramide levels by decreasing the intestinal production of ceramide [66]
Glucagon like peptide-1 agonist	Semaglutide	Approved	NAFLD	Semaglutide exhibits the capacity to lower blood glucose levels, mitigate the buildup of liver fat, and exert anti-inflammatory effects in advanced NAFLD attributed to the impacts of a high-fat diet [67]
Fibroblast growth factor 19 mimetics	Aldafermin	Phase IIb	NASH	Functioning as an FGF19 analogue, curbs CYP7A1 activity via the FGFR4-βKlotho receptor complex on hepatocytes. This, in turn, leads to diminished levels of hydrophobic and glycine-conjugated bile acids in patients with NASH [68]
Fibroblast growth factor 21 mimetics	Pegbelfermin	Clinical investigation	NAFLD	Pegbelfermin decreased DCA levels, suppressed gene expression, and influenced microbiome-driven secondary BA synthesis in NASH [69]
	Efruxifermin	Phase IIa	NASH cirrhosis	Efruxifermin decreases liver fat and markers of liver injury, reduces fibrosis, improves glucose and lipid metabolism, and lowers hyperuricemia. Furthermore, a weight loss trend is observed [70]
Peroxisome proliferator-activated receptor (PPAR)	Seladelpar (MBX-8025) PPARδ	Clinical investigation	Diabetic NAFLD, NASH	Seladelpar enhanced multiple aspects of glucose regulation and liver tissue structure, addressing issues like inflammation and fat buildup [71]

Table 1 (continued)

Target	Drug	Clinical Status	Disease	Impact
	Saroglitazar (PPARα and PPARγ agonist)	Clinical investigation	NASH	Improves hepatic steatosis, and decreases plasma ALT levels. In addition, it positively affected all histologic characteristics associated with NASH [72, 73]
Thyroid hormone receptor beta (THR-B) agonist	VK2809	Clinical investigation	NAFLD	Reduction in hepatic TAG content in NAFLD [74]
	ASC41	Advancing to phase II	NAFLD, NASH	Hypolipidemic activity in healthy volunteers [75]
	TERN-501	Phase I	Hyperlipidemia and NASH	Reduced serum cholesterol levels and attenuated liver steatosis and fibrosis [76]
	Resmetrirom (MGL -3196)	Phase III		TRβ agonist reduces hepatic fat and markers of inflammation and fibrosis and reduces elevated liver enzymes [77]
	Clostridium butyricum combined with Rosuvastatin	Clinical investigation	NAFLD	Gut microbiota and HMG-CoA reductase Inhibitor [78]

data to fully support its use in this particular context. Vitamins E and D show certain effectiveness although uncertainty remains regarding their long-term safety and therapeutic efficacy. On the other hand, Statins can lower serum LDL levels and mitigating cardiovascular problems, but they do not address the progression of liver disease. Currently, there is no FDA-approved treatment for NAFLD. However, targeted therapies are in different phases of clinical trials. Table 1 outlines a number of encouraging drug contenders at various stages of clinical development for NAFLD.

Fecal microbiota transplantation (FMT)

FMT presents a novel approach for restoring and rebalancing the diversity of the gut's microorganisms, aiming to address various diseases, including *Clostridioides difficile* infection [79]. Additionally, FMT has shown promise in treating metabolic diseases, tumors, autoimmune disorders, and hepatic encephalopathy [80–82]. Studies on animals have indicated that FMT can effectively improve the manifestations of NAFLD by addressing gut microbiota dysbiosis [83–85]. As a result, FMT has become an appealing option for NAFLD patients. However, there have been only a limited number of studies exploring the clinical efficacy of FMT in NAFLD treatment. One randomized control trial revealed that FMT has the potential to reduce small intestinal permeability in NAFLD patients [86, 87]. Moreover, FMT from healthy donors has been found to impact hepatic gene expression and plasma metabolites related to inflammation and lipid metabolism, demonstrating the significant interplay between gut microbiota composition and NAFLD.

Management of gut dysbiosis

Patients with NAFLD often follow high-calorie diets rich in carbohydrates and fats, contributing to obesity. Mitigating NAFLD risk involves replacing saturated and trans fats with healthier unsaturated fats, particularly omega-3 fatty acids. Opting for low-glycemic index foods such as fruits, vegetables, and whole grains is recommended as they have a milder effect on blood glucose compared to high-glycemic index foods like white bread and potatoes. Sugary beverages, notably high in sucrose and fructose, are linked to NAFLD and should be avoided [88, 89]. NAFLD's connection to obesity emphasizes the need for gradual weight loss through balanced eating and exercise. Shedding 7 to 10% of body weight through diet and physical activity notably improves NAFLD and its more severe form, NASH, decreasing liver fat content and addressing fibrosis.

Regular physical activity, aiming for 150 min of moderate-intensity or 75 min of vigorous-intensity exercise weekly, positively impacts gut microbiome and liver health [90]. Emerging research indicates the significance of probiotics, prebiotics, and synbiotics in gastrointestinal health. These therapies target disrupted gut microbiota, which plays a pivotal role in NAFLD development. Probiotic and prebiotic supplementation have shown promise in reducing liver enzymes AST and ALT in damaged liver patients [91–94]. The intricate gut microbiota is essential for digestion, vitamin synthesis, immune training, and pathogen prevention. Antibiotic use, particularly fluoroquinolones, can disrupt this ecosystem, leading to reduced diversity and opportunistic infections.

Conclusion

The human gut microbiota plays a crucial role in maintaining various physiological processes and overall health. The intricate interactions between the gut microbiome, liver function, and immune responses have significant implications for the development and progression of non-alcoholic fatty liver disease (NAFLD). The dysbiosis of gut microbiota, characterized by alterations in microbial composition and metabolic activity, has been associated with NAFLD through its influence on digestion, energy metabolism, inflammation, and immune function. This review article has highlighted the role of short-chain fatty acids (SCFAs), bile acids, and gut-derived endotoxins in the development of NAFLD. SCFAs, produced by the fermentation of dietary fibers, have been shown to influence energy homeostasis, lipid metabolism, and inflammation. Bile acids, beyond their role in digestion, regulate various aspects of liver health, including lipid metabolism and inflammation. Dysbiosis-related alterations in SCFAs and bile acids contribute to liver inflammation and lipid accumulation, pivotal factors in NAFLD progression. Moreover, the disruption of the intestinal barrier integrity allows the translocation of bacterial products, including lipopolysaccharides (LPS), into the liver. This initiates an inflammatory response and oxidative stress, further promoting liver damage. The interplay between gut microbiota and the immune system has been shown to impact the progression of NAFLD, with dysbiosis promoting inflammation through the activation of pattern recognition receptors.

Diagnosis and management of NAFLD have also seen advancements in recent years. Non-invasive techniques such as transient elastography and blood tests have emerged as alternatives to liver biopsy for assessing liver fibrosis. Targeted therapies, including FXR agonists and antagonists, GLP-1 agonists, and thyroid hormone receptor agonists, are being investigated for their potential to address NAFLD at the molecular level. Furthermore, the potential of fecal microbiota transplantation (FMT) has garnered attention as a novel approach to restoring gut microbiota balance in NAFLD patients. Promising results

from animal studies and limited clinical trials suggest that FMT could influence gut-liver crosstalk and potentially mitigate NAFLD-associated conditions. Lifestyle interventions remain crucial for managing NAFLD. Dietary modifications, physical activity, and weight loss continue to be cornerstones of NAFLD management, as they can positively impact gut microbiota composition and diversity. Probiotics, prebiotics, and synbiotics also hold promise in improving gut health and mitigating NAFLD risk.

In summary, the intricate relationship between gut microbiota, liver health, and NAFLD underscores the importance of understanding these interactions for the development of targeted therapeutic strategies. Advances in diagnostic techniques, treatment options, and lifestyle interventions are paving the way for a comprehensive approach to managing NAFLD by addressing gut microbiota dysbiosis and its implications for overall health. Further research in this field holds the potential to revolutionize our approach to preventing and treating NAFLD, a growing global health concern.

Abbreviations

GM	Gut microbiota
NAFLD	Non-alcoholic fatty liver disease
BAs	Bile acids
SCFAs	Short-chain fatty acids
CA	Cholic acid
CDCA	Chenodeoxycholic acid
LCA	Lithocholic acid
DCA	Deoxycholic acid
UDCA	Ursodeoxycholic acid
HCC	Hepatocellular carcinoma
TMA	Trimethylamine
TMAO	Trimethylamine N-oxide (TMAO)
VLDL	Very low-density lipoproteins
HFD	High-fat diet
FMT	Fecal microbiota transplantation

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DMS, SD, and VVSRP wrote and edited the manuscript. JN and SP drew the images. All authors read and approved the final manuscript.

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