International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Gut-Liver Axis: Molecular Mechanisms and Therapeutic Targeting in Liver Disease

Liang Ma[1], He Wang[2], Qiuyu Jin[3], Zhiwen Sun[3], Shuang Yu[4], Yang Zhang[3]

[1]First Clinical Medical College, Heilongjiang University of Chinese Medicine, Harbin, 150040, People's Republic of China; [2]Department of Cardiology, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, 150040, People's Republic of China; [3]Department of Gastroenterology, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, 150040, People's Republic of China; [4]College of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin, 150040, People's Republic of China

Correspondence: Yang Zhang, Department of Gastroenterology, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, No. 26 Heping Street, Xiangfang District, Harbin, Heilongjiang, 150006, People's Republic of China, Email zhangyanghljucm@126.com

Abstract: The gut microbiota, often termed the "second genome", demonstrates profound therapeutic potential through its intricate biological network connecting multiple distal organs. Although microbial diversity is strongly correlated with intestinal health, its systemic implications on overall physiological homeostasis remain incompletely understood. This review synthesizes the latest evidence from clinical trials, randomized controlled trials (RCTs), systematic reviews, and meta-analyses to elucidate the biological pathways and therapeutic applications of the gut–liver axis. Through comprehensive schematic illustrations, we delineate the molecular mechanisms underlying bidirectional gut–liver communication, including microbial metabolite signaling, immune modulation networks, and enterohepatic circulation dynamics. Although interventional studies have confirmed the beneficial physiological effects of microbial modulation, current mechanistic insights are predominantly derived from animal models with limited clinical translation. While large-scale cohort studies with long-term follow-up data remain imperative, the existing evidence strongly supports the clinical value of microbiome-targeted strategies for treating hepatic diseases and related complications. These findings establish a critical theoretical framework for the development of next-generation microbial therapeutics targeting the gut–liver axis. The novelty of this review lies in its systematic classification of gut microbiota and their metabolites in the pathogenesis and treatment of various liver diseases, its detailed elaboration on signaling pathways, and its dedicated focus on the role of Traditional Chinese Medicine (TCM) in modulating the gut–liver axis.

Keywords: gut microbiome, gut-liver axis, biological pathways, immune response, liver diseases, non-alcoholic fatty liver disease

Introduction

Liver diseases represent a significant global health burden, with etiologies ranging from viral infections and alcohol abuse to metabolic disorders. Among these, metabolic dysfunction-associated steatotic liver disease (MASLD, historically known as non-alcoholic fatty liver disease or NAFLD) has emerged as the most prevalent chronic liver condition worldwide, affecting approximately 25% of the global population. Its more severe form, metabolic dysfunction-associated steatohepatitis (MASH, historically known as non-alcoholic steatohepatitis or NASH), is characterized by hepatic steatosis, lobular inflammation, and ballooning degeneration, which can progress to fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC).[1,2] The clinical spectrum of MASLD is often intertwined with obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia, making its management complex. Current pharmacological strategies have evolved significantly. While older approaches such as pioglitazone (an insulin sensitizer) and vitamin E (an antioxidant) show modest efficacy in improving liver histology, they are associated with side effects including weight gain and potential increased risk of prostate cancer, respectively. Obeticholic acid, a farnesoid X receptor (FXR) agonist, showed promise but is linked to pruritus and an unfavorable lipid profile.[3] Recently, breakthrough therapies have emerged. Resmetirom, a thyroid hormone receptor-β agonist, became the first FDA-approved medication for non-cirrhotic MASH with moderate-to-advanced fibrosis (F2-F3) in March 2024, demonstrating significant MASH resolution

Received: 4 July 2025
Accepted: 6 December 2025
Published: 15 December 2025

and fibrosis improvement in the Phase 3 trial.[4] Similarly, semaglutide, a GLP-1 receptor agonist, received FDA indication for MASH with fibrosis in August 2025 based on the phase 3 ESSENCE trial, which showed high rates of MASH resolution.[5] Despite these advances, challenges such as specific patient eligibility, the need for long-term adherence, and the pursuit of even greater efficacy remain. The lack of a universally optimal therapeutic option continues to underscore the need for novel drug targets and treatment strategies.

The therapeutic landscape for MASLD/MASH has evolved significantly, as evidenced by the latest Global Consensus Recommendations for MASLD/MASH (2025) and the AASLD Practice Guidance on NAFLD/MASLD (updated 2023).[6,7] These guidelines establish lifestyle intervention as the fundamental management approach, while also recognizing important advances in pharmacotherapy. Notably, the thyroid hormone receptor-beta (THR-β) agonist resmetirom has gained approval as the first drug specifically indicated for treating MASH with fibrosis, representing a milestone in targeted therapy for this condition.[8] Beyond this specific indication, the guidelines also address the role of other pharmacological agents: GLP-1 agonists are recognized as preferred treatments for patients with concomitant type 2 diabetes and/or obesity, while SGLT2 inhibitors are considered appropriate treatments for type 2 diabetes in individuals with or without MASH, though both classes are currently used off-label for MASH-specific treatment.[9,10] In addition to these established therapies, several investigational products are currently in clinical trials, reflecting the dynamic nature of MASLD research. These include FXR agonists (eg, tropifexor and cilofexor), fibroblast growth factor-21 (FGF21) analogues/mimetics (eg, efruxifermin, also known as AKR-001), ACC/DGAT/lipid metabolism inhibitors, and anti-inflammatory/anti-fibrotic agents such as cenicriviroc (a CCR2/5 antagonist).[11–15] These developments highlight the progressive refinement of therapeutic strategies for MASLD/MASH, while simultaneously underscoring the ongoing need for novel approaches that address the complex pathophysiology of this prevalent liver disease.

Recent advancements in biomedical science have increasingly highlighted the critical roles of the microbiome and gut microbiota in the pathogenesis of various diseases.[16–18] Notably, non-communicable diseases, particularly metabolic disorders, are supported by a wealth of evidence-based research.[19,20] Abnormal bile acid (BA) synthesis and metabolism are multifactorial processes in the liver, with MASLD and MASH emerging as key contributors to liver dysfunction, significantly increasing the risk of cirrhosis and HCC.[21] The gut-liver axis, which underscores the indispensable relationship between the intestine and liver, is pivotal in maintaining normal physiological metabolism. Focusing on biliary and lipid metabolism can provide valuable insights into the pathogenesis and etiology of liver diseases.[22] In chronic liver diseases (CLD), the gut-liver axis has drawn particular attention to the role of gut microbiota in liver cirrhosis.[23,24]

Beyond pharmacological interventions, recent research has increasingly focused on the role of gut microbiota in the pathogenesis and treatment of liver diseases. Gut microbiota therapy has demonstrated efficacy in addressing insulin resistance and fasting insulin levels through the use of prebiotics, probiotics, and synbiotics (combinations of the former two).[25] For patients with hepatic damage, this therapeutic approach holds promise, provided the right species combination, optimum dosage, and the absence of confounding factors are ensured.[26] Additionally, the emerging field of reverse bacteriophage therapy, which involves modulating bacterial composition to treat viral infections, has shown that fecal microbiota transplantation (FMT) is both safe and effective in clearing viral infections. This treatment improved inflammatory episodes and clinical outcomes in cases of hepatitis B, COVID-19, human immunodeficiency virus (HIV), and cytomegalovirus colitis, with no reports of severe adverse events.[27–30]

Clinical trials have demonstrated that CLD are closely associated with microbiota-derived metabolites including short-chain fatty acids (SCFAs), choline, and tryptophan.[31] In the context of alcohol addiction, probiotics show therapeutic potential by targeting neurotransmitter pathways involved in addiction, restoring the gut microbiota balance, and reducing neuroinflammation.[32] Furthermore, probiotics have been shown to mitigate alcoholic liver disease (ALD) by modulating the gamma-aminobutyric acid (GABA), dopamine, and glutamate pathways, thereby reducing the desire for alcohol consumption. Next-generation probiotics (NGPs), which combine the dual function of producing SCFAs and inhibiting oxidative stress, hold promise for reversing both MASLD and its late stage, MASH.[33] Silibinin capsules, a component derived from milk thistle used in TCM practices, have been shown to significantly improve clinical symptoms by lowering blood lipids and enhancing liver function through gut microbiota modulation.[34]

The increased prevalence of small intestinal bacterial overgrowth (SIBO) in patients with CLD, especially those with portal hypertension, variceal bleeding, and spontaneous bacterial peritonitis, underscores its association with cirrhosis.[35] Evidence primarily from preclinical and small human studies indicates that *Saccharomyces boulardii* can reduce intestinal barrier permeability, suppress *Escherichia* (*Proteobacteria*) growth, and, with the increase in *Bacteroidetes* being inconsistent across studies, modulate gut microbiota. These actions may help mitigate bacterial translocation, endotoxemia, inflammation, and liver steatosis. It also inhibits the expression of α-smooth muscle actin (α-SMA) and transforming growth factor-beta (TGF-β), decreases collagen deposition, and reduces liver fibrosis, thereby addressing MASLD.[36] However, despite these advancements, evidence for gut microbiota modification in liver diseases remains inconsistent. For instance, studies on dietary glycation compounds have failed to demonstrate significant health benefits, and exposure to various doses of dicarbonyl compounds did not reverse renal injury, glucose intolerance, or insulin resistance.[37] This finding highlights the need for more robust and conclusive research in this field.

Given the recent advances in understanding how the gut microbiota modulates the pathogenesis of liver diseases, this review aims to unravel the underlying biological pathways and mechanisms involved. The novelty of this work lies in its comprehensive synthesis of the gut-liver axis's role across the spectrum of liver diseases, its detailed mechanistic exploration of pro-inflammatory pathways and microbial metabolites, its systematic classification of microbiota and metabolites, its critical analysis of TCM's multifaceted role, and its forward-looking perspective on future therapeutic strategies.

Articles Search Strategy

A systematic literature search was conducted in PubMed, Scopus, Web of Science, and Embase for studies published between 2015 and 2025. The search strategy incorporated both current and historical terminology to ensure comprehensive coverage. Search terms included: "gut microbiome", "gut microbiota", "gut-liver axis", "MASLD", "MAFLD", "NAFLD", "MASH", "NASH", "probiotics", "bile acids", "SCFAs", "FMT", and "Traditional Chinese Medicine". These terms were combined using appropriate Boolean operators and adapted for each database. The initial search yielded 587 records. After removing 208 duplicates, 379 unique records were screened by title and abstract. Of these, 245 records were excluded. The remaining 134 articles underwent full-text review and 55 were excluded due to irrelevance, being review article, insufficient outcome data, or not meeting population criteria. Ultimately, 79 studies were deemed suitable and included in the qualitative synthesis Figure 1.

The Role of Gut Microbiota in Specific Chronic Liver Diseases

The impact of the gut microbiota is not uniform across all liver diseases; its influence varies significantly depending on the etiology and pathophysiology of the condition.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Gut dysbiosis in MASLD is characterized by a decrease in beneficial bacteria like *Lactobacillus* and *Bifidobacterium* and an increase in pro-inflammatory bacteria such as *Escherichia coli* and *Bacteroides*. This shift leads to increased gut permeability, allowing pathogen-associated molecular patterns (PAMPs) like lipopolysaccharide (LPS) to enter the portal circulation. LPS activates Toll-like receptor 4 (TLR4) on Kupffer cells, initiating a pro-inflammatory cascade via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) that promotes hepatic insulin resistance, de novo lipogenesis, and steatohepatitis.[38–40] Furthermore, microbial metabolites like trimethylamine N-oxide (TMAO) and decreased SCFA production exacerbate metabolic dysfunction.[41,42]

Alcoholic Liver Disease (ALD)

Alcohol consumption directly damages the intestinal epithelium and alters microbiota composition, favoring Gram-negative *Proteobacteria* (*Enterobacteriaceae*) and reducing *Bacteroidetes*.[41,43] This dysbiosis increases gut permeability, facilitating the translocation of live bacteria and LPS into the liver. The ensuing activation of hepatic innate immune responses drives inflammation, oxidative stress, and ultimately hepatocyte injury, contributing to the spectrum of ALD from steatosis to hepatitis and cirrhosis.

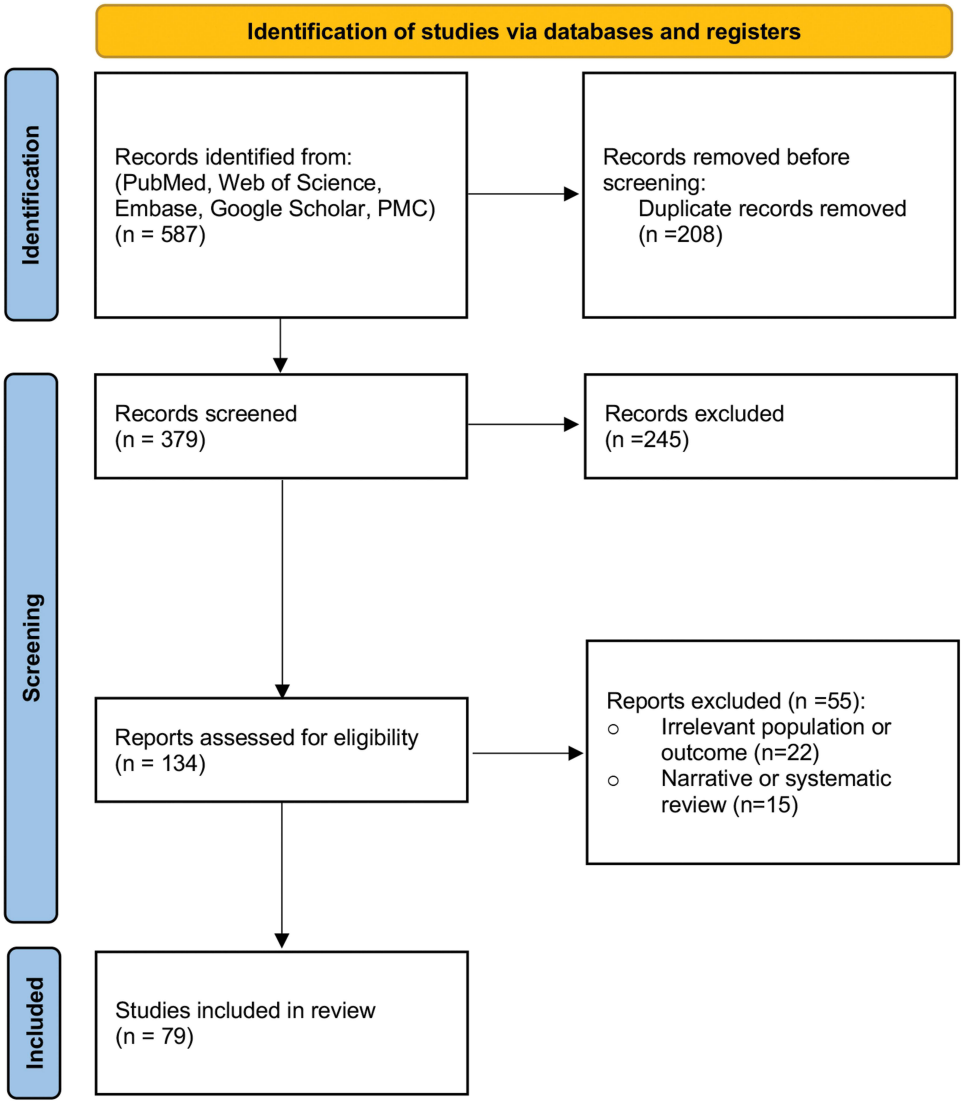

Figure 1 Flowchart of the article screening process.

Viral Hepatitis (HBV/HCV)

Chronic viral hepatitis can alter gut microbiota composition, often reducing diversity. Conversely, gut dysbiosis may influence viral persistence and the progression of liver fibrosis. Notably, FMT has shown potential to enhance viral clearance in patients with hepatitis B virus (HBV).[28,30] However, it is crucial to highlight that these promising findings are based on small pilot studies, and evidence remains preliminary, not yet validated in large controlled trials. The gut-viral-liver interaction represents a complex interplay where microbiota modulation could serve as an adjuvant therapy.

Liver Cirrhosis and HCC

Advanced cirrhosis is marked by severe dysbiosis and a profound increase in gut permeability, leading to continuous bacterial translocation and endotoxemia. This state of chronic inflammation drives fibrogenesis and increases the risk of complications like hepatic encephalopathy and spontaneous bacterial peritonitis.[23,44] In HCC, gut microbiota-derived metabolites, such as deoxycholic acid (DCA), can cause DNA damage and create an immunosuppressive tumor microenvironment (TME), promoting hepatocarcinogenesis.[45,46]

Autoimmune Liver Disease

Emerging evidence suggests a link between gut dysbiosis and autoimmune liver diseases like autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Molecular mimicry between microbial and self-antigens or a dysregulated immune response due to altered microbiota may break tolerance and trigger autoimmunity, though it remains unclear if dysbiosis is a cause or consequence[47] Table 1

Mechanistic Pathway of Gut-Liver Axis

The gut-liver axis constitutes a bidirectional communication system where the liver influences intestinal health via bile secretion, and the gut impacts liver function via microbial metabolites and translocated products. In the context of alcohol consumption, this axis involves interconnected levels, including the gut microbiota, epithelial barrier, mucus layer, and production of antimicrobial peptides. This pathway connects the gut, gut microbiota, and liver through signaling pathways influenced by dietary, genetic, and environmental factors, which collectively induce pro-inflammatory conditions and increase microbial exposure in the liver.[38]

The induction of pro-inflammatory conditions primarily occurs through the translocation of microbial products. Dysfunction of the intestinal barrier, mediated by alcohol, high-fat diets, or pathogens, allows bacteria and their products to translocate through compromised tight junctions. Key bacterial toxins such as cytolysin (from *Enterococcus faecalis*) and candidalysin (from *Candida albicans*) directly damage epithelial cells.[43] Once in the portal circulation, PAMPs like LPS bind to pattern recognition receptors (PRRs), notably TLR4, on hepatic immune cells (Kupffer cells) and hepatic stellate cells (HSCs). This binding triggers two main signaling pathways: the myeloid differentiation primary response 88 (MyD88)-dependent pathway, which rapidly activates NF-κB and activator protein 1 (AP-1), leading to the production of pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6], IL-1β); and the TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathway, which induces type I interferons.[44] These cytokines perpetuate liver inflammation, recruit neutrophils, and activate HSCs, driving fibrogenesis.

Dietary factors, genetic predispositions, and environmental toxins significantly influence microbial metabolic activities. For example, certain gut microbes like *Desulfovibrionaceae* and *Enterobacteriaceae* metabolize dietary choline into trimethylamine (TMA), which is subsequently oxidized in the liver to TMAO. Elevated TMAO levels are associated with impaired BA metabolism and increased inflammation, contributing to the progression of MASLD.[41] In BA metabolism, bacteria such as *Clostridium scindens*, which possess the *bai* operon, perform 7α-dehydroxylation to convert primary BAs into secondary BAs. High concentrations of DCA, a secondary BA, can induce hepatotoxicity and DNA damage, thereby promoting HCC.[45,65] Additionally, some bacteria, including *Klebsiella pneumoniae* and *Escherichia coli*, are capable of producing endogenous ethanol through fermentation. This occurs even in non-alcoholic individuals and contributes to oxidative stress and the pathogenesis of MASLD.

Classification of Gut Microbiota and Metabolites in Liver Disease

The gut microbiota can be systematically classified into protective and pathogenic groups based on their roles in liver disease. Protective bacterial taxa are often depleted in liver disease and are associated with anti-inflammatory and barrier-strengthening effects. These include *Lactobacillus* spp.,[66,67] *Bifidobacterium* spp.,[36,66] *Akkermansia muciniphila*,[47] and *Faecalibacterium prausnitzii*.[68] In contrast, pathogenic bacteria are often enriched in liver disease and contribute to inflammation, barrier disruption, and harmful metabolite production. These include *Escherichia coli* (and other *Proteobacteria*),[36,43] *Enterococcus faecalis*,[43] *Staphylococcus aureus*, and certain strains of *Bacteroides* spp.[48]

Microbial metabolites are crucial for gut-liver axis communication and have both beneficial and harmful effects. Beneficial metabolites include SCFAs like acetate, propionate, and butyrate. These SCFAs are produced by *Lactobacillus, Bifidobacterium, Faecalibacterium*, and *Roseburia* through dietary fiber fermentation.[48,66] Indoles and derivatives, such as indole-3-propionic acid, are tryptophan metabolites produced by *Lactobacillus* spp. and *Clostridium* spp.[53,69] Certain secondary BAs like urso-DCA (UDCA) are also beneficial and are produced by gut bacteria.

In contrast, deleterious metabolites include endotoxins such as LPS from Gram-negative bacteria like *E. coli* and *Enterobacteriaceae*.[44] Ethanol is produced by *Klebsiella pneumoniae* and *E. coli*. TMAO is derived from dietary choline/

https://doi.org/10.2147/IJGM.S551494

Table 1 Overview of Studies Examining the Relationship Between Gut Microbiota and Liver Health

Aim of Study	Methods	Main Findings	Conclusion	Reference
▪ Sulforaphane on insulin resistance in MASLD	▪ Mice model and randomized controlled trial (RCT)	▪ Increased level of ○ Insulin sensitivity ○ GLP1 ▪ Reduced levels of ○ GSK-3 ○ PEPCK activity ○ Phosphorylation of serine residues of IRS-2 ○ Blood glucose ○ HOMA-IR ▪ Elevated abundance of ○ *Bacteroidaceae* ○ *Lactobacillaceae* ○ *Bifidobacteriaceae*	▪ Sulforaphane alleviates insulin resistance in MASLD via the Bacteroides and Lactobacillus SCFAs-GPR41/43-GLP1 axis	[48]
▪ Repurposing disulfiram for MASH via gut-liver axis modulation	▪ Mouse model, self-controlled clinical trial	▪ Modulated: Gut microbiota ▪ Inhibited: *Clostridium* ▪ Reduced: 7α-dehydroxylation activity ▪ Activated: Hepatic FXR signaling	▪ Disulfiram ameliorates MASH by modulating the gut microbiota and BA metabolism.	[49]
▪ Synbiotics on MASLD	▪ RCT, double-blinded, seven-week intervention	▪ Reduced: ALT ▪ No change: Microbial composition	▪ Synbiotics can delay the progression of MASLD.	[50]
▪ Evaluate oral nutrition supplement combined with probiotics on liver function	▪ Comparative study	▪ Improved ○ Liver function ○ Gut microbiota ▪ No change: ○ Nutrition ○ Immune status ○ Blood lipids	▪ Probiotics may regulate the gut-liver axis, improving liver function and gut microbiota.	[51]
▪ Rifaximin-α for liver fibrosis in patients with alcohol-related liver disease	▪ Randomized, double-blind, placebo-controlled Phase 2 trial	▪ No difference: Fibrosis reduction ▪ Reduced: Fibrosis progression in per-protocol analysis ▪ Similar: Safety profiles	▪ Rifaximin-α may reduce fibrosis progression.	[52]
▪ Effect of inulin supplementation on fecal and blood metabolome	▪ Randomized, double-blind, placebo-controlled study	▪ Increased: N8-acetylspermidine ▪ Reduced: ○ Indole-3-butyric acid ○ 5-AVAB ○ BAs ○ 3-methylhistidine ▪ Higher levels ○ Long-chain fatty acids ○ Medium-chain acylcarnitines ○ Sphingomyelins	▪ Inulin supplementation alters metabolome and may influence liver function	[53]

▪ Effect of a specific *Escherichia coli Nissle* 1917 strain on hepatic encephalopathy	▪ Prospective, single-center, open-label, randomized study	▪ Reduced ○ Serum ammonia ○ Pathogenic Enterobacteria ○ IL-6, IL-8, and IFN-γ ▪ Increased ○ *Bifidobacteria* ○ *Lactobacilli* ▪ Improved: Reaction time	▪ *Escherichia coli Nissle* is safe, effective, and superior to lactulose for HE treatment	[54]
▪ Oral exposure to titanium dioxide nanoparticles (TiO2 NPs) on liver enzymes	▪ Meta-analysis	▪ Elevated: AST and ALT ▪ Dysbiosis: Gut microbiota leading to hepatotoxicity	▪ Gut-liver axis affects gut microbiota, suggesting gut-hepatotoxicity of TiO2 NPs	[55]
▪ Evaluating probiotic supplementation on hepatic fibrosis	▪ Double-blind, placebo-controlled clinical trial	▪ Decreased: APRI ▪ No change: Gut microbiota composition	▪ Probiotics alone are not sufficient to improve inflammatory parameters and gut microbiota in MASH	[56]
▪ Effects of probiotics in the treatment of MASLD	▪ RCT	▪ Influenced by: Age, baseline BMI, intervention duration	▪ Probiotic supplementation can reduce liver enzyme levels and regulate glycometabolism in MASLD	[57]
▪ Alcohol use and FMT	▪ Animal model	▪ Reduced: Ethanol acceptance, intake, preference ▪ Associated: Microbial taxa with lower alcohol intake and preference	▪ A gut-liver-brain axis through FMT can reduce alcohol consumption	[58]
▪ Different lifestyle interventions on gut microbiota composition in MASLD patients	▪ RCT	▪ Synergistic effect: Physical activity and Mediterranean diet on liver protection	▪ Diet and physical activity programs synergistically affect gut microbiota in MASLD patients	[59]
▪ Efficacy of probiotics in the treatment of MASLD	▪ Meta-analysis	▪ Reduced: Serum indices ▪ No change: BMI	▪ Gut microbiota modulation may improve liver function and reduce blood lipid levels	[60]
▪ Effect of probiotics on hepatic steatosis in MASLD patients	▪ Randomized, double-blind, placebo-controlled trial	▪ No change: Hepatic steatosis, fibrosis levels ▪ Reduced: CD8+ T lymphocytes	▪ Probiotics have no significant clinical improvement in MASLD patients	[61]
▪ *Lachnospiraceae* and *Ruminococcaceae* on hepatic encephalopathy	▪ RCT	▪ Reduced: IL-6, LBP ▪ Improved: EncephalApp ▪ Higher: Deconjugation and secondary BA formation	▪ Gut microbiota function in cirrhosis is beneficially affected by capsular FMT	[62]
▪ Therapeutic potential of a prebiotic on MASH	▪ TCT pilot trial	▪ Improved: Liver steatosis ▪ Enhanced: *Bifidobacterium* ▪ Reduced: *Clostridium cluster XI*	▪ Prebiotic supplementation reduced histologically-confirmed steatosis in patients with MASH	[63]
▪ *Lactobacillus reuteri* with guar gum and inulin on MASH	▪ RCT	▪ Reduced: Steatosis, weight, BMI, waist circumference ▪ No improvement: Intestinal permeability, LPS levels	▪ Synbiotic supplementation with nutritional counseling is superior to counseling alone for MASH	[64]

carnitine by *Desulfovibrionaceae* and *Enterobacteriaceae*.[41] Harmful secondary BAs include DCA and lithocholic acid (LCA), produced by *Clostridium scindens* and other bacteria.[45,65] Phenylacetic acid is produced by various pathobionts.[70]

Biological Pathways

The gut-liver axis influences hepatic pathophysiology through a complex network of signaling pathways. Probiotics and other interventions target these pathways to exert therapeutic effects.

AMPK/Nrf2 Pathway

AMP-activated protein kinase (AMPK) is a central regulator of cellular energy homeostasis. Its activation inhibits lipid synthesis and promotes fatty acid oxidation. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of antioxidant response. Probiotics like *Lactobacillus plantarum* and *Bifidobacterium bifidum* can activate AMPK/Nrf2 signaling, reducing hepatic oxidative stress and improving lipid metabolism in MASLD.[66]

AMPKα/PGC-1α Pathway

AMPK activation also stimulates peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α), a key regulator of mitochondrial biogenesis and function. This pathway enhances mitochondrial fatty acid β-oxidation, reducing lipid accumulation in hepatocytes.[71]

SREBP-1/FAS and SREBP-1/ACC Pathways

Sterol regulatory element-binding protein 1 (SREBP-1) is a transcription factor that controls the expression of lipogenic genes like fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Activation of SREBP-1 leads to increased de novo lipogenesis, a key process in MASLD development. Microbial metabolites and probiotics can inhibit SREBP-1 activation, thereby downregulating FAS and ACC expression and reducing hepatic lipid synthesis and accumulation.[72]

LPS/TLR4/NF-κB Pathway

This is a primary pro-inflammatory pathway in liver disease. Gut-derived LPS binds to TLR4 on Kupffer cells and HSCs, triggering downstream signaling via MyD88/NF-κB. This results in the massive production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), which drive hepatic inflammation, insulin resistance, and HSC activation, leading to fibrosis. Modulating the gut microbiota to reduce LPS producers and increase barrier-protective species is a key strategy to inhibit this pathway.[73]

Immune Responses

The gut microbiota profoundly regulates liver immune homeostasis. SCFAs, particularly butyrate, propionate, and acetate, are crucial mediators of these effects. Their anti-inflammatory mechanisms are multi-faceted:

HDAC Inhibition

Butyrate acts as a histone deacetylase (HDAC) inhibitor. This leads to hyperacetylation of histones in the promoter regions of genes, facilitating a more open chromatin structure and promoting the transcription of genes involved in anti-inflammatory responses and gut barrier integrity.[48]

GPR Activation

SCFAs bind to G-protein-coupled receptors (GPR41, GPR43, GPR109a) on immune and epithelial cells. This binding inhibits NF-κB signaling, reduces the production of pro-inflammatory cytokines (TNF-α, IL-6), and promotes the differentiation of regulatory T cells (Tregs), which are essential for maintaining immune tolerance and suppressing excessive inflammation.[48,67]

Enhancing Barrier Function

Butyrate is the primary energy source for colonocytes. Adequate butyrate levels strengthen the intestinal epithelial barrier by promoting the assembly of tight junction proteins (occludin, ZO-1), thereby reducing the translocation of pro-inflammatory microbial products into the portal circulation.[66] This is supported by recent studies on natural compounds. For instance, *Artemisia argyi* polysaccharide was shown to alleviate inflammation by increasing SCFA-producing

bacteria and enhancing intestinal barrier function.[74] Similarly, *Dendrobium officinale* oligosaccharides modulated gut microbiota and increased SCFA levels, which correlated with reduced colitis severity.[75]

Beyond SCFAs, the gut microbiota regulates other immune aspects. *Lactobacillus plantarum* and *Bifidobacterium bifidum* have been shown to modulate the balance between CD4+ T helper cells and Tregs, shifting the immune response away from a pro-inflammatory state.[67] Furthermore, reduced microbial diversity can lead to the release of toxic metabolites that inhibit apoptosis and promote cancer growth, mediated through mechanisms involving DCA, LPS, and HSC activation via TLR4[44] Figure 2.

Prospects on Gut-Liver Axis

The gut-liver axis plays a pivotal role in systemic health, extending beyond lipid metabolism to influence insulin sensitivity, systemic inflammation, and energy homeostasis. Alterations in the gut microbiota significantly affect these processes. For instance, lignans, essential plant components, exert lipid-lowering effects and modulate metabolic pathways through their interactions with the gut-liver axis.[76–78] SCFAs derived from gut microbiota mitigate hepatic injury by conferring anti-inflammatory properties, reducing oxidative stress, and mediating apoptosis. Additionally, gut

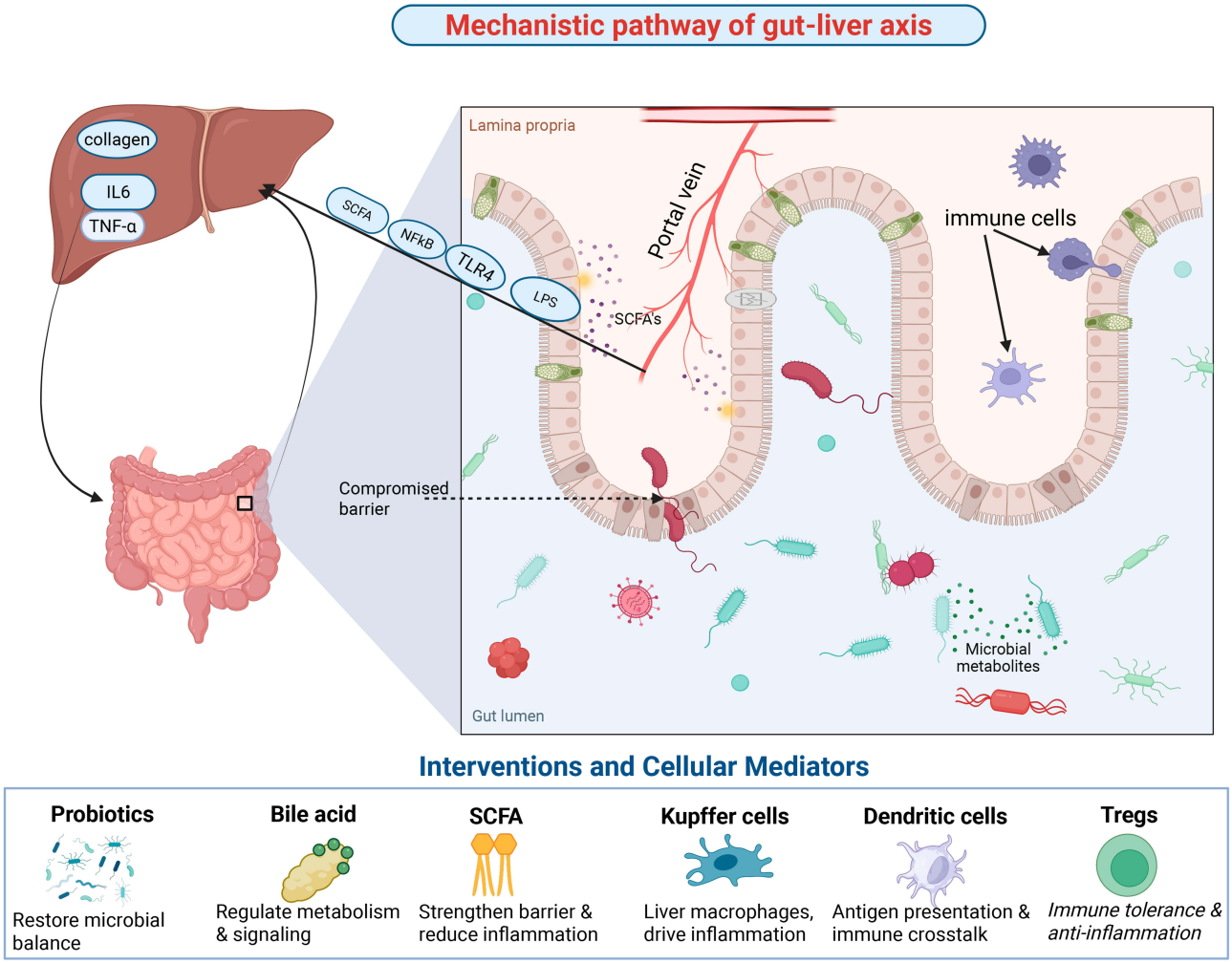

Figure 2 Mechanistic pathway of the gut–liver axis and its regulation by interventions and cellular mediators. Disruption of the intestinal barrier allows microbial metabolites and endotoxins such as lipopolysaccharides (LPS) to translocate via the portal vein to the liver, triggering inflammatory signaling cascades (eg, NF-κB, TLR4) and promoting fibrosis through collagen deposition and cytokine release (IL-6, TNF-α). Short-chain fatty acids (SCFAs) and other microbial metabolites can exert protective effects by strengthening barrier integrity and modulating immune responses. Interventions including probiotics, bile acids, and SCFAs restore microbial balance, regulate metabolism, and reduce inflammation. Cellular mediators such as Kupffer cells, dendritic cells, and regulatory T cells (Tregs) further shape immune crosstalk, antigen presentation, and tolerance, collectively influencing liver inflammation and gut–liver homeostasis.

https://doi.org/10.2147/IJGM.S551494

microbiota-synthesized cytokines exhibit hepatoprotective effects, offering therapeutic strategies for hepatic ischemia-reperfusion injury (HIRI) and other liver dysfunctions.[68] Neuropsychiatric sequelae after liver transplantation may also be ameliorated through interventions targeting immune inflammation, gastrointestinal flora, and vagus nerve activity, thereby improving a patient's quality of life.[79] Therefore, interventions that modulate these pathways show potential to improve cognitive and psychological outcomes, although robust clinical evidence is still lacking.

Probiotics have emerged as promising therapeutic tools for modulating immune checkpoint inhibitors to regulate inflammation, immune response, and metabolic processes. This not only provides a safe therapeutic strategy for HCC but also offers effective interventions for other conditions.[80] For example, probiotics improve MASLD following bariatric surgery by releasing metabolites or neurotransmitters.[81] Hepatotoxicity induced by alcoholism, carbon tetrachloride, acetaminophen, and thioacetamide is often mediated by increased intestinal permeability and can be mitigated by probiotics. These non-invasive, economical, and safe agents suppress inflammatory mediators, reverse toxin effects, and modulate mucosal immunity.[82]

Intestinal failure-associated liver disease (IFALD) is closely linked to SIBO and intraluminal BA signaling.[83] Polysaccharide-based strategies are promising for the treatment of liver diseases.[84] The abundance of *Ruminococcus gnavus* is correlated with liver fat accumulation, suggesting a potential role for the gut microbiota in the pathogenesis of MASLD and its comorbidities.[85] Consequently, interventions such as FMT, probiotics, and dietary modifications can modulate MASLD and potentially improve cognitive decline.[86] Reduced alpha diversity in the gut microbiota is a marker of MASLD severity, and gut microbiota modulation can enhance gut permeability, alter BA metabolism, and reduce endotoxin-producing bacteria.[87]

The bidirectional gut-liver relationship underscores the potential of pan-omics approaches for understanding hepatic disease progression and developing targeted therapies.[88] TCM provides diverse mechanisms, both direct and indirect, for drug development against liver diseases.[89] The anatomical proximity between the gut and liver facilitates their intimate connection, which is crucial for liver regeneration and transplantation success.[90] Targeting gut microbiota holds promise for treating T2DM related to MASLD, potentially reversing cardiovascular outcomes through molecular interactions along the gut-liver axis, though confirmatory large-scale clinical evidence is still needed.[91]

Emerging research highlights the gut-liver-brain axis as a key mechanism influencing gut-liver, gut-brain, and brain-liver communication.[92] The microbiota-BA axis in cholestatic liver diseases (CLD) represents another innovative therapeutic target.[93] The liver-brain axis, mediated by hepatocyte secretion, transmits signals throughout the body, with the gut playing a central role. The neural and humoral pathways, involving the autonomic nervous system and hypothalamic nuclei, are integral to the gut-liver-brain axis.[94] Additionally, *Porphyromonas gingivalis* involvement in the oral gut-liver pathway offers strategies for managing periodontitis-associated MASLD.[95] Natural products facilitate gut-liver communication through the bile ducts and portal veins, playing a critical role in the dysregulation observed in portal hypertension.[96,97]

Crosstalk between the gut-liver axis and microplastics is also an emerging area of study because microplastic-induced dysbiosis can disrupt the gut barrier.[98] Gut microbiota can damage the gut vascular barrier and non-tolerogenic immunologic environments and cause detrimental metabolic changes, including impairment of unconjugated BA metabolism mediated by the FXR-gut-liver axis.[99] In addition, the role of gut microbiota in nicotinamide adenine dinucleotide (NAD) metabolic therapy offers prospects for treating MASLD, drug-induced liver damage, hepatobiliary diseases, and AIH, though evidence in autoimmune hepatitis remains preliminary.[100–102] Although gut microbiota alterations are correlated with autoimmune liver diseases, it remains unclear whether these changes drive disease progression or are a consequence of the disease.[47]

Future Perspectives and Discussion

The therapeutic landscape for the gut-liver axis is rapidly evolving beyond conventional probiotics. NGPs and live biotherapeutic products (LBPs) are being developed, including defined bacterial consortia containing *Akkermansia muciniphila* or *Faecalibacterium prausnitzii* for conditions like MASH.[33,68] Postbiotics and metabolite-based therapies involve direct administration of beneficial metabolites, such as SCFA supplements or engineered mimetic molecules.[68,103] Phage therapy offers a highly specific strategy to target pathogens like cytolysin-producing

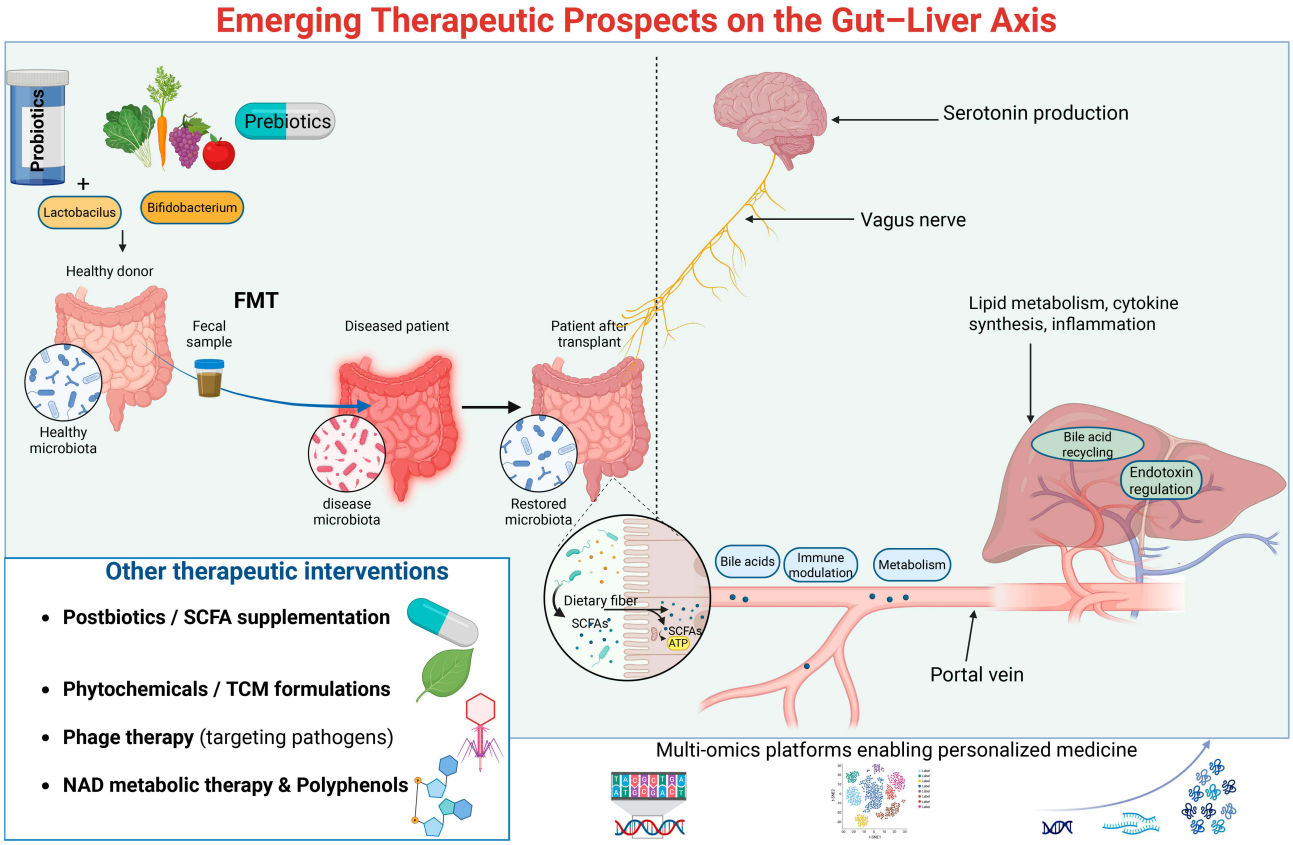

Figure 3 Emerging therapeutic prospects targeting the gut–liver axis. Alterations in the gut microbiota influence systemic health by modulating lipid metabolism, insulin sensitivity, inflammation, and energy homeostasis. Prospective therapeutic strategies include probiotics, prebiotics, fecal microbiota transplantation (FMT), next-generation probiotics (eg, Akkermansia muciniphila, Faecalibacterium prausnitzii), postbiotics and SCFA supplementation, polyphenols, NAD metabolic therapy, phage therapy, and phytochemical or TCM formulations. These interventions restore microbial balance, regulate bile acid recycling, improve gut barrier function, and reduce endotoxin load. The gut–liver–brain axis further mediates crosstalk through vagus nerve activity and serotonin production, while multi-omics approaches provide opportunities for personalized microbiome-based diagnostics and therapies. Collectively, these prospects highlight an evolving therapeutic landscape for liver diseases and metabolic dysfunctions.

Enterococcus faecalis in ALD.[43] Synergistic approaches with Traditional Chinese Medicine (TCM) focus on identifying active components, standardizing extracts, and conducting high-quality RCTs, supported by preclinical studies that elucidate their mechanisms and therapeutic potential.[104,105] Advanced FMT protocols emphasize standardization, encapsulated formulations, and optimal donor identification.[27–30] Integration of multi-omics data enables personalized microbiome-based diagnostics and therapeutics.[88] Prospective interventions include prebiotics, probiotics (*Faecalibacterium prausnitzii*), or direct butyrate supplementation to ameliorate hepatic HIRI and inflammation.[68] These are complemented by phytochemical formulations like Xiao-Chai-Hu decoction (XCHD) for hepatitis, fibrosis, and HCC.[105] Graveoline inhibits JAK1/STAT3 signaling in acute injury.[106] Saikosaponin D, Oroxin B, myricetin, and *Polygala tenuifolia* seed oil alleviate MASLD by modulating gut microbiota and strengthening the intestinal barrier.[107–110] Novel cell-based therapies also show promise for treating liver failure.[111] These approaches collectively highlight a multi-faceted therapeutic strategy Figure 3.

Conclusion

This review highlights the immense potential for significant advancements in the treatment of liver diseases by using gut microbiota-targeted therapies. This field has garnered substantial interest among biomedical scientists, particularly because of its promise as a non-invasive therapeutic approach. The beneficial effects of gut microbiota modifications achieved through probiotics, prebiotics, dietary supplements, and TCM demonstrate considerable promise as adjuncts to standard care strategies. However, robust, multi-country, and multi-regional studies involving diverse populations are

essential to address potential confounding factors and validate these findings. The future of gut-liver axis therapeutics lies in precision medicine, using multi-omics to guide the selection of specific bacterial strains, metabolites, or herbal compounds tailored to an individual's unique microbial signature and disease phenotype. Currently, the gut-liver axis is a well-established therapeutic target with proven efficacy. This review underscores the need for large-scale cohort studies to evaluate both the short- and long-term outcomes of gut microbiota-based interventions to ensure their safety and effectiveness in the management of liver diseases.

Abbreviations

ACC, Acetyl-CoA Carboxylase; AIH, Autoimmune Hepatitis; ALD, Alcoholic Liver Disease; AMPK, AMP-activated Protein Kinase; AP-1, Activator Protein 1; α-SMA, Alpha-Smooth Muscle Actin; BA, Bile Acid(s); BMI, Body Mass Index; CLD, Cholestatic Liver Disease (also used for Chronic Liver Disease in some contexts); DCA, Deoxycholic Acid; FAS, Fatty Acid Synthase; FMT, Fecal Microbiota Transplantation; FXR, Farnesoid X Receptor; GABA, Gamma-Aminobutyric Acid; GPR, G-protein-coupled Receptor; HCC, Hepatocellular Carcinoma; HDAC, Histone Deacetylase; HIRI, Hepatic Ischemia-Reperfusion Injury; HIV, Human Immunodeficiency Virus; HSC, Hepatic Stellate Cell(s); IFALD, Intestinal Failure-Associated Liver Disease; IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; LBP, Live Biotherapeutic Products (also, Lipopolysaccharide-Binding Protein in a table context); LCA, Lithocholic Acid; LPS, Lipopolysaccharide; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; MASH, Metabolic Dysfunction-Associated Steatohepatitis; MyD88, Myeloid Differentiation Primary Response 88; NAD, Nicotinamide Adenine Dinucleotide; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; NGPs, Next-Generation Probiotics; Nrf2, Nuclear factor erythroid 2-related factor 2; PAMPs, Pathogen-Associated Molecular Patterns; PBC, Primary Biliary Cholangitis; PGC-1α, Peroxisome Proliferator-Activated Receptor-gamma Coactivator 1-alpha; PRRs, Pattern Recognition Receptors; PSC, Primary Sclerosing Cholangitis; RCT, Randomized Controlled Trial; SCFAs, Short-Chain Fatty Acids; SIBO, Small Intestinal Bacterial Overgrowth; SREBP-1, Sterol Regulatory Element-Binding Protein 1; T2DM, Type 2 Diabetes Mellitus; TCM, Traditional Chinese Medicine; TGF-β, Transforming Growth Factor-Beta; THR-β, Thyroid Hormone Receptor-beta; TMA, Trimethylamine; TMAO, Trimethylamine N-oxide; TME, Tumor Microenvironment; TNF-α, Tumor Necrosis Factor-Alpha; TRIF, TIR-domain-containing adapter-inducing interferon-β; TLR4, Toll-like Receptor 4; Tregs, Regulatory T cells; UDCA, Ursodeoxycholic Acid; XCHD, Xiao-Chai-Hu Decoction.

Acknowledgments

Figures were created using https://BioRender.com.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The Longjiang Science and Technology Talents Spring Goose Support Program (No. 2022CYQN0027), National Natural Science Foundation of China Project (No. 81973601), and Heilongjiang Provincial Natural Science Foundation Project (No. LH2023H059), Heilongjiang Provincial Traditional Chinese Medicine Scientific Research Project (No. ZYW2024–018).

Disclosure

The authors declare no competing interest.

References

1. Kalligeros M, Henry L, Younossi ZM. Metabolic dysfunction-associated steatotic liver disease and its link to cancer. *Metabolism*. 2024;160:156004. doi:10.1016/j.metabol.2024.156004
2. Lekakis V, Papatheodoridis GV. Natural history of metabolic dysfunction-associated steatotic liver disease. *Eur J Intern Med*. 2024;122:3–10. doi:10.1016/j.ejim.2023.11.005
3. Do A, Zahrawi F, Mehal WZ. Therapeutic landscape of metabolic dysfunction-associated steatohepatitis (MASH). *Nat Rev Drug Discov*. 2025;24(3):171–189. doi:10.1038/s41573-024-01084-2
4. Bhushan S, Sohal A, Noureddin M, Kowdley KV. Resmetirom: the first approved therapy for treating metabolic dysfunction associated steatohepatitis. *Expert Opin Pharmacother*. 2025;26(6):663–675. doi:10.1080/14656566.2025.2478917
5. Sanyal AJ, Newsome PN, Kliers I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med*. 2025;392(21):2089–2099. doi:10.1056/NEJMoa2413258
6. Younossi ZM, Zelber-Sagi S, Lazarus JV, et al. Global consensus recommendations for metabolic dysfunction-associated steatotic liver disease and steatohepatitis. *Gastroenterology*. 2025;169(5):1017–1032.e1012. doi:10.1053/j.gastro.2025.02.044
7. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology*. 2023;77(5):1797–1835. doi:10.1097/hep.0000000000000323
8. Suvarna R, Shetty S, Pappachan JM. Efficacy and safety of Resmetirom, a selective thyroid hormone receptor-β agonist, in the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD): a systematic review and meta-analysis. *Sci Rep*. 2024;14(1):19790. doi:10.1038/s41598-024-70242-8
9. Elsayed NA, Aleppo G, Bannuru RR, etal. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S52–s76. doi:10.2337/dc24-S004
10. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet*. 2021;398(10296):262–276. doi:10.1016/s0140-6736(21)00536-5
11. Tang Y, Fan Y, Wang Y, et al. A Current Understanding of FXR in NAFLD: the multifaceted regulatory role of FXR and novel lead discovery for drug development. *Biomed Pharmacother*. 2024;175:116658. doi:10.1016/j.biopha.2024.116658
12. Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nature Med*. 2021;27(7):1262–1271. doi:10.1038/s41591-021-01425-3
13. Calle RA, Amin NB, Carvajal-Gonzalez S, et al. ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-alcoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trials. *Nat Med*. 2021;27(10):1836–1848. doi:10.1038/s41591-021-01489-1
14. Esler WP, Bence KK. Metabolic targets in nonalcoholic fatty liver disease. *Cell Mol Gastroenterol Hepatol*. 2019;8(2):247–267. doi:10.1016/j.jcmgh.2019.04.007
15. Anstee QM, Neuschwander-Tetri BA, Wong VW-S, et al. Cenicriviroc for the treatment of liver fibrosis in adults with nonalcoholic steatohepatitis: aurora Phase 3 study design. *Contemporary Clin Trials*. 2020;89:105922. doi:10.1016/j.cct.2019.105922
16. Bajinka O, Simbilyabo L, Tan Y, Jabang J, Saleem SA. Lung-brain axis. *Crit Rev Microbiol*. 2022;48(3):257–269. doi:10.1080/1040841X.2021.1960483
17. Wang M, Ren F, Zhou Y, He Y, Du T, Tan Y. Age-related sarcopenia and altered gut microbiota: a systematic review. *Microb Pathog*. 2024;195:106850. doi:10.1016/j.micpath.2024.106850
18. Jiaman WU, Yan N, Liya T, Fei MA, Yanting L, Yuanyuan Z. Difference of the gut microbiota of premature ovarian insufficiency in two traditional Chinese syndromes. *J Tradit Chin Med*. 2025;45(1):132–139. doi:10.19852/j.cnki.jtcm.2025.01.012
19. Bajinka O, Tan Y, Darboe A, Ighaede-Edwards IG, Abdelhalim KA. The gut microbiota pathway mechanisms of diabetes. *AMB Express*. 2023;13(1):16. doi:10.1186/s13568-023-01520-3
20. Li D, Li Y, Yang S, Lu J, Jin X, Wu M. Diet-gut microbiota-epigenetics in metabolic diseases: from mechanisms to therapeutics. *Biomed Pharmacother*. 2022;153:113290. doi:10.1016/j.biopha.2022.113290
21. Zhang S, Ren X, Zhang B, Lan T, Liu B. A systematic review of statins for the treatment of nonalcoholic steatohepatitis: safety, efficacy, and mechanism of action. *Molecules*. 2024;29(8). doi:10.3390/molecules29081859
22. Wang H, Gong J, Chen J, Zhang W, Sun Y, Sun D. Intestinal microbiota and biliary system diseases. *Front Cell Infect Microbiol*. 2024;14:1362933. doi:10.3389/fcimb.2024.1362933
23. Di Ciaula A, Khalil M, Baffy G, Portincasa P. Advances in the pathophysiology, diagnosis and management of chronic diarrhoea from bile acid malabsorption: a systematic review. *Eur J Intern Med*. 2024;128:10–19. doi:10.1016/j.ejim.2024.07.008
24. Zhu X, Zhou Z, Pan X. Research reviews and prospects of gut microbiota in liver cirrhosis: a bibliometric analysis (2001-2023). *Front Microbiol*. 2024;15:1342356. doi:10.3389/fmicb.2024.1342356
25. Vakilpour A, Amini-Salehi E, Soltani Moghadam A, et al. The effects of gut microbiome manipulation on glycemic indices in patients with non-alcoholic fatty liver disease: a comprehensive umbrella review. *Nutr Diabetes*. 2024;14(1):25. doi:10.1038/s41387-024-00281-7
26. Amini-Salehi E, Hassanipour S, Keivanlou MH, et al. The impact of gut microbiome-targeted therapy on liver enzymes in patients with nonalcoholic fatty liver disease: an umbrella meta-analysis. *Nutr Rev*. 2024;82(6):815–830. doi:10.1093/nutrit/nuad086
27. Ebrahimi R, Masouri MM, Salehi Amniyeh Khozani AA, Ramadhan Hussein D, Nejadghaderi SA. Safety and efficacy of fecal microbiota transplantation for viral diseases: a systematic review of clinical trials. *PLoS One*. 2024;19(10):e0311731. doi:10.1371/journal.pone.0311731
28. Chauhan A, Kumar R, Sharma S, et al. Fecal microbiota transplantation in hepatitis B e antigen-positive chronic hepatitis B patients: a pilot study. *Dig Dis Sci*. 2021;66(3):873–880. doi:10.1007/s10620-020-06246-x
29. Lau RI, Su Q, Ching JYL, et al. Fecal microbiota transplantation for sleep disturbance in post-acute COVID-19 syndrome. *Clin Gastroenterol Hepatol*. 2024;22(12):2487–2496e2486. doi:10.1016/j.cgh.2024.06.004
30. Serrano-Villar S, Talavera-Rodriguez A, Gosalbes MJ, et al. Fecal microbiota transplantation in HIV: a pilot placebo-controlled study. *Nat Commun*. 2021;12(1):1139. doi:10.1038/s41467-021-21472-1
31. Mac Cann R, Newman E, Devane D, et al. HIV, the gut microbiome and clinical outcomes, a systematic review. *PLoS One*. 2024;19(12):e0308859. doi:10.1371/journal.pone.0308859

32. Vidya Bernhardt G, Shivappa P, RP J, et al. Probiotics-role in alleviating the impact of alcohol liver disease and alcohol deaddiction: a systematic review. *Front Nutr*. 2024;11:1372755. doi:10.3389/fnut.2024.1372755
33. Zhu Y, Tan JK, Liu J, Goon JA. Roles of traditional and next-generation probiotics on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review and network meta-analysis. *Antioxidants*. 2024;13(3). doi:10.3390/antiox13030329
34. Zhang X, Jiang Z, Jin X, Zhou Q. Efficacy of traditional Chinese medicine combined with Silibinin on nonalcoholic fatty liver disease: a meta-analysis and systematic review. *Medicine*. 2024;103(5):e37052. doi:10.1097/MD.0000000000037052
35. Shah A, Spannenburg L, Thite P, et al. Small intestinal bacterial overgrowth in chronic liver disease: an updated systematic review and meta-analysis of case-control studies. *EClinicalMedicine*. 2025;80:103024. doi:10.1016/j.eclinm.2024.103024
36. Maslennikov R, Benuni N, Levshina A, et al. Effect of saccharomyces boulardii on liver diseases: a systematic review. *Microorganisms*. 2024;12(8):1678. doi:10.3390/microorganisms12081678
37. Hellwig M, Diel P, Eisenbrand G, et al. Dietary glycation compounds - implications for human health. *Crit Rev Toxicol*. 2024;54(8):485–617. doi:10.1080/10408444.2024.2362985
38. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. *J Hepatol*. 2020;72(3):558–577. doi:10.1016/j.jhep.2019.10.003
39. Raya Tonetti F, Eguileor A, Mrdjen M, et al. Gut-liver axis: recent concepts in pathophysiology in alcohol-associated liver disease. *Hepatology*. 2024;80(6):1342–1371. doi:10.1097/HEP.0000000000000924
40. Shahid A, Chambers S, Scott-Thomas A, Bhatia M. Gut microbiota and liver dysfunction in sepsis: the role of inflammatory mediators and therapeutic approaches. *Int J Mol Sci*. 2024;25(24):13415. doi:10.3390/ijms252413415
41. Tarantino G, Cataldi M, Citro V. Could chronic opioid use be an additional risk of hepatic damage in patients with previous liver diseases, and what is the role of microbiome? *Front Microbiol*. 2024;15:1319897. doi:10.3389/fmicb.2024.1319897
42. Mignini I, Galasso L, Piccirilli G, et al. Interplay of oxidative stress, gut microbiota, and nicotine in metabolic-associated steatotic liver disease (MASLD). *Antioxidants*. 2024;13(12). doi:10.3390/antiox13121532
43. Li W, Gao W, Yan S, Yang L, Zhu Q, Chu H. Gut microbiota as emerging players in the development of alcohol-related liver disease. *Biomedicines*. 2024;13(1):74. doi:10.3390/biomedicines13010074
44. Hao Y, Hao Z, Zeng X, Lin Y. Gut microbiota and metabolites of cirrhotic portal hypertension: a novel target on the therapeutic regulation. *J Gastroenterol*. 2024;59(9):788–797. doi:10.1007/s00535-024-02134-7
45. Saadh MJ, Ahmed HH, Al-Hussainy AF, et al. Bile's hidden weapon: modulating the microbiome and tumor microenvironment. *Curr Microbiol*. 2024;82(1):25. doi:10.1007/s00284-024-04004-0
46. Ohtani N, Hara E. Gut-liver axis-mediated mechanism of liver cancer: a special focus on the role of gut microbiota. *Cancer Sci*. 2021;112 (11):4433–4443. doi:10.1111/cas.15142
47. Schneider KM, Kummen M, Trivedi PJ, Hov JR. Role of microbiome in autoimmune liver diseases. *Hepatology*. 2024;80(4):965–987. doi:10.1097/HEP.0000000000000506
48. Tian S, Lei Y, Zhao F, et al. Improving insulin resistance by sulforaphane via activating the bacteroides and lactobacillus SCFAs-GPR-GLP1 signal axis. *Food Funct*. 2024;15(17):8644–8660. doi:10.1039/d4fo01059k
49. Lei Y, Tang L, Chen Q, et al. Disulfiram ameliorates nonalcoholic steatohepatitis by modulating the gut microbiota and bile acid metabolism. *Nat Commun*. 2022;13(1):6862. doi:10.1038/s41467-022-34671-1
50. Mantri A, Kohlmoos A, Schelski DS, et al. Impact of synbiotic intake on liver metabolism in metabolically healthy participants and its potential preventive effect on metabolic-dysfunction-associated fatty liver disease (MAFLD): a randomized, placebo-controlled, double-blinded clinical trial. *Nutrients*. 2024;16(9):1300. doi:10.3390/nu16091300
51. Li X, Gong W, Tang K, Kang J, Song F, Wang Y. The effect of oral nutritional supplementation combined with probiotics on the liver function and intestinal microflora in lung cancer chemotherapy patients through the gut-liver axis. *Sci Rep*. 2025;15(1):10063. doi:10.1038/s41598-025-95005-x
52. Israelsen M, Madsen BS, Torp N, et al. Rifaximin-alpha for liver fibrosis in patients with alcohol-related liver disease (GALA-RIF): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8(6):523–532. doi:10.1016/S2468-1253(23)00010-9
53. Amadieu C, Ahmed H, Leclercq S, et al. Effect of inulin supplementation on fecal and blood metabolome in alcohol use disorder patients: a randomised, controlled dietary intervention. *Clin Nutr ESPEN*. 2025;66:361–371. doi:10.1016/j.clnesp.2025.01.046
54. Manzhalii E, Moyseyenko V, Kondratiuk V, Molochek N, Falalyeyeva T, Kobyliak N. Effect of a specific Escherichia coli Nissle 1917 strain on minimal/mild hepatic encephalopathy treatment. *World J Hepatol*. 2022;14(3):634–646. doi:10.4254/wjh.v14.i3.634
55. Ma Y, Yu N, Lu H, et al. Titanium dioxide nanoparticles: revealing the mechanisms underlying hepatotoxicity and effects in the gut microbiota. *Arch Toxicol*. 2023;97(8):2051–2067. doi:10.1007/s00204-023-03536-x
56. Escouto GS, Port GZ, Tovo CV, et al. Probiotic supplementation, hepatic fibrosis, and the microbiota profile in patients with nonalcoholic steatohepatitis: a randomized controlled trial. *J Nutr*. 2023;153(7):1984–1993. doi:10.1016/j.tjnut.2023.05.019
57. Wang Q, Wang Z, Pang B, et al. Probiotics for the improvement of metabolic profiles in patients with metabolic-associated fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. *Front Endocrinol*. 2022;13:1014670. doi:10.3389/fendo.2022.1014670
58. Wolstenholme JT, Saunders JM, Smith M, et al. Reduced alcohol preference and intake after fecal transplant in patients with alcohol use disorder is transmissible to germ-free mice. *Nat Commun*. 2022;13(1):6198. doi:10.1038/s41467-022-34054-6
59. Calabrese FM, Disciglio V, Franco I, et al. A low glycemic index mediterranean diet combined with aerobic physical activity rearranges the gut microbiota signature in NAFLD patients. *Nutrients*. 2022;14(9):1773. doi:10.3390/nu14091773
60. Yang R, Shang J, Zhou Y, Liu W, Tian Y, Shang H. Effects of probiotics on nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2021;15(12):1401–1409. doi:10.1080/17474124.2022.2016391
61. Mohamad Nor MH, Ayob N, Mokhtar NM, et al. The effect of probiotics (MCP((R)) BCMC((R)) Strains) on hepatic steatosis, small intestinal mucosal immune function, and intestinal barrier in patients with non-alcoholic fatty liver disease. *Nutrients*. 2021;13(9):3192. doi:10.3390/nu13093192
62. Bajaj JS, Salzman N, Acharya C, et al. Microbial functional change is linked with clinical outcomes after capsular fecal transplant in cirrhosis. *JCI Insight*. 2019;4(24). doi:10.1172/jci.insight.133410

63. Bomhof MR, Parnell JA, Ramay HR, et al. Histological improvement of non-alcoholic steatohepatitis with a prebiotic: a pilot clinical trial. *Eur J Nutr*. 2019;58(4):1735–1745. doi:10.1007/s00394-018-1721-2
64. Ferolla SM, Couto CA, Costa-Silva L, et al. Beneficial effect of synbiotic supplementation on hepatic steatosis and anthropometric parameters, but not on gut permeability in a population with nonalcoholic steatohepatitis. *Nutrients*. 2016;8(7):397. doi:10.3390/nu8070397
65. Wang J, Wang X, Zhuo E, Chen B, Chan S. Gut-liver axis in liver disease: from basic science to clinical treatment (Review). *Mol Med Rep*. 2025;31(1). doi:10.3892/mmr.2024.13375
66. Lu J, Shataer D, Yan H, et al. Probiotics and non-alcoholic fatty liver disease: unveiling the mechanisms of lactobacillus plantarum and bifidobacterium bifidum in modulating lipid metabolism, inflammation, and intestinal barrier integrity. *Foods*. 2024;13(18):2992. doi:10.3390/foods13182992
67. Yang W, Cong Y. Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cell Mol Immunol*. 2021;18(4):866–877. doi:10.1038/s41423-021-00661-4
68. Wang J, Yun Y, Dong X, et al. Gut-liver axis: modulating the gut microbiota and its metabolic products as a potential therapeutic strategy for the treatment of hepatic ischemia-reperfusion injury. *Discov Med*. 2024;36(189):1955–1972. doi:10.24976/Discov.Med.202436189.181
69. Shukla S, Hsu CL. Alcohol use disorder and the gut-brain axis: a narrative review of the role of gut microbiota and implications for treatment. *Microorganisms*. 2025;13(1):67. doi:10.3390/microorganisms13010067
70. Bhardwaj M, Mazumder PM. The gut-liver axis: emerging mechanisms and therapeutic approaches for nonalcoholic fatty liver disease and type 2 diabetes mellitus. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;397(11):8421–8443. doi:10.1007/s00210-024-03204-6
71. Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α is a master regulator of mitochondrial lifecycle and ROS stress response. *Antioxidants*. 2023;12(5). doi:10.3390/antiox12051075
72. Song X, Liu Y, Zhang X, Weng P, Zhang R, Wu Z. Role of intestinal probiotics in the modulation of lipid metabolism: implications for therapeutic treatments. *Food Sci Human Wellness*. 2023;12(5):1439–1449. doi:10.1016/j.fshw.2023.02.005
73. Li Z, Wan M, Wang M, Duan J, Jiang S. Modulation of gut microbiota on intestinal permeability: a novel strategy for treating gastrointestinal related diseases. *Int Immunopharmacol*. 2024;137:112416. doi:10.1016/j.intimp.2024.112416
74. Ning E-J, Sun C-W, Wang X-F, et al. Artemisia argyi polysaccharide alleviates intestinal inflammation and intestinal flora dysbiosis in lipopolysaccharide-treated mice. *Food Med Homol*. 2024;1(1):9420008. doi:10.26599/FMH.2024.9420008
75. Shi D-C, Wang P-Y, Xu L, et al. Potential of Dendrobium officinale oligosaccharides to alleviate chronic colitis by modulating inflammation and gut microbiota. *Food Med Homol*. 2025;2(3):9420077. doi:10.26599/FMH.2025.9420077
76. Yuan X, Ouedraogo SY, Jammeh ML, et al. Can microbiota gut-brain axis reverse neurodegenerative disorders in human? *Ageing Res Rev*. 2025;104:102664. doi:10.1016/j.arr.2025.102664
77. Peng LH, Tan Y, Bajinka O. The influence of maternal diet on offspring's gut microbiota in early life. *Arch Gynecol Obstet*. 2024;309(4):1183–1190. doi:10.1007/s00404-023-07305-0
78. Chu Z, Hu Z, Luo Y, Zhou Y, Yang F, Luo F. Targeting gut-liver axis by dietary lignans ameliorate obesity: evidences and mechanisms. *Crit Rev Food Sci Nutr*. 2025;65(2):243–264. doi:10.1080/10408398.2023.2272269
79. Jing W, Bi C, Fang Z, et al. Neuropsychiatric sequelae after liver transplantation and their possible mechanism via the microbiota-gut-liver-brain axis. *Biomed Pharmacother*. 2023;163:114855. doi:10.1016/j.biopha.2023.114855
80. Chen P, Yang C, Ren K, et al. Modulation of gut microbiota by probiotics to improve the efficacy of immunotherapy in hepatocellular carcinoma. *Front Immunol*. 2024;15:1504948. doi:10.3389/fimmu.2024.1504948
81. Zhang X, Wu M, Wang J, Chen J, Yu W, Pan H. Research progress of probiotics regulating intestinal micro-ecological environment in obese patients after bariatric surgery. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2024;53(5):659–666. doi:10.3724/zdxbyxb-2024-0060
82. Noor S, Ali S, Summer M, Riaz A, Nazakat L, Aqsa. Therapeutic role of probiotics against environmental-induced hepatotoxicity: mechanisms, clinical perspectives, limitations, and future. *Probiotics Antimicrob Proteins*. 2024;17(2):516–540. doi:10.1007/s12602-024-10365-6
83. Fan SX, Wang J, Li Q, Li YS, Guan WX, Li JS. Mechanism of gut-microbiota-liver axis in the pathogenesis of intestinal failure-associated liver disease. *Zhonghua Wei Chang Wai Ke Za Zhi*. 2021;24(1):94–100. doi:10.3760/cma.j.cn.441530-20201009-00550
84. Yang Y, Fan G, Lan J, Li X, Li X, Liu R. Polysaccharide-mediated modulation of gut microbiota in the treatment of liver diseases: promising approach with significant challenges. *Int J Biol Macromol*. 2024;280(Pt 1):135566. doi:10.1016/j.ijbiomac.2024.135566
85. Meadows V, Antonio JM, Ferraris RP, Gao N. Ruminococcus gnavus in the gut: driver, contributor, or innocent bystander in steatotic liver disease? *FEBS J*. 2024;e17327. doi:10.1111/febs.17327
86. Meroni M, Longo M, Paolini E, Dongiovanni P. A narrative review about cognitive impairment in metabolic dysfunction-associated steatotic liver disease (MASLD): another matter to face through a holistic approach. *J Adv Res*. 2025;68:231–240. doi:10.1016/j.jare.2024.02.007
87. Saeed H, Diaz LA, Gil-Gomez A, et al. Microbiome-centered therapies for the management of metabolic dysfunction-associated steatotic liver disease. *Clin Mol Hepatol*. 2024;31(Suppl):S94–S111. doi:10.3350/cmh.2024.0811
88. Jeyaraman N, Jeyaraman M, Mariappan T, et al. Insights of gut-liver axis in hepatic diseases: mechanisms, clinical implications, and therapeutic potentials. *World J Gastrointest Pharmacol Ther*. 2024;15(6):98146. doi:10.4292/wjgpt.v15.i6.98146
89. Zhai YJ, Wang XX, Wang X, Dou YJ, Xu YY, Li YB. Research progress on indirect action and mechanism of traditional Chinese medicine based on gut-gut microbiota-target organ talks. *Zhongguo Zhong Yao Za Zhi*. 2024;49(22):5977–5987. doi:10.19540/j.cnki.cjcmm.20240722.401
90. Kiseleva YV, Zharikova TS, Maslennikov RV, et al. Gut microbiota and liver regeneration: a synthesis of evidence on structural changes and physiological mechanisms. *J Clin Exp Hepatol*. 2024;14(6):101455. doi:10.1016/j.jceh.2024.101455
91. Smith ML, Wade JB, Wolstenholme J, Bajaj JS. Gut microbiome-brain-cirrhosis axis. *Hepatology*. 2024;80(2):465–485. doi:10.1097/HEP.0000000000000344
92. Sun D, Xie C, Zhao Y, et al. The gut microbiota-bile acid axis in cholestatic liver disease. *Mol Med*. 2024;30(1):104. doi:10.1186/s10020-024-00830-x
93. Yang X, Qiu K, Jiang Y, Huang Y, Zhang Y, Liao Y. Metabolic crosstalk between liver and brain: from diseases to mechanisms. *Int J Mol Sci*. 2024;25(14). doi:10.3390/ijms25147621
94. Mei EH, Yao C, Chen YN, Nan SX, Qi SC. Multifunctional role of oral bacteria in the progression of non-alcoholic fatty liver disease. *World J Hepatol*. 2024;16(5):688–702. doi:10.4254/wjh.v16.i5.688

95. Ming Z, Ruishi X, Linyi X, Yonggang Y, Haoming L, Xintian L. The gut-liver axis in fatty liver disease: role played by natural products. *Front Pharmacol*. 2024;15:1365294. doi:10.3389/fphar.2024.1365294
96. Lombardi M, Troisi J, Motta BM, Torre P, Masarone M, Persico M. Gut-liver axis dysregulation in portal hypertension: emerging frontiers. *Nutrients*. 2024;16(7):1025. doi:10.3390/nu16071025
97. Wang X, Deng K, Zhang P, et al. Microplastic-mediated new mechanism of liver damage: from the perspective of the gut-liver axis. *Sci Total Environ*. 2024;919:170962. doi:10.1016/j.scitotenv.2024.170962
98. Nicastro E, D'Antiga L. Nutritional interventions, probiotics, synbiotics and fecal microbiota transplantation in steatotic liver disease: pediatric fatty liver and probiotics. *Adv Exp Med Biol*. 2024;1449:113–133. doi:10.1007/978-3-031-58572-2_7
99. Gao T, Wang S, Zhu Z, et al. Components from curcuma longa (turmeric) against hepatobiliary diseases based on gut-liver axis: pharmacotherapeutic properties and potential clinical applications. *Am J Chin Med*. 2024;52(2):387–415. doi:10.1142/S0192415X24500162
100. Lu X, Yang R, Chen Y, Chen D. NAD metabolic therapy in metabolic dysfunction-associated steatotic liver disease: possible roles of gut microbiota. *iScience*. 2024;27(3):109174. doi:10.1016/j.isci.2024.109174
101. Sun C, Zhu D, Zhu Q, He Z, Lou Y, Chen D. The significance of gut microbiota in the etiology of autoimmune hepatitis: a narrative review. *Front Cell Infect Microbiol*. 2024;14:1337223. doi:10.3389/fcimb.2024.1337223
102. Tao W, Fan Q, Wei J. Gut-liver axis as a therapeutic target for drug-induced liver injury. *Curr Issues Mol Biol*. 2024;46(2):1219–1236. doi:10.3390/cimb46020078
103. Wang C, Liu Z, Zhou T, et al. Gut microbiota-derived butyric acid regulates calcific aortic valve disease pathogenesis by modulating GAPDH lactylation and butyrylation. *Imeta*. 2025;4(4):e70048. doi:10.1002/imt2.70048
104. Luo T, Che Q, Guo Z, Song T, Zhao J, Xu D. Modulatory effects of traditional Chinese medicines on gut microbiota and the microbiota-gut-x axis. *Front Pharmacol*. 2024;15:1442854. doi:10.3389/fphar.2024.1442854
105. Wang Z, Li Y, Wang X, et al. Precision strike strategy for liver diseases trilogy with xiao-chai-hu decoction: a meta-analysis with machine learning. *Phytomedicine*. 2025;142:156796. doi:10.1016/j.phymed.2025.156796
106. He J, Feng X, Liu Y, et al. Graveoline attenuates D-GalN/LPS-induced acute liver injury via inhibition of JAK1/STAT3 signaling pathway. *Biomed Pharmacother*. 2024;177:117163. doi:10.1016/j.biopha.2024.117163
107. Gu Y, Duan S, Ding M, et al. Saikosaponin D attenuates metabolic associated fatty liver disease by coordinately tuning PPARα and INSIG/SREBP1c pathway. *Phytomedicine*. 2022;103:154219. doi:10.1016/j.phymed.2022.154219
108. Huang Y, Wang C, Wang M, et al. Oroxin B improves metabolic-associated fatty liver disease by alleviating gut microbiota dysbiosis in a high-fat diet-induced rat model. *Eur J Pharmacol*. 2023;951:175788. doi:10.1016/j.ejphar.2023.175788
109. Xin M, Wang H, Wang M, et al. Attenuating effect of Polygala tenuifolia Willd. seed oil on progression of MAFLD. *Front Pharmacol*. 2023;14:1253715. doi:10.3389/fphar.2023.1253715
110. Sun WL, Li XY, Dou HY, et al. Myricetin supplementation decreases hepatic lipid synthesis and inflammation by modulating gut microbiota. *Cell Rep*. 2021;36(9):109641. doi:10.1016/j.celrep.2021.109641
111. Chen F, Wang Z, Yao H, et al. Large-scale manufacturing of human gallbladder epithelial cell products and derived hepatocytes via a chemically defined approach. *Trends Biotechnol*. 2025;43(10):2646–2664. doi:10.1016/j.tibtech.2025.04.009