

Insights of gut-liver axis in hepatic diseases: Mechanisms, clinical implications, and therapeutic potentials

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade C

Scientific Significance: Grade B

P-Reviewer: Shi JJ

Received: June 18, 2024

Revised: August 6, 2024

Accepted: September 10, 2024

Published online: November 5, 2024

Processing time: 128 Days and 4.4 Hours



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Abstract

With the rising prevalence of chronic liver diseases worldwide, there exists a need to diversify our artillery to incorporate a plethora of diagnostic and therapeutic methods to combat this disease. Currently, the most common causes of liver disease are non-alcoholic fatty liver disease, hepatitis, and alcoholic liver disease. Some of these chronic diseases have the potential to transform into hepatocellular carcinoma with advancing fibrosis. In this review, we analyse the relationship

between the gut and liver and their significance in liver disease. This two-way relationship has interesting effects on each other in liver diseases. The gut microbiota, through its metabolites, influences the metabolism in numerous ways. Careful manipulation of its composition can lead to the discovery of numerous therapeutic potentials that can be applied in the treatment of various liver diseases. Numerous cohort studies with a pan-omics approach are required to understand the association between the gut microbiome and hepatic disease progression through which we can identify effective ways to deal with this issue.

Key Words: Gut-liver axis; Dysbiosis; Liver disease; Probiotics; Fecal microbiota transplantation; Precision medicine

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Core Tip: We explore the bidirectional impact of gut-liver interactions on liver disease, highlighting how gut microbiota metabolites affect metabolism. It suggests that altering gut microbiota composition could unveil new treatments for liver ailments. Future cohort studies using pan-omics will be crucial in understanding gut microbiome links to liver disease progression and finding effective interventions.

Citation: Jeyaraman N, Jeyaraman M, Mariappan T, Muthu S, Ramasubramanian S, Sharma S, Santos GS, da Fonseca LF, Lana JF. Insights of gut-liver axis in hepatic diseases: Mechanisms, clinical implications, and therapeutic potentials. *World J Gastrointest Pharmacol Ther* 2024; 15(6): 98146

URL: <https://www.wjgnet.com/2150-5349/full/v15/i6/98146.htm>

DOI: <https://dx.doi.org/10.4292/wjgpt.v15.i6.98146>

INTRODUCTION

The liver and gut microbiota exhibit a complex, bidirectional relationship essential for maintaining metabolic equilibrium. Metabolic byproducts from the gut microbiome are transported to the liver *via* the portal vein, while the liver contributes to gut health by secreting bile and immunoglobulins into the intestinal tract[1]. This physiological exchange is crucial for sustaining a well-balanced metabolic state[2]. In various hepatic disorders, there is a notable perturbation of this equilibrium, a condition known as dysbiosis. Such imbalance is characterized by a decrease in microbial diversity and proliferation of pathogenic bacteria within the gut[3,4]. This altered microbial landscape is indicative of the significant role that the gut microbiota plays in the pathology of liver diseases. Dysbiosis is influenced by a confluence of genetic factors, environmental exposures, and lifestyle choices, which collectively contribute to the progression of liver diseases.

The mechanisms through which dysbiosis exacerbates liver disease are multifaceted. Primarily, it leads to immune dysregulation, which allows for the unchecked progression of disease. Additionally, alterations in energy utilization occur, and there is an increase in intestinal permeability. This heightened permeability facilitates the translocation of toxic metabolites from the gut into the liver. Once in the liver, these toxic substances trigger a pro-inflammatory response. This inflammatory state not only worsens liver function but also promotes the progression of liver disease, establishing a deleterious cycle that further impairs both liver and gut health[4-7]. Thus, understanding the interplay between the gut microbiota and liver function is critical for identifying potential therapeutic targets aimed at restoring this crucial physiological balance. This manuscript describes the pathways connecting the gut microbiota with liver diseases, explores the clinical relevance of the gut-liver axis across different liver conditions, and evaluates the effectiveness of treatments involving probiotics, prebiotics, synbiotics, and faecal microbiota transplantation.

ANATOMY AND PHYSIOLOGY OF GUT-LIVER AXIS

The gut and liver are interlinked majorly through the portal circulation[8-10]. This acts as a medium through which gut metabolites reach the liver. In between there exists a selectively permeable barrier through which nutrients and essential microbial products are translocated. It also acts as a barrier to harmful bacterial products and microbes. This function is achieved through tight junctions between enterocytes which predominantly consist of desmosomes, claudins, occludins, E-cadherins, and adhesion proteins. The short-chain fatty acids produced by the microbiota by the breakdown of dietary fibres have diverse roles such as energy production for intestinal cells, regulating motility of the gut, immune regulation, absorption of nutrients and anti-inflammatory products, and more importantly, altering carbohydrate and lipid metabolism[11]. Butyric acid is essential for maintaining the intestinal barrier[12]. Based on studies on mice, butyric acid and acetic acid act as the principal source of energy for intestinal cells, and their absence increases utilization of glucose and eventually leads to lipogenesis[13]. Added to this, it was found that activation of sterol and cholesterol regulatory element binding protein was inhibited by butyric acid which results in inhibition of lipogenesis[14]. Unlike butyric and acetic acid, propionic acid (mostly produced by pathogenic bacteria) was found to have an adipogenic effect that plays a major role in non-alcoholic fatty liver disease (NAFLD)[15], which summarizes the effects of the microbiota on the liver.

The effects of primary bile acids (PBAs) on the gut microbiota are significant as they control the overproduction of pathogenic bacteria. In the gut, the PBAs are converted to secondary bile acids by bacteria. These bile acids act on farnesoid X receptor (FXR) receptors and activate the transcription of protective genes. FXR also decreases the expression of SREBP-1c and LXR, which results in decreased lipogenesis and gluconeogenesis[16]. Another study stated that FXR enhanced glycogenesis through upregulation of GLUT-4, PPAR-gamma, GLP-1, *etc.*, thus improving insulin sensitivity as well[17]. The culmination of all the abovementioned effects is vital to establish homeostasis. The overall gut-liver axis and the role of gut microbiota in maintaining the liver homeostasis is illustrated in **Figure 1**.

ROLE OF GUT MICROBIOTA IN LIVER DISEASES

The human gut is host to 2172 taxonomically distinct species, predominantly composed of the phyla Firmicutes, Bacteroidetes, Fusobacteria, Actinobacteria, Proteobacteria, and Verrucomicrobia[18-21]. Each harbours a unique microbial composition, influenced by factors such as age, sex, genetics, environmental exposures, lifestyle choices, medications, and disease states. Commonly, in the context of disease, the gut microbiota is characterized in terms of the Gram-positive Firmicutes and the Gram-negative Bacteroidetes, which are crucial in regulating the immune response and metabolic processes, and maintaining gut homeostasis[22]. Short-chain fatty acids (SCFAs) not only support the integrity of the intestinal barrier but also stimulate the production of antimicrobial peptides like immunoglobulin A. This is facilitated by alterations in mucin layers on the intestinal epithelium and increased mucin production *via* microbial products[20]. Another pathway involves the sustained activation of Toll-like receptors that boost mucin and antimicrobial peptide levels[23]. Additionally, the gut microbiota modifies bile acids that influence FXR signalling pathways, thereby modulating inflammatory responses, neutralizing endotoxins, and preventing bacterial proliferation[24]. Li *et al*[25] observed that SCFAs produced by *Faecalibacterium*, *Coprococcus*, and *Ruminococcus* had a suppressive effect on pro-inflammatory mediators.

In alcoholic individuals, an increase in Proteobacteria, Streptococci, and Enterobacteria, and a decrease in Bacteroidetes, *Faecalibacterium prausnitzii*, *Clostridium leptum*, and *Lactobacillus* have been documented[25,26], which led to reduced anti-inflammatory molecule production and enhanced endotoxemia. NAFLD patients show a rise in alcohol-producing bacteria (Proteobacteria-Enterobacteriaceae), which disrupt gut epithelial integrity and facilitate ethanol transport to the liver, thereby inducing oxidative stress and liver damage[27]. In non-alcoholic steatohepatitis (NASH), there is an increase in Firmicutes and a reduction in Bacteroidetes, Proteobacteria, and Actinobacteria[28,29]. A recent study indicated that high levels of alcohol-producing *Klebsiella pneumoniae* could lead to fatty liver disease *via* the 2,3-butanediol fermentation pathway, with subsequent alcohol transport to the liver mirroring previously described mechanisms[30]. Patients with hepatitis B virus infections show elevated levels of *Veillonella*, *Fusobacteria*, *Prevotella*, and *Acinetobacter*[31]. In cirrhosis patients, a reduction in the *Bifidobacterium*/Enterobacteriaceae ratio, a key indicator of microbial colonization resistance, correlates with increased endotoxemia and IL-6 levels, thereby exacerbating liver inflammation[32]. Bajaj *et al*[33] demonstrated that improvements in microbiome diversity following liver transplantation were associated with amelioration of liver cirrhosis symptoms. The various interactions between the gut microbiota and liver conditions are summarized in **Table 1**.

As cirrhosis progresses from compensated to uncompensated to acute-on-chronic liver failure, there is a marked reduction in metagenomic richness.

MECHANISMS LINKING GUT MICROBIOTA TO HEPATIC DISEASES

The onset of liver pathology is often precipitated by dysbiosis, which leads to enhanced intestinal permeability. Various factors, including diet, environment, lifestyle, medications, age, and gender, can alter the gut microbiome[34]. This alteration facilitates the release of lipopolysaccharide (LPS), endotoxins, pathogen-associated molecular patterns, damage-associated molecular patterns, and other gut-derived metabolites into the bloodstream. Once in circulation, LPS interacts with Toll-like receptor 4 (TLR4) on endothelial cells, Kupffer cells, and hematopoietic stem cells, and with TLR9 on dendritic cells. Activation of TLR4 also stimulates liver stellate cells, initiating fibrogenesis and the release of pro-inflammatory and profibrotic mediators like TNF- α , IL-1 β , and interleukin (IL)-6, along with chemokines such as CCL2, CXCL2, and CXCL10[35,36]. These inflammatory responses and metabolic disruptions elevate serum-free fatty acid and triglyceride levels, leading to their accumulation in the liver and further inflammatory changes[37]. LPS also affects the secretion of adipokines such as adiponectin, IL-6, and leptin, which enhance hepatic inflammation[38,39]. Moreover, LPS reduces adrenergic stimulation, diminishes the protective effects of IL-10, and decreases reactive oxygen species (ROS) production[40-42]. Enhanced TLR signalling in the colonic mucosa also increases the expression of the inflammasome nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 in patients with NASH rather than simple steatosis[43].

Another pathway of liver injury involves alterations in bile acid metabolism. Normally, PBAs are converted into secondary bile acids such as lithocholic acid and deoxycholic acid (DCA) through 7 α -dehydroxylation by bacteria like *Lachnospiraceae* and *Blautia*[9,44]. In chronic liver conditions, the inflammatory mediators released inhibit PBA synthesis *via* CYP7A1, creating a conducive environment for pathogenic bacteria such as Enterobacteriaceae and Porphyromonadaceae due to the reduced production of antimicrobial agents typically stimulated by PBAs[45]. Alternatively, activation of sterol 27-hydroxylase (CYP27A1) results in the production of chenodeoxycholic acid but not cholic acid (CA). This decrease in CA leads to reduced DCA levels, which otherwise inhibit bacterial overgrowth by displaying potent anti-

Table 1 Summary of published studies on gut microbiota and hepatic diseases

Ref.	Population	Disease focus	Key findings	Implications
Chen <i>et al</i> [87], 2011	36 cirrhosis patients; 24 healthy controls	Cirrhosis	↑ Proteobacteria; ↑ Fusobacteria; ↑ Enterobacteriaceae; ↑ Veillonellaceae; ↑ Streptococcaceae; ↓ Bacteroidetes; ↓ Lachnospiraceae	Dysbiosis due to increased Enterobacteriaceae and Streptococcaceae may affect the prognosis of cirrhosis patients
Liu <i>et al</i> [88], 2012	Cirrhosis patients <i>vs</i> healthy controls	Cirrhosis	↓ Bifidobacterium; ↓ Bacteroidetes; ↑ Proteobacteria; ↑ Fusobacteria; ↑ Enterobacteriaceae; ↑ Enterococcus	On releasing endotoxin by enterobacteriaceae, intestinal permeability is increased
Bajaj <i>et al</i> [89], 2012	25 cirrhosis patients: 17 with HE and 8 without HE; 10 healthy controls	Cirrhosis	↑ Bacteroidetes; ↑ Veillonellaceae in HE; ↑ Enterobacteriaceae; ↑ Alcaligenaceae; ↑ Porphyromonadaceae; ↑ Fusobacteriaceae; ↓ Ruminococcaceae; ↓ Lachnospiraceae	Dysbiosis was found in patients with HE compared to healthy individuals; endotoxemia, impaired cognition, and inflammation in the liver were seen in patients with HE
Mutlu <i>et al</i> [26], 2012	ALD patients <i>vs</i> healthy control	ALD	↑ Proteobacteria; ↓ Bacteroidetes; ↓ Firmicutes; ↑ Enterobacteriaceae; ↓ Bacteroidetes; ↓ Lactobacillus	Decreased beneficial bacteria and increased intestinal permeability result in systemic endotoxemia
Zhang <i>et al</i> [90], 2013	26 cirrhosis patients with HE; 25 cirrhosis patients without HE; 26 healthy controls	Cirrhosis	↑ <i>Streptococcus salivarius</i> in HE; ↑ Streptococcaceae; ↑ Veillonellaceae	<i>Streptococcus salivarius</i> was found in patients with HE due to increased ammonia
Wong <i>et al</i> [91], 2013	NASH patients and healthy controls	NASH	↓ Firmicutes; ↓ Clostridiales (Faecalibacterium & Anaerostorobacte); ↑ Bacteroidetes (Parabacteroides & Allisonella)	
Mouzaki <i>et al</i> [92], 2013	33 NAFLD patients; 11 steatosis patients; 22 NASH patients; 17 normal controls	NAFLD; NASH; steatosis	↑ <i>C. Coccoides</i> in NASH; ↓ Bacteroidetes in NASH	The relationship between Bacteroidetes and liver disease state was independent of increase in BMI
Zhu <i>et al</i> [51], 2013	22 NASH patients; 25 obese people; 16 healthy controls	NASH	↑ Bacteroides (Prevotella); ↑ Proteobacteria (Escherichia); ↓ Firmicutes; ↓ Actinobacteria	Increased population of ethanol producing bacteria in patients with NASH contributed to disease progression; increased ethanol-producing bacteria (Escherichia) was due to the use of antibiotics
Raman <i>et al</i> [30], 2013	30 NAFLD patients; 30 healthy controls	NAFLD	↑ Proteobacteria; ↑ Firmicutes; ↓ Bacteroidetes	Faecal ester volatile organic compounds could negatively influence the microbiome composition of patients with NAFLD
Kakiyama <i>et al</i> [93], 2013	47 cirrhosis patients; 14 healthy controls	Cirrhosis	↑ Staphylococcaceae; ↑ Enterobacteriaceae; ↑ Enterococcaceae; ↓ Lachnospiraceae; ↓ Ruminococcaceae; ↓ Clostridiales XIV; ↓ Blautia	Increased pathogenic bacteria as a result of gut dysbiosis in cirrhotic patients with altered bile acid composition
Qin <i>et al</i> [94], 2014	98 cirrhosis patients; 83 controls	Cirrhosis	↑ Proteobacteria; ↑ Veillonella; ↑ Streptococcus; ↓ Bacteroidetes; ↓ Lachnospiraceae; ↓ Ruminococcaceae; ↓ Blautia	Oral commensals were found in the gut of cirrhotic patients
Bajaj <i>et al</i> [4,95,96], 2014, 2016, and 2019	HE patients <i>vs</i> healthy control	HE due to cirrhosis	↑ Megasphaera; ↑ Enterococcus; ↑ Burkholderia; ↑ Veillonellaceae; ↓ Faecalibacterium; ↓ Blautia; ↓ Roseburia; ↓ Dorea	Increased pathogenic bacteria are linked with poor cognition and inflammation
Bajaj <i>et al</i> [97], 2014	Cirrhosis patients <i>vs</i> healthy controls	Cirrhosis	↑ Veillonella spp.; ↑ Streptococcus spp.; ↓ Bacteroidetes; ↓ Firmicutes	
Grat <i>et al</i> [98], 2016	15 HCC patients; 5 patients without HCC; all participants with cirrhosis underwent liver transplantation	HCC	↑ <i>E. coli</i> ; ↑ Enterobacteriaceae; ↑ Enterococcus; ↑ Lactobacillus; ↑ H2O2-producing Lactobacillus species	Increased faecal counts of <i>E. coli</i> were noted in the cirrhotic-HCC group, indicating its association with HCC development
Llopis <i>et al</i> [27], 2016	Severe AH patients <i>vs</i> healthy control	Alcoholic hepatitis	↑ Bifidobacteria; ↑ Streptococci; ↑ Enterobacteria; ↓ <i>Clostridium leptum</i> ; ↓ <i>Faecalibacterium prausnitzii</i>	Decreased anti-inflammatory bacteria and enhanced intestinal dysbiosis result in gut permeability which facilitates microbiota translocation
Chen <i>et al</i> [99], 2016	30 cirrhosis patients; 28 healthy controls	Cirrhosis	↑ Veillonella; ↑ Megasphaera; ↑ Dialister; ↑ Atopobium; ↑ Prevotella; ↑ Firmicutes	Raised oral commensal bacteria were found in duodenal mucosal microbiota of cirrhotic patients
Ahluwalia <i>et al</i> [100], 2016	87 patients with HE; 40 healthy controls	Cirrhosis	↑ Enterobacteriaceae; ↓ Lachnospiraceae; ↓ Ruminococcaceae	Specific bacterial families were associated with astrocytic and neuronal MRI changes; gut dysbiosis in cirrhosis was linked with systemic inflammation, elevated ammonia

				levels, and neuronal dysfunction
Yang <i>et al</i> [101], 2017	ALD patients <i>vs</i> healthy controls	ALD	↑ <i>Candida</i> ; ↓ <i>Epicoccum</i> ; ↓ <i>Galactomyces</i>	
Dubinkina <i>et al</i> [102], 2017	ALD patients <i>vs</i> healthy controls	ALD	↑ <i>Bifidobacterium</i> ; ↑ <i>Streptococcus</i> spp; ↑ <i>Lactobacillus</i> spp; ↓ <i>Prevotella</i> ; ↓ <i>Paraprevotella</i> ; ↓ <i>Alistipes</i>	
Chierico <i>et al</i> [29], 2017	61 NASH/NAFLD patients; 54 healthy controls	NAFLD; NASH	↑ <i>Actinobacteria</i> ; ↑ <i>Bradyrhizobium</i> ; ↑ <i>Anaerococcus</i> ; ↑ <i>Peptoniphilus</i> ; ↑ <i>P.acnes</i> ; ↑ <i>Enterobacteriaceae</i> (<i>Escherichia coli</i>); ↑ <i>Dorea</i> ; ↑ <i>Ruminococcus</i> ; ↓ <i>Bacteroidetes</i> ; ↓ <i>Oscillospira</i> ; ↓ <i>Rikenellaceae</i>	Increased microbial diversity in NASH/NAFLD; decreased <i>Bacteroidaceae</i> and <i>Bacteroides</i> were observed in NAFLD and NASH, while they were increased in obese patients compared to controls; increased ethanol-producing bacteria (<i>Enterobacteriaceae</i>) in NAFL/NASH compared to controls
Loomba <i>et al</i> [103], 2017	NAFLD patients and healthy controls	NAFLD	↑ <i>Escherichia coli</i> ; ↑ <i>Bacteriodes vulgatus</i> ; ↓ <i>Ruminococcus</i> spp.; ↓ <i>Eubacterium rectale</i> ; ↓ <i>Faecalibacterium prausnitzii</i>	
Liu <i>et al</i> [104], 2018	36 cirrhosis patients; 20 healthy controls	Cirrhosis	↑ <i>Firmicutes</i> ; ↓ <i>Bacteroidetes</i>	Microbial dysbiosis in cirrhotic patients with Child-Pugh scores > 5 led to decreased gut motility
Ren <i>et al</i> [105], 2019	75 early HCC patients; 40 Liver cirrhosis patients; 75 healthy controls	HCC	↑ <i>Actinobacteria</i> ; ↑ <i>Gemmiger</i> ; ↑ <i>Parabacteroides</i> ; ↑ <i>Paraprevotella</i> ; ↑ <i>Klebsiella</i> ; ↑ <i>Haemophilus</i> ; ↓ <i>Verrucomicrobia</i> ; ↓ <i>Alistipes</i> ; ↓ <i>Phascolarctobacterium</i> ; ↓ <i>Ruminococcus</i> ; ↓ <i>Oscillibacter</i> ; ↓ <i>Faecalibacterium</i> ; ↓ <i>Clostridium</i> IV; ↓ <i>Coprococcus</i>	Decreased butyrate-producing bacteria and increased LPS-producing bacteria observed in early HCC
Ponziani <i>et al</i> [106], 2019	21 NAFLD-related cirrhosis patients with HCC; 20 NAFLD related cirrhosis patients without HCC; 20 healthy controls	HCC	↑ <i>Bacteroides</i> ; ↓ <i>Ruminococcaceae</i> ; ↑ <i>Bifidobacterium</i>	Increased faecal calprotectin in HCC patients is an indicator of inflammatory state
Piñero <i>et al</i> [107], 2019	407 cirrhosis patients: 25 with HCC; 25 without HCC; 25 healthy controls	HCC	↑ <i>Erysipelotrichaceae</i> ; ↑ <i>Odoribacter</i> ; ↑ <i>Butyricimonas</i> ; ↓ <i>Leuconostocaceae</i> ; ↓ <i>Fusobacterium</i> ; ↓ <i>Lachnospiraceae</i>	Decreased <i>Prevotella</i> in cirrhotic patients with HCC, is associated with activation of several inflammatory pathways
Ni <i>et al</i> [108], 2019	68 primary HCC patients: (23 Stage I, 13 Stage II, 30 Stage III, 2 Stage IV); 18 healthy controls	HCC	↑ Dysbiosis index <i>Proteobacteria</i> (<i>Enterobacter</i> , <i>Haemophilus</i>); ↓ <i>Desulfococcus</i> ; ↑ <i>Prevotella</i> ; ↑ <i>Veillonella</i> ; ↓ <i>Cetobacterium</i>	Dysbiosis is seen in patients with primary HCC when compared to healthy controls
Liu <i>et al</i> [69], 2019	57 HCC patients (35 with HBV related HCC, 22 with non-HBV non-HCV related HCC); 33 healthy controls	HCC	↑ <i>Bifidobacterium</i> ; ↑ <i>Lactobacillus</i> ; ↓ <i>Proteobacteria</i> ; ↓ <i>Firmicutes</i>	Decreased anti-inflammatory and increased pro-inflammatory bacteria in non-HBC non-HCV related HCC patients are positively correlated with alcohol consumption
Schwimmer <i>et al</i> [109], 2019	87 NAFLD patients; 37 healthy controls	NAFLD	↑ <i>Bacteroidetes</i> ; ↑ <i>Proteobacteria</i> ; ↓ <i>Firmicutes</i>	Decreased α -diversity in NAFLD was associated with differences in bacterial abundance rather than an increase in specific phyla or genus; increased bacterial pro-inflammatory products (LPS) were seen in patients with NAFLD
Duarte <i>et al</i> [110], 2019	NASH patients; healthy controls	NASH	↑ <i>Bacteroides</i> ; ↑ <i>Proteobacteria</i> ; ↑ <i>Enterobacteriaceae</i> ; ↑ <i>Escherichia</i> ; ↓ <i>Firmicutes</i> ; ↓ <i>Actinobacteria</i> ; ↑ <i>Klebsiella pneumoniae</i>	Increased alcohol-producing bacteria supply a constant source of ROS which results in liver inflammation
Kravetz <i>et al</i> [111], 2020	44 NAFLD patients; 29 healthy controls	NAFLD	↓ <i>Bacteroidetes</i> ; ↓ <i>Prevotella</i> ; ↓ <i>Gemmiger</i> ; ↓ <i>Oscillospira</i>	Decreased bacterial diversity in patients with NAFLD is associated with an increase in the rate of inflammation in NAFLD
Lang <i>et al</i> [65], 2020	NAFLD patients and healthy controls	NAFLD	↓ <i>Virus</i> and bacteriophage diversity; ↑ <i>Escherichia</i> ; ↑ <i>Enterobacteria</i> ; ↑ <i>Lactobacillus</i> phage	
Lang <i>et al</i> [112], 2021	NAFLD patients and healthy controls	NAFLD	↑ <i>Gemmiger</i> ; ↓ <i>Faecalibacterium</i> ; ↓ <i>Bacteroides</i> ; ↓ <i>Prevotella</i>	
Behary <i>et al</i> [113], 2021	32 NAFLD-HCC patients; 28 NAFLD-cirrhosis patients; 30 non-NAFLD controls	HCC	↑ <i>Proteobacteria</i> ; ↑ <i>Enterobacteriaceae</i> ; ↑ <i>Bacteroides xylanisolvens</i> ; ↑ <i>B. caecimuris</i> ; ↑ <i>Ruminococcus gnavus</i> ; ↑ <i>Clostridium bolteae</i> ; ↑ <i>Veillonella parvula</i> ; ↑ <i>Bacteroides caecimuris</i> ; ↑ <i>Veillonella parvula</i> ; ↑ <i>Clostridium bolteae</i> ; ↑ <i>Ruminococcus gnavus</i> ; ↓ <i>Oscillospiraceae</i> ; ↓ <i>Erysipelotrichaceae</i> ; ↓ <i>Eubacteriaceae</i>	Increased <i>B. caecimuris</i> and <i>Veillonella parvula</i> distinguish NAFLD-HCC from NAFLD-cirrhosis and non-NAFLD controls; decreased gut microbial α -diversity and increased SCFAs serum levels in NAFLD-HCC result in immunosuppression

Trebicka <i>et al</i> [114], 2021	Cirrhosis patients <i>vs</i> healthy controls	Cirrhosis	↑ Enterobacteriaceae; ↑ Alcaligenaceae; ↑ Streptococcaceae; ↑ Veillonellaceae; ↑ Fusobacteriaceae; ↓ Bacteroidetes; ↓ Ruminococcaceae; ↓ Lachnospiraceae	Pathogenic organisms' overgrowth results in accelerated disease progression and endotoxemia which results in reduction of organisms that can produce SCFAs and anti-bacterial peptides
Solé <i>et al</i> [115], 2021	182 cirrhosis patients	Cirrhosis	↑ Enterococcus; ↑ Streptococcus in ACLF; ↑ Faecalibacterium; ↑ Ruminococcus; ↑ Eubacterium in decompensated patients	As cirrhosis progressed from compensated to uncompensated to ACLF, there was a marked reduction in metagenomic richness

ACLF: Acute-on-chronic liver failure; ALD: Alcohol-related liver diseases; SCFAs: Short chain fatty acids; NAFLD: Non-alcoholic fatty liver disease; HCC: Hepatocellular carcinoma; ROS: Reactive oxygen species; LPS: Lipopolysaccharide; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Non alcoholic steatohepatitis; HE: Hepatic encephalopathy; BMI: Body mass index.

crobal activity[46-48]. Another study observed a reduction in the secondary to primary bile acids (BAs) ratio and a decrease in total faecal BA concentration in the terminal stages of cirrhosis[49]. These shifts result in diminished FXR activation and increased damage mediated by ROS[50]. Consequently, these changes foster bacterial overgrowth and dysbiosis, perpetuating the vicious cycle of increased permeability, immune dysregulation, metabolic imbalance, and hepatocellular damage. **Figure 2** illustrates the complex interactions within the gut-liver axis and the mechanisms of its failure, leading to liver injury.

CLINICAL IMPLICATIONS OF GUT-LIVER AXIS IN HEPATIC DISEASES

NAFLD

NAFLD has been linked to gut dysbiosis influenced by dietary and lifestyle factors. Elevated levels of Proteobacteria, Enterobacteriaceae, and Escherichia, which are known alcohol-producing bacteria, have been observed in patients with NASH[51]. These bacteria may cause liver damage by enabling the translocation of toxins through the portal circulation. In cases of NAFLD or NASH, there is an increase in Bacteroidetes, Proteobacteria, and Actinobacteria[24,28,29,52-54]. Conversely, other studies indicate an increase in Firmicutes and a decrease in Bacteroidetes, Proteobacteria, and Actinobacteria in NASH patients[28,29]. Moreover, the presence of metabolic syndrome in patients with NAFLD correlates with more severe disease due to increased Bacteroidetes and Ruminococcus[55]. A decrease in Coprococcus, Faecalibacterium, and Ruminococcus was noted in NAFLD patients, resulting in a reduction of their anti-inflammatory effects[55].

Alcoholic liver disease

Alcohol consumption disrupts the gut microbiota. Research involving ethanol-fed mice showed intestinal cell death, which increases permeability due to the deterioration of tight junctions[56]. A significant rise in endotoxemia was observed in alcoholics, patients with alcoholic hepatitis, and those with cirrhosis compared to the general population[57]. Mutlu *et al*[26], in 2012, noted a reduction in Bacteroidetes and Firmicutes and an increase in Proteobacteria. Severe alcoholic liver disease is associated with a higher proportion of Streptococci, Bifidobacteria, and Enterobacteria, and a reduction in anti-inflammatory microorganisms like *Faecalibacterium prausnitzii*[27]. Furthermore, *Parasutterella excrementihominis*, absent in alcoholic mouse microbiota but present in non-alcoholic ones, suggests a protective role for this bacterium.

Liver cirrhosis

Cirrhotic patients exhibit a decline in Lachnospiraceae, Clostridia, Ruminococcaceae [Firmicutes phylum], and Bacteroidetes[58-60], along with an increase in pathogenic bacteria such as Veillonellaceae, Enterobacteriaceae, and Streptococcaceae[58,61,62]. This shift towards pathogenic bacteria leads to a reduction in SCFAs and an increase in LPS production. The reduced favourable microbiota is associated with decreased 7 α -hydroxylation, which subsequently lowers bile acid levels. This reduction can facilitate the translocation of oral commensals like *Streptococcus salivarius*[61] and Veillonella species[63] into the gut, driven by urease production, leading to endotoxemia and exacerbating liver inflammation, which may progress to steatosis, hepatitis, and fibrosis.

Hepatocellular carcinoma

The LPS-TLR4 axis is implicated in promoting carcinogenesis *via* activation of stellate and Kupffer cells, chronic inflammation, and fibrosis, though it does not initiate carcinogenesis[64]. Another pathway involves the activation of the nuclear factor- κ B pathway through TLR-4, which stimulates the release of inflammatory cytokines such as IL-1B and IL-18[65,66]. LPS can also trigger epithelial-mesenchymal transition[67]. A common alteration in the gut microbiota in hepatocellular carcinoma (HCC) is an increased Firmicutes/Bacteroidetes ratio[68]. There is also an elevation in inflammatory bacteria like Enterococcus, Escherichia, and Shigella, alongside a reduction in Faecalibacterium, Ruminococcus, and Ruminoclostridium in HCC patients[69]. Additionally, Zheng *et al*[66] found a decrease in butyrate-producing bacteria such as Clostridium, Coprococcus, and Ruminococcus, and an increase in LPS-producing bacteria like Neisseria, Enterobacteriaceae, and Veillonella in patients with HCC and cirrhosis. These microbial shifts could serve as potential biomarkers for HCC.

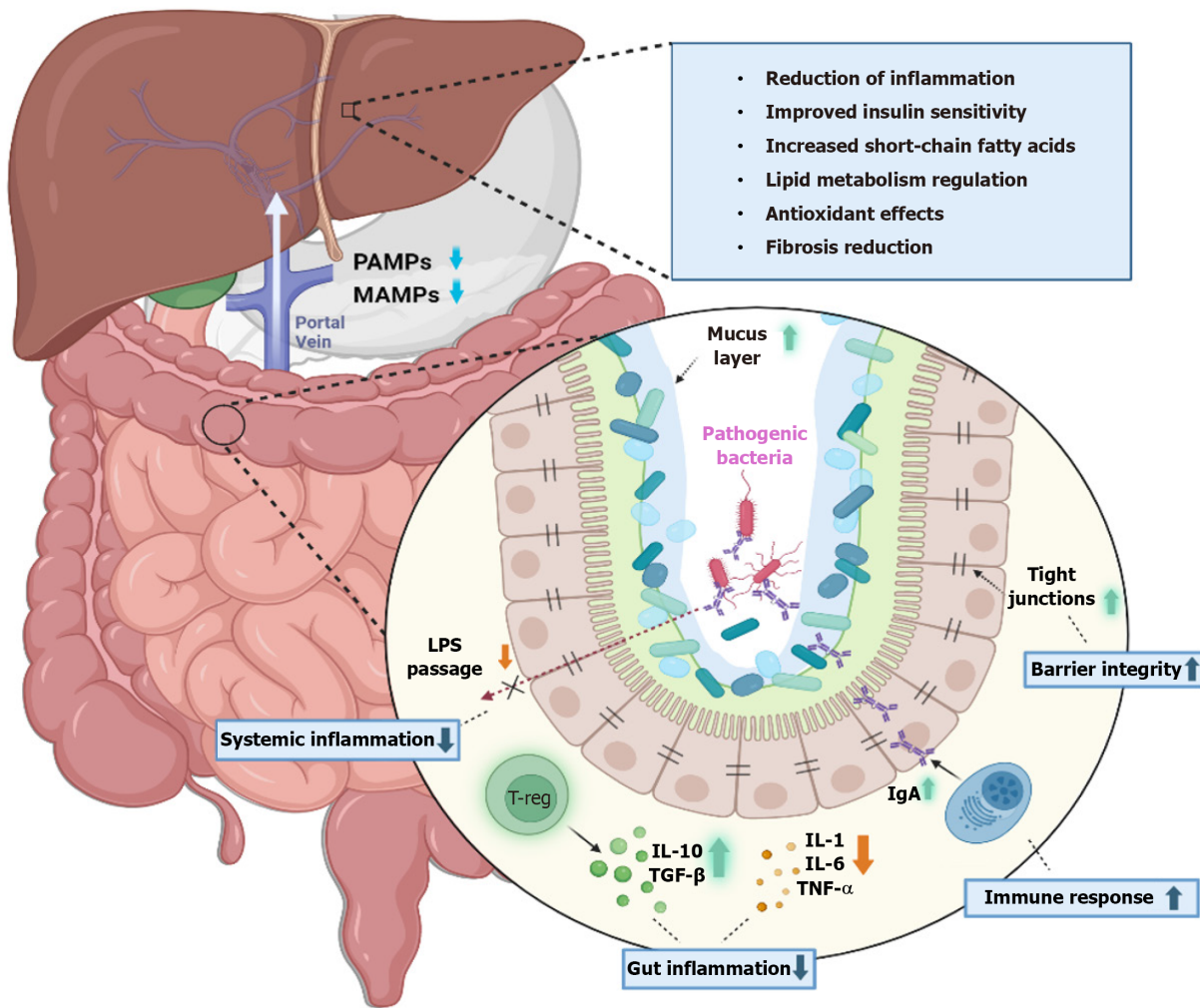


Figure 1 Role of gut microbiota in maintaining liver homeostasis. IgA: Immunoglobulin A; IL: Interleukin; MAMP: Microbe-associated molecular patterns; PAMP: Pathogen-associated molecular patterns; TGF: Transforming growth factor; TNF: Tumor necrosis factor.

Autoimmune hepatitis

The pathogenesis of this condition is primarily dependent on the interplay between genetic and environmental factors. It has been found that genetically susceptible individuals have HLA-DRB1 0301 and HLA-DRB1 0401 genotypes which, on interaction with environmental factors such as viruses (cytomegalovirus, hepatitis A, B, C, and E viruses, and Epstein-Barr virus) or drugs (minocycline), leads to a dysregulated pro-inflammatory response where the antigen presenting cells set off a cascade of events where helper T cells get activated. Activated helper T cells release a stream of cytokines which in turn activate cytotoxic T cells to release a group of cytokines resulting in an antibody-mediated cell toxicity, eventually leading to hepatocellular injury.

Another mechanism in the development of autoimmune hepatitis is through molecular mimicry where the antibodies directed against environmental antigens become self-directed to self-antigens due to similarities of environmental antigens with self-antigens *as per* Floreani *et al* [67]. In individuals with AIH, there were significant reductions in species of *Bifidobacterium* and *Lactobacillus*, which resulted in increased gut permeability and enhanced translocation of bacteria indicated by increased lipopolysaccharide levels that were positively correlated with the disease severity *as per* Lin *et al* [70].

Viral hepatitis and other liver diseases

These pathologies show an increased association between disease progression and dysbiosis. A decrease in *Bacteroides*, *Lactobacillus*, *Bifidobacterium* and an increase in *Enterococcus* and *Enterobacteriaceae*, which resulted in altered gut microbiome, were seen in chronic hepatitis B. With limited studies on hepatitis C and gut dysbiosis, it was found that there was a reduction in alpha-diversity and altered gut microbiome. One of the reasons for altered microbiome is that a reduction in bile production leads to an increase in pathogenic species in the gut [71-73].

Another interesting correlation was observed between primary sclerosing cholangitis (PSC) and gut dysbiosis. According to Bajer *et al* [74], in patients with PSC and PSC-IBD there was an increase in *Veillonella*, *Enterococcus*, *Clostridium*, *Streptococcus*, *Rothia*, and *Hemophilus* and a decrease in *Coprococcus*. This observation is explained by the fact that the pro-inflammatory state set by PSC leads to increased gut permeability and the products of bacteria such as SCFAs and bile acids lead to disease progression [74].

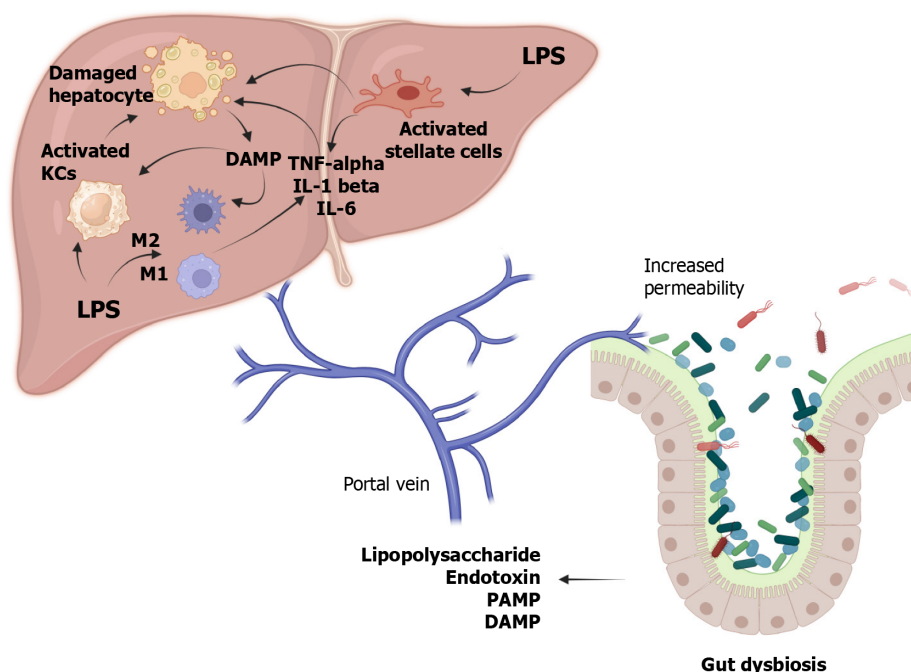


Figure 2 Dysbiotic gut-liver axis resulting in liver damage. IL: Interleukin; LPS: Lipopolysaccharide; M: Macrophage; KCs: Kupffer cells; DAMP: Damage-associated molecular patterns; PAMP: Pathogen-associated molecular patterns; TNF: Tumor necrosis factor.

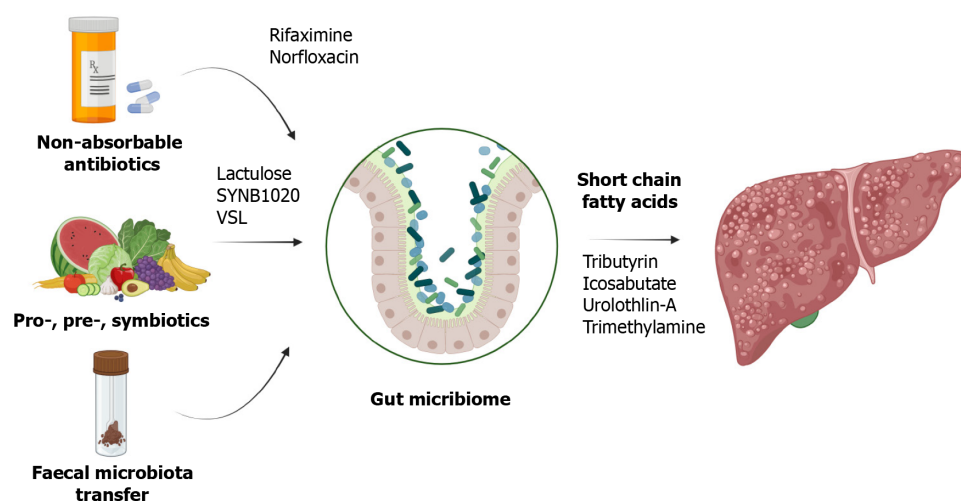


Figure 3 Therapeutic potential of intestinal microbiome in liver disease management.

In primary biliary cholangitis (PBC), a study by Lv *et al*[75] stated that there was an increase in *Veillonella*, *Bifidobacterium*, *Neisseria*, and *Klebsiella* and a decrease in *Ruminococcus*, *Bacteroides eggertii*, and *Hallella*. But further studies are required for establishing treatments that alter the gut microbiome in patients with PBC and PSC/PSC-IBD.

THERAPEUTIC POTENTIALS AND INTERVENTIONS

Targeted changes in human microbiota are achieved through probiotics, prebiotics, and synbiotics as shown in Figure 3.

Probiotics

Probiotics, which are live organisms, are administered as supplements to supplant pathogenic bacteria. Research has demonstrated that a mixture of *Lactobacillus*, *Streptococcus thermophilus*, and *Bifidobacteria* ameliorated steatosis in mice induced by a high-fat diet[76]. *Lactobacillus* GG was shown to mitigate intestinal oxidative stress, leakage, and liver damage in rat models of alcoholic steatohepatitis[77]. Additionally, combinations of probiotics have been effective in

slowing the progression of HCC in mice by reducing TH17 cells[78]. *Akkermansia muciniphila* has been noted to strengthen tight junctions and maintain intestinal permeability in alcoholic steatohepatitis models[79]. There is also evidence suggesting that probiotic therapy can enhance the efficacy of immunotherapy in cancer patients[80].

Prebiotics

Studies have shown that pectin can modify the intestinal microbiota in mice, prevent steatosis, and decrease inflammation. Common prebiotics include oligosaccharides, polyunsaturated fatty acids, and polyphenols[81]. A meta-analysis involving 1309 patients with NAFLD reported significant reductions in body mass index, liver enzymes, serum cholesterol, and triglycerides following prebiotic administration[82].

Synbiotics

The combined use of prebiotics and probiotics, known as synbiotics, has shown enhanced benefits. According to Hadi *et al*[83], synbiotic consumption led to improvements in lipid profiles and metabolic hepatic steatosis. Malaguarnera *et al*[84] found that after 6 mo of administering *Bifidobacterium longum* and Fructo-oligosaccharide to 66 patients with NASH, there were significant reductions in serum AST, LPS, inflammatory mediators, fat denaturation, and the NASH activity index.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) aims to replace the intestinal flora with a healthier one, improving gut permeability and reducing endotoxemia and inflammatory molecules through the increased production of anti-microbial peptides. In a study by Ferrere *et al*[85], fecal bacteria from alcohol-resistant mice were transplanted to alcohol-sensitive receptor mice, effectively preventing alcohol-induced intestinal disorders and fatty liver hepatitis. This treatment altered the bacterial composition, decreasing Bacteroides and increasing Actinobacteria and Firmicutes. In a recent randomized, double-blind trial, patients with alcohol-related liver disease and cirrhosis received FMT from a donor with a Lachnospiraceae and Ruminococcaceae rich microbiota. Results from this trial showed reductions in IL-6 and LPS-binding protein levels and an increase in butyrate/isobutyrate levels on day 15 in the FMT group, in contrast to the control and placebo groups[86](Table 2).

CHALLENGES AND FUTURE DIRECTIONS

The therapeutic landscape for liver diseases is complex, due to challenges such as tissue specificity, drug resistance, and selectivity, complicating the establishment of clear relationships between specific liver conditions and causative organisms. Current research often relies on animal models, primarily mice, which differ significantly in gut microbial diversity from humans. This variation limits the direct applicability of findings to human models. Although advancements in microbial analysis have begun to elucidate the relationships between gut metabolites and specific microbes, many metabolites remain unlinked to distinct microbial agents. Deeper microbial and metabolomic investigations are imperative for understanding the molecular mechanisms underlying liver pathology. The variability in gut microbiota compositions among individuals, influenced by genetic, dietary, and environmental factors, poses a significant challenge in translating microbiota research into clinical applications. This diversity necessitates the development of personalized therapeutic interventions tailored to individual microbiome profiles. Most studies to date have been cross-sectional, restricting the ability to establish causality between microbiota changes and liver disease progression. Longitudinal and multi-centric studies are crucial for tracking microbiota evolution over time and validating findings across diverse populations to enhance the generalizability of the research.

The current understanding of how microbial metabolites affect liver pathology is limited, and further research is needed to identify key microbial strains or metabolites critical in disease progression. This could pave the way for targeted therapies. Moreover, there is a pressing need for non-invasive biomarkers that reflect the gut-liver axis accurately, facilitating early disease diagnosis and monitoring. Advances in metagenomic and metabolomic technologies are pivotal in identifying such biomarkers by profiling microbial communities and their metabolic outputs. The clinical efficacy of microbiota-targeted therapies, such as probiotics, prebiotics, and synbiotics, varies due to differences in formulations, dosages, and patient demographics. Standardized intervention protocols and rigorous clinical trials are essential to ascertain the most effective therapeutic compositions. Furthermore, the safety of therapies like FMT must be thoroughly assessed to mitigate risks associated with the transfer of pathogenic organisms or undesirable genetic materials. Establishing stringent regulatory frameworks and standardized protocols will be critical as these therapies progress toward routine clinical use. Integrating microbiota-modulating therapies with conventional liver disease treatments—such as pharmacotherapy and lifestyle interventions—may enhance therapeutic outcomes. It is also vital to explore how these therapies interact with emerging treatments like gene therapy and immunotherapy to adopt a holistic approach to managing hepatic diseases. Additionally, public health initiatives should integrate gut microbiota research findings to develop guidelines that promote a microbiota-friendly lifestyle through dietary recommendations, lifestyle modifications, and urban planning, thereby preventing liver diseases at a population level and alleviating the broader public health burden.

Table 2 Potential therapeutic interventions targeting the gut-liver axis

Interventions	Mechanism of action	Targeted disease	Clinical outcomes	Ref.
Prebiotics (pectin)	Restore <i>Bacteroides</i> level	Alcoholic liver disease	Control dysbiosis	Ferrere <i>et al</i> [85], 2017
Prebiotics (Fructo-oligosaccharide)	Promote fatty acid oxidation	NAFLD	Reduced hepatocyte damage and inflammation	Matsumoto <i>et al</i> [116], 2017
Probiotics (<i>E. coli</i> Nissle strain)	↑ <i>Lactobacillus</i> species; ↑ <i>Bifidobacterium</i> species; ↓ <i>Proteus</i> hauseri; ↓ <i>Citrobacter</i> species; ↓ <i>Morganella</i> species	Cirrhosis (humans)	Significant improvement in gut microbiome with decreased endotoxemia, bilirubin, and ascites	Lata <i>et al</i> [117], 2007
Probiotics (<i>Lactobacillus reuteri</i> GMNL-263)	↑ <i>Bifidobacteria</i> ; ↑ <i>Lactobacilli</i> ; ↓ <i>Clostridia</i>	Hepatic steatosis (rats)	↓ Blood glucose levels, TNF- α and IL-6 production by adipose tissue	Hsieh <i>et al</i> [118], 2013
Probiotics	↑ <i>Parabacteroides</i> ; ↑ <i>Allisonella</i> ; ↓ <i>Faecalibacterium</i> ; ↓ <i>Anaerosporebacter</i>	NASH (humans)	↑ <i>Bacteroidetes</i> ↓ <i>Firmicutes</i>	Wong <i>et al</i> [91], 2013
Probiotic: VSL#3 (8 probiotic mixture)	GLP-1	NAFLD	Decrease BMI and increase GLP-1 and activated GLP1	Alisi <i>et al</i> [119], 2014
Probiotics (VSL #3)	↑ <i>Lactobacillus</i> species	Cirrhosis (humans)	Reduced hospitalization due to HE with daily intake of probiotic for 6 mo	Dhiman <i>et al</i> [120], 2014
Probiotics (<i>Lactobacillus</i> GG)	↑ <i>Firmicutes</i> species; ↓ <i>Enterobacteriaceae</i> ; ↓ <i>Porphyromon adacea</i> ;	Cirrhosis (humans)	↓ Endotoxemia and TNF- α after 8 wk; ↓ dysbiosis due to decreased <i>Enterobacteriaceae</i> and increased <i>Firmicutes</i> species	Bajaj <i>et al</i> [95], 2014
Probiotics (cholesterol lowering probiotics and anthraquinone from <i>Cassia obtusifolia</i> L)	↑ <i>Bacteroides</i> ; ↑ <i>Lactobacillus</i> P; ↑ <i>Arabacteroides</i> ; ↓ <i>Oscillospira</i>	NAFLD (rats)	Improve intestinal barrier and decrease endotoxemia and inflammatory cytokines	Mei <i>et al</i> [121], 2015
Probiotics (Prohep: <i>Lactobacillus rhamnosus</i> GG (LGG), viable <i>Escherichia coli</i> Nissle 1917 (EcN), and heat-inactivated VSL#3)	↑ <i>Alistipes</i> ; ↑ <i>Butyricimonas</i> ; ↑ <i>Mucispirillum</i> ; ↑ <i>Oscillibacter</i> ; ↑ <i>Parabacteroides</i> ; ↑ <i>Paraprevotella</i> ; ↑ <i>Prevotella</i> ; ↑ <i>Bacteroidetes</i> ; ↓ <i>Firmicutes</i> ; ↓ <i>Proteobacteria</i>	HCC (mice)	↑ Anti-inflammatory bacteria; ↓ Th17-inducing bacteria and segmented filamentous pro inflammatory bacteria	Li <i>et al</i> [77], 2016
Probiotics	↑ <i>Ruminococcus</i> ; ↑ <i>Saccharibacteria</i> (TM7 phylum); ↓ <i>Verrucomicrobia</i> ; ↓ <i>Veillonella</i>	NAFLD (rats)	↓ TC, TG, lipid deposition, and inflammation	Liang <i>et al</i> [122], 2019
Six probiotic mixtures	Gut microbiota	NAFLD	Reduce intrahepatic fat and body weight	Ahn <i>et al</i> [123], 2019
Probiotics (multispecies strain)	↑ <i>Lactobacillus</i> (<i>brevis</i> , <i>salivarius</i> , <i>lactis</i>); ↑ <i>Faecalibacterium prausnitzii</i> ; ↑ <i>Syntrophococcus sucromutans</i> ; ↑ <i>Alistipes shahii</i> ; ↑ <i>Bacteroides vulgatus</i> ; ↑ <i>Prevotella</i>	Cirrhosis (humans)	Gut microbiome enrichment in compensated cirrhosis patients and improved gut barrier function	Horvath <i>et al</i> [124], 2020
Probiotics (<i>Bifidobacterium animalis</i> spp. <i>Lactis</i> 420)	↑ <i>Lactobacillus</i> ; ↑ <i>Alistipes</i> ; ↑ <i>Rikenella</i> ; ↑ <i>Clostridia</i> ; ↓ <i>Bacteroides</i> ; ↓ <i>Ruminococcus</i>	HCC (Mice)	Reduced liver injury and improved immune homeostasis <i>via</i> : Increment in tight junction proteins; ↓ Serum endotoxin levels; ↑ fecal SCFAs; ↑ α -diversity regulation of pro-inflammatory cytokines; (-) RIP3-MLKL signalling pathway of liver macrophages	Zhang <i>et al</i> [125], 2020
Probiotics (<i>Bifidobacterium</i> and <i>Lactobacillus</i>)	↑ <i>Bacteroidetes</i> ; ↑ <i>Bifidobacterium</i> ; ↑ <i>Bacteroides</i> ; ↑ <i>Clostridium</i> ; ↑ <i>Ruminococcus</i> ; ↑ <i>Anaerostipes</i> ; ↑ <i>Blautia</i> ; ↓ <i>Firmicutes</i> ; ↓ <i>Faecalibacterium</i> ; ↓ <i>Helicobacter</i> ; ↓ <i>Staphylococcus</i>	HCC (Mice)	↑ T _{reg} cell differentiation; ↑ SCFAs; ↓ infiltration of inflammatory cells in the liver; ↓ ALT, AST; ↓ Th1, Th17 cells; (-) LPS translocation to the liver; (-) activation of the TLR/NF- κ B pathway	Liu <i>et al</i> [126], 2021
Probiotic	Gut barrier	NAFLD		Mohamad <i>et al</i> [127], 2021
FMT	↑ <i>Lactobacillaceae</i> ; ↑ <i>Bifidobacteriaceae</i> ; ↑ <i>Bacteroidetes</i> ; ↑ <i>Firmicutes</i>	HE	Improves dysbiosis and SCFAs	Bajaj <i>et al</i> [86], (2017)
FMT	Gut microbiota	Cirrhosis	Reduced systemic inflammation	Bajaj <i>et al</i> [128], 2019
FMT	Allogenic FMT: ↑ <i>Ruminococcus</i> ↑ <i>Eubacterium hallii</i> ; ↑ <i>Faecalibacterium</i> ; ↑	NAFLD	Decreased steatosis and liver inflammation and enhanced liver endothelial function	Witjes <i>et al</i> [129], 2020

	<i>Prevotella copri</i> ; Autologous FMT: ↑ Lachnospiraceae			
FMT	Gut microbiota	NAFLD	Reduced intestinal permeability	Craven <i>et al</i> [130], 2020
FMT	↑ <i>Bifidobacterium</i> ; ↑ <i>Lactobacillus</i> ; ↓ <i>Escherichia coli</i>	HCC	Decreased AST, ALT, and serum IgG levels and prevented progression of alcohol induced hepatitis	Liang <i>et al</i> [131], 2021
FMT	Gut microbiota	NAFLD	Reduces gut dysbiosis and decreases fat accumulation	Xue <i>et al</i> [132], 2022
Synbiotics [<i>Bifidobacterium longum</i> and Fructo-oligosaccharide]	Gut microbiota	NASH	Reduced liver inflammation and hepatocyte damage	Malaguarnera <i>et al</i> [84], 2012
Synbiotics [<i>Bifidobacterium animalis</i> and inulin]	Gut microbiota	NAFLD	Improved steatosis and liver enzyme levels	Lambert <i>et al</i> [133], 2015
Synbiotics	Gut microbiota	NAFLD	Increased levels of <i>Bifidobacterium</i> and <i>Faecalibacterium</i> , and decreased <i>Oscillibacter</i> and <i>Alistipes</i>	Scorletti <i>et al</i> [134], 2020

NAFLD: Non-alcoholic fatty liver disease; NASH: Non alcoholic steatohepatitis; HCC: Hepatocellular carcinoma; FMT: Faecal microbial transplantation; HE: Hepatic encephalopathy; TC: Total cholesterol; TG: Triglycerides; SCFAs: Short chain fatty acids; LPS: Lipopolysaccharide; GLP: Glucagon like peptide.

CONCLUSION

Our article highlights the potential of gut microbiome manipulation as a transformative approach to liver disease treatment, with fewer side effects and complications compared to traditional methods. Therapeutic strategies such as the administration of probiotics, prebiotics, synbiotics, and FMT have shown promise in modulating the gut microbiota to enhance liver health. As we move forward, the integration of these interventions into personalized medicine is essential, utilizing detailed individual microbiome profiles to tailor therapies. The future of liver disease management will be shaped by continued research and innovation. Longitudinal studies and clinical trials are imperative to validate the therapeutic potentials identified and to refine these strategies, propelling us into a new era of precision medicine in hepatology.

FOOTNOTES

Author contributions: Jeyaraman M, Mariappan T, and Jeyaraman N contributed to conceptualization; Mariappan T and Ramasubramanian S contributed to acquiring the clinical data and performing the data analysis; Jeyaraman M, Mariappan T, and Ramasubramanian S contributed to manuscript writing; Jeyaraman M, Santos GS, Fonseca LF, and Lana JF helped in manuscript revision; Muthu S contributed to image acquisition; Jeyaraman M contributed to proofreading; Jeyaraman M and Lana JF contributed to administration. All authors have agreed to the final version to be published and agree to be accountable for all aspects of the work.

Conflict-of-interest statement: The authors declare no conflict of interest in publishing the manuscript.

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S-Editor: Liu JH

L-Editor: Wang TQ

P-Editor: Wang WB

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