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Perspective

# Gut microbiome and liver diseases

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ABSTRACT

Symbiotic microbiota plays a crucial role in the education, development, and maintenance of the host immune system, significantly contributing to overall health. Through the gut-liver axis, the gut microbiota and liver have a bidirectional relationship that is becoming increasingly evident as more research highlights the translocation of the gut microbiota and its metabolites. The focus of this narrative review is to examine and discuss the importance of the gut-liver axis and the enterohepatic barrier in maintaining overall health. Additionally, we emphasize the crucial role of the gut microbiome in liver diseases and explore potential therapeutic strategies for liver diseases by manipulating the microbiota.

## 1. Introduction

The gut and liver interact via several pathways, including the portal vein and biliary and circulatory systems. Anatomically, the portal vein accumulates venous blood from the intestines and provides most of the blood supply [1]. The liver is exposed to almost all bile acids, microbial metabolites, and nutrients, along with a few gut-derived microbes, via the portal vein. Consequently, these gut-derived factors mediate liver functions, including synthetic and secretory functions and immune responses [1,2]. The gut lumen houses a diverse array of microorganisms, including bacteria, fungi, helminths, viruses, and archaea, with combined populations reaching trillions. The liver produces bile acids (BAs), immunoglobulin A (IgA), and antimicrobial molecules that influence the gut microbiome. Maintaining balance in the microbial community is important for the fitness of the host liver [3,4].

*Abbreviations:* 3-sucCA, 3-succinylated cholic acid; ABS, auto-brewery syndrome; AFLD, alcoholic fatty liver disease; AH, alcoholic hepatitis; AMPs, antimicrobial peptides; AhR, aryl hydrocarbon receptor; BAs, bile acids; CLCA, calcium-activated chloride channel regulator; CAID, cirrhosis-associated immune dysfunction; CLAs, conjugated linoleic acids; CAR, constitutive androstane receptor; DCA, deoxycholic acid; DPP4, dipeptidyl peptidase 4; EcN, *E. coli* Nissle 1917; FXR, farnesoid X receptor; FMT, Fecal microbiota transplantation; FAH, fumarylacetoacetate hydrolase; GPCR, G protein-coupled receptors; GLP-1, glucagon-like peptide 1; HE, Hepatic encephalopathy; HSCs, hepatic stellate cells; HBV, hepatitis B virus; HCC, hepatocellular cancer; HiAlc Kpn, high-alcohol-producing *Klebsiella pneumoniae*; IgG4-SC, IgG4-related sclerosing cholangitis; *Il1b*, interleukin-1 beta; ILC3, type 3 innate lymphoid; ICAM-1, intercellular adhesion molecule 1; IgA, Immunoglobulin A; IBD, inflammatory bowel diseases; ISAPP, International Scientific Association for Probiotics and Prebiotics; LGG, *Lactobacillus rhamnosus* GG; LPS, lipopolysaccharides; LSECs, liver sinusoidal endothelial cells; Lypd8, Ly6/plaur domain-containing protein 8; MASH, metabolic dysfunction-associated steatohepatitis; MAFLD, metabolic-associated fatty liver disease; MadCAM-1, mucosal vascular addressin cell adhesion molecule 1; MAMPs, microbe-associated molecular patterns; MHI, microbial-host-isozyme; MUCs, mucins; NK, natural killer cells; NKT, natural killer T cells; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAMPs, pathogen-associated molecular pattern; PRRs, pattern recognition receptors; PGN, peptidoglycan; PUFAs, polyunsaturated fatty acids; PXR, pregnane X receptor; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PGE2, prostaglandin E2; rCDI, recurrent *Clostridium difficile* infection; sIgA, secretory immunoglobulin A; SCFAs, Short-chain fatty acids; TLR4, Toll-like receptor 4; TFF, trefoil factor; TMA, trimethylamine; TMAO, trimethylamine N-oxide; *Tnf*, tumor necrosis factor; HT1, tyrosinemia type 1; UDP-GlcNAc, uridine diphospho-N-acetylglucosamine; UDCA, ursodeoxycholic acid; VAP1, vascular adhesion protein-1; VCAM-1, vascular cell adhesion protein 1; VDR, vitamin D receptor; ZG16, zymogen granule protein 16.

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Herein, we provide a concise summary of the anatomical foundation of the gut-liver interaction, including the gut-liver axis and the enterohepatic barrier. We have structured the involvement of microbial factors in hepatic disease development, specifically the translocation of microbes *per se*, and its metabolites. In addition, we have discussed microbiome-based therapeutic strategies for chronic and infectious liver conditions.

## 2. The gut-liver axis and the enterohepatic barrier

### 2.1. Gut-liver axis

The gut and liver are connected through the biliary system and the portal vein, enabling bidirectional crosstalk known as the "gut-liver axis" [3]. In the liver, various primary BAs are produced, conjugated with either glycine or taurine and ultimately transported to the intestine via the biliary system. The composition of the intestinal microbial community is influenced by both the composition and pH of the biliary system. Conversely, gut microbes metabolize endogenous and exogenous substrates, including BAs, amino acids, and diet, to maintain intestinal homeostasis. Through unconjugation, dehydrogenation, and dehydroxylation, the gut microbiota converts primary BAs into secondary BAs. Approximately 95% of these products are reabsorbed into the portal vein at the terminal ileum and are transported back to the liver [5]. "Enterohepatic circulation" refers to the release of BAs from the liver into the gut, followed by their reabsorption from the gut back into the liver, and is a potent driver for reshaping the gut microenvironment and liver biofunction.

### 2.2. Enterohepatic barrier

(1) Intestinal barrier

The intestinal barrier is essential for protection against harmful substances and pathogens [2]. Compromise of the intestinal barrier integrity, known as the "leaky gut" phenomenon, creates a pathway for gut-derived microorganisms, microbial stimuli, and dietary constituents to enter the systemic circulation and the portal vein, which is the etiological basis for ectopic dysfunction, such as liver disease (via the gut-liver axis) [3], cognitive disorder (via the "gut-brain axis") [6,7], and even reproductive system dysfunction (via the "gut-ovary axis") [8].

The intestinal barrier typically comprises various barriers, including microbial, chemical, physical, and immunological barriers. Healthy adults have approximately $1 \times 10^{12}$ symbiotic microbes per gram of lumen, which is characterized as a microbial barrier against pathogenic invasion [9]. BAs, plasma cells producing secretory immunoglobulin A (sIgA), and Paneth cells producing antimicrobial peptides (AMPs) function as chemical barriers. The mucus layer, which serves as part of the physical barrier, is composed of two distinct layers in a lamellar structure: a tightly packed inner layer and a loosely arranged outer layer. The mucus layer, which serves as a highly hydrated and complex viscoelastic medium, consists of various components, with MUC2 among the 21 members of the mucin (MUC) family serving as an essential skeletal component. By working together with the trefoil factor (TFF) family, the calcium-activated chloride channel regulator (CLCA) family of zinc-dependent metalloproteinases, zymogen granule protein 16 (ZG16), and Ly6/plaur domain-containing protein 8 (Lypd8), MUC2 plays a crucial role in maintaining the structure of the mucosal barrier and regulating the local microenvironment homeostasis [10]. The epithelial cells below the mucus layer are connected by tight junctions, forming another part of the physical barrier, which allows molecules with specific sizes and charges to cross the paracellular pathways, namely the pore and leak pathways [11]. A significant number of immune cells are found in the lamina propria and mainly function to engulf microorganisms that enter the body. These immune cells include macrophages, dendritic cells, T and B lymphocytes, as well as innate lymphoid cells, among others [2].

Additionally, a newly identified gut-vascular barrier comprising endothelial cells has been shown to regulate the spread of bacteria throughout the body (Fig. 1) [12,13].

(2) Hepatic barrier

Via the trafficking of intestinal blood into the portal vein, the gut material can access the liver and influence hepatic function. Apart from the intestinal barrier, liver sinusoidal endothelial cells (LSECs) are the most abundant non-parenchymal cells and act as gatekeepers against gut-derived antigens and stimuli [14,15]. These cells line the low-shear sinusoidal capillary channels of the liver (Fig. 1). Functionalization of LSECs enables them to perform essential tasks such as filtration, endocytosis, antigen presentation, and leukocyte recruitment. LSECs play a crucial role in hepatic function by releasing various paracrine factors through angiocrine signaling, which in turn affects hepatic blood microcirculation, immune response, liver metabolism, and regeneration [15]. Several chronic liver diseases, including hepatitis B, primary sclerosing cholangitis (PSC), autoimmune hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), fibrosis, and hepatocellular cancer (HCC) [14,16], have been extensively studied, with previous research highlighting the involvement of LSECs in their development. Clinically, numerous patients with inflammatory bowel disease (IBD) have disrupted gut barriers, but do not have liver dysfunction. Recent evidence suggests that LSECs, also known as the hepatic barrier, play a critical role in protecting the liver against invasive factors originating from the gut. In cases of barrier damage, the recruitment and activation of hepatic neutrophils occur in colitis-induced liver injury, which can be attributed to the presence of gut-derived lipopolysaccharides (LPSs) [17].

Safeguarding the liver from intestinal pathogenic factors in the gut-liver axis relies heavily on maintaining the integrity of the enterohepatic barrier. In contrast, the disruption of the enterohepatic barrier is the underlying mechanism in most cases of liver disease.

## 3. Gut microbe-derived hepatotoxic factors

As mentioned above, along with BAs via enterohepatic circulation, gut-derived microbes, metabolites, and other hepatotoxic factors may access the liver. When the integrity of the enterohepatic barrier is preserved, gut-derived hepatotoxic factors cannot reach the liver and cause liver disorders. However, various factors derived from gut microbes can affect hepatic biofunction, as described below (Fig. 2 and Table 1).

### 3.1. Microbiota-derived metabolites

(1) Ethanol

In addition to ethanol from food sources, intestinal microorganisms can produce ethanol through saccharolytic fermentation. Ethanol and its metabolite, acetaldehyde, directly and indirectly, induce hepatic damage by disturbing the integrity of gut barrier function [1]. Meijnikman and colleagues demonstrated the direct link between the severity of advanced liver disease and the concentration of microbiome-derived ethanol in the portal vein [18]. Yuan et al. replicated an alcohol-fed phenotype in a murine model by administering a gavage of high-alcohol-producing *Klebsiella pneumoniae* (HiAlc Kpn) bacteria obtained from a patient with a rare case of non-alcoholic steatohepatitis (NASH) and auto-brewery syndrome (ABS) [19]. These results confirmed the association of endogenous with NASH pathogenesis [20].

(2) BAs

BAs are synthesized from cholesterol in hepatocytes and are transformed into secondary BAs by the gut microbiota once secreted into the intestinal lumen [21]. To regulate the balance of BAs within the body, BAs utilize specific receptors, such as nuclear and G protein-

**Table 1**
**The summarized information for gut microbe-derived hepatotoxic factors**.

| Category | Names | Resource | Effects | Liver disease | References |
|---|---|---|---|---|---|
| *Microbiota-derived metabolites* | Ethanol | 1) food;<br>2) saccharolytic fermentation;<br>3) ethanol-producing bacteria (*e.g.*, HiAlc Kpn), *etc*. | 1) disrupt the gut barrier;<br>2) liver toxicity. | N/MAFLD, N/MASH,<br>AFLD, Cirrhosis, HCC | [1,18-20] |
| | BAs | 1) liver synthesis (primary BAs);<br>2) microbial metabolism (secondary BAs, 3-sucCA, *etc.*) | 1) regulating liver BA synthesis;<br>2) mediating immune response via FXR, TGR5, *etc*. | N/MAFLD, N/MASH,<br>PSC, PBC, Cirrhosis, HCC | [21-24] |
| | SCFAs | 1) anaerobic fermentation of indigestible proteins and fibers | 1) cellular energy supply;<br>2) anti-inflammation. | Decreased and involving in most of liver diseases | [1,25,26] |
| | Tryptophan and indoles | 1) foods like vegetables, fish, and eggs, *etc.* | 1) host metabolizing via the kynurenine and serotonin pathway;<br>2) anti-inflammation via indole and indole-related derivatives | Decreased and involving in most of liver diseases | |
| | TMA and TMAO | 1) food choline | 1) regulating microbial community;<br>2) affecting LSECs integrity. | N/MAFLD, AFLD, PSC | [1,31-33] |
| | Microbiota-derived hepatotoxins | 1) bacterial PGN, LPS, *etc.*<br>2) fungal chitin, $\beta$-glucans, *etc.* | 1) triggering gut immune response;<br>2) arriving liver via portal vein and launching liver immune response. | Increased and involving in most of liver diseases | [34,35] |
| | Microbial-host-isozyme | 1) microbial enzymes (such as *Bacteroides* spp.) | 1) mimic function of host enzyme like DPP4; 2) impair host metabolic homeostasis | MAFLD | [36,37] |
| *Gut microbial translocation* | Gut microbes | 1) alive gut microbes. | 1) translocating and transplanting into the mesenteric lymph nodes and liver via leaky gut; 2) impairing the gut barrier including epithelial and vascular barriers; 3) sparking a local immune response. | N/MAFLD, N/MASH, HCC | [38,39] |
| *Gut-liver immune trafficking* | Microbes-activated immune cells | 1) gut immune cells | 1) a rolling interaction mediated by selectins, integrins; 2) trafficking into the liver and mediating immune response. | Involving in most of liver diseases | [43-50] |

Abbreviations (Alphabetically): 3-sucCA, 3-succinylated cholic acid; AFLD, alcoholic fatty liver disease; BAs, bile acids; DPP4, dipeptidyl peptidase 4; FXR, farnesoid X receptor; HCC, hepatocellular cancer; HiAlc Kpn, high-alcohol-producing *Klebsiella pneumoniae*; LPS, lipopolysaccharides; LSECs, liver sinusoidal endothelial cells; MASH, metabolic dysfunction-associated steatohepatitis; MAFLD, metabolic-associated fatty liver disease; MAMPs, microbe-associated molecular patterns; MHI, microbial-host-isozyme; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PAMPs, pathogen-associated molecular pattern; PGN, peptidoglycan; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SCFAs, Short-chain fatty acids; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

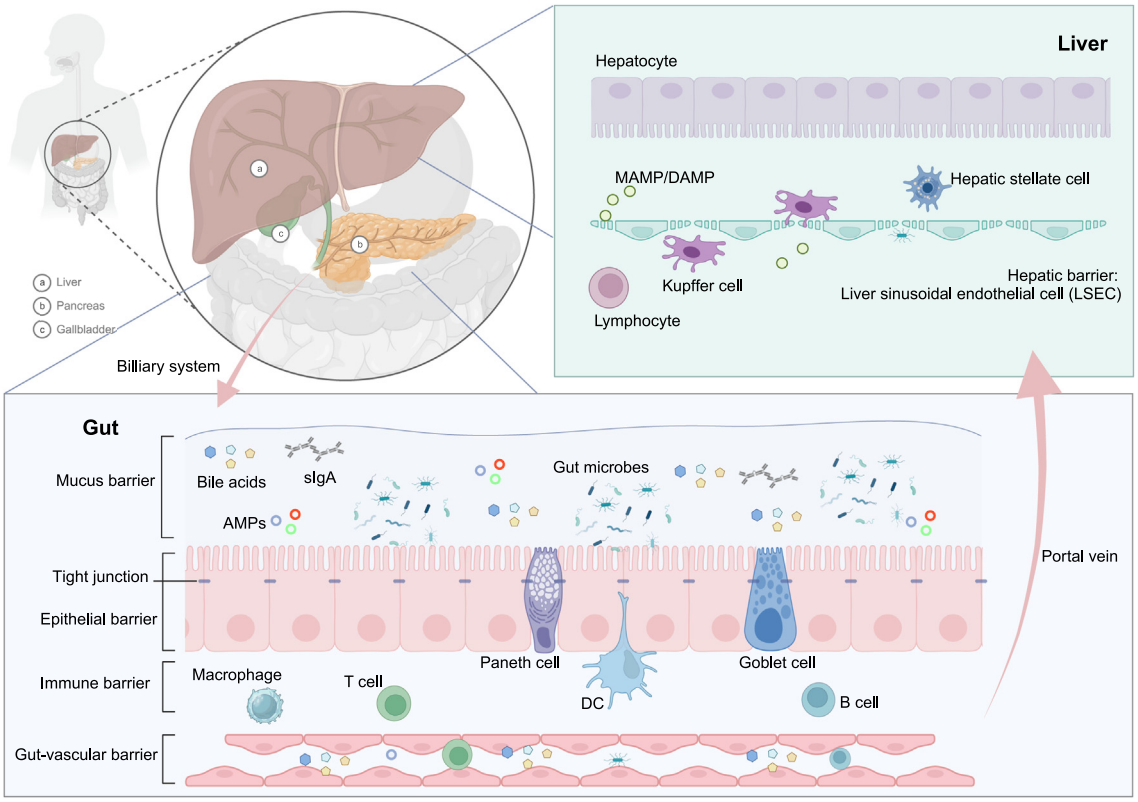


**Fig. 1. The enterohepatic barrier. The intestinal barrier is involved the mucus, epithelial, immune (lamina propria), gut-vascular barriers.** The hepatic barrier is meaningly constituted by the liver sinusoidal endothelial cell; around it, the Kupffer cell and hepatic stellate cell can respond to gut-derived stimulating signals, such as the MAMP and/or PAMP. AMP, antimicrobial peptides; sIgA, secretory immunoglobulin A; DC, dendritic cell; MAMP/PAMP, microbe- or pathogen-associated molecular patterns. This figure was created using the BioRender website (https://app.biorender.com/), and assigned a publication agreement number of BS26WJG0JD.

coupled receptors (GPCR), during their metabolism and transport in the enterohepatic circulation. In addition to the gut microbiome, BA-activated nuclear receptors, including farnesoid X receptor (FXR, also known as NR1H4), pregnane X receptor (PXR, also known as NR1I2), constitutive androstane receptor (CAR, also known as NR1I3), and vitamin D receptor (VDR, also known as NR1I1), play crucial roles in regulating various aspects of host BA metabolism and transport and lipid and glucose metabolism in enterohepatic circulation. These receptors primarily maintain BA homeostasis and influence innate and adaptive immunity within the enterohepatic system [22]. Takeda G protein-coupled receptor 5 (TGR5) is a GPCR that regulates immunometabolism and mediates the immunosuppressive effects of BAs on innate immune cells [23]. BA receptors disrupt BA transport and homeostasis, leading to cholestatic disorders and various liver diseases [21].

Jiang et al. identified different microbial-derived BAs, one of which was a newly discovered compound, 3-succinylated cholic acid (3-sucCA). This metabolite is found exclusively in the lumen and alleviates metabolic dysfunction-associated steatohepatitis (MASH) by promoting the growth of *Akkermansia muciniphila* [24].

(3) Short-chain fatty acids (SCFAs)

SCFAs, including butyrate, propionate, and acetate, are produced through anaerobic fermentation of indigestible proteins and fibers by the gut microbiota. These SCFAs are then transported to the liver through the portal circulation and contribute approximately 30% of the hepatic energy supply [1,25]. SCFAs also exert an anti-inflammatory role by directly influencing the differentiation of phagocytes, B cells, and plasma cells, as well as regulatory and effector T cells. However, its inability to properly respond to microbial dysbiosis has been linked to various liver disorders, including immune-related illnesses. Kupffer cells, a type of macrophage, reside in the liver and have a remarkable ability to self-sustain. Furthermore, in cases of liver injury, these cells quickly accumulate in organs. Butyrate exerts its anti-inflammatory effects by specifically targeting Kupffer cells in the liver. In rodent models, the administration of butyrate increases the production of immunosuppressive arachidonic acid and prostaglandin E2 (PGE2) by Kupffer cells, while simultaneously reducing the expression of pro-inflammatory cytokine genes such as interleukin-1 beta (*Il1b*) and tumor necrosis factor (*Tnf*) [25,26].

(4) Tryptophan and indoles

Tryptophan is found in various foods such as vegetables, fish, and eggs. Hosts can utilize tryptophan in two main ways: direct absorption and metabolism by host cells via the kynurenine and serotonin pathways or catabolization into indole and indole-related derivatives by intestinal bacterial microbes expressing the enzyme tryptophanase [27]. Indole derivatives can serve as ligands for various BA receptors, including the aryl hydrocarbon receptor (AhR) and PXR. Activation of these receptors, which are expressed in lymphocytes within the gut and liver, leads to decreased inflammation [28,29].

(5) TMA and TMAO

The gut microbiota can convert dietary choline into trimethylamine (TMA) in the colon, which is further oxidized by hepatic monooxygenases from the liver to trimethylamine N-oxide (TMAO) [30]. TMA and TMAO are linked to cardiovascular disease, and patients with NAFLD had higher serum levels of TMAO, which is associated with increased severity of hepatic steatosis and higher all-cause mortality [1,31,32]. Moreover, research on mechanics has shed light on the role of TMAO in promoting communication between microbiota and liver blood ves-

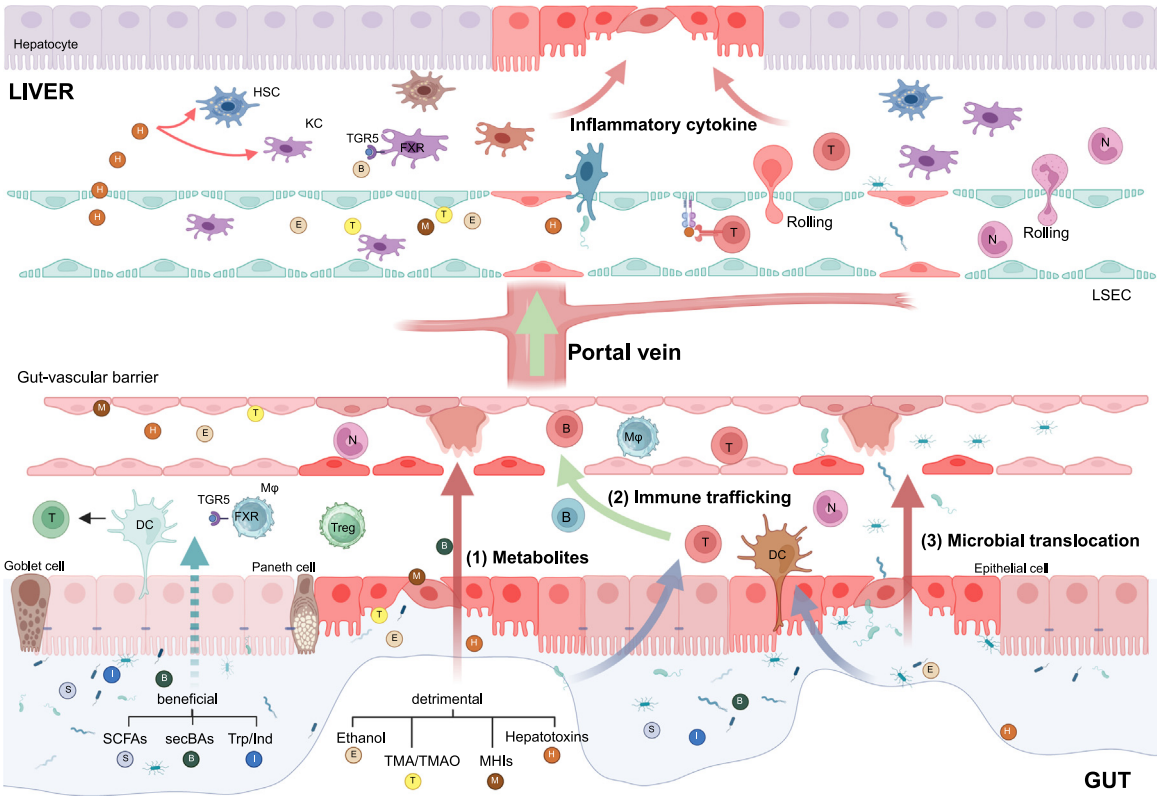


**Fig. 2. The gut microbe-derived representative hepatotoxic factors in the liver diseases.** Three factors are depicted in the figure: microbiota-derived metabolites, gut microbial translocation, and gut-liver immune trafficking. Ethanol, bile acids, SCFAs, tryptophan and indoles, TMA and TMAO, microbiota-derived hepatotoxins, and microbial-host-isozymes are the seven key microbiota-derived metabolites that play a role in mediating liver diseases. SCFAs, short-chain fatty acids; TMA, trimethylamine; TMAO, trimethylamine N-oxide. DC, dendritic cell; Treg, regulatory T celll; M$\varphi$, macrophage; KC, kupffer cell; HSC, hepatic stellate cell; LSEC, liver sinusoids endothelial cell; N, neutrophil. FXR, Farnesoid X Receptor; TGR5, G protein-coupled receptor Gpbar1. This figure was created using the BioRender website (https://app.biorender.com/), and assigned a publication agreement number of PD26YA4351.

sels by regulating the composition of the gut microbial community and ensuring LSEC integrity [33].

(6) Microbiota-derived hepatotoxins

Host pattern recognition receptors (PRRs) in immune cells recognize microbe-specific molecules, also known as microbe- or pathogen-associated molecular patterns (MAMPs or PAMPs). These molecules include bacterial peptidoglycans (PGN), LPS, fungal chitin, and $\beta$-glucan. Owing to the high concentrations of liver-specific Kupffer, natural killer (NK), and natural killer T (NKT) cells, the liver displays innate immune features and reacts quickly to multiple stimuli. Microbe-specific MAMPs and PAMPs have detrimental effects on innate immune cells during immune-mediated liver injury, underscoring their significance in this process [34,35].

(7) Microbial-host-isozyme

Wang et al. demonstrated that microbial-host-isozymes (MHI) can enhance the interactions between the microbiota and the host, thereby connecting microbial enzyme activity with host physiological functions [36]. The authors developed an MHI screening system and showed that *Bacteroides* spp. produce bacterial dipeptidyl peptidase 4 (DPP4), which can break down active glucagon-like peptide 1 (GLP-1) in leaky gut and impair host metabolic homeostasis [36]. This cutting-edge research highlights how targeting MHI can effectively treat metabolic disorders, paving the way for new directions in understanding the gut-liver axis [37].

### 3.2. Gut microbial translocation

Beyond microbiota-derived metabolites, emerging evidence suggests that commensal bacteria in the gut can traverse the intestinal barrier and influence the development of a wide range of immune-mediated diseases [38]. Yi et al. reported that mucosal-adapted strains of *Enterococcus gallinarum* possess unique traits that differentiate them from ancestral and luminal strains. These strains can evade immune system detection and clearance, exhibit enhanced translocation to and survival within the mesenteric lymph nodes and liver, and cause increased inflammation in the intestines and liver [38]. Zhang et al., reported that the introduction of *Escherichia coli* NF73–1 derived from patients with NASH aggravated NAFLD development in mice. This finding was attributed to the ability of bacteria to migrate to the liver and stimulate M1 polarization, as reported previously [39]. Gut microbial translocation may be connected to various mechanisms, involving within-host evolution [38], Paneth cell dysfunction [40], and intestinal epithelial and vascular permeability [41].

### 3.3. Gut-liver immune trafficking

The process of gut-liver immune trafficking is initiated when liver immune cells recognize antigens originating from the gut [42]; that is, hepatocytes, LSECs, Kupffer cells, and other PRR-expressing lymphocytes recognize and bind to PAMPs and DAMPs. When these cells are exposed to these molecules while responding to invasive pathogens, leukocytes must first migrate from the blood vessels into the liver through a rolling interaction [43]. In the traditional sense, the process of tethering and rolling in tissues is facilitated by the expression of selectins on leukocytes, endothelial cells, and platelets, specifically L-selectin, E-selectin, and P-selectin, respectively. These selectins bind to glycans to mediate this process [31]. Subtle connections between integrins in immune cells and ligands in endothelial cells are also involved in this process [44].

However, the rolling process in the liver primarily relies on the latter mechanism, which is the most important interaction [45]. $\alpha 4$ (such as $\alpha 4\beta 1$ and $\alpha 4\beta 7$, expressed by lymphocytes and monocytes) and $\beta 2$ integrins (expressed by all types of leukocytes) mediate the gut-liver immune trafficking via binding to vascular cell adhesion protein 1 (VCAM-1), mucosal vascular addressin cell adhesion molecule 1 (MadCAM-1), and intercellular adhesion molecule 1 (ICAM-1) expressed by LSECs [46,47]. Vascular adhesion protein-1 (VAP1) and CD44 are two other glycoproteins that traffic immune cells to the liver [48,49]. Along with rolling, the interaction between chemokines and chemokine receptors is crucial for facilitating the direct chemotaxis of immune cells in response to stimuli. Liver-infiltrating effector T cells rely heavily on chemokine receptors such as CXCR3, CXCR6, CCR5, CCR2, and CCR1 for recruitment [43,50].

## 4. Relationships between the gut microbiome and liver diseases

### 4.1. NAFLD and non-alcoholic steatohepatitis

NAFLD and its more advanced stage, NASH, are better known as metabolic-associated fatty liver disease (MAFLD) and MASH, respectively [51]. For consistency, this review uses the original descriptions; *i.e.*, NAFLD and NASH. The gut microbial community is also closely associated with NAFLD. For example, transplanting fecal microbiota from obese mice of the same weight into germ-free recipients reproduces most NAFLD characteristics [52]. Despite the variations in study cohorts and literature, studies have reported consistent findings regarding the microbial signature associated with NAFLD. Compared with healthy individuals, patients with NAFLD show increased proportions of Proteobacteria phylum, Enterobacteriaceae family, and *Escherichia, Dorea, Peptoniphilus* genera, along with decreased proportions of the Rikenellaceae and Ruminococcaceae families and *Anaerosporobacter, Coprococcus, Eubacterium, Faecalibacterium* and *Prevotella* genera [53,54]. Patients with NASH also show unique microbial signatures at the phylum, family, and genus levels compared with healthy individuals [53,55]. At the species level, the abundance of *E. coli* and *Propionibacterium acnes* are increased, while those of *Clostridium coccoides* and *B. fragilis* are decreased in patients with NAFLD and NASH [53]. Various hypotheses have been proposed regarding the mechanisms for how the pathways of gut microbiota contribute to the development of NAFLD and NASH. In brief, intestinal permeability causes the release of LPS, bile acids, and other bacterial metabolites (including TMAO, choline, and ethanol) into the liver tissue, which affects the immune status and triggers inflammation [1,18,19,24,53,56]. Additionally, microbial translocation into the liver directly leads to immunological disturbances, dysbiosis of hepatic triglyceride metabolism, and NAFLD progression [39,41].

### 4.2. Alcoholic fatty liver disease (AFLD)

Excessive alcohol consumption can result in dysbiosis of the gut microbial community, which in turn contributes to AFLD onset and progression. Dysbiotic microbiota in patients with AFLD includes decreased microbial diversity and beneficial *Akkermansia] muciniphila*, along with increased pathogenic *Enterococci* [1,57]. Moreover, the increased occurrence of *Enterobacteria* and *Lactococcus* phages in fecal samples from individuals with alcoholism suggests a more progressive liver condition [58,59]. AFLD pathogenesis is associated with microbial-derived MAMPs such as LPS, cytolysin, and candidalysin, as well as metabolites including BAs, SCFAs, indole, and TMAO [1]. Moreover, AFLD development involves disruption of the intestinal barrier. Around 50% of patients with alcohol abuse show increased intestinal permeability [60]. Due to a leaky gut, MAMPs can travel to the liver through the portal vein, which triggers the activation of PRRs on the membranes of immune cells in the liver, ultimately leading to liver disease progression [61]. The cytolysin exotoxin secreted by *Enterococcus faecalis* is a pore-forming toxin consisting of two subunits and has been detected in individuals with alcohol-associated liver disease rather than in those diagnosed with NAFLD [62,63]. Candidalysin, a peptide toxin secreted by *Candida albicans*, can form pores and also trigger a response in Th17 cells and activate macrophages and dendritic cells to exacerbate ethanol-induced liver disease and damage hepatocytes [64,65]. Fecal samples from patients with alcohol-associated liver disease demonstrate reduced levels of SCFAs and indoles, both of which are derived from tryptophan metabolism and positively affect bacterial metabolites. These metabolites demonstrate hepatoprotective properties by inducing the production of anti-inflammatory cytokines, particularly interleukin (IL)−22 in type 3 innate lymphoid (ILC3) cells [66,67].

### 4.3. PSC

Inflammation, fibrosis, and strictures of the intra- and extrahepatic bile ducts in PSC lead to chronic complications. A strong and undeniable connection between the gut and liver axes is indicated by the fact that a significant percentage (60–80%) of patients with PSC experience complications related to IBD [68]. Clinical evidence suggests that intestinal inflammation, leaky gut, and antibiotics may affect the disease course of PSC, providing a rationale for the relationship between the gut microbiome and PSC pathogenesis [69-71]. Patients with PSC show decreased gut microbial diversity but increased abundance of *Veillonella* spp., *Streptococcus* spp., *Enterococcus*, and *Fusobacterium* compared with healthy individuals [72,73]. Conversely, individuals with PSC exhibit elevated fungal biodiversity, characterized by a higher prevalence of *Exophiala Candida*, and *Trichocladium griseum* and a decreased prevalence of *Saccharomyces cerevisiae* [74,75]. The gut microbiota also differs between the PSC-like hepatic phenotype and the PSC itself. This phenomenon can be illustrated by examining the numerous clinical similarities between IgG4-related sclerosing cholangitis (IgG4-SC) and PSC. However, distinct microbial and metabolic features, including significantly decreased *Blautia* and increased succinic acid levels, underscore the distinctiveness of IgG4-SC. Furthermore, patients with IgG4-SC show a consistent decrease in *Eubacterium* and microbiota-derived metabolites, including secondary BAs [76]. In contrast, patients with PSC exhibit increased levels of circulating intestinal fatty acid-binding protein, LPS, and zonulin, suggesting a disturbance in the intestinal barrier and potential microbial translocation. Thus, the activation of particular microbes induces T-cell production of the pro-inflammatory cytokine IL-17 to potentially trigger inflammation in PSC [77,78]. Additionally, the pathogenic process of PSC also involves microbial metabolites such as BAs, SCFAs, amino acids and derivatives, B vitamins, and TMA/TMAO [1,68,79].

### 4.4. Primary biliary cholangitis (PBC)

The distinguishing feature of PBC is the ongoing destruction of small bile ducts inside the liver, ultimately leading to the development of cholangitis, fibrosis, and potentially cirrhosis. Microbial diversity is decreased at the individual level in PBC, including a distinctive pattern characterized by a reduced prevalence of four genera (*Bacteroides, Sutterella, Oscillospira*, and *Faecalibacterium*) and an increased prevalence of eight genera (*Haemophilus, Veillonella, Clostridium, Lactobacillus, Streptococcus, Pseudomonas, Klebsiella*, and an unidentified genus within the Enterobacteriaceae family). In addition, a more pronounced decrease in Faecalibacterium was observed in gp210-positive patients with PBC [80]. The use of ursodeoxycholic acid (UDCA) as an initial treatment for PBC can restore the gut microbial community in patients who exhibit a positive response, especially in individuals with elevated levels of secondary and tertiary fecal BAs and SCFAs [80-83].

### 4.5. Cirrhosis

Fibrotic tissue replacing functional hepatocytes signifies the development of cirrhosis, the ultimate stage of chronic liver disease, along with

a reduction in the influx of BAs into the gut lumen and ensuing dysbiosis within the microbial community. A notable decline in the abundance of *Bacteroides* at the genus level has been observed in patients diagnosed with cirrhosis. In individuals with cirrhosis, the abundance of *Veillonella, Streptococcus, Clostridium*, and *Prevotella* among the remaining genera was higher, whereas *Eubacterium* and *Alistipes* exhibited decreased levels. Moreover, the cirrhosis group was enriched in four *Streptococcus* spp. and six *Veillonella* spp., implying the potential importance of these two genera in the pathogenesis of liver cirrhosis [69]. Another study confirmed these results: it has been reported that the abundance of *E. coli, Acidaminococcus* spp. D21 and *K. pneumoniae* are increased, whereas *E. eligens, E. r*ectale, *D. longicatena*, and *Faecalibacterium prausnitzii* are reduced in patients with cirrhosis [1].

The fecal virome is negatively correlated with *Faecalibacterium* phages and end-stage liver disease scores, while *Escherichia* phages show a positive correlation [84]. Additionally, a reduced *Bacteroidetes* to *Ascomycota* ratio is associated with the hospitalization of individuals with cirrhosis, suggesting a connection between fungal and bacteria-fungi interactions in cirrhosis advancement [85].

The development of liver cirrhosis is attributed to chronic inflammation and liver injury. As intestinal permeability increases during the pathogenic process, the entry of MAMPs into the portal vein initiates systemic inflammation, which subsequently leads to hepatic cirrhosis-associated immune dysfunction (CAID) and decompensation [1,86]. Liver cell necrosis is a result of the action of pro-inflammatory cytokines such as TNF-$\alpha$, IL-1, IL-6, and interferon-gamma (IFN-$\gamma$), ultimately leading to the development of liver fibrosis. Moreover, the profibrotic mechanisms of liver cirrhosis may involve inflammasomes and chemokines such as chemokine ligand 2 (CCL2)/MCP-1 [87]. The dysbiotic metabolism of fecal BAs is also involved in cirrhosis pathogenesis [88,89]. By modulating BA profiles and activating BA receptors such as FXR, cirrhosis can be alleviated by enhancing tight-junction protein expression and restoring the vascular barrier in the gut [90].

### 4.6. HCC

Globally, HCC is responsible for the third-highest number of cancer-related deaths. Accumulating evidence suggests that microbial dysbiosis plays a crucial role in hepatocarcinogenesis. The etiology of HCC is multifaceted and encompasses alcohol, hepatitis viruses, and aflatoxins. Diverse microbial signatures have been observed in HCC phenotypes originating from different etiologies. Patients diagnosed with cirrhosis, show increases in certain bacterial families (*Bacteroidetes, Ruminococcaceae, Gemmiger*, and *Parabacteroides*) and decreases in others (*Bifidobacterium* and *Verrucomicrobia*), which contributed to HCC development [91,92]. *Escherichia-Shigella* and *Enterococcus* are indicative of HCC in patients with hepatitis B virus (HBV) infection, whereas *Faecalibacterium, Ruminococcus*, and *Ruminoclostridium* exhibit diminished presence [93,94]. HCC progression is marked by the accumulation of bacteria such as *Enterococcus* and *Enterobacteriaceae*, whereas *Bifidobacteriaceae, Lachnospiraceae*, and *Peptostreptocpccaceae* are depleted in patients with late-stage HCC [95]. The interaction between microbially derived MAMPs and host PRRs, specifically TLRs, is a vital factor in hepatocarcinogenesis and occurs because of a leaky gut [96]. Toll-like receptor 4 (TLR4) is a PRR found in various cell types within the liver, including Kupffer cells, LSECs, hepatic stellate cells (HSCs), and hepatocytes. MAMPs originating from the compromised intestinal barrier bind to TLRs and facilitate HCC development through the activation of the nuclear factor kappa B (NF-$\kappa$B) pathway. This process also triggers the production of pro-inflammatory cytokines, including TNF-$\alpha$ and IL-6. Moreover, the presence of microbial metabolites, specifically deoxycholic acid (DCA) synthesized by *Clostridium* bacteria via 7$\alpha$-dehydroxylation, stimulates a senescence-associated secretory phenotype in HSCs, linking it to HCC development [97].

A recent study demonstrated that high dietary fructose promotes HCC progression by increasing levels of uridine diphospho-N-acetylglucosamine (UDP-GlcNAc) and O-GlcNAcylation through acetate derived from microbiota [98].

## 5. Microbiome-based therapeutic strategies

As stated previously, dysbiosis of the gut microbiome plays a crucial role in the development of liver diseases. Translocation of the gut microbiota and its metabolites, combined with the orchestration of gut-liver immune trafficking, triggers the development of liver diseases. Studies investigating the etiology of this process have revealed new therapeutic targets for liver diseases. Herein, we provide a brief overview of microbiome-based therapeutic strategies for treating liver diseases (Fig. 3).

### 5.1. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) was initially implemented as a therapeutic approach to rectify microbial dysbiosis in patients with recurrent *Clostridium difficile* infection (rCDI). Currently, interest is increasing in the utilization of FMT to address intra- and extra-intestinal diseases beyond rCDI, including IBD, irritable bowel syndrome (IBS), and liver disease. As of May 16, 2024, 52 clinical trials related to the treatment or assessment of FMT-associated liver disease were registered at https://www.clinicaltrials.gov/. Hepatic encephalopathy (HE), alcoholic hepatitis (AH), cirrhosis, NAFLD, and NASH are liver diseases that are the focus of FMT treatment (Table 2). Approximately two-thirds of patients with severe SAH do not meet the criteria for historical steroid therapy. Philips et al. conducted a consecutive seven-day-FMT administration to patients with SAH who were ineligible for steroid treatment. The results showed a significant improvement in survival rates at one year (87.5% *vs*. 33.3%) compared with historical controls [99]. Individuals with cirrhosis exhibit gut microbiota dysbiosis and compromised immune systems. FMT is a safe and well-tolerated therapeutic approach for patients with cirrhosis, leading to improvements in microbial dysbiosis, hospitalization rates, cognitive function, and the occurrence of HE events [29]. Regarding NAFLD and NASH, randomized clinical trial data have demonstrated that FMT effectively enhances treatment outcomes for patients with NAFLD, particularly in lean individuals. This is achieved by mitigating hepatic fat build-up by improving gut microbial dysbiosis and intestinal permeability and modulating liver DNA methylation [100-102]. These findings shed light on the potential application of FMT in the management of liver diseases. Nevertheless, addressing the clinical obstacles surrounding FMT, including its clinical application, efficacy, durability, and safety, requires close adherence to international consensus guidelines regulating the quality of donor stool and stool banking [103,104].

### 5.2. Bacteriophages

Bacteriophages are naturally occurring viruses that have specific affinities for bacterial cells. Bacteriophages play a crucial role in the colonization of intestinal bacteria and the regulation of bacterial metabolism [84]. Owing to their remarkable genetic adaptability, bacteriophages can undergo a wide range of surface modifications, which can be utilized for prophylactic, diagnostic, and therapeutic approaches in liver disease [105]. Approximately 80% of patients diagnosed with AH show *E. faecalis* in their feces; among these patients, 5.59% of fecal bacteria are *Enterococcus spp*., compared with scarcely any in healthy controls. Additionally, cytolysin, a bacterial exotoxin synthesized by *E. faecalis*, can worsen ethanol-induced liver diseases. However, bacteriophages targeting gut cytolytic *E. faecalis* abolished ethanol-induced liver disease in gnotobiotic mice [106,107]. Furthermore, a strain of *K. pneumoniae* with a high alcohol-producing capability (HiAlc Kpn) is one factor contributing to NAFLD, and the use of bacteriophage specifically targeting HiAlc Kpn may mitigate

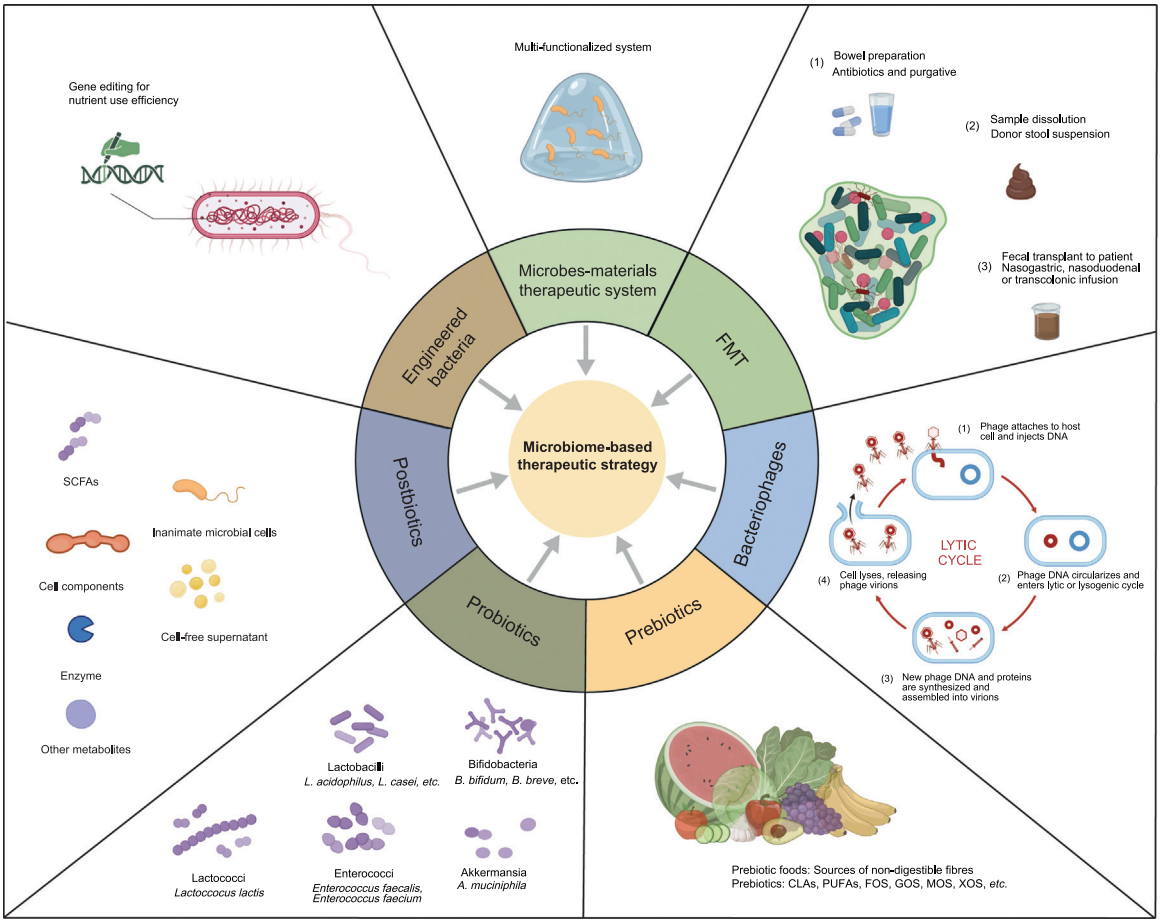


**Fig. 3. The representative microbiome-based therapeutic strategies. Five strategies are shown in this figure, including FMT, bacteriophages, prebiotics, probiotics, postbiotics, engineered bacteria and novel microbes-materials therapeutic system.** FMT, fecal microbiota transplantation; CLAs, conjugated linoleic acids; PUFAs, polyunsaturated fatty acids; FOS, fructooligosaccharides; GOS, galactooligosaccharides; MOS, mannanoligosaccharide; XOS, xylooligosaccharides. This figure was created using the BioRender website (https://app.biorender.com/), and assigned a publication agreement number of ZF26YJBX4I.

**Table 2**
**Registered FMT clinical trials in the** https://www.clinicaltrials.gov/.

| Treatment Strategy | Liver Disease Type | Number | NCT Number |
|---|---|---|---|
| FMT | Hepatic Encephalopathy | 10 | NCT05229289, NCT06368895, NCT06040814, NCT03439982, NCT03420482, NCT02255617, NCT05669651, NCT05421351, NCT03796598, NCT02636647 |
| FMT | Alcoholic Hepatitis | 8 | NCT05285592, NCT03827772, NCT06307964, NCT02458079, NCT05548452, NCT05006430, NCT03091010, NCT05448144 |
| FMT | Cirrhosis | 8 | NCT04330469, NCT04842539, NCT04591522, NCT02862249, NCT03416751, NCT03014505, NCT04932577, NCT02019784 |
| FMT | NAFLD and related Fibrosis | 7 | NCT02496390, NCT03648086, NCT04594954, NCT04465032, NCT05607745, NCT04371653, NCT06024681 |
| FMT | NASH and related Cirrhosis | 6 | NCT02469272, NCT03803540, NCT05821010, NCT05622526, NCT02721264, NCT02868164 |
| FMT | Liver Transplant | 4 | NCT04621812, NCT02223468, NCT03507140, NCT03666312 |
| FMT | Liver Failure (chronic and acute) | 3 | NCT03363022, NCT05170971, NCT02689245 |
| FMT | HBV and related Cirrhosis | 3 | NCT03429439, NCT04431375, NCT03437876 |
| | Liver Cancer | 3 | NCT05750030, NCT04303286, NCT05690048 |

the development of steatohepatitis caused by HiAlc Kpn [19,108]. In the context of HBV infection, bacteriophages have been utilized for the surface display of HBcAg to generate anti-HBcAg monoclonal antibodies that detect and neutralize HBV infections [105]. Bacteriophages are also a potential approach for managing infections in immunocompromised patients, such as those with cirrhosis or liver transplantation [109,110].

### 5.3. Probiotics

Probiotics are considered safe and vital for maintaining host health but require an optimal level of viable bacteria [111]. *Lactobacillus* and *Bifidobacterium* are two traditional probiotic bacteria. The genus *Lactobacillus* comprises approximately 300 bacterial species, including L. *rhamnosus* GG (LGG), L. *paracasei* F19, L. *acidophilus*, L. *bulgaricus*, L.

*casei*, L. *plantarum*, and others. These species show positive effects on various liver diseases, including NAFLD, AFLD, liver fibrosis, cirrhosis, and HCC [112]. The mechanisms of action attributed to these effects include antimicrobial activity, immunomodulation, microbiota modulation, metabolite production, and antitumor activity [112].

LGG was the first strain within the *Lactobacillus* genus shown to withstand the pH of gastric acid, thriving in bile-containing environments, and adhering to enterocytes. LGG exerts a protective effect in patients with NAFLD and NASH by inhibiting pathogens through lectin-like proteins 1 and 2, while also promoting type 1 immune responsiveness and enhancing IL-10, IL-12, and tumor necrosis alpha (TNF-$\alpha$) production [113-115]. The genus *Bifidobacterium* comprises more than 45 species and subspecies. These gram-positive bacteria are polymorphic, rod-shaped, and commonly found in the gastrointestinal tract of humans and animals [116]. *Bifidobacteria* enhance the intestinal barrier and mediate the immune response of the liver to exert beneficial effects [117]. For example, *B. pseudolongum* inhibits NAFLD-HCC formation by producing acetate, restoring the healthy composition of the gut microbiome, enhancing gut barrier function, suppressing proliferation, and inducing apoptosis in cancer cells [118]. A clinical trial involving patients with HCC showed that the oral administration of a probiotic bacterial cocktail containing *B. longum* led to significant improvements, including reduced rates of delayed recovery, shorter hospital stays, and improved overall 1-year survival, resulting from the metabolism of three substances: 5-hydroxytryptamine, secondary BAs, and SCFAs [119]. *B. animalis* ssp. Lactis 420 downregulates serum endotoxin levels and suppresses the receptor-interacting kinase 3 (RIP3) signaling pathway in liver macrophages by increasing fecal SCFA and upregulating tight junction proteins in autoimmune hepatitis models [120]. In addition to conventional probiotics, *A. muciniphila* is a promising new class of beneficial microorganisms because of its involvement in maintaining the gut microbial balance and a robust gut barrier, regulating BA metabolism and host immune response, and suppressing inflammation onset [121]. *A. muciniphila* is also effective in enhancing the treatment of hepatic disorders such as hepatic steatosis, AFLD, and MAFLD [121-123].

### 5.4. Prebiotics

In 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) published a consensus statement on the definition and scope of prebiotics [124]. Prebiotics are food ingredients that, although non-digestible, provide benefits to the host by enhancing the activity of probiotics through microbial fermentation. These compounds include conjugated linoleic acid (CLAs), polyunsaturated fatty acids (PUFAs), oligosaccharides (*e.g.* inulin, fructooligosaccharides, galactooligosaccharides, mannan oligosaccharides, and xylooligosaccharides), and human milk oligosaccharides, *etc*. In contrast to dietary fibers such as pectins, cellulose, and xylans, prebiotics exclusively elicit metabolism in host-beneficial microbes [124]. These prebiotics affect gut microbes via fermentation, influencing the composition of the microbial community and providing energy for host cells [125]. Among the fermentative products of prebiotics, SCFAs are important contributors to overall well-being. As mentioned previously, SCFAs exert anti-inflammatory effects by shaping the immune community and its biofunction [25].

### 5.5. Postbiotics

The term “postbiotics” refers to the utilization of dead microorganisms and/or their elements (metabolites or cells) to bestow advantageous effects on the host [126]. According to this definition, heat-killed bacteria and microbial metabolites can serve as postbiotics to enhance host fitness. For instance, heat-killed lactic acid bacteria such as *Lactobacillus reuteri* GMNL-263 (Lr263), L. *plantarum* L-137 (HK L-137), L. *pentosus* strain S-PT84, and L. *pentosaceus* LP28 (LP28) are viable treatments for alleviating NAFLD and NASH phenotypes [127]. Additionally, as mentioned earlier, the pathogenesis of liver diseases involves microbially produced metabolites, including TMAO, tryptophan derivatives, and SCFAs [111]. Therefore, postbiotics exert effects through five mechanisms: modulating resident microbiota, enhancing epithelial barrier function, modulating host immune responses, influencing host metabolic responses, and producing signals via the nervous system [126].

### 5.6. Engineered bacteria

Certain bacteria residing in the human body are harmless and can be genetically modified to serve as live diagnostic and therapeutic agents with specific properties, offering potential treatments for various diseases [128]. Several studies have sought to treat liver disease using engineered bacteria. The administration of engineered L. *reuteri* in mice reduced ethanol-induced liver disease via IL-22 production and induction of regenerating family member 3 gamma (REG3G) expression in the intestine [67]. Deficiency in fumarylacetoacetate hydrolase (FAH) activity causes hereditary tyrosinemia type 1 (HT1), leading to potentially fatal liver damage. Genetic modification of *E. coli* Nissle 1917 (EcN) to incorporate genes related to tyrosine metabolism resulted in tyrosine degradation and mitigation of fatal liver damage in the HT1 mouse model [129]. Furthermore, the introduction of bacteria engineered to deliver GLP-1 to the gastrointestinal tract may enhance insulin production and circulating insulin levels, thus establishing a connection to NAFLD [130].

### 5.7. Novel microbe-materials therapeutic system

The use of engineered microbes has raised new concerns, including the decreased vitality of dosed bacteria owing to low overall bioavailability, as well as the risk of infectious side effects when bacteria migrate from the gut to distant organs. The exploration of new methods for disease treatment includes the combination of novel materials with engineered microbes to enhance biofunctional specificity, therapeutic targetability, and spatiotemporal controllability. For example, bacterial micro- and micro-encapsulation have been developed for bacterial surface decoration and encapsulation to enhance bacterial targeting and vitality, as well as *in vivo* sensing and *in vitro* control [131,132]. Furthermore, an engineered bacteria-activated multi-functionalized delivery system that combines living *Lactococcus* and a heparin-poloxamer thermoresponsive hydrogel promoted diabetic wound healing in a dynamic-temporal manner [133]. Moreover, a platform for surface nanocoating was developed to enhance the resilience of living therapeutics, allowing them to better withstand challenging host environmental conditions [134]. These research efforts underscore the significance of improving microbial therapy to address a wide array of liver diseases and offer new possibilities for combating human ailments.

## 6. Conclusion and perspectives

Liver diseases are primarily caused by the gut. The bidirectional relationship between the gut microbiota and liver, facilitated through the gut-liver axis, is well documented, with a growing body of evidence supporting this connection. This relationship involves not only the gut microbiota, but also the translocation of its metabolites. This review highlighted the crucial role of enterohepatic barriers in maintaining overall health. Additionally, we investigated the pathophysiological impact of the gut microbiome on liver diseases to shed light on its significance. Notably, based on the close connection between the gut and liver axis, there remain many unexplained mechanisms of intestinal factors involved in the development of liver diseases. As mentioned above, edge-cutting studies on microbial-host isozymes and newly identified microbial metabolites (such as 3-sucCA) have suggested the tremendous potential for the use of gut-derived factors to elucidate the pathogenesis of liver and other extraintestinal diseases. Meeting this need requires

the development of new technologies (such as microbial culture systems and product screening systems) and concepts (such as microbial-host isozymes).

Liver diseases are treated in the gut. Although some uncertainty may exist regarding certain aspects, research has demonstrated that many liver diseases are caused by factors originating from the gut. Thus, one can infer that these liver diseases can be treated by managing and adjusting the conditions of the gut. To conclude our discussion, we have shifted our focus towards the exploration of microbiota-based therapeutic strategies, highlighting their promising potential for the treatment of liver diseases. Numerous therapeutic strategies have been developed using microorganisms. The successful use of FMT and bacteriophages in treating infectious and refractory liver diseases is one valuable example. Additionally, the promising potential of prebiotics, probiotics, and engineered bacteria presents an exciting opportunity for the effective management of chronic liver disease. Apart from the aforementioned concerns, other important considerations include the potential for infectious risks, the bioavailability of the microbial substance, and the ability to control its spatiotemporal aspects. This novel microbe-material therapeutic system represents a promising trend for treatments in clinical practice. Nevertheless, balancing its clinical benefits and the potential risks and ethical concerns is crucial.

## Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

## Ackonwledgments

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