



Review Article

The Gut–Liver Axis in Liver Diseases: From Dysbiosis Mechanisms to Precision Niche Remodeling



Xinqiang Li^{1,2#}, Ruidong Ding^{1,2#}, Peng Jiang^{1,2}, Xueting Wang^{1,2}, Ge Guan^{1,2}, Xin Wang^{1,2}, Chuanshen Xu^{1,2}, Huan Liu^{1,2}, Kai Zhao^{1,2*} , Feng Wang^{1,2*} and Jinzhen Cai^{1,2,3*}

¹Organ Transplantation Center, Affiliated Hospital of Qingdao University, Qingdao, Shandong, China; ²Institute of Organ Donation and Transplantation, Medical College of Qingdao University, Qingdao, Shandong, China; ³Organ Transplant Center, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

Received: April 18, 2026 | Revised: May 26, 2026 | Accepted: June 05, 2026 | Published online: June 23, 2026

Abstract

The gut microbiota engages in a complex, bidirectional dialogue with the liver via the gut–liver axis, and its dysbiosis plays a central role in the initiation and progression of various liver diseases. This review comprehensively integrates recent advances in the common features and etiology-specific patterns of gut microbial dysbiosis in liver diseases, signal decoding of key microbial metabolite axes, gut–liver immune crosstalk mechanisms, the accelerating role of gut barrier disruption, and recent progress in the use of the microbiome as diagnostic and prognostic biomarkers. We focus on analyzing the common patterns of reduced diversity, depletion of beneficial bacteria, and enrichment of pathogenic bacteria associated with gut flora dysbiosis across different liver diseases, ranging from nonalcoholic fatty liver disease and alcoholic liver disease to cirrhosis and hepatocellular carcinoma, as well as their unique etiology-related characteristics. Core findings reveal that microbial metabolites act as key chemical messengers that precisely drive liver disease progression by modulating host metabolic, immune, and inflammatory pathways. Meanwhile, the translocation of microbes and their products resulting from disruption of gut barrier integrity serves as a key accelerator, exacerbating liver injury and related complications. Based on these mechanisms, this review further explores ecological niche remodeling strategies targeting the gut microbiota, including the existing evidence and limitations of fecal microbiota transplantation and probiotics/prebiotics, as well as the prospects of emerging precision interventions such as phage therapy, microbial enzyme inhibitors, and engineered bacteria. Finally, we emphasize the potential and personalized implementation pathways of synergistically integrating microbiota modulation with existing therapies such as antivirals, antifibrotics, immunotherapy, and metabolic surgery. Future research must focus on promoting the translation of microbiome research from association studies to clinical applications through multi-omics integration and prospective clinical trials, ultimately achieving precise prevention and treatment of liver diseases based on gut–liver axis regulation.

Keywords: Liver disease; Gut–liver axis; Gut microbial dysbiosis; Microbial metabolites; Gut barrier; Ecological niche remodeling; Therapeutics; Multi-omics.

***Correspondence to:** Kai Zhao, Organ Transplantation Center, Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China. ORCID: <https://orcid.org/0009-0005-0318-1243>. Tel: +86-13920053073, E-mail: zhaokai7801@126.com; Feng Wang, Organ Transplantation Center, Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China. ORCID: <https://orcid.org/0000-0002-3893-6467>. Tel: +86-18661800709, E-mail: wangfengrr@yeah.net; Jinzhen Cai, Organ Transplantation Center, Affiliated Hospital of Qingdao University, Qingdao, Shandong 266000, China. ORCID: <https://orcid.org/0000-0001-5414-1050>. Tel: +86-18661800188, E-mail: caijinzhen@qdu.edu.cn

[#]These authors contributed equally to this work.

How to cite this article: Li X, Ding R, Jiang P, Wang X, Guan G, Wang X, *et al.* The Gut–Liver Axis in Liver Diseases: From Dysbiosis Mechanisms to Precision Niche Remodeling. *J Transl Gastroenterol* 2026;4(2):112–144. doi: 10.14218/JTG.2026.00016.

Introduction

Liver diseases are one of the leading causes of death and disability worldwide, with a broad spectrum ranging from metabolic dysfunction–associated steatotic liver disease (MASLD)/nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and viral hepatitis to cirrhosis and hepatocellular carcinoma (HCC). These diseases not only impose a heavy burden on global public health systems but also constitute major clinical challenges due to their high incidence, complex pathogenesis, and limited treatment options.^{1–3} In recent years, with the deepening of microbiome research, the core role of the gut microbiota as a key hub connecting the environment, genetics, and host health in the development of liver diseases has become increasingly prominent. Ample evidence indicates that gut microbial dysbiosis is a common pathological

feature of various liver diseases. Through the gut–liver axis, a bidirectional communication network, dysbiotic flora and their metabolic products continuously influence the liver's immune, metabolic, and repair processes, thereby driving disease progression.^{4–6} Therefore, deeply analyzing the role of the gut microbiota in liver diseases is not only crucial for understanding the nature of the disease but also provides unprecedented opportunities for developing novel diagnostic markers and therapeutic strategies. It is important to note that a recent multi-society Delphi consensus updated the disease nomenclature from NAFLD to MASLD, and from nonalcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatohepatitis (MASH). Because much of the cited literature in this review used earlier nomenclature, the terms NAFLD, NASH, and metabolic dysfunction-associated fatty liver disease (MAFLD) are retained when referring to specific original studies to maintain historical and methodological accuracy. Otherwise, the updated MASLD/MASH terminology is used throughout the manuscript where appropriate.

Current research has comprehensively depicted the common patterns and etiology-specific characteristics of liver disease–related gut microbial dysbiosis. Commonly, patients with liver disease exhibit reduced α -diversity and shifted β -diversity in gut flora. The core features include the depletion of beneficial bacteria that produce short-chain fatty acids (SCFAs) (such as Lachnospiraceae and Ruminococcaceae) and the enrichment of potential pathogens with pro-inflammatory potential (such as Enterobacteriaceae and Streptococcaceae).^{4,7} This imbalance disrupts gut barrier integrity, leading to the translocation of microbes and their products (such as lipopolysaccharides (LPS)), which triggers and sustains inflammation by activating hepatic innate immunity.^{8,9} Simultaneously, the remodeling of microbial metabolite axes, including bile acids, SCFAs, and tryptophan derivatives, has been confirmed as a key mechanism regulating intrahepatic signaling. For example, microbes remodel the bile acid pool through bile salt hydrolases (BSH) and 7 α -dehydroxylases, affecting farnesoid X receptor (FXR) signaling, thereby regulating hepatic lipid metabolism and inflammation^{10,11}; SCFAs like butyrate exert anti-inflammatory and metabolic homeostasis-maintaining effects by inhibiting histone deacetylases (HDACs) and activating G-protein-coupled receptors¹²; tryptophan metabolites finely tune hepatic immune balance by activating the aryl hydrocarbon receptor (AhR).¹³ These studies collectively construct a framework of “altered microbial composition—metabolic dysfunction—hepatic pathological response,” positioning the gut microbiota as a core regulator of liver disease progression.

Despite significant progress, critical knowledge gaps and challenges remain in this field. First, while most studies reveal strong correlations, establishing causality between gut microbial changes and liver disease progression remains challenging. Although intervention studies like fecal microbiota transplantation (FMT) provide some causal evidence, the immense heterogeneity of the microbiome between individuals makes it difficult to draw universal conclusions.¹⁴ Second, existing studies mostly focus on bacterial communities, while little is known about the roles of the gut mycobiome, virome, and their cross-kingdom interactions with bacteria in liver diseases, limiting our understanding of the full picture of gut microecology.^{15,16} Furthermore, there is a bottleneck in translating microbiome features into clinical applications. Although diagnostic tools based on machine learning models show high accuracy, their robustness across different populations, regions, and etiologies of liver disease awaits validation in large-scale prospective cohorts.^{17,18} More importantly, existing ecological niche re-

modeling strategies, such as broad-spectrum probiotics, prebiotics, or FMT, exhibit significant individual differences and uncertainty in efficacy and may even produce harmful results, highlighting the urgent necessity of shifting from “broad-spectrum” interventions to “precision” targeting.^{19,20}

Therefore, this review aims to comprehensively integrate the latest evidence regarding the role of the gut microbiota in liver diseases, moving beyond simple flora–disease association descriptions to deeply dissect its core mechanisms as an “accelerator” of liver disease progression, and to critically evaluate its translational potential as non-invasive biomarkers and novel therapeutic targets. By critically analyzing the efficacy and limitations of existing niche remodeling strategies and looking forward to the future direction of precision targeting strategies (such as specific strains, phage therapy, and microbial enzyme inhibitors), this review aims to provide a theoretical basis and roadmap for constructing a new paradigm of multidimensional, personalized liver disease management based on the gut–liver axis, ultimately promoting a paradigm shift in liver disease diagnosis and treatment from “targeting the liver” to “regulating the intestinal niche” (Fig. 1).

Common features and etiology-specific patterns of gut microbial dysbiosis in liver diseases

Common features of gut microbial dysbiosis in liver diseases

Various liver diseases, including NAFLD/MASLD, ALD, viral hepatitis, cirrhosis, and HCC, all exhibit common characteristics of gut microbial dysbiosis (Table 1).^{4,5,7,21–62} The core manifestation is a systemic reduction in microbial diversity and disruption of specific flora structures. Studies consistently find that, compared with healthy controls, the α -diversity (e.g., Shannon index, Chao1 index) of gut flora in liver disease patients is significantly reduced, and β -diversity (community structure) shifts significantly, indicating that the gut microbial ecosystem tends toward simplification and disorder in disease states.^{4,5,7,21} This common pattern of dysbiosis typically manifests as the depletion of “beneficial bacteria” and the enrichment of “harmful bacteria.” Specifically, SCFA-producing bacteria, such as *Faecalibacterium prausnitzii*, *Roseburia*, and *Butyrivibrio* within the Lachnospiraceae and Ruminococcaceae families, are universally reduced in liver disease patients.^{7,22,23} Conversely, bacterial taxa with pro-inflammatory potential significantly increase, such as Enterobacteriaceae (e.g., *Escherichia-Shigella*, *Klebsiella*), Streptococcaceae, and *Veillonella* within the Proteobacteria phylum.^{4,5,23} This imbalance pattern of “reduced protective flora—increased pathogenic flora” disrupts gut barrier function, increases the translocation of endotoxins like LPS, and continuously drives liver inflammation and injury through the gut–liver axis, constituting the common microbial background for the occurrence and development of various liver diseases.^{24,25} For example, in patients with NAFLD, the reduction in gut flora α -diversity is negatively correlated with the severity of hepatic steatosis,²⁶ while gut flora dysbiosis in cirrhosis patients is closely related to the occurrence of complications such as portal hypertension and hepatic encephalopathy (HE).²⁷

Microbial characteristics of MASLD/NAFLD

Gut flora dysbiosis in MASLD has distinct characteristics closely linked to obesity, insulin resistance, and hepatic steatosis. A significant change in the gut flora of MASLD patients is an elevated Firmicutes/Bacteroidetes (F/B) ratio, which is typically associated with increased energy absorption and metabolic disorders.^{28,29} At

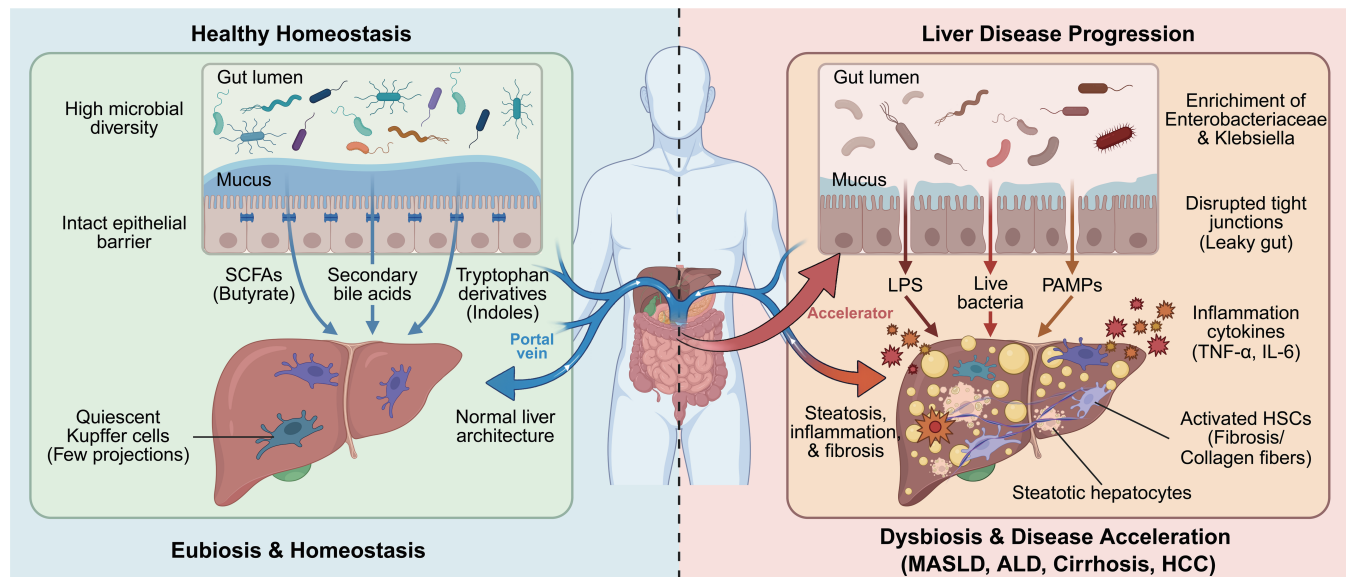


Fig. 1. The Gut–liver axis: Dysbiosis as an accelerator of liver disease progression. This figure illustrates the transition from healthy homeostasis to liver disease progression mediated by the gut–liver axis. The left panel depicts a healthy state characterized by high microbial diversity, an intact epithelial barrier, and the production of beneficial metabolites like SCFAs that maintain normal liver architecture. The right panel shows the progression of liver diseases (MASLD, ALD, cirrhosis, HCC), marked by gut dysbiosis with reduced diversity and the enrichment of pathogenic taxa such as Enterobacteriaceae and Klebsiella. This imbalance disrupts tight junctions (causing a “leaky gut”), facilitating the translocation of microbes and products like lipopolysaccharide (LPS) to the liver. Acting as an “accelerator,” these translocated signals activate hepatic innate immunity (e.g., Kupffer cells via TLR4/NF- κ B), driving steatosis, inflammation, and fibrosis. This figure was created with BioRender (<https://biorender.com/>). ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; IL-6, interleukin-6; LPS, lipopolysaccharides; MASLD, metabolic dysfunction-associated steatotic liver disease; NF- κ B, nuclear factor kappa B; PAMPs, pathogen-associated molecular patterns; SCFAs, short-chain fatty acids; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor-alpha.

the genus level, changes in specific flora are related to disease severity. For instance, the abundance of *Blautia*, *Ruminococcus*, and *Dorea* is often elevated in MASLD patients and positively correlated with liver fat content and inflammatory markers.^{30–32} Conversely, *Akkermansia muciniphila*, a bacterium capable of improving gut barrier function and metabolic health, is significantly reduced in MASLD patients, and its abundance is negatively correlated with the degree of hepatic steatosis.^{33–35} Furthermore, MASLD, especially its more severe form, nonalcoholic steatohepatitis (NASH), is also associated with gut mycobiome dysbiosis, characterized by the enrichment of fungi such as *Candida* and *Mucor*.^{15,32} These microbial characteristics are not only related to disease phenotypes, but microbial signatures constructed based on machine learning models can also distinguish MASLD patients from healthy individuals with high precision and even predict the severity of hepatic steatosis and fibrosis.^{36–38} For example, a study found that the ability of the gut microbiome alone to predict liver disease risk is comparable to traditional risk factors, while combining microbiome features with traditional risk factors can significantly improve prediction performance.³⁹ Specific metabolites, such as gut flora-derived acetate entering the liver to fuel tumor growth, may represent a potential mechanism for gut microbe-mediated early recurrence of HCC.⁴⁰ Additionally, gut flora dysbiosis is associated with the occurrence of metabolic diseases such as NAFLD, and regulating the gut microbiome through drugs, prebiotics, probiotics, and FMT may become a feasible method for treating NAFLD.^{41,63}

Microbial characteristics of ALD

Gut flora dysbiosis in ALD presents a unique pattern directly related to alcohol metabolism and toxicity. Long-term alcohol intake

causes drastic changes in gut flora, characterized by a significant enrichment of Proteobacteria, especially Enterobacteriaceae bacteria, which exacerbates gut barrier damage and endotoxemia.^{8,9} A specific increase in the abundance of Fusobacteria is also observed in the stages of alcoholic hepatitis and cirrhosis.⁸ Functionally, the gut microbial metabolic profile of ALD patients undergoes profound changes, highlighted by the depletion of SCFAs (such as butyrate and propionate) and anti-inflammatory microbial metabolites (such as indole-3-propionic acid (IPA)), alongside increased production of microbially derived ethanol and endotoxins.^{8,42} Notably, specific bacteria carrying virulence factors are associated with poor prognosis in ALD. For example, *Escherichia coli* carrying the capsular polysaccharide synthesis gene *kpsM* can evade hepatic immune clearance and aggravate liver injury, while the activity of trimethylamine (TMA)-producing microbes is enhanced, and their inhibitors could be potential therapeutic targets.^{43,44} These characteristics make the microbial profile of ALD not only valuable for diagnosis but also provide a basis for developing precise microbial-targeted therapies. Gut flora imbalance in mice with ALD also leads to reduced vitamin B6 synthesis, thereby affecting hepatic amino acid metabolism and glutathione synthesis, exacerbating the disease process.⁴⁵ In addition, FGF-19 dysregulation during alcohol consumption, and the resulting changes in bile acid synthesis and composition, may be contributing factors to ALD and gut flora dysbiosis.⁴⁶

Microbial characteristics of viral hepatitis and cirrhosis

Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and the resulting cirrhosis are accompanied by progressively worsening gut flora dysbiosis, the degree of which parallels disease progression. In chronic HBV infection, as the disease progresses

Table 1. Common features and etiology-specific patterns of gut microbial dysbiosis in liver diseases

Disease stage/etiology	Key characteristics & diversity changes	Enriched taxa (pathogens/risk factors)	Depleted taxa (beneficial/protective)	Pathophysiological impact
Common features ^{4,5,7,21–27}	Reduced α -diversity and shifted β -diversity (simplification and disorder of ecosystem)	Proteobacteria: Enterobacteriaceae (e.g., <i>Escherichia-Shigella</i> , <i>Klebsiella</i>), Streptococcaceae	SCFA-producers: Lachnospiraceae, Ruminococcaceae (e.g., <i>Faecalibacterium prausnitzii</i> , <i>Roseburia</i>)	Gut barrier disruption, increased endotoxin (LPS) translocation, activation of hepatic TLR4/NF- κ B pathway
MASLD / NAFLD ^{28–41}	High Firmicutes/Bacteroidetes (F/B) ratio linked to energy absorption	<i>Blautia</i> , <i>Ruminococcus</i> , <i>Dorea</i> , <i>Collinsella</i> . Fungi: <i>Candida</i> , <i>Mucor</i> (in NASH)	<i>Akkermansia muciniphila</i> , <i>Bacteroides</i>	Associated with hepatic steatosis severity, insulin resistance, and inflammation
Alcoholic liver disease (ALD) ^{42–46}	Drastic changes driven by alcohol metabolism; profound metabolic profile shifts	Proteobacteria (Enterobacteriaceae), Fusobacteria (in hepatitis/cirrhosis). Virulent <i>E. coli</i>	SCFA and Indole-3-propionic acid producers	Exacerbated gut barrier damage, endotoxemia, and evasion of hepatic immune clearance
Viral hepatitis (HBV/HCV) ^{47,48}	Progressive decline in diversity from immune tolerance to active phases	<i>Streptococcus</i> , <i>Veillonella</i> , <i>Enterococcus</i> . Oral Lactobacillales (HCV)	Bacteroidetes, Clostridiales	Dysbiosis parallels disease progression and fibrosis severity; associated with bile acid dysmetabolism
Cirrhosis ^{49–54}	Extreme ecological dysregulation; “Oralization” of gut flora	Oral-origin bacteria: <i>Streptococcus</i> , <i>Veillonella</i> . Pathogens: Enterobacteriaceae, <i>Klebsiella</i>	Lachnospiraceae, Ruminococcaceae, <i>Faecalibacterium</i> , <i>Bacteroides</i>	Collapse of gut barrier, translocation of ammonia/bacteria driving complications like hepatic encephalopathy
Hepatocellular carcinoma (HCC) ^{55–62}	Specific patterns related to tumor environment and treatment response	LPS-producing bacteria. <i>Bacteroides</i> , <i>Ruminococcus gnavus</i> (non-viral HCC). <i>Prevotella</i> (linked to Rx resistance)	SCFA-producing bacteria (<i>Faecalibacterium</i> , <i>Agathobacter</i> , <i>Coprococcus</i>)	Dysbiosis promotes immunosuppressive microenvironment; intratumoral microbes can predict prognosis

F/B, Firmicutes/Bacteroidetes ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; LPS, lipopolysaccharide; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF- κ B, nuclear factor kappa B; Rx, treatment; SCFA, short-chain fatty acid; TLR4, Toll-like receptor 4.

from the immune tolerance phase to the active phase and cirrhosis phase, gut flora diversity continues to decline; beneficial bacteria such as Bacteroidetes decrease, while potential pathogens like *Streptococcus*, *Veillonella*, and *Enterococcus* gradually become enriched.^{5,47,48} Cirrhosis, especially decompensated cirrhosis, represents an extreme state of intestinal ecological dysregulation. At this time, gut flora richness drops to a minimum, and resident symbiotic bacteria with protective functions (such as Lachnospiraceae and Ruminococcaceae) are largely replaced by bacteria of oral origin (such as *Streptococcus* and *Veillonella*) and typical intestinal pathogens (such as Enterobacteriaceae), a phenomenon known as “oralization”.^{23,49} This severe dysbiosis leads to the collapse of gut barrier function, allowing bacteria and their products (such as LPS and ammonia) to translocate to the portal vein and systemic circulation, directly driving the occurrence of fatal complications such as HE and spontaneous bacterial peritonitis (SBP).^{25,50,51} Therefore, the gut microbial characteristics of cirrhosis patients can serve as powerful biomarkers for predicting complication risk and prognosis. For instance, the peripheral blood microbiome profile of cirrhosis patients is significantly different from healthy controls, and the enrichment of specific genera is associated with severe portal hypertension.⁵² In patients with chronic hepatitis B-related cirrhosis, disease progression and antiviral treatment are two major factors leading to changes in gut flora and metabolite composition, and gut flora dysbiosis and metabolomics play important roles in disease progression.⁵³ Furthermore, gut flora analysis shows that

the diversity of gut flora in HBV-related cirrhosis patients is significantly reduced, and changes in specific genera and metabolites are closely related to disease severity and inflammatory status.⁵⁴

Microbial characteristics of HCC

Gut microbial dysbiosis in HCC integrates the characteristics of its underlying liver disease (such as viral hepatitis, cirrhosis, and MASLD) and further develops specific patterns related to the tumor immune microenvironment and treatment response. HCC patients exhibit significantly reduced gut flora diversity and altered composition.^{55,56} Studies have found that, regardless of etiology, HCC patients are often accompanied by a reduction in SCFA-producing bacteria (such as *Faecalibacterium* and *Agathobacter*) and an increase in LPS-producing bacteria.^{21,56} However, microbial characteristics also possess etiology specificity: virus-related HCC is enriched in *Faecalibacterium* and *Coprococcus*, while non-virus-related HCC (such as MASLD-HCC) is enriched in *Bacteroides* and the *Ruminococcus gnavus* group, with the depletion of SCFA producers being more pronounced in the latter.⁵⁵ More importantly, specific gut microbial profiles are closely related to HCC progression and therapeutic efficacy. For example, flora features rich in *Lachnospiraceae* and *Veillonella* are associated with better objective response and survival in immune checkpoint inhibitor (ICI) treatment, whereas flora rich in *Prevotella* 9 are associated with treatment resistance.^{57,58} In addition, the intratumoral microbiome itself exhibits heterogeneity; the enrichment of specific bacteria

(such as *Stenotrophomonas maltophilia*) can promote liver cancer progression by modulating hepatic stellate cell phenotypes, and intratumoral microbial features can also serve as independent predictors for HCC prognosis.^{59–61} Genera such as *Dialister*, *Veillonella*, *Eubacterium coprostanoligenes* group, and *Lactobacillus* in the gut microbiota, as well as species like *Streptococcus pneumoniae* and *Bifidobacterium faecale*, are associated with early recurrence of HBV-related HCC.⁴⁰ Liver tissue microbial analysis shows a key link between liver microbial composition/function and HCC tumor staging, suggesting it may play a critical role in HCC development.⁶² Furthermore, gut microbes are significantly associated with various gastrointestinal diseases, eight of which are related to HCC, indicating they may serve as novel biomarkers for the prevention and treatment of these diseases.⁶⁴

Microbial metabolite axes: Intrahepatic signal decoding from bile acids, SCFAs to tryptophan derivatives

Bile acid metabolism remodeling and intrahepatic signal regulation

Gut microbes, through key enzymes they encode, such as BSH and 7 α -dehydroxylase, deconjugate and dehydroxylate host primary bile acids to generate secondary bile acids, thereby profoundly remodeling the composition and signaling function of the bile acid pool. In NAFLD, gut flora dysbiosis often leads to reduced BSH activity, manifested as the accumulation of conjugated bile acids (such as taurocholic acid and taurochenodeoxycholic acid) in feces and serum, while unconjugated and secondary bile acids (such as deoxycholic acid (DCA) and lithocholic acid) decrease.^{10,11} This compositional change affects host metabolism via the gut–liver axis: conjugated bile acids act as antagonists of FXR in the intestine, inhibiting the intestinal FXR-FGF15/19 signaling pathway, leading to upregulation of hepatic cholesterol 7 α -hydroxylase expression and accelerating the conversion of cholesterol to bile acids, but may also promote hepatic lipogenesis.^{65,66} Conversely, secondary bile acids like DCA and lithocholic acid are potent agonists of hepatic FXR and TGR5 receptors. Studies have found that serum levels of conjugated DCA (such as glycodeoxycholic acid) are significantly reduced in HCC patients, and glycodeoxycholic acid can directly inhibit the growth and migration of HCC cells *in vitro*, revealing the direct role of specific bile acid profile changes in liver cancer tumorigenesis.¹¹ Furthermore, novel bile acids produced by microbial metabolism, such as tauro- β -muricholic acid, have been found to indirectly regulate hepatic lipid metabolism and inflammation by antagonizing intestinal FXR, providing new targets for interventions based on the microbe–bile acid axis.⁶⁷ In MAFLD, n-3 polyunsaturated fatty acid supplementation upregulates the CYP7B1-mediated alternative bile acid synthesis pathway by activating hepatic PPAR α signaling, increasing the synthesis of the secondary bile acid hyodeoxycholic acid. As an intestinal FXR antagonist, hyodeoxycholic acid can reduce ceramide accumulation in the gut and liver, thereby improving the MAFLD phenotype.⁶⁸ Additionally, large-leaf yellow tea polysaccharides remodel the gut microbiota by reducing BSH-producing genera and increasing taurine-metabolizing genera, thereby altering colonic bile acid composition, increasing levels of conjugated bile acids and non-12OH bile acids, inhibiting ileal FXR receptors and hepatic bile acid reabsorption, promoting bile acid synthesis and fecal excretion, and subsequently inhibiting NAFLD progression.⁶⁹ In patients with chronic hepatitis C, even in the early stages of the disease, their bile acid profile differs from that of healthy

populations, characterized by significantly reduced fecal deoxycholic acid and dominance of lithocholic acid or ursodeoxycholic acid. This change is associated with reduced commensal Clostridiales and increased oral Lactobacillales, and the transcription level of CYP8B1, a key enzyme in bile acid synthesis, is reduced, indicating that HCV infection alters bile acid metabolism through the gut–microbiota–liver axis.⁷⁰

Intrahepatic metabolic regulation and immune homeostasis by SCFAs

SCFAs produced by gut microbial fermentation of dietary fiber, mainly including acetate, propionate, and butyrate, are key metabolic messengers connecting gut flora and liver health. These SCFAs enter the liver via the portal vein and exert protective effects through multiple mechanisms. Butyrate and propionate are ligands for G-protein-coupled receptors (such as GPR41 and GPR43), and their activation can inhibit hepatic de novo lipogenesis. For example, acetate produced by *Bifidobacterium longum* inhibits the carcinogenic IL-6/JAK1/STAT3 signaling pathway by activating hepatocyte GPR43, thereby preventing the progression of NAFLD-related liver cancer (NAFLD–HCC).⁷¹ SCFAs, especially butyrate, are also effective inhibitors of HDACs. In a portal hypertension model, FMT enriched butyrate-producing bacteria, and the resulting butyrate activated the PI3K/Akt/eNOS signaling pathway by inhibiting HDAC3 activity in liver sinusoidal endothelial cells, increasing nitric oxide production and thereby reducing intrahepatic vascular resistance.¹² Moreover, SCFAs indirectly mitigate liver inflammation by maintaining gut barrier integrity and reducing LPS translocation. For example, kudzu resistant starch improves the gut barrier, inhibits the LPS/Toll-like receptor 4 (TLR4)/NF- κ B inflammatory pathway, and alleviates hepatic steatosis by increasing the abundance of butyrate-producing bacteria (such as *Coprococcus* and *Bifidobacterium*) and elevating plasma butyrate levels.⁷² In chronic hepatitis B patients, those achieving functional cure have a higher abundance of butyrate-producing bacteria in their gut, and *in vitro* experiments confirmed that butyrate can directly inhibit HBsAg production in HBV-infected cells, revealing the potential role of SCFAs in antiviral immunity.⁷³ Genistein improves liver function, blood lipids, and inflammation in MAFLD rats by increasing gut microbiota-derived butyrate production, which subsequently activates the SIRT1 signaling pathway.⁷⁴ In patients with MASLD and chronic kidney disease, fecal Butyryl-CoA:acetate CoA-transferase (BCoAT) gene expression levels are positively correlated with estimated glomerular filtration rate, and compared with MASLD patients, chronic kidney disease patients have lower BCoAT and higher plasma intestinal fatty acid-binding protein levels, revealing shared and unique gut microbiota dysbiosis and related biomarkers in both diseases.⁷⁵ Additionally, fructooligosaccharides and galactooligosaccharides alleviate MASLD by increasing the abundance of acetate-producing bacteria (such as *Bacteroides acidifaciens* and *Bacteroides dorei*) and inducing POMC/GPR43-positive neurons in the hypothalamic arcuate nucleus, indicating the existence of gut microbiota–brain axis signal regulation.⁷⁶

Tryptophan metabolites and the AhR-mediated intrahepatic signaling network

Gut microbes metabolize dietary tryptophan into a series of bioactive molecules, including indole, indole-propionic acid, indole-3-carboxaldehyde (ICA), and indole-3-acetic acid (I3A). These metabolites regulate hepatic immunity and metabolic homeostasis primarily by activating AhR within host cells. AhR activation has

dual roles in liver diseases, with effects highly dependent on the ligand and cellular environment. In autoimmune hepatitis and T-cell-mediated hepatitis models, gut microbiota-derived ICA induces the expression of PI3K-interacting protein 1 by activating AhR in CD8⁺ T cells, thereby inhibiting the PI3K/Akt/mTOR pathway, limiting excessive activation of effector T cells, and attenuating liver injury.^{13,77} Supplementation with *Lactobacillus reuteri*, a bacterium capable of producing ICA, increases circulating ICA levels and exerts hepatoprotective effects.¹³ However, in the context of hepatocarcinogenesis, gut flora dysbiosis may shift tryptophan metabolism in a harmful direction. Studies have found that depletion of gut flora impairs tryptophan metabolism and reduces the production of AhR agonists, thereby relieving AhR's post-translational suppression of sterol regulatory element binding protein 2, promoting cholesterol synthesis and liver cancer initiation.⁷⁸ Furthermore, the tryptophan metabolite IPA is often reduced in patients with ALD and NAFLD. IPA exerts anti-inflammatory effects in macrophages by activating AhR and can promote intestinal IL-22 production, which mitigates oxidative stress and ferroptosis in drug-induced liver injury via STAT3 signaling.⁷⁹ Therefore, targeting the microbial tryptophan metabolism-AhR axis by supplementing specific probiotics (such as IPA-producing bacteria) or their beneficial metabolites is a potential strategy for regulating hepatic inflammation and metabolic disorders. Pseudopunicic acid B improves high-fat diet-induced MAFLD by significantly down-regulating gut flora positively correlated with liver injury and enriching tryptophan metabolic pathways, elevating the level of its microbial metabolite cinnamic acid. Cinnamic acid can stably bind and activate AhR, subsequently downregulating hepatic lipogenesis genes through the AhR-mediated IL-22/JAK1/STAT3 signaling pathway.⁸⁰ In a gossypol-induced Nile tilapia fatty liver model, *Lactobacillus plantarum* YC17 reduced hepatic free fatty acid content and alleviated liver injury by restoring the abundance of *Lactobacillus*, *Clostridium*, and *Cetobacterium* in the gut and significantly increasing serum concentrations of microbial tryptophan metabolites IPA and I3A. This strain activates the AhR, promotes P53 protein ubiquitination and degradation to inhibit the P53 signaling pathway, and upregulates the expression of free fatty acid esterification genes.⁸¹ Additionally, CB2R knockout mice exhibit gut flora dysbiosis similar to that of NAFLD patients and model mice. Microbial functional analysis and metabolomics showed that tryptophan metabolism is clearly disturbed in NAFLD patients, model mice, and CB2R knockout mice, where increased tryptophan metabolites like indole lactate are correlated with NAFLD severity indicators. *In vitro* and *in vivo* validation experiments confirmed that indole lactate aggravates the NAFLD phenotype, indicating that CB2R participates in the NAFLD process by regulating gut microbiota-mediated tryptophan metabolism.⁸²

Intrahepatic mechanisms of other key microbial metabolites

Beyond the three major classes mentioned above, gut microbes produce a series of other metabolites that precisely regulate hepatic pathophysiology. Microbial-derived D-lactate is elevated in obesity and can be metabolized in the liver into pyruvate, tricarboxylic acid cycle intermediates, lipids, and glucose, thereby directly participating in host glucose and lipid metabolism. Oral administration of a biocompatible polymer that captures intestinal D-lactate and promotes its fecal excretion can significantly reduce blood glucose, insulin resistance, liver inflammation, and fibrosis in mice with obesity and MAFLD.⁸³ Trimethylamine N-oxide (TMAO) is a product of choline and carnitine metabolism by gut microbes. High levels of TMAO are associated with the

severity of fatty liver, and the mechanism may involve activation of the AMPK signaling pathway and interaction with oxidative phosphorylation pathways, thereby promoting hepatic lipid accumulation.^{84,85} In liver fibrosis, the microbial metabolite 2-oleoylglycerol (2-OG) has been identified as a key mediator. It is produced by the gut bacterium *Blautia producta* and drives macrophage priming and hepatic stellate cell activation by activating the GPR119/TAK1/NF- κ B/TGF- β 1 signaling pathway, thereby promoting inflammation and fibrosis.⁸⁶ These findings reveal the precise and complex regulatory roles of microbial metabolites as direct signaling molecules or through affecting the epigenetic and metabolic states of host cells in liver disease progression. In high-fat diet-induced obese mice, the abundance of *Blautia producta* in the gut flora increases, leading to elevated 2-OG levels. This metabolite enhances hepatic de novo lipogenesis by activating ChREBP and SREBP-1 pathways and induces mitochondrial dysfunction, thereby promoting hepatic steatosis. In human MASLD patients, serum 2-OG levels in grade II and III hepatic steatosis patients are significantly higher than those in healthy subjects, suggesting that circulating 2-OG acts as a potential predictive biomarker for hepatic steatosis.⁸⁷ Furthermore, zinc supplementation increases *Blautia producta* abundance and promotes p-coumaric acid production by altering the gut microbiota. P-coumaric acid is negatively correlated with liver injury parameters in patients with cholestatic liver disease, directly binds NADPH oxidase 2, and inhibits reactive oxygen species production in hepatocytes, thereby preventing hepatocyte death and liver injury. This reveals a new mechanism by which zinc supplementation stimulates host-microbiota interactions to alleviate cholestatic liver injury.⁸⁸ In NAFLD patients, plasma histidine levels are strongly negatively correlated with steatosis and are associated with hepatic transcriptomic signatures involving insulin signaling, inflammation, and trace amine-associated receptor 1. Circulating histidine is negatively correlated with Proteobacteria and positively correlated with bacteria lacking the histidine utilization system. Histidine supplementation improves NAFLD and reduces de novo lipogenesis in different animal models. FMT from low-histidine donors and mono-colonization of germ-free fruit flies with *Enterobacter cloacae* increase triglyceride accumulation and decrease histidine content, revealing interactions between microbiota, histidine catabolism, and NAFLD.⁸⁹

Integration and interactive regulation of multi-metabolite networks

In the progression of liver disease, different microbial metabolite axes do not operate in isolation but form a dynamic, interactive network that collectively shapes the liver microenvironment. For example, bile acids and SCFAs can synergistically regulate the same signaling pathway. Butyrate, as an HDAC inhibitor, can enhance FXR expression and activity, thus synergizing with bile acid signaling to jointly inhibit hepatic lipogenesis.¹² Cross-talk also exists between tryptophan metabolism and bile acid metabolism: tryptophan can modulate gut microbiota–bile acid crosstalk by altering BSH-enriched microbes and intestinal FXR signaling, thereby influencing hepatic bile acid synthesis.⁹⁰ The imbalance of this multi-metabolite network is central to liver disease deterioration. In patients progressing from NASH to liver fibrosis, an increase in secondary bile acid (e.g., DCA) generation is observed alongside a decrease in anti-inflammatory tryptophan metabolites (e.g., IPA) and an increase in pro-fibrotic metabolites (e.g., 2-OG); this multi-axis dysregulation jointly drives the disease phenotype.^{86,91} Therefore, future therapeutic strategies should not be limited to single

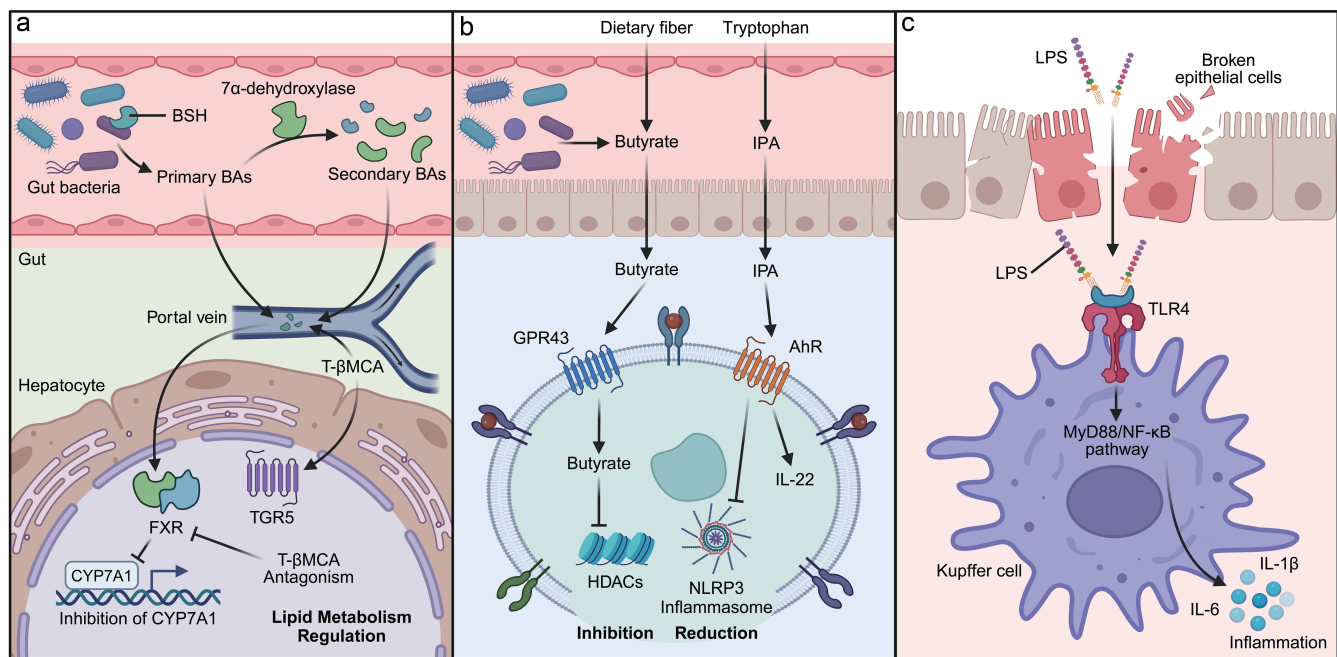


Fig. 2. Deciphering intrahepatic signaling: Metabolites, immunity, and barrier integrity. This figure details the core mechanisms by which gut microbial signals regulate hepatic pathophysiology. Panel A highlights the bile acid axis, where bacterial enzymes like bile salt hydrolase (BSH) and 7 α -dehydroxylase remodel the bile acid pool (converting primary to secondary bile acids), influencing hepatic FXR and TGR5 signaling to regulate lipid metabolism and CYP7A1 expression. Panel B illustrates the SCFA and Tryptophan Axes, showing how fiber-derived butyrate inhibits histone deacetylases (HDACs) and activates GPR43, while tryptophan metabolites like IPA activate AhR to modulate immunity. Panel C depicts the Immune-Barrier Axis, where disrupted barrier integrity leads to LPS translocation, triggering the TLR4–MyD88–NF- κ B pathway in Kupffer cells and the release of pro-inflammatory cytokines like TNF- α , IL-1 β , and IL-6. This figure was created with BioRender (<https://biorender.com/>). AhR, aryl hydrocarbon receptor; BAs, bile acids; BSH, bile salt hydrolase; FXR, farnesoid X receptor; GPR43, G protein-coupled receptor 43; HDACs, histone deacetylases; IL-1 β , interleukin-1 beta; IL-22, interleukin-22; IL-6, interleukin-6; IPA, indole-3-propionic acid; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response 88; NF- κ B, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; SCFA, short-chain fatty acid; TGR5, Takeda G protein-coupled receptor 5; TLR4, Toll-like receptor 4; T- β MCA, tauro- β -muricholic acid.

metabolites or pathways but should focus on rebuilding healthy microbial metabolite networks. By comprehensively correcting disorders across multiple metabolite axes through dietary interventions (such as supplementing specific prebiotics and fibers), probiotic/postbiotic therapies, or small-molecule inhibitors (such as targeting microbial enzymes CutC/D to inhibit TMAO generation), it is expected that more fundamental and effective management of liver diseases can be achieved. In NAFLD patients, two heterogeneous subgroups based on gut microbial composition were identified: PHC-like patients and P-patients. PHC-like patients have significant enrichment of Enterobacteriaceae in feces, and metabolic pathway analysis suggests enrichment of dicarboxylic acid sugar degradation products; the glyceric acid produced may reduce IL-6 levels and fat accumulation through the PPAR- α pathway. P-patients have significant colonization of *Prevotella* in feces, accompanied by enrichment of heme b biosynthesis and sulfate reduction metabolic pathways; the protoporphyrin IX/heme produced may participate in liver injury, and endogenous hydrogen sulfide may elevate serum IL-6 levels. These findings offer possibilities for personalized treatment of NAFLD.⁹² Furthermore, in an NAFLD mouse model, gut flora imbalance—specifically the increase of pathogenic *Blautia* and *Helicobacter* and the decrease of beneficial *Allobaculum*—is an important cause of intestinal metabolic disorder. This disorder reduces serum unsaturated fatty acid content, especially eicosapentaenoic acid and docosahexaenoic acid, while branched-chain fatty acids accumulate, subsequently

leading to significantly elevated liver injury indicators. This may exacerbate the progression of NAFLD and obesity (Fig. 2).⁹³

Gut–liver immune crosstalk: microbiota shaping of hepatic innate and adaptive immunity

Microbiota Regulation of hepatic innate immune cells

The gut microbiota and its products continuously shape the function of liver-resident innate immune cells through the portal circulation, among which Kupffer cells, as the major macrophage population in the liver, are key sentinels sensing gut-derived signals. Microbial-associated molecular patterns, such as LPS, translocate to the liver through the damaged gut barrier, are recognized by TLR4 on the surface of Kupffer cells, activate the downstream MyD88/NF- κ B signaling pathway, drive the massive release of pro-inflammatory cytokines (such as TNF- α , IL-1 β , IL-6), and thereby initiate and maintain the inflammatory state of the liver, which is crucial in the pathogenesis of ALD and NASH.^{8,9} Besides direct activation, the gut microbiota also indirectly regulates innate immunity through its metabolic products. For example, the reduction of SCFAs (such as butyrate) caused by gut microbiota dysbiosis weakens their inhibitory effect on HDACs, thereby enhancing the pro-inflammatory phenotype of Kupffer cells.¹² In HCC models, cyclic di-AMP from gut microbiota was found to act as an agonist for STING receptors, activating intrahepatic in-

nate immunity and enhancing antitumor immune responses, while microbiota dysbiosis inhibits this pathway, leading to radiotherapy resistance.⁹⁴ Additionally, gut microbiota affects the function of hepatic natural killer (NK) cells and natural killer T cells. Studies have found that supplementing specific probiotics or regulating microbiota can increase the infiltration and activation of hepatic NK cells and natural killer T cells, thereby enhancing the clearance capability against tumors or virus-infected cells.⁹⁵ In MASLD mouse models, early antibiotic exposure accelerates the progression of MASLD-HCC by continuously disrupting hepatocyte function, immune balance, and metabolic homeostasis, manifested as disorders of various immune cells such as T cells, B cells, NK cells, and macrophages in the liver.⁹⁶ Moreover, in cystic fibrosis transmembrane conductance regulator gene knockout mice, gut microbiota dysbiosis leads to increased neutrophils, macrophages, and T cells in the periportal region of the liver and activates pro-inflammatory and pathogen-mediated immune pathways. Treatment with non-absorbable antibiotics improves intestinal permeability and liver inflammation.⁹⁷

Microbiota shaping of hepatic adaptive immunity

The gut microbiota profoundly influences hepatic adaptive immune responses by regulating antigen presentation and T cell differentiation. In HCC, gut microbiota dysbiosis inhibits the cGAS-STING-IFN-I pathway, impairing the antigen presentation function of dendritic cells and weakening the activation and function of effector CD8⁺ T cells, leading to primary resistance to radiotherapy or ICI.⁹⁴ Conversely, specific beneficial microbiota can promote antitumor immunity. For example, in HCC mouse models, stigmasterol remodels gut microbiota, increases *Lactobacillus* abundance, leads to a decrease in the proportion of regulatory T cells (Tregs) in the tumor microenvironment, and simultaneously increases the proportion of IFN- γ ⁺ CD8⁺ T cells with killing function, thereby enhancing antitumor immunity.⁹⁸ In autoimmune hepatitis, gut microbiota dysbiosis plays a driving role. Berberine regulates gut microbiota, increases beneficial bacteria, decreases harmful bacteria, and enhances the gut barrier, thereby reducing LPS translocation and its mediated TLR4/NF- κ B pathway activation to inhibit liver inflammation. Meanwhile, it can also regulate the T cell balance in the spleen and liver, reducing the proportion of pro-inflammatory Th17 cells and increasing anti-inflammatory Tregs and IL-10 levels, thereby alleviating autoimmune liver injury.⁹⁹ This evidence indicates that gut microbiota is a key regulator of local and systemic adaptive immune responses in the liver. In MAFLD, washed microbiota transplantation (WMT) promotes the migration of group 3 innate lymphoid cells (ILC3s) to the liver via the CXCL16/CXCR6 axis by upregulating CXCR6 expression on ILC3s, thereby mitigating hepatic steatosis through IL-22 release, suggesting that targeting liver-homing ILC3s is a potential therapeutic strategy.¹⁰⁰ Additionally, in an autoimmune hepatitis mouse model, *Bifidobacterium* triple viable capsules alleviated liver injury by downregulating IL-33 production and inhibiting TLR2/4 signaling pathways, restoring the Treg/Th17 balance.¹⁰¹

Microbial translocation and establishment of the hepatic immune microenvironment

In advanced liver diseases like cirrhosis, gut barrier function is severely impaired, leading to massive translocation of live bacteria and their products (such as LPS) to the liver, directly participating in shaping the local immune microenvironment. This translocation not only activates Kupffer cells but also leads to the detection of bacterial DNA in the liver. Studies have found distinct bacte-

rial communities in tumor tissues and non-tumor tissues of HCC patients, where bacteria enriched in metastatic nodules, such as *Enterococcus* and *Streptococcus anginosus*, can induce an immunosuppressive microenvironment and promote tumor progression through epithelial-mesenchymal transition.¹⁰² Similarly, in patients with MASLD, universal translocation of obesity-induced gut bacteria to the liver and adipose tissue is observed. The abundance of *Enterococcus* and *Granulicatella* is positively correlated with liver immune cell counts and inflammatory gene expression levels, and they are significantly enriched in steatohepatitis (MASH) patients, suggesting that these translocated bacteria may directly drive disease severity.¹⁰³ Furthermore, translocated microbes or their components can act as antigens, continuously stimulating the hepatic immune system and breaking immune tolerance, which may play an important role in the pathogenesis of autoimmune liver diseases such as primary biliary cholangitis.¹⁰⁴ In a liver fibrosis mouse model, dihydromyricetin alleviates liver fibrosis by remodeling gut microbiota and host metabolism to improve inflammatory responses.¹⁰⁵ In an ALD rat model, gut microbiota dysbiosis induced by bismuth quadruple therapy led to damaged gut barrier, elevated serum LPS levels, activation of the hepatic NLRP3 inflammasome pathway, increased IL-18 and IL-1 β , and exacerbated liver injury.¹⁰⁶ Moreover, in an autoimmune hepatitis mouse model, dextran sulfate sodium-induced gut microbiota dysbiosis may aggravate liver inflammation and injury by disrupting the gut barrier and leading to microbiota translocation to the liver.¹⁰⁷ Furthermore, this microbial crosstalk is pivotal in liver transplantation. Perioperative ischemia-reperfusion injury severely compromises the intestinal barrier, facilitating the translocation of gut-derived signals that exacerbate graft damage. Notably, specific commensals like Lachnospiraceae have been identified to alleviate hepatic ischemia-reperfusion injury (HIRI), particularly in steatotic donor livers, by inhibiting ferroptosis.¹⁰⁸ Post-transplantation, the resulting dysbiosis actively modulates the recipient's hepatic immune microenvironment, potentially dictating the critical balance between immune tolerance and acute cellular rejection.^{109,110}

Crucially, across all these diverse hepatic pathologies and clinical interventions, the paradigms of microbial translocation are actively evolving. Beyond direct bacterial infiltration and the passive diffusion of free microbial products, bacterial extracellular vesicles have recently emerged as a pivotal, independent communication modality along the gut–liver axis.¹¹¹ Unlike whole bacteria, these nanosized vesicles can efficiently traverse both intact and compromised intestinal barriers, entering the portal circulation without requiring severe mucosal damage.¹¹² Upon reaching the liver, bacterial extracellular vesicles function as highly targeted delivery vehicles, independently unloading concentrated packages of virulence factors, microbial small RNAs, and active metabolites directly into hepatic non-parenchymal cells. This vesicle-mediated transport mechanism allows the gut microbiota to profoundly shape the hepatic immune microenvironment and drive localized inflammatory cascades, even in the complete absence of viable bacteremia.¹¹³

Microbial metabolites as immune regulatory signaling molecules

Gut flora-derived metabolites are core chemical messengers remotely regulating hepatic immunity. SCFAs like butyrate, besides serving as energy substrates, are important immune modulators. Butyrate, by inhibiting HDACs and activating G-protein-coupled receptors (such as GPR109A), can promote the differentiation of macrophages and dendritic cells toward anti-inflammatory pheno-

types (M2, tolerogenic dendritic cells) and enhance the function of Tregs, thereby alleviating liver inflammation in ALD and non-alcoholic fatty liver models.^{12,114} Tryptophan metabolites, such as I3A and IPA, play key roles in immune regulation by activating AhR. AhR activation can inhibit inflammasome (such as NLRP3) activation, reduce the production of pro-inflammatory factors like IL-1 β , and promote IL-22 secretion, which has a protective effect on hepatocytes and can reduce oxidative stress and steatosis.^{79,115} In an autoimmune hepatitis model, Yinchenhao Tang alleviated liver injury by regulating gut microbiota, increasing the release of SCFAs like butyrate, and subsequently restoring the Th1/Treg balance in the spleen and hepatic hilar lymph nodes through G-protein-coupled receptor-mediated mechanisms.¹¹⁶ These metabolites constitute the molecular language of the fine dialogue between gut flora and the hepatic immune system. In a NASH mouse model, Paeonol inhibited NOD-like receptor protein 3 inflammasome production and inflammation by regulating gut microbiota, reducing the abundance of certain Gram-negative tryptophan-metabolizing bacteria, and significantly increasing the level of the metabolite indole acetic acid, which enhanced the expression of AhR-related pathway proteins.¹¹⁷ Additionally, in an ALD mouse model, Galangin effectively alleviated alcohol-induced liver disease by regulating gut microbiota dysbiosis and increasing SCFA levels, improving intestinal microecological imbalance, and thus inhibiting the inflammatory cascade through the gut–liver axis mediated by gut microbiota.¹¹⁸

To fully decode how these microbial metabolite signals orchestrate the hepatic immune system, it is crucial to move beyond traditional bulk tissue analysis.¹¹⁹ Recent breakthroughs utilizing single-cell RNA sequencing and spatial multi-omics (such as spatial transcriptomics and proteogenomics) have revolutionized our understanding of hepatic niches.¹²⁰ These advanced technologies have mapped the precise spatial zonation of immune responses, revealing how distinct subpopulations of hepatic non-parenchymal cells, such as specific lipid-associated macrophages localized at fibrotic zones or bile ducts, uniquely respond to gut-derived metabolic signals.¹²¹ Incorporating this high-resolution spatial dimension is indispensable for deciphering exactly where and how these specific molecules trigger inflammatory or fibrotic remodeling within the liver lobule.¹²²

Therapeutic prospects of targeting the microbe-immune axis

Based on the deep understanding of gut–liver immune dialogue mechanisms, targeting the microbiota to regulate hepatic immunity has become a highly promising therapeutic strategy. By holistically remodeling the gut ecosystem, FMT has been proven to improve survival rates in patients with severe alcoholic hepatitis (SAH) and cirrhosis, with mechanisms closely related to increasing beneficial flora, reducing pathogenic bacteria, and thereby alleviating systemic and hepatic inflammation.^{123,124} The application of probiotics and synbiotics is more precise. For example, combined probiotic and prebiotic treatment for autoimmune hepatitis can act by remodeling gut microbiota, maintaining the gut barrier, blocking LPS/TLR4/NF- κ B pathway activation, and restoring immune imbalance, with effects superior to probiotics or prebiotics alone.¹²⁵ Furthermore, small molecule drugs targeting specific microbial enzymes or metabolic pathways are under development. For instance, inhibiting microbial TMA lyase (CutC/D) to reduce TMAO generation, or using D-lactate scavengers, have shown potential in preclinical models to improve metabolic liver disease and inflammation.⁸³ In the future, combining microbiome sequencing and immune profiling is expected to enable personalized microbial

interventions, such as transplanting “beneficial” flora to sensitize HCC patients ineffective to ICI therapy, or customizing probiotic formulas regulating immune balance for autoimmune liver disease patients, truly realizing the immune therapy paradigm shift from “targeting the liver” to “targeting the intestinal niche.” In HCC patients, the treatment regimen of nivolumab combined with oral vancomycin and tadalafil led to changes in the gut microbiome, reduced secondary bile acids, and significant changes in peripheral blood monocyte subsets; although the expected clinical efficacy was not observed, it provided an exploratory direction for immunotherapy combined with microbial regulation.¹²⁶ In an ALD mouse model, combined *Lactobacillus rhamnosus* GG and metformin treatment corrected immune response dysregulation by enhancing the gut microbiome, restoring mucosal barrier integrity, regulating immune function, and reducing liver injury, thereby improving ALD.¹²⁷ Additionally, in cirrhosis patients, a 12-month multifactorial intervention (home exercise, branched-chain amino acids, and multi-strain probiotics) improved the Liver Frailty Index, while a decrease in *Akkermansia muciniphila* abundance and an increase in multiple *Bifidobacterium* species abundance were observed, indicating that the improvement in frailty status occurs synchronously with changes in gut flora composition.¹²⁸

Disruption of gut barrier integrity and microbial translocation: The accelerator of liver disease progression

Pathophysiological changes in gut barrier structure and function

As a key physical and immunological defense line separating intestinal lumen contents from the host’s internal environment, the integrity of the gut barrier suffers systemic destruction during the progression of liver diseases. Pathophysiological changes involve multiple levels: at the cellular level, the expression of tight junction proteins (such as ZO-1, occludin, and the claudin family) is significantly downregulated, leading to the loss of the “sealing” function between intestinal epithelial cells and increased intestinal permeability.^{129–131} At the chemical barrier level, mucins (such as MUC2) secreted by goblet cells decrease, thinning the mucus layer covering the intestinal epithelium and failing to effectively block direct contact between bacteria and the epithelium.¹³² Simultaneously, the expression of antimicrobial peptides (such as lysozyme and defensins) secreted by Paneth cells decreases, weakening the innate immune defense capability against commensal and pathogenic bacteria.¹³³ This multi-level barrier dysfunction is not an isolated event but forms a vicious cycle with gut flora dysbiosis. For example, in ALD models, ethanol and its metabolites directly induce necroptosis and endoplasmic reticulum stress in intestinal epithelial cells, while altering the bile acid profile to further impair barrier protein expression.^{134,135} In MASLD, high-fat diet-induced oxidative stress and the release of inflammatory cytokines (such as TNF- α) directly downregulate the transcription and translation of tight junction proteins by activating signaling pathways like NF- κ B.^{131,132} These structural and functional changes collectively constitute the pathological basis of gut barrier “leakiness,” opening the gateway for subsequent translocation of microbes and their products. In high-severity patients after liver transplantation, gut barrier function is more persistently and severely impaired, with a higher proportion of pathogens like *Escherichia coli* and *Shigella flexneri* in their feces, while butyrate producers like *Roseburia intestinalis* are positively correlated with albumin levels, suggesting an interconnection between dysbiosis and barrier damage.¹³⁶ Chronic apical periodontitis damages gut barrier integrity by altering gut flora and their

metabolites, disrupting intestinal tight junction protein and mucin expression, thereby promoting liver fibrosis progression in NAFLD.¹³⁷ Arsenic exposure significantly reduces the expression of gut barrier proteins occludin, ZO-1, and MUC2 in mice, elevates serum FITC levels indicating increased intestinal permeability, and FMT experiments confirm that arsenic-induced dysbiosis and barrier dysfunction play a key role in liver injury.¹³⁸ In patients with compensated cirrhosis, duodenal epithelial permeability is increased, and the mucosal microbial community structure is related to barrier function, where beneficial bacteria like *Lactobacillus* and *Bifidobacterium* have a protective effect on duodenal permeability.¹³⁹ Splenectomy improves cirrhosis by restoring gut barrier function and maintaining gut microbiota balance. *Veillonella* is a key genus whose conditioned medium promotes hepatic stellate cell activation and induces hepatocyte pyroptosis.¹⁴⁰ Nanoplastic exposure alters gut flora composition in mice, disrupts the gut barrier, leads to increased circulating LPS, and promotes liver cell pyroptosis and inflammation. Recipient mice receiving fecal transplants from nanoplastic-treated mice also develop similar gut barrier damage and liver inflammation.¹⁴¹ Methamphetamine administration leads to impaired gut barrier, increased circulating LPS, and promotes liver dysfunction and inflammation by disturbing the cecal microbiota and impairing bile acid homeostasis.¹⁴² In a bile duct ligation-induced liver fibrosis rat model, intervention with cinnamaldehyde nanoemulsion formulated with vitamin A exerts therapeutic effects by restoring gut flora, increasing SCFA concentration, and improving gut integrity.¹⁴³ A hyperammonemia mouse model shows decreased gut microbial load, diversity, and aerobic/facultative anaerobic bacteria ratio, and gut flora diversity decreases in a time-dependent manner; data suggest that ammonia-induced motor coordination deficits may develop through direct and indirect pathways acting on the gut–brain axis, indicating impaired barrier function.¹⁴⁴ IL-17 deficiency leads to gut flora dysbiosis, inhibiting probiotic growth while pathogenic bacteria overproliferate, triggering higher endotoxemia and more severe gut barrier defects; transplanting flora from IL-17-deficient mice to germ-free mice exacerbates gut barrier damage and promotes the development of NASH.¹⁴⁵ *Helicobacter pylori*-infected high-fat diet mice exhibit more severe hepatic steatosis; infection triggers gastric flora dysbiosis, leading to significant enrichment of the *Helicobacter* genus. Gastric tissue energy metabolomics analysis shows elevated glycolytic pathway activity after infection, and the disturbance of the gastric flora–metabolic axis is significantly positively correlated with the severity of hepatic steatosis and inflammation.¹⁴⁶ Oral exposure to high concentrations of microplastics for six weeks, even without inducing leaky gut syndrome, leads to elevated serum lipid levels and exacerbated fatty liver function in mice. Exposure does not affect gut innate lymphoid cell numbers or SCFAs but increases NK cell numbers, alters gut flora, induces gut inflammation, and regulates the expression of genes related to nutrient transport in the gut.¹⁴⁷ In an intrahepatic cholestasis of pregnancy rat model, 17 α -ethinylestradiol treatment leads to reduced gut flora α -diversity and significantly altered structure; resveratrol intervention partially rescues gut flora dysbiosis and improves biochemical abnormalities.¹⁴⁸ Cognitive impairment caused by HIRI exhibits circadian oscillation; FMT from ZT12-HIRI mice can induce cognitive impairment behavior in recipient mice, and gut flora composition and metabolite analysis show significant enrichment of differential fecal metabolites in lipid metabolism pathways.¹⁴⁹ In specific pathogen-free mice, a low-iron diet reduces serum triglycerides and induces MAFLD, while germ-free mice on a low-iron diet show elevated serum triglycerides and do not develop hepatic steatosis;

significant changes in hepatic lipid metabolism and increased insulin resistance depend on the presence of gut flora.¹⁵⁰ Chronic fructose intake leads to gut flora dysbiosis, tight junction protein down-regulation, secretory cell depletion, and elevated pro-inflammatory cytokines, thereby disrupting the gut barrier and triggering endotoxemia-mediated liver inflammation and fibrosis. Calcitriol intervention significantly restores vitamin D receptor expression, enhances autophagy flux, stimulates mucin/antimicrobial peptide production, and inhibits NF- κ B-mediated inflammatory responses.¹⁵¹ Multi-donor FMT significantly improves liver fat accumulation in high-fat diet-fed mice, increases relative protein levels of gut barrier proteins (claudin-1, occludin, and E-cadherin), and reduces serum LPS levels.¹⁵² Fecal microbiomes of cirrhosis patients treated with oral L-ornithine L-aspartate show higher abundances of *Flavonifractor* and *Oscillospira*, but there are no differences in intestinal permeability or inflammatory markers.¹⁵³ Patchoulene epoxide significantly reduces the disease activity index and alleviates colon atrophy in ulcerative colitis mice, improving pathological changes in the colon and liver by protecting tight junctions and mucus connections and inhibiting pro-inflammatory cytokine and LPS generation. These beneficial effects are attributed to patchoulene epoxide's ability to regulate colonic microbiota and metabolic processes.¹⁵⁴ Long-term high-energy diet reduces anti-infective, immune, and antioxidant functions, increases cell death, and leads to liver inflammation and activation of cytokine/chemokine signaling pathways by altering rumen and jejunum microbiomes; meanwhile, indoxyl sulfate and p-cresol sulfate increase while triterpenoids decrease in the liver.¹⁵⁵ In an ALD mouse model, NLRP6 deficiency has no effect on hepatic steatosis and injury but slightly interferes with intestinal homeostasis by affecting intestinal epithelial function and gut flora, and unexpectedly significantly reduces hepatic immune cell infiltration.¹⁵⁶ Hepatic ischemia/reperfusion injury mice induce a depression-like phenotype via the subdiaphragmatic vagus nerve-mediated gut–microbiota–liver–brain axis, manifested as splenomegaly, systemic inflammation, reduced synaptic protein expression in the prefrontal cortex, abnormal gut flora composition, and altered blood metabolites and lipids; subdiaphragmatic vagotomy significantly blocks these changes.¹⁵⁷ An NAFLD mouse model induced by a high-fat, high-sugar diet for 6 months exhibits hypercholesterolemia, glucose intolerance, and hyperinsulinemia, accompanied by severe hepatic macro- and microvesicular steatosis and human-like pericellular fibrosis, along with hepatic stellate cell activation, CD68⁺ macrophage infiltration, and elevated hepatic pro-inflammatory factors p65-NF- κ B, IL-6, and TNF- α protein levels. Gut flora analysis shows reduced bacterial diversity, enriched Firmicutes and Proteobacteria, and reduced Bacteroidetes and Fusobacteria.¹⁵⁸ Oral exposure to cylindrospermopsin leads to reduced gut bacterial phylum diversity, accompanied by increased *Clostridioides difficile* abundance and reduced beneficial flora like *Roseburia*, *Akkermansia*, and *Bacteroides thetaiotaomicron* (*B. theta*). This feature is closely related to gut and liver pathology, and gut flora dysbiosis is also associated with increased intestinal Claudin2 protein, a marker of leaky gut and endotoxemia.¹⁵⁹ In a nonalcoholic fatty liver mouse model, the β -diversity of cecal microbiota changes significantly, where *Blautia*, *Unidentified-Lachnospiraceae*, *Romboutsia*, *Faecalibaculum*, and *Ileibacterium* abundance increase significantly, while *Allobaculum* and *Enterorhabdus* decrease significantly. Metabolomics analysis identifies 167 differential metabolites involving amino acids, lipids, bile acids, and nucleotides.¹⁶⁰ Combined triptonide and triptonide treatment causes intestinal bleeding and microbial dysbiosis, subsequently elevating plasma LPS levels and exacerbating

triptolide-induced liver injury. Metabolomics and flora analysis confirm that the toxic metabolite p-cresol sulfate is significantly associated with gut barrier damage, and p-cresol sulfate supplementation *in vivo* verifies its ability to promote combined medication hepatotoxicity.¹⁶¹ In gut microbiota analysis of early-stage liver fibrosis (F0–F2), 50% of disease-associated taxa are Enterobacteriaceae, Pseudomonadaceae, Flavobacteriaceae, and Burkholderiaceae, among which Flavobacteriaceae and Xanthomonadaceae can distinguish F0 from F1 stages. Predictive metagenomics analysis finds that preQ0 biosynthesis and potential pathways involving glucopyranose and glycogen degradation are negatively correlated with F1–F2 fibrosis.¹⁶² Copper exposure significantly elevates duck liver AST and ALT levels and induces liver inflammation by upregulating pro-inflammatory cytokines and activating the LPS/TLR4/NF- κ B signaling pathway. Meanwhile, copper exposure alters gut flora composition, significantly reduces the expression of gut barrier-related proteins (occludin, claudin-1, ZO-1), and promotes the secretion of intestinal pro-inflammatory cytokines. FMT experiments further confirm that transplanting fecal samples from copper-exposed ducks to microbiota-depleted ducks disrupts intestinal function, leading to impaired liver function and activation of liver inflammation.¹⁶³ In the high liver fat group (>5%), fecal abundances of Prevotellaceae NK3B31 group and *Bacteroides* are lower, while lysine and histidine degradation product levels are higher. Elevated plasma caffeine and its metabolite levels indicate reduced hepatic CYP1A2 activity, and fecal 6 β -hydroxytestosterone (metabolized by CYP3A4) levels are lower.¹⁶⁴ Oxaliplatin-induced drug-induced fatty liver disease in a tree shrew model manifests as early severe hepatocyte steatosis and ballooning, late mild steatosis with sinusoidal dilation, and persistent hepatic oxidative stress. Hepatic transcriptome analysis identifies 1,503 differentially expressed genes, 601 of which differ in both early and late disease stages, involving significant dysregulation of oxidative stress and lipid metabolic pathways. Gut microbial analysis shows increased relative abundance of potentially harmful bacteria (such as *Parabacteroides*, *Rikenella*, *Alistipes*, and *Faecalitalea*) and decreased abundance of antioxidant bacteria (such as *Lactococcus* and *Flavobacterium*).¹⁶⁵ Oral nano-silica for 12 weeks leads to gut flora dysbiosis, metabolite imbalance, and gut barrier damage in mice, causing liver-specific silicon accumulation, which subsequently triggers hepatic lipid deposition, senescence, and fibrosis via the microbe–gut–liver axis. 16S rRNA sequencing shows that nano-silica reduces the abundance of beneficial bacteria *Muribaculum* and *Ligilactobacillus* and increases pathogenic *Helicobacter*.¹⁶⁶ In overweight and obese Iranian children and adolescents, the only significant gut flora change associated with MASLD is reduced *Coprococcus* abundance. After adjusting for age, gender, and body mass index, *Coprococcus* count is negatively correlated with MASLD prevalence odds and ALT levels; conversely, *Prevotella* is significantly positively correlated with ALT and AST levels.¹⁶⁷ Long-term skin exposure to UVB not only triggers liver inflammation and oxidative stress but also leads to abnormal hepatic lipid metabolism, specifically significant changes in glyceride, sphingolipid, and glycerophospholipid metabolism. Meanwhile, UVB exposure disrupts gut flora structure and function. Co-culturing fecal supernatant from UVB-exposed mice with HepG2 cells induces increased inflammatory factor IL-8 secretion, MDA accumulation, reduced SOD activity, and reduced hepatocyte lipid content.¹⁶⁸ Cadmium exposure leads to gut flora dysbiosis, reduced fecal BSH activity, and elevated intestinal tauro- β -muricholic acid levels in mice, subsequently inhibiting the intestinal FXR/FGF-15 signaling pathway, promoting hepatic bile acid synthesis, and ultimately triggering bile duct pro-

liferation, inflammation, and injury. Mice receiving fecal microbiota transplants from cadmium-treated mice recapitulate signal inhibition, increased bile acid synthesis, and liver injury, while antibiotic clearance of flora blocks these effects.¹⁶⁹ The synergistic action of fructose and potassium sorbate significantly induces liver pathological changes of MASLD, including steatosis, inflammation, and fibrosis, accompanied by elevated liver function markers and altered lipid profiles. These changes are associated with significant alterations in gut bacterial and fungal communities, gut barrier function disruption, and enhanced pro-inflammatory responses in mesenteric lymph nodes.¹⁷⁰ Gentiopicroside significantly attenuates weight loss and disease activity index scores in dextran sulfate sodium-induced colitis mice, restores intestinal tight junction protein expression, and improves colonic permeability. Simultaneously, it regulates gut flora, significantly increasing the abundance of beneficial bacteria like *Bacteroides* and *Clostridium* cluster IV. Mechanistically, it inhibits colonic and hepatic inflammatory responses by suppressing TLR4/MyD88/NF- κ B and JAK2/STAT3 signaling pathways.¹⁷¹ In NAFLD patients, no significant association is observed between dietary n-6/n-3 fatty acid ratio and gut flora composition or disease severity. However, the abundance of specific bacteria like *Catenibacterium* and *Lactobacillus ruminis* is positively correlated with dietary n-6 fatty acid intake, while *Clostridium* abundance is negatively correlated.¹⁷² *Bacillus subtilis* C10 intervention improves hepatic lipid metabolism and oxidative stress in an alcoholic liver injury mouse model by regulating gut flora balance, reducing harmful bacteria numbers, and increasing beneficial bacteria. Specific mechanisms include regulating key hepatic lipid metabolism factors and interfering with the Nrf-2/HO-1 signaling pathway, while reducing harmful metabolites and increasing beneficial metabolites by regulating multiple hepatic metabolic pathways such as glutathione metabolism, purine metabolism, pantothenate and CoA biosynthesis, ABC transporters, and the HIF-1 signaling pathway.¹⁷³

Mechanisms and consequences of microbial and product translocation

The direct consequence of gut barrier integrity disruption is the translocation of microbes and their metabolic products from the intestinal lumen to the portal circulation and systemic circulation, a process that is a core accelerator driving liver disease deterioration. Translocated substances mainly include live bacteria, bacterial fragments (such as LPS and peptidoglycans), and microbial metabolic products (such as D-lactate and TMAO). LPS, as a cell wall component of Gram-negative bacteria, is the most representative translocated product. In patients and animal models of cirrhosis, ALD, and NASH, serum LPS levels are significantly elevated and positively correlated with disease severity.^{130,131,174} Translocated LPS reaches the liver via the portal vein, is recognized by TLR4 on the surface of liver sinusoidal endothelial cells and Kupffer cells, activates the downstream MyD88/NF- κ B signaling pathway, triggers a strong pro-inflammatory response, releases large amounts of cytokines such as TNF- α , IL-1 β , and IL-6, and exacerbates liver inflammation and cell injury.^{8,9,174} Besides LPS, translocation of live bacteria is equally harmful. Studies confirm that gut-derived bacteria (such as *Klebsiella pneumoniae* and *Escherichia coli*) can be detected in the liver tissues of HCC patients and animal models; colonization by these bacteria can directly activate carcinogenic signaling pathways (such as TLR4) within hepatocytes, promoting tumor occurrence and progression.¹⁷⁵ Microbial translocation also leads to “metabolic endotoxemia,” an abnormal elevation of microbial-derived metabolite levels in circulation. For example,

elevated serum levels of D-lactate, a bacterial fermentation product, act as a sensitive marker for increased intestinal permeability, while TMAO is associated with the degree of hepatic steatosis and inflammation, possibly promoting disease by affecting cholesterol metabolism and macrophage foam cell formation.^{83,84} These translocated microbial components act together to transform local intestinal disturbances into systemic and sustained hepatic inflammatory attacks. In HCC patients, the microbiome differs between tumor and peritumoral tissues; tumor tissues are enriched in Lactobacillales, Veillonellaceae, *Rhodobacter*, and *Megasphaera*, while peritumoral tissues are enriched in *Pseudochrobactrum*. Patients with capsular invasion exhibit higher α -diversity at the genus level in liver tissues.¹⁷⁶ In operable HBV-related HCC patients, there is a significant difference in gut flora β -diversity between the microvascular invasion (MVI) group and the non-MVI group. A random forest model based on nine optimal microbial markers achieved areas under the curve of 79.76% and 79.80% for predicting MVI risk in training and independent validation sets, respectively.¹⁷⁷ Significant heterogeneity exists between multifocal tumor nodules in HCC.

The microbiome as non-invasive biomarkers for liver disease diagnosis and prognosis: From association to application

Liver disease diagnosis models based on gut microbial features

Gut microbiome features have moved beyond simple association studies to develop into high-precision non-invasive diagnostic tools for liver disease. In the field of MASLD, machine learning models constructed based on fecal 16S rRNA or metagenomic sequencing data demonstrate superior diagnostic performance. For instance, a study using a classifier containing ten core microbial genera achieved an area under the curve (AUC) as high as 0.93 for predicting fatty liver disease in insulin-resistant individuals, with accuracy comparable to or better than traditional fatty liver indices.¹⁷ Another study focusing on pediatric MASLD also confirmed that diagnostic models based on gut flora features possess high discriminatory power.¹⁷⁸ In Chinese children with NAFLD, a microbial model based on fecal flora also showed a high AUC, capable of distinguishing NAFLD patients from healthy individuals.¹⁷⁹ For HCC, the construction of diagnostic models is even more refined. Research integrating oral and gut microbial markers developed a consensus classifier that achieved an AUC of 0.9405 in distinguishing HCC from controls; when combined with serum α -fetoprotein, the AUC further improved to 0.9811, significantly surpassing the diagnostic capability of single biomarkers.¹⁸ Furthermore, a diagnostic model constructed based on the urine microbiome achieved an AUC of 0.94 and an accuracy of 88.4% in an independent validation cohort, providing a brand-new avenue for non-invasive HCC detection.¹⁸⁰ These models not only distinguish disease from health but can also identify different liver disease types. For example, a classification model based on eight gut bacterial genera can distinguish HCC, cholangiocarcinoma, and healthy controls with high precision, with AUCs reaching 0.967, 0.920, and 0.989 for the three groups in the validation cohort.¹⁸¹ Similarly, specific gut fungal signatures (such as *Scopulariopsis* and *Cluyveromyces*) achieved an AUC of 0.93 in distinguishing ALD from NAFLD and an AUC of 0.99 in distinguishing advanced fibrosis.¹⁸² In elderly HCC patients, a random forest model constructed based on specific genera like *Eggerthella*, *Anaerostipes*, and the *Lachnospiraceae* ND3007 group also showed good predictive ability (AUCs of 0.791, 0.766, and 0.730, respectively).¹⁸³ Machine

learning models based on gut microbes also performed well in predicting HBV-related HCC risk, with AUC values of seven models reaching 0.821–0.898 and 0.813–0.885 in training and validation sets, respectively.¹⁸⁴ In viral hepatitis patients, prediction models constructed based on gut flora α -diversity and key microbial markers such as *Butyrivibrio* and *Escherichia-Shigella* also had AUC values exceeding 0.7.¹⁸⁵

Microbial biomarkers predicting disease progression and liver fibrosis

The gut microbiome shows immense prognostic value in predicting liver disease progression, particularly the severity of liver fibrosis. In patients with chronic hepatitis B-related liver disease, changes in the abundance of specific genera are tightly linked to fibrosis stages. For example, the relative abundance of *Dorea* decreases significantly with increasing liver fibrosis severity, serving as a potential microbial marker for identifying fibrosis occurrence and progression.¹⁸⁶ In MASLD patients, the gut flora characteristics of the moderate-to-severe fibrosis (F2–F4) group manifest as enrichment of *Fusobacterium* and *Escherichia-Shigella* and reduction of *Lachnospira*; a random forest classifier constructed based on three bacterial genera could distinguish fibrosis degree with high precision (AUC of 0.93).¹⁸⁷ In NAFLD patients, severe fibrosis (F3–F4) patients show reduced abundance of anti-inflammatory species (such as *Eubacterium ventriosum* and *Alistipes finegoldii*) and increased abundance of genera like *Enterobacter* and *Klebsiella* in feces.^{188,189} Additionally, microbial markers can predict the progression of liver disease to end-stage events. In cirrhosis patients, specific patterns of gut flora dysbiosis are associated with adverse clinical outcomes. Studies found that as the disease progresses from compensated to decompensated cirrhosis and liver cancer, gut flora diversity progressively declines, *Bacteroides*, *Prevotella*, and *Faecalibacterium* gradually decrease, while *Klebsiella*, *Haemophilus*, and *Streptococcus* increase. A predictive nomogram constructed based on these features achieved AUC values of 0.865 and 0.848 in training and external validation cohorts, respectively.¹⁹⁰ More specifically, in cirrhosis patients, a denser, more uniform bacterial–archaeal–viral network centered on Ruminococcaceae and Christensenellaceae at baseline is associated with the risk of future decompensation events.¹⁹¹ In cirrhosis patients, gut flora dysbiosis is significantly associated with 90-day mortality and hospitalization rates; Firmicutes/Bacteroidetes and Firmicutes/Proteobacteria ratios progressively decrease and are significantly correlated with 90-day mortality.¹⁹² These findings indicate that gut microbiome features can dynamically reflect the accumulation of hepatic pathological injury and are powerful tools for non-invasive assessment of disease stage and prognosis prediction.

Microbiome predicting treatment response and efficacy

Gut microbiome profiles are becoming novel biomarkers for predicting patient response to specific treatments, especially in the fields of immunotherapy and antiviral therapy for HCC. In HCC patients, those achieving durable clinical benefit prior to ICI treatment have significantly higher overall gut bacterial and fungal diversity compared to non-durable benefit patients. A study established a prediction model containing 18 bacterial species to predict whether immunotherapy would yield sustained benefits, achieving an AUC of 75.63%.¹⁹³ Another study also found that patients with higher baseline gut flora α -diversity respond better to immunotherapy, and a machine learning classifier based on serum metabolites performed better (AUC 0.793) than a classifier based on gut flora in

predicting potential beneficiaries of immunotherapy.¹⁹⁴ In chronic hepatitis B treatment, gut flora features are closely related to antiviral efficacy. Research found that a gut flora cluster dominated by *Bacteroides* is associated with a higher probability of undetectable plasma HBV-DNA (OR 3.49), and patients in this cluster have higher plasma ursodeoxycholic acid levels and secondary bile acid biotransformation activity; whereas a cluster dominated by *Blautia* is associated with increased risk of advanced liver fibrosis (OR 2.74).¹⁹⁵ Additionally, in *Fasciola hepatica*-infected patients, gut microbiome characteristics differ significantly between responders and non-responders to triclabendazole treatment both before and after therapy. Responders have higher abundance of Firmicutes A and *Bacteroides* species and phospholipid synthesis pathways in their microbiome, suggesting that gut flora may play a role in modulating drug efficacy.¹⁹⁶ In nonalcoholic fatty liver and pre-diabetic patients, personalized gut flora networks at baseline can predict individual hepatic fat response to exercise intervention.¹⁹⁷ These evidences promote the potential application of pre-treatment microbiome testing in clinical decision-making.

Application of microbial biomarkers in warning of liver disease complications

Gut microbiome features have significant value for predicting common and fatal complications of cirrhosis, providing a window for early intervention. Regarding the prediction of HE, microbial markers show high specificity. Studies found that the gut flora of HE patients is dominated by *Escherichia/Shigella*, Burkholderiales, and Lactobacillales, while non-HE patients are characterized by *Veillonella* and *Bacteroides*. A rapid fecal test model based on 20 microbes can serve as an effective tool to rule out HE and avoid misdiagnosis.¹⁹⁸ Deeper mechanistic studies discovered that urease-positive *Streptococcus salivarius* producing ammonia is significantly enriched in the gut of HE patients, while urease-negative *R. gnavus* enriched in rifaximin non-responders can enhance the ammonia-producing activity of surrounding urease-positive bacteria; the sensitivity of these two bacteria to rifaximin depends on conjugated secondary bile acid levels, providing targets for personalized treatment.¹⁹⁹ Regarding the prediction of HE after transjugular intrahepatic portosystemic shunt, increased abundance of *Phocaeicola vulgatus* in the gut pre-surgery is significantly associated with elevated postoperative blood ammonia levels and HE occurrence; multiple machine learning models indicate *P. vulgatus* can serve as an important microbial marker for predicting postoperative complications.²⁰⁰ In HBV-related cirrhosis patients, the occurrence of postoperative HE in patients receiving transjugular intrahepatic portosystemic shunt treatment is associated with an increase in non-probiotic bacteria and the appearance of *Morganella* in the gut flora.²⁰¹ For SBP, gut flora features can also provide early warning. SBP patients have significantly reduced gut flora richness and increased diversity, dominated by pathogens like *Klebsiella pneumoniae* and *Serratia marcescens*, whereas non-SBP decompensated cirrhosis patients are dominated by beneficial bacteria like *Faecalibacterium prausnitzii* and *Lactobacillus reuteri*. A model based on five optimal microbial markers discriminated SBP from decompensated cirrhosis with an AUC of 0.8383.²⁰² Additionally, serum metabolites and gut flora features at admission are associated with the occurrence of nosocomial infections in cirrhosis patients; combining metabolites with clinical variables improved the AUC for predicting nosocomial infection from 0.74 to 0.77.²⁰³ In cirrhosis patients, during colonization by toxigenic *Clostridioides difficile* (pre-CDI), gut microbial richness and diversity significantly decreased, relative abundance of oppor-

tunistic pathogen *Enterococcus* increased, while beneficial commensals like *Faecalibacterium* decreased; a model based on three biomarkers distinguished pre-CDI from non-colonized controls with an AUC as high as 0.81.²⁰⁴

Challenges and future directions toward clinical translation

Although the gut microbiome shows immense potential as biomarkers for liver disease, its move toward large-scale clinical application still faces multiple challenges such as standardization, causality, and personalization. Current research is mostly based on observational associations, urgently requiring prospective large-cohort studies to validate the robustness of markers. For example, although many diagnostic models perform excellently in discovery cohorts, validation in independent populations, different regions, and races still needs strengthening.^{180,181} Standardization of microbial testing (including sample collection, DNA extraction, sequencing platforms, and bioinformatics pipelines) is a prerequisite for result reproducibility and comparability. Furthermore, distinguishing whether microbial changes are the cause or result of liver disease is crucial for the disease specificity of markers. Analysis tools like Mendelian randomization help infer causality; for instance, studies confirmed that Lachnospiraceae increases cirrhosis risk, while Lactobacillaceae, *Butyrivibrio*, and *Lactobacillus* have protective effects.²⁰⁵ Future development directions lie in developing composite biomarker panels integrating multi-omics data. For example, combining gut microbial features with serum metabolites (such as bile acids and tryptophan metabolites), clinical indicators (such as liver function and fibrosis scores), and even imaging features is expected to build more powerful prediction models. One study combined gut flora and serum metabolites, achieving a diagnostic accuracy (AUC) of 0.93 for MAFLD and its severity.²⁰⁶ Another study found that multi-kingdom markers integrating oral-gut-tumor microbiota can greatly improve early detection efficiency for HCC.¹⁸ In MAFLD patients, the combination of phenomics and metabolomics had the highest accuracy for MAFLD diagnosis (AUC = 0.97), while the combination of phenomics and metagenomics had the highest accuracy for predicting MAFLD hepatic steatosis progression (AUC = 0.94).²⁰⁷ In HCC patients, a diagnostic combination of gut flora (such as *Odoribacter splanchnicus* and *Ruminococcus bicirculans*) and serum metabolites (such as ouabain and taurochenodeoxycholic acid) had diagnostic value superior to α -fetoprotein.²⁰⁸ Ultimately, locking in key microbial or genetic markers through low-cost, rapid detection technologies (such as qPCR and microarrays) and conducting interventional clinical trials to verify their value in guiding treatment decisions and improving patient outcomes is the only way for microbiome markers to move from the laboratory to the clinical consultation room.

Ecological niche remodeling strategy i: evidence and limitations of FMT, probiotics, and prebiotics

Efficacy and challenges of FMT in liver disease treatment

As the most direct “niche remodeling” strategy, FMT has shown therapeutic potential in various liver diseases by holistically importing a healthy donor’s gut microbial ecosystem, yet its efficacy coexists with challenges (Fig. 3). In patients with SAH, a study showed that the 90-day survival rate of patients receiving healthy donor FMT treatment was as high as 87.5%, significantly better than patients receiving only corticosteroid treatment (64.3%) or high-dose probiotic infusion (55%), and FMT significantly im-

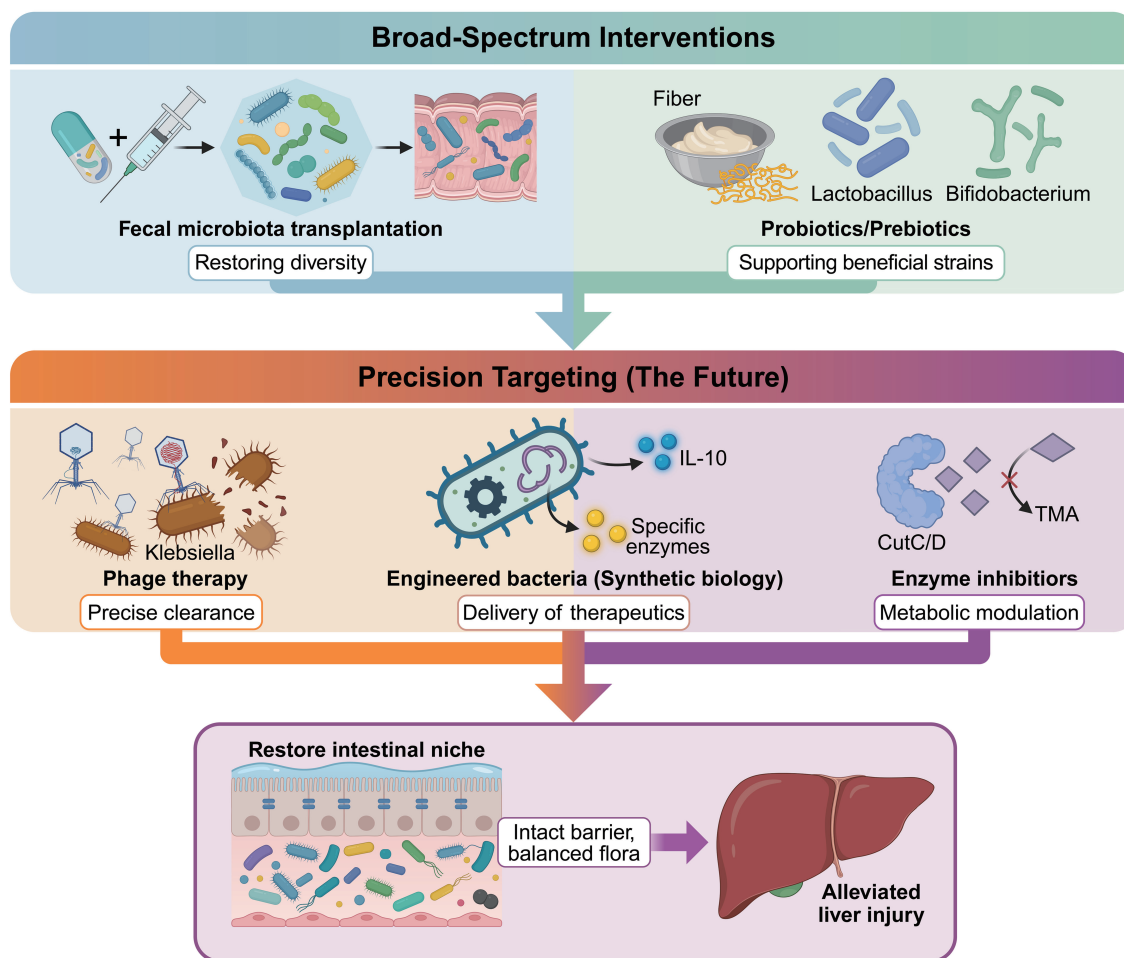


Fig. 3. Strategies for ecological niche remodeling: From broad-spectrum to precision targeting. This figure summarizes therapeutic approaches for modulating the intestinal niche. The upper section presents broad-spectrum interventions, including fecal microbiota transplantation to restore diversity and the use of probiotics and prebiotics to support beneficial strains. The middle section highlights future precision targeting strategies, such as phage therapy for the precise clearance of pathogens like *Klebsiella*, engineered bacteria for the synthetic delivery of therapeutic molecules (e.g., IL-10), and microbial enzyme inhibitors targeting pathways like CutC/D to reduce harmful metabolites such as TMA/TMAO. The bottom section depicts the therapeutic goal: a restored intestinal niche with an intact barrier and balanced flora, leading to alleviated liver injury. This figure was created with BioRender (<https://biorender.com/>). IL-10, interleukin-10; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

proved gut flora dysbiosis, increased beneficial flora, and reduced pathogenic bacteria.¹⁹ In cirrhosis patients, FMT also demonstrates potential for improving the gut barrier and clinical outcomes. For example, a study using vegan donor FMT for cirrhosis patients found it induced significant changes in gut flora (such as *Eubacterium siraeum* and *Blautia wexlerae*) and plasma metabolites (such as phenylacetylcarnitine) and affected hepatic DNA methylation profiles, suggesting FMT may act through multi-omics-level meta-organism pathways.²⁰⁹ In an acute liver failure mouse model, FMT significantly improved liver injury and inflammation by regulating gut flora composition and hepatic metabolites.²¹⁰ However, the efficacy of FMT is not universally consistent and faces significant challenges. A 12-week randomized controlled trial in patients with MASLD found that, compared to autologous FMT, allogenic FMT did not significantly reduce liver fat fraction or improve glucose tolerance; although patient fecal microbiota composition diverged, no microbial signatures clearly associated with treatment response were found, and colonization of donor flora presented donor specificity rather than efficacy specificity.¹⁴ In an ALD rat model, oral

FMT effectively reversed alcohol-induced liver injury by improving gut flora disorders and metabolic patterns.²¹¹ In a cirrhosis portal hypertension model, FMT improved visceral circulation and vascular reactivity, indicating microbial intervention may affect portal hypertension by regulating visceral circulation.²¹² In SAH patients, compared to corticosteroid treatment, FMT treatment altered the abundance of specific gut bacteria associated with alcohol relapse, such as *Pedobacter* genus and *Streptophyta* species, and non-relapsers had elevated levels of SCFA-producing bacterial taxa.²¹³ In cirrhosis patients, FMT improved intestinal mucosal mitochondrial oxidative phosphorylation function, thereby influencing the gut barrier.²¹⁴ In Budd-Chiari syndrome patients, mice transplanted with patient flora developed liver injury and gut flora dysbiosis, indicating that flora dysbiosis may lead to the disease through immune dysregulation.²¹⁵ In MAFLD patients, WMT improved hepatic fat deposition by regulating tongue coating microbial structure.²¹⁶ In an intrahepatic cholestasis of pregnancy mouse model, microbiota transplantation from patients induced the intrahepatic cholestasis of pregnancy phenotype, while Yinchenhao

Tang intervention partially restored flora balance.²¹⁷ In liver fibrosis macaques, significant differences existed in gut flora α - and β -diversity compared to normal macaques, with beneficial bacteria like *Lactobacillus* significantly reduced.²¹⁸ In Wilson's disease mice, healthy microbiota transplantation increased *Lactobacillus* abundance, reduced hepatic copper concentration, and alleviated liver injury.²¹⁹ In HCC mouse models, FMT from healthy donors alleviated intrahepatic metastasis promoted by dysbiotic flora.²²⁰ In an NAFLD mouse model, FMT from FGF21-treated mice produced improvement effects similar to FGF21 treatment.²²¹ In an NAFLD mouse model, FMT from silymarin-treated mice confirmed that changes in gut flora and their metabolites are the cause of NAFLD improvement.²²² In a MAFLD mouse model, FMT from patients supplemented with hydroxytyrosol improved the Western diet-induced MAFLD phenotype.²²³ In an ALD mouse model, FMT from urolithin A-treated mice achieved protective effects comparable to direct treatment.²²⁴ In drug-induced liver injury mice, FMT from *Codonopsis pilosula* polysaccharide-intervened mice alleviated liver injury.²²⁵ In APAP-induced liver injury mice, reconstruction of gut flora structure from *Broussonetia papyrifera* polysaccharide-treated mice effectively alleviated liver injury symptoms.²²⁶ In pseudo-germ-free MAFLD rats, the efficacy of receiving fecal microbiota from rats treated with Shenling Jianpiwei Granule was drastically reduced, indicating that the anti-MAFLD effect of this formula is largely gut microbiota-dependent.²²⁷ In antibiotic-induced pseudo-germ-free MAFLD rats, the efficacy of hawthorn ethanol extract was affected, revealing its action mediated by the gut microbiota.²²⁸ In CCl₄-induced liver fibrosis mice, FMT from metformin-treated mice alleviated liver fibrosis in recipient mice.²²⁹ In an NAFLD mouse model, FMT from mice treated with Ginsenoside Rg5 also demonstrated similar NAFLD improvement effects.²³⁰ In an NAFLD mouse model, FMT from mice treated with Tangshen formula confirmed the key role of gut flora in its efficacy.²³¹ In an NAFLD mouse model, FMT from mice treated with Qushi Huayu decoction confirmed that its induced gut flora remodeling partially mediated the efficacy.²³² In mice with antibiotic-cleared gut flora, vine tea extract lost its hepatoprotective effect, indicating its efficacy depends on the gut microbiota.²³³ However, in drug-induced liver injury mice, transplantation of fecal microbiota suspension from Sangyu Granule-treated mice did not produce a therapeutic effect.²³⁴ This highlights the core bottlenecks currently facing FMT: strong donor dependence, lack of standardization in preparation processes, complex and obscure mechanisms of action, and significant individual differences in efficacy. Compounding these clinical challenges is a significant translational barrier: current mechanistic studies rely heavily on commercialized cell lines and rodent models. The inherent discrepancies in immune-metabolic baselines, gastrointestinal anatomy, and foundational gut microbiota composition between these preclinical models and humans partially explain the inconsistent efficacies frequently observed in clinical trials.^{235,236}

Therefore, although the concept of FMT is highly attractive, its large-scale clinical application still needs to resolve key issues such as donor screening, preparation standardization, elucidation of mechanisms, and long-term safety assessment (Table 2).^{209–225,227,229–232,237–288} In direct response to the specific bottlenecks regarding preparation and safety, WMT has recently emerged as a standardized clinical evolution of traditional FMT. By employing automated purification systems and rigorous consensus-based protocols, WMT explicitly addresses the demands for preparation standardization and enhanced safety. This methodology effectively eliminates pro-inflammatory mediators and undigested

particles present in crude feces, thereby significantly reducing adverse events and improving clinical reproducibility. Consequently, WMT paves a promising pathway toward the large-scale, safe clinical application of microbiome interventions.^{289,290}

Evidence and strain specificity of probiotics in improving liver disease phenotypes

Probiotics regulate gut microecology by supplementing specific live beneficial bacteria and have accumulated extensive preclinical and partial clinical evidence in liver disease management, but their efficacy is highly dependent on strain specificity. In the field of NAFLD, multiple studies have confirmed the benefits of specific probiotic strains. For example, supplementation with *Bifidobacterium breve* CM02-09T can alleviate liver injury and fat accumulation in high-fat diet mice by reducing the Firmicutes/Bacteroidetes ratio, increasing beneficial bacteria abundance, and enhancing lipid metabolism function.²³⁹ *Lactobacillus plantarum* ZGHY combined with entecavir treatment for 24 weeks in chronic hepatitis B liver fibrosis patients effectively increased gut flora diversity, reduced potential pathogens (such as *Klebsiella* and *Enterococcus*), and simultaneously increased beneficial bacteria like *Bacteroides*, showing a positive role in assisting flora regulation.²⁴⁰ In ALD, the novel exopolysaccharide BVP1 from *Lactobacillus plantarum* CGMCC 24752 significantly improved hepatic steatosis and inflammation in mouse models by remodeling gut flora and fecal metabolite profiles and upregulating hepatocyte lipid degradation gene expression.²⁴¹ *Lactobacillus paracasei* N1115 supplementation for 12 weeks significantly increased gut microbial diversity in hepatitis B cirrhosis patients, improved liver function, and reduced inflammatory factor levels.²⁴² In a T2DM+HCC mouse model, *Lactobacillus brevis* intervention improved blood glucose and insulin resistance and delayed disease progression.²⁴³ In an NAFLD rat model, ZW3 probiotic improved liver injury and inflammation by regulating gut flora and inhibiting the TLR4-MyD88/JNK pathway.²⁴⁴ In a MAFLD mouse model, EcNI and EcNA intervention improved the recovery process, reducing liver fat and plasma cholesterol.²⁴⁵ In an NAFLD mouse model, T3L probiotic improved obesity-induced NAFLD by regulating gut–liver axis pathways.²⁴⁶ In an ALD rat model, fermented milk containing *Bifidobacterium animalis* subsp. *lactis* Probio-M8 effectively maintained gut flora stability and alleviated liver injury.²⁴⁷ In NAFLD children, probiotic intervention regulated gut flora and maintained gut barrier integrity, providing a potential strategy for treatment.²⁴⁸ In a MAFLD rat model, *Bifidobacterium* combined with rosuvastatin treatment regulated gut flora, promoted gastrointestinal emptying, and improved liver pathology and function better than monotherapy.²⁴⁹ In NAFLD patients, *Clostridium butyricum* capsules combined with rosuvastatin treatment improved efficacy and ameliorated gut flora imbalance.²⁵⁰ In an ALD mouse model, pretreatment with various lactic acid bacteria improved liver injury and gut flora dysbiosis, with JN-8 showing superior effects in improving hepatic antioxidant capacity.²⁵¹ Screened from 498 lactic acid bacteria strains, *Lactobacillus brevis* SR52-2 and *Lactobacillus delbrueckii* subsp. *bulgaricus* Q80 inhibited HBsAg and HBsAg expression *in vitro* and improved the gut microenvironment in a liver cancer group.²⁵² *Lacticaseibacillus paracasei* HP-B1337 showed good probiotic properties and was confirmed to effectively alleviate fatty liver disease in a mouse model.²⁵³ In an obese mouse model, *Lactobacillus plantarum* 1-2-3 alleviated obesity, glycolipid metabolism abnormalities, and liver injury by regulating the gut–liver axis.²⁵⁴ In an obese mouse model, *Lactobacillus plantarum* NCUH001046 and *Lactobacillus fermentum* alleviated obesity development by regulating the hepatic AMPK signaling pathway and

Table 2. Ecological niche remodeling strategies: Mechanisms, evidence, and limitations

Therapeutic strategy	Core mechanism	Key evidence & efficacy	Current limitations & challenges
Fecal microbiota transplantation (FMT) ^{209–225,227,229–232,237,238}	Holistically imports a healthy donor ecosystem to restore diversity and barrier function	High 90-day survival (87.5%) in severe alcoholic hepatitis. Improves portal hypertension and cognition in cirrhosis	Strong donor dependence; efficacy is not universally consistent (e.g., in MASLD); risk of pathogen transmission; lack of standardization
Probiotics ^{239–258}	Supplementing specific live beneficial bacteria to regulate microecology and immune response	<i>B. breve</i> reduces fat in NAFLD mice. <i>L. plantarum</i> combined with antivirals improves fibrosis	Efficacy is strain-specific. Some strains (e.g., <i>E. faecalis</i>) or high doses in severe disease may be harmful or ineffective
Prebiotics & synbiotics ^{259–276}	Dietary fibers act as substrates for beneficial bacteria to produce SCFAs; Synbiotics combine this with probiotics	Resistant starch reduces liver triglycerides by ~9% in NAFLD. Synbiotics reduce hepatic steatosis and inflammation	Effects depend on the patient's baseline flora (responders vs. non-responders); without weight loss, prebiotic efficacy may be limited
Phage therapy ^{277–279}	Specifically lyses target pathogenic bacteria without disrupting the broader community	Effectively targets alcohol-producing <i>Klebsiella pneumoniae</i> to alleviate steatohepatitis in mice	Narrow host range; potential for bacterial resistance; challenges in delivery to target sites
Microbial enzyme inhibitors ^{280–283}	Blocks production of harmful metabolites without killing bacteria	CutC/D inhibitors reduce TMAO generation. BSH regulation alters bile acid pools to improve NAFLD	Requires high specificity to avoid affecting host enzymes; ensuring effective intestinal concentration
Engineered bacteria ^{284–286}	Synthetic biology modification to deliver therapeutic molecules (e.g., IL-10, metabolites)	<i>Sporosolibacterium</i> pathways identified for insulin-sensitizing metabolites. Potential for tumor microenvironment modulation	Biosafety concerns (gene transfer, stability); ethical and regulatory hurdles regarding “live drugs”
Integrated/Combined therapy ^{287,288}	Synergizes microbiota modulation with standard care (drugs, surgery)	Improves antiviral efficacy (HBV). Sensitizes HCC to immunotherapy (overcoming resistance)	Requires precision stratification (multi-omics) to identify optimal combinations; lack of large-scale RCTs

BSH, bile salt hydrolase; FMT, fecal microbiota transplantation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IL-10, interleukin-10; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease; RCTs, randomized controlled trials; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide.

gut flora via the microbe-fat-liver axis.²⁵⁵ In an NAFLD mouse model, supplementation with Prohep probiotic mixture alleviated hepatic steatosis and prevented the progression from MAFLD to MASH.²⁵⁶ In an NAFLD mouse model, *Faecalibacterium prausnitzii* strains LC49 and LB8 had significant anti-NAFLD and flora-regulating effects.²⁵⁷ However, the efficacy of probiotics is not always positive. In SAH patients, high-dose probiotic infusion (containing four *Lactobacillus* and four *Bifidobacterium* species) had a 90-day survival rate (55%) even lower than corticosteroids and failed to significantly improve bacterial α -diversity, instead leading to an increase in pathogenic bacteria (such as *Bilophila* and *Roseburia*) and harmful expansion of fungal communities.¹⁹ Supplementation with commensal *Bacteroides fragilis* exacerbated NAFLD progression in high-fat diet mice, increasing hepatic lipid accumulation.²⁰ In children with obesity and NAFLD, isolated *Enterococcus faecalis* B6 and its metabolite tyramine significantly exacerbated NAFLD symptoms in mice.²⁵⁸ This warns us that probiotic interventions may produce vastly different or even harmful results depending on the disease background, strain combination, dosage, and route of administration. Therefore, future probiotic therapies must be based on a deep understanding of specific strain functions, host-microbe interactions, and the disease microenvironment, moving toward “strain-level” precision application.

Prebiotics and synbiotics modulating the gut–liver axis via dietary fibers

Prebiotics (mainly non-digestible dietary fibers) and synbiotics

(combinations of probiotics and prebiotics) indirectly remodel gut flora by providing selective fermentation substrates for beneficial host bacteria, representing a more sustainable and safer niche modulation strategy. Resistant starch, as a classic prebiotic, absolutely reduced intrahepatic triglyceride content by 9.08% after 12 weeks of intervention in NAFLD patients; its mechanism involves regulating gut flora (such as *Bacteroides stercoris*) and serum branched-chain amino acids, and causality was confirmed via mouse FMT.²⁵⁹ Synbiotic intervention also shows promise. A study on metabolically healthy men found that 12-week synbiotic intervention significantly reduced serum alanine aminotransferase levels, with a 20.70% reduction in the subgroup with elevated body fat percentage, and significant changes in gut microbiome composition occurred in this subgroup, suggesting synbiotics may exert hepatoprotective effects on specific populations by regulating gut flora.²⁶⁰ Another randomized controlled trial in MASLD patients showed that 12-week synbiotic intervention significantly reduced hepatic steatosis and enriched beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* in the gut, while reducing *Ruminococcus* and *Enterobacter*.²⁶¹ In an obese mouse model, synbiotic treatment containing *Lactobacillus acidophilus*, *Bifidobacterium infantis*, and konjac glucomannan oligosaccharides improved obesity, fatty liver, and gut flora dysbiosis.²⁶² Fructooligosaccharide treatment alleviated metabolic changes and hepatic steatosis in an NAFLD mouse model and remodeled gut flora structure.²⁶³ Flaxseed meal intervention for 12 weeks improved hepatic lipid deposition, body composition, and lipid metabolism

in NAFLD patients, and increased beneficial bacteria while reducing harmful bacteria by regulating gut flora.²⁶⁴ In long-term alcohol drinkers, a 60-day intervention regulated flora imbalance, increased beneficial bacteria abundance, and reduced opportunistic pathogens.²⁶⁵ In NAFLD patients, sulforaphane intervention increased GLP-1 levels, revealing a new pathway for alleviating insulin resistance through the gut flora-SCFA-GPR41/43-GLP1 axis.²⁶⁶ In MAFLD patients, butyrate supplementation had potential benefits for specific patient subgroups.²⁶⁷ In NAFLD patients, curcumin intervention reduced liver fat content, an effect associated with regulating gut flora-dependent bile acid metabolism and activating the TGR5 pathway.²⁶⁸ In type 2 diabetes patients with nonalcoholic fatty liver, exenatide combined with metformin treatment regulated gut flora while improving metabolism.²⁶⁹ In NAFLD patients, a Mediterranean diet combined with aerobic exercise intervention had a synergistic effect on gut microbiota composition.²⁷⁰ In NAFLD patients, the Dietary Index for Gut Microbiota was negatively correlated with NAFLD prevalence.²⁷¹ In MAFLD patients, daily consumption of 400 g “Navelina” oranges for 28 days identified specific flora and volatile organic compound combinations associated with MAFLD.²⁷² In NAFLD patients, a freshwater fish diet significantly reduced hepatic steatosis more than a diet alternating freshwater fish with red meat, and increased the enrichment of fecal SCFAs and unconjugated bile acids.²⁷³ In cirrhosis patients, intermittently replacing meat with vegetarian meals may help reduce ammonia production.²⁷⁴ However, the efficacy of prebiotics/synbiotics also has limitations and controversies. A study using inulin-type fructans to treat NAFLD patients for 12 weeks found that, although it increased fecal *Bifidobacterium* content, it failed to significantly reduce liver fat content or improve metabolic and inflammatory mediators, indicating that without weight loss, prebiotic intervention alone may be insufficient to improve NAFLD.²⁷⁵ In MAFLD patients, the beneficial effects of fish oil combined with vitamin D3 supplementation on nonalcoholic fatty liver may be partially attributed to its regulation of gut microbiota and fecal metabolites.²⁷⁶ In NAFLD patients, no significant association was observed between dietary n-6/n-3 fatty acid ratio and gut flora composition or disease severity.¹⁷² Additionally, the effect of prebiotics is highly dependent on the individual’s original gut flora structure, and the quantity and type of fermentation products (such as SCFAs) generated vary from person to person, which may lead to significant individual differences in efficacy. Therefore, developing personalized prebiotic/synbiotic formulas based on individual microbiome characteristics is a key direction for improving their efficacy and reliability.

Prebiotic-like components in traditional herbs and natural products

Many traditional herbs and natural food extracts are rich in polysaccharides, polyphenols, and other components. Although not prebiotics by traditional definition, these substances can exert significant “prebiotic-like” effects by regulating gut flora, providing rich resources for liver disease management. For example, hawthorn fruit polysaccharides alleviate NAFLD in mice by improving gut flora dysbiosis (affecting Lachnospiraceae and *Dubosiella*), increasing intestinal acetate levels, and subsequently correcting hepatic amino acid, lipid, and vitamin metabolic disorders; *in vitro* experiments confirmed no direct effect, highlighting the mechanism mediated by the gut–liver axis.²⁹¹ *In vitro* fermentation of kudzu starch specifically increased the abundance of *Lactobacillus*, *Bifidobacterium*, and *Turicibacter*, reduced *Desulfovibrio*, and alleviated inflammation and hepatic steatosis in an NAFLD

mouse model, supporting its use as a functional prebiotic.²⁹² Fuzhuan brick tea intervention significantly regulated gut flora (increasing *Blautia* and *Fusicatenibacter*, inhibiting *Prevotella*), affected SCFA, bile acid, and LPS levels, and improved hepatic steatosis and inflammation in NAFLD mice dependent on gut flora.²⁹³ Lingguizhugan decoction improved NAFLD by remodeling gut flora structure and metabolism, with flora-derived SCFAs and bile acids as potential mediators.²⁹⁴ Qushi Huayu formula exerted therapeutic effects by regulating specific gut flora and their metabolites.²⁹⁵ Honeysuckle-Cassia seed extract, after co-fermentation, had increased bioactive component content in its mixed bacterial fermentation broth and improved liver injury, oxidative stress, and gut flora dysbiosis in a mouse ALD model.²⁹⁶ Shenling Jianpiwei Granule improved MAFLD by restoring gut flora dysbiosis, and most of its anti-MAFLD effect was gut flora-dependent.²²⁷ Baoganning Decoction alleviated liver fibrosis by enriching beneficial bacteria and reducing pathogenic bacteria to remodel gut flora, while simultaneously regulating bile acid homeostasis.²⁹⁷ Saikosaponin improved fatty liver in laying hens by regulating the gut flora-bile acid-intestinal FXR axis pathway.²⁹⁸ Berberine improved fatty liver hemorrhagic syndrome in laying hens by remodeling gut flora.²⁹⁹ *Swertia* alleviated liver inflammation and injury by regulating oxidative stress and restoring gut flora.³⁰⁰ Jianggan Jiangzhi pill had good effects on treating NAFLD, and its mechanism may be closely related to improving gut flora dysbiosis.³⁰¹ Glycyrrhizic acid’s effect in improving NAFLD may be related to improving gut flora dysbiosis.³⁰² Ganfule capsule exerted anti-liver cancer effects via the microbe-metabolic axis.³⁰³ THSWD exerted anti-liver cancer effects via the gut flora-metabolite-lysosomal autophagy axis.³⁰⁴ Zhizi Chi Decoction alleviated liver inflammation and injury by regulating the microbe-gut–liver axis via pleiotropic mechanisms.³⁰⁵ These natural products usually contain diverse active ingredients, which may regulate microbe-host interactions through multi-target and multi-pathway synergistic effects. However, their complex composition, difficult quality control, and unclear mechanisms of action are bottlenecks restricting their standardization and widespread application. Future research needs to combine metabolomics, metagenomics, and culturomics technologies to elucidate their key active ingredients, specific microbial targets of action, and downstream host signaling pathways, thereby elevating them from empirical application to the level of precision intervention.

Ecological niche remodeling strategy ii: precision targeting—from specific strains, phages to microbial enzyme inhibitors

Isolation and application of specific beneficial strains

Going beyond broad-spectrum probiotics, isolating and applying specific bacterial strains with distinct hepatoprotective functions represents the frontier of precision niche remodeling. Multiple studies have successfully identified single strains with therapeutic potential. For example, a *Bacteroides eggerthii* strain isolated from healthy human feces significantly attenuated hepatic lipid peroxidation and lobular inflammation in a MASLD mouse model by improving gut flora disorders; although its improvement of hyperlipidemia and steatosis was limited, it suggests its potential as a biotherapeutic candidate.³⁰⁶ In an ALD model, a *Bacteroides acidifaciens* strain isolated from the gut of gentamicin-treated mice was confirmed to reduce CD95/CD95L-mediated hepatocyte apoptosis by inhibiting hepatocyte surface CD95 expression, thereby exerting protective effects against both Concanavalin A-

and alcohol-induced liver injury.³⁰⁷ In the field of NAFLD, the abundance of *B. theta* is positively correlated with the remission of metabolic syndrome; administering *B. theta* to high-fat diet mice regulated gut flora composition, increased gut–liver folate levels and hepatic polyunsaturated fatty acid ratio, thereby preventing hepatic steatohepatitis and liver injury.³⁰⁸ Furthermore, *Prevotella plebeius* isolated from healthy donor feces is significantly reduced in abundance in cirrhosis patients; supplementing this strain significantly improved phenotypes and biochemical indicators in flora-depleted cirrhosis models, exerting multifunctional biotherapeutic effects by downregulating the expression of genes related to liver inflammation, fibrosis, and hepatotoxicity.³⁰⁹ These studies provide a solid experimental basis for developing “live biotherapeutics” based on specific, culturable beneficial strains. Notably, in NAFLD patients, the abundance of *Adlercreutzia equolifaciens* decreases with disease progression and disappears in the end stage; its anti-inflammatory properties suggest that supplementing this bacterium may be a promising live biotherapeutic strategy.³¹⁰ Similarly, in MASLD patients, the relative abundance of *Bacteroides dorei* is negatively correlated with disease severity; its cell-free supernatant improved hepatic lipid accumulation and inflammation in animal models by increasing β -oxidation gene expression and inhibiting inflammatory responses, indicating it holds promise as a candidate for novel microbiome-based therapeutic strategies.³¹¹

Precision clearance of specific pathogens by phage therapy

Phage therapy, by specifically lysing target bacteria, offers a highly promising tool for precise deletion of pathogenic bacteria in the gut, avoiding the overall destruction of flora caused by broad-spectrum antibiotics. In NAFLD, high alcohol-producing *Klebsiella pneumoniae* was identified as a key pathogen. Phage therapy targeting this bacterium effectively alleviated steatohepatitis, improved liver function, and reduced the expression of inflammatory cytokines and lipogenic genes in mouse models, without causing significant pathological changes in liver/kidney function or gut flora composition, proving its efficacy and safety.²⁷⁷ In sensitizing HCC to immunotherapy, phage therapy also shows potential. Oncolytic virus VSV δ 51 treatment causes gut flora dysbiosis, reducing commensal *Lactobacillus*, thereby weakening efficacy; supplementing *Lactobacillus acidophilus* restored tumor sensitivity to VSV δ 51 by restoring the disrupted gut barrier and flora homeostasis, suggesting that targeting specific microbes (such as through phage modulation) may improve the efficacy of oncolytic virus therapies.²⁷⁸ Additionally, in MASLD patients, gut virome perturbations coexist with bacterial dysbiosis; the expansion of phages targeting typical oral bacteria corresponds to the expansion of their bacterial hosts in the gut, implying the possibility of using phages to regulate cross-kingdom microbial networks.¹⁶ Despite broad prospects, phage therapy still faces challenges, including narrow phage host ranges, potential rapid development of bacterial resistance, and how to safely and effectively deliver phages to target sites in the gut. Future development needs to combine metagenomics to identify key pathogens and develop targeted phage cocktail therapies to achieve precise clearance of specific harmful members in complex flora. For example, in MAFLD and steatohepatitis patients, *Mushu* phage was identified as a key hub species in disease pathogenesis, suggesting it may become a target for precision intervention.²⁷⁹

Building upon the concept of precision niche remodeling, CRISPR-armed bacteriophages represent a transformative frontier in microbiome engineering. Unlike conventional lytic phages that obligately kill their bacterial targets and may inadvertently per-

turb community dynamics, this advanced technology utilizes engineered phages as highly specific delivery vectors for CRISPR-Cas machinery or base editors.³¹² This enables in situ targeted silencing or excision of specific virulence factors and detrimental metabolic pathways without killing the host bacterium.³¹³ By selectively disarming pathogenic functions while preserving the host cell, CRISPR-phage therapy facilitates highly precise therapeutic modulation along the gut–liver axis while strictly maintaining overall microbiome stability and colonization resistance.

Intervention in harmful metabolic pathways by microbial enzyme inhibitors

Developing small molecule inhibitors against specific harmful metabolic enzymes encoded by gut microbes is a strategy for precision intervention at the functional level, aiming to block the production of pathogenic metabolites without directly affecting bacterial survival. TMA lyase (such as CutC/D) is a well-studied target, which converts dietary choline into TMA; TMA is then oxidized in the host liver to TMAO, which is associated with increased risks of fatty liver and cardiovascular disease. Developing CutC/D inhibitors to reduce TMAO generation at the source has shown potential to improve metabolic liver disease in preclinical models.³¹⁴ Another key target is microbial BSH. Excessive BSH activity leads to premature deconjugation of conjugated bile acids, affecting bile acid signaling. Studies found that Ginsenoside Re altered bile acid synthesis pathways by regulating microbial genera associated with BSH, thereby improving NAFLD; while antibiotic co-administration counteracted its effect, confirming the microbial dependence of its action.²⁸⁰ Similarly, nobiletin slowed the progression of MAFLD by increasing the abundance of BSH-producing bacteria, promoting bile acid excretion, and downregulating hepatic FXR signaling.²⁸¹ Furthermore, microbial D-lactate generation is also an intervention target. Oral administration of a biocompatible polymer that captures intestinal D-lactate and promotes its fecal excretion significantly improved metabolic phenotypes in obese and MASLD mice.⁸³ The advantage of these enzyme inhibitor strategies lies in their clear mechanism of action and potential to avoid drastic perturbations to flora structure. However, the challenge lies in ensuring inhibitor specificity (targeting only microbial enzymes without affecting host homologs), achieving effective concentration in the gut, and ensuring long-term safety. For example, in an NAFLD mouse model, the efficacy of obeticholic acid depends on the gut microbiota; its intervention significantly increased the abundance of beneficial bacteria like *Akkermansia muciniphila* and regulated the host bile acid pool, indicating that specific gut microbes mediated the alleviation effect of obeticholic acid by regulating host bile acid metabolism.²⁸² Similarly, in an NAFLD mouse model, the protective effect of fenofibrate on NAFLD depended on the TFEB-autophagy axis and significantly regulated gut flora composition.²⁸³

Engineered bacteria and metabolite delivery systems

Utilizing synthetic biology techniques to modify engineered bacteria so they can colonize the gut and continuously produce therapeutic molecules is a revolutionary strategy for precision-targeted therapy. For example, research revealed the pathway by which the common gut commensal *Sporosalibacterium* produces the metabolite 3-phenylpropionic acid, which possesses insulin-sensitizing and antisteatotic activities.²⁸⁴ This provides a blueprint for engineering this bacterium or other safe strains to stably and efficiently produce 3-phenylpropionic acid or other beneficial metabolites (such as IPA and butyrate). In HCC treatment, the ap-

plication of engineered bacteria also shows promise. Some studies plan to evaluate advanced HCC patients ineffective to immunotherapy receiving FMT from responders or healthy donors via colonoscopy to alter the tumor microenvironment and overcome drug resistance.²⁸⁵ Although this is not strictly engineered bacteria, it embodies the concept of utilizing microbes as therapeutic vectors or regulatory factors. A further strategy is to design “smart” engineered bacteria capable of sensing disease states (such as specific metabolites or pH changes) and responsively releasing therapeutic proteins (such as anti-inflammatory cytokines and enzyme inhibitors). For example, engineered bacteria can be designed to locally deliver IL-10 or TGF- β in the intestinal inflammatory environment to regulate hepatic immunity. However, engineered bacterial therapy faces severe biosafety, ethical, and regulatory challenges, including the stability of engineered bacteria *in vivo*, risks of horizontal gene transfer, immunogenicity, and controllable clearance from the body. Nevertheless, with advances in synthetic biology and microbiomics, engineered bacteria as “live drugs” have immeasurable potential in precisely regulating the gut–liver axis. For instance, the gut microbe *Rikenella microfus* promotes intestinal absorption of the isoflavone biochanin A through its β -galactosidase activity, thereby alleviating acute liver injury caused by acetaminophen overdose, revealing a new mechanism by which microbiome composition affects the severity of acute liver injury by regulating isoflavone absorption.²⁸⁶

Future prospects of multi-target precision combination strategies

Future precision niche remodeling will tend toward multi-target, personalized combination strategies to address complex microbial disturbances in liver diseases. This includes the organic integration of the different strategies mentioned above. For example, first using a phage cocktail to precisely clear identified key pathogens (such as ethanol-producing *Klebsiella pneumoniae*), followed by supplementing combinations of screened probiotic strains capable of producing specific beneficial metabolites (such as butyrate and indole-propionic acid) to fill the ecological niche and restore function. Concurrently, small molecule inhibitors targeting remaining harmful metabolic pathways (such as CutC/D inhibitors) can be administered. This combination of “subtraction” (clearing harmful bacteria) + “addition” (supplementing beneficial bacteria/functions) + “regulation” (inhibiting harmful functions) is expected to rebuild a healthy gut ecological niche more comprehensively and durably. Realizing this vision depends on advances in precision diagnostic technologies. It is necessary to integrate multi-omics data such as gut metagenomics, metatranscriptomics, and metabolomics, combined with machine learning, to map unique “microbe-metabolic dysfunction landscapes” for each patient, identifying key pathogens, defective beneficial bacteria, and dysregulated core metabolic pathways. On this basis, true individualized precision intervention plans can be formulated. For instance, for a MASLD patient characterized by enrichment of a specific pathogen and lack of SCFAs, the treatment plan might include phages targeting that pathogen, supplementation with specific butyrate-producing strains, and dietary guidance rich in fermentable fibers. This paradigm shift from “broad-spectrum” to “precision,” and from “flora composition” to “functional output,” will elevate ecological niche management of liver diseases to a completely new height, laying the foundation for achieving efficient and safe “targeted gut microbial niche” therapy. For example, in HCC patients, gut microbe-associated feature scores showed cancer-type-specific genomic alterations and immune microenvironment feature associations,

and can serve as potential clinical biomarkers for immunotherapy responsiveness and recurrence in multiple malignancies, providing a comprehensive framework for quantifying microbe-driven transcriptional activity and its clinical significance in cancer.²⁸⁷ Additionally, in a NASH mouse model, combined AFO-202 and N-163 treatment significantly increased gut microbial diversity, maximized Bacteroidetes abundance, and reduced Firmicutes abundance, exhibiting anticancer activity, suggesting the potential of combined intervention.²⁸⁸

Integrated intervention: Synergizing microbiota modulation with existing therapies

Synergistic potentiation of microbiota modulation and antiviral therapy

The synergistic effect of gut microbiota modulation and antiviral therapy for HBV has been preliminarily validated, with mechanisms involving improved immune response and restoration of metabolic homeostasis (Fig. 4). Research found that a gut flora profile dominated by *Bacteroides* is associated with a higher probability of undetectable plasma HBV-DNA, and patients in this flora cluster have higher plasma ursodeoxycholic acid levels and secondary bile acid biotransformation activity, suggesting specific flora structures may enhance antiviral efficacy through metabolite axes.¹⁹⁵ In terms of clinical intervention, Jianpi Shugan formula combined with lifestyle intervention for 12 weeks in NAFLD patients significantly improved liver function, liver stiffness, and glucolipid metabolism compared to lifestyle intervention alone; its efficacy was associated with up-regulating beneficial genera like *Coprococcus*, *Lachnospiraceae_NK4A136 group*, and *Ruminococcus*, revealing the potential of traditional Chinese medicine to treat NAFLD by regulating flora.³¹⁵ Notably, although tenofovir disoproxil fumarate treatment can significantly alter the gut flora of HBV-infected individuals, it failed to fully restore it to a healthy state, and serum inflammatory cytokine concentrations did not improve significantly, suggesting that treatment duration may affect flora recovery and inflammation remission.³¹⁶ In the field of HCV infection, after achieving viral clearance with direct-acting antivirals, some studies observed an increasing trend in gut flora α -diversity and a decreasing trend in potential pathogens (such as Enterobacteriaceae); this microbial improvement was more pronounced in patients without cirrhosis, indicating that viral eradication and partial recovery of gut microbiota may promote each other.³¹⁷ However, some studies also pointed out that chronic hepatitis C patients did not show significant gut flora dysbiosis, and curing HCV infection via direct-acting antivirals was not associated with significant changes in the gut microbiome.³¹⁸ In patients achieving sustained virologic response for HCV, the β -diversity of mucosa-associated microbiota, especially in the ascending colon, was associated with liver fibrosis progression, and multiple SCFA-producing genera were reduced in the ascending colon of cirrhosis patients.³¹⁹ These evidences collectively support the sequential or combined application of microbial modulation strategies such as probiotics, prebiotics, or traditional Chinese medicine with antiviral drugs to optimize viral clearance, alleviate liver inflammation, and improve long-term prognosis.

Microbiota modulation sensitizing HCC immunotherapy

The gut microbiota is a key regulator determining the response of HCC patients to ICI therapy, and flora-based intervention strategies are becoming new avenues to overcome immunotherapy resistance. Clinical observations found that HCC patients with

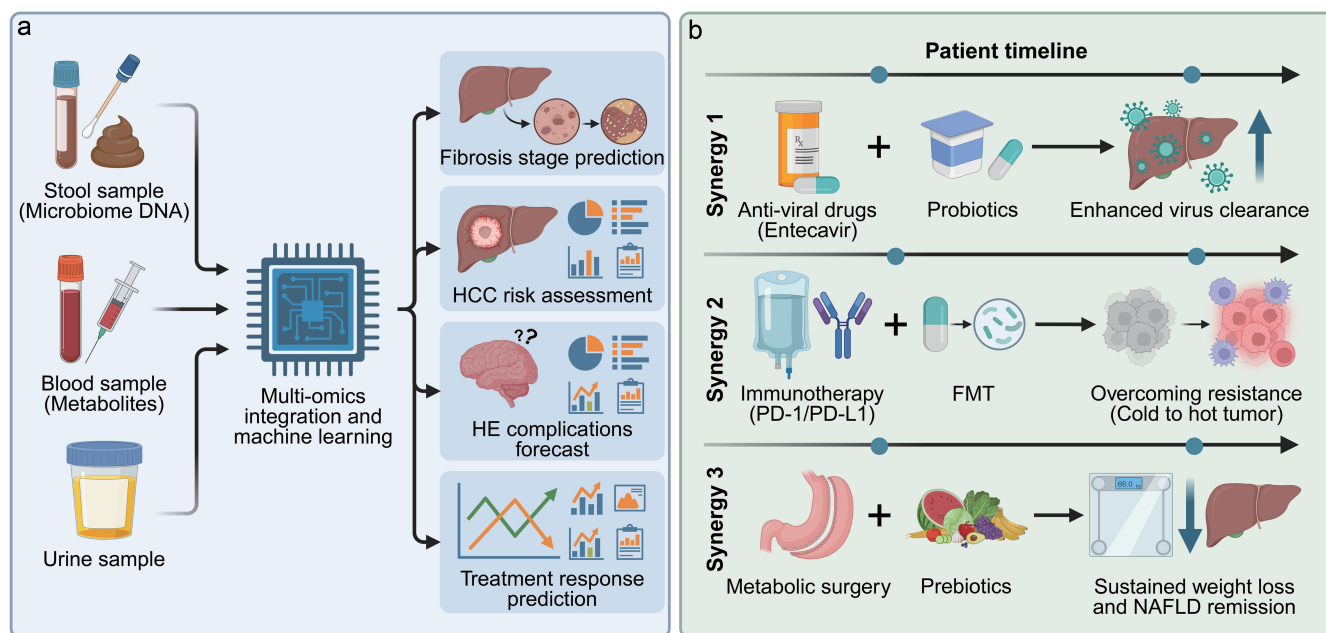


Fig. 4. Clinical translation: Microbiome as biomarkers and integrated therapy. This figure outlines the translational potential of the microbiome in liver disease management. Panel a demonstrates the use of non-invasive biomarkers derived from stool (microbiome DNA), blood (metabolites), and urine, integrated via multi-omics and machine learning to predict fibrosis stages, assess HCC risk, forecast complications like HE, and predict treatment responses. Panel b illustrates integrated intervention strategies that synergize microbiota modulation with standard therapies, including combining antivirals with probiotics to enhance viral clearance, using FMT to sensitize tumors to immunotherapy by overcoming resistance, and pairing metabolic surgery with prebiotics to sustain weight loss and NAFLD remission. This figure was created with BioRender (<https://biorender.com/>). FMT, fecal microbiota transplantation; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; NAFLD, nonalcoholic fatty liver disease; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1.

higher baseline gut flora α -diversity respond better to ICI therapy, and classifiers based on serum metabolites perform excellently in predicting potential beneficiaries of immunotherapy, providing a basis for patient stratification via microbial features before treatment.¹⁹⁴ Mechanistically, specific beneficial flora can shape a favorable tumor immune microenvironment. For example, in HCC mouse models, *Stigmastol* remodels gut flora, increases *Lactobacillus* abundance, leads to a decrease in the proportion of Tregs in the tumor microenvironment, and simultaneously increases the proportion of IFN- γ^+ CD8 $^+$ T cells with killing function, thereby enhancing antitumor immunity.⁹⁸ Clinical translational studies are underway; for instance, trials plan to evaluate advanced HCC patients ineffective to ICI receiving FMT from treatment responders or healthy donors via colonoscopy, aiming to alter the tumor microenvironment and overcome resistance.²⁸⁵ Additionally, traditional Chinese medicine also shows potential in sensitizing immunotherapy via flora modulation. Jiedu Granule treatment in advanced HCC patients significantly prolonged median overall survival and caused dose-dependent changes in gut flora, such as reducing *Peptostreptococcaceae* associated with liver carcinogenesis and maintaining *Akkermansia muciniphila* abundance associated with immunotherapy efficacy, revealing the potential microbial mechanism of its efficacy.³²⁰ Notably, significant differences exist in microbial communities in HCC tumor tissues, where the abundance of bacteria with antitumor effects like *Pseudomonadaceae* is reduced, and their reduction is linearly correlated with patient prognosis.³²¹ Meanwhile, significant microbial heterogeneity exists between multifocal tumor nodules in HCC, with specific bacterial communities enriched in metastatic clones, driving epithelial-mesenchymal transition and immune suppression.³²² These findings strongly support the combined or sequential treatment of

FMT, specific probiotics/synbiotics, or flora-regulating traditional Chinese medicines with ICIs to expand the beneficiary population of immunotherapy and enhance efficacy.

Synergistic action of microbiota modulation and metabolic surgery

The significant improvement of NAFLD by metabolic surgery (such as sleeve gastrectomy) is partly attributed to its remodeling of the gut microbiota, providing a theoretical basis for combined microbial intervention in the perioperative period. Studies found that six months after sleeve gastrectomy, clinical parameters of NAFLD patients improved significantly, while gut flora changed, including increases in beneficial bacteria like *Lactobacillus crispatus* and *Lactobacillus iners*, and decreases in harmful bacteria like *Erysipelotrichia*.³²³ Key mechanistic studies indicate that changes in gut flora of postoperative patients reduced glucose-dependent insulinotropic polypeptide (GIP) signaling; transplanting postoperative patient feces to antibiotic-treated mice effectively resisted diet-induced obesity and NAFLD, and this resistance was associated with reduced GIP levels in mice.³²⁴ Furthermore, the gut microbiome characteristics of patients with NAFLD remission after bariatric surgery manifested as higher abundance of *Bacteroides*, *Akkermansia*, and multiple genera of SCFA-producing *Clostridia* (such as *Blautia*, *Faecalibacterium*); these specific gut microbes and accompanying bile acid changes may jointly promote liver disease remission.³²⁵ Notably, patients after pancreaticoduodenectomy exhibit gut flora dysbiosis; at 6 months post-surgery, their β -diversity still differs significantly from healthy volunteers, and the abundance of *Lactobacillus gasseri* in patients developing fatty liver post-surgery is significantly lower than in healthy volunteers,

indicating that the occurrence of postoperative fatty liver may be related to significant differences in gut flora composition.³²⁶ These evidences suggest that actively applying prebiotics, probiotics, or synbiotics before and after metabolic surgery to further optimize and consolidate surgically induced favorable flora changes may produce synergistic effects, accelerating NAFLD reversal and preventing recurrence. For example, postoperative supplementation with polyphenol-rich prebiotics (such as Camu Camu) or specific probiotic strains may further increase beneficial bacterial colonization and promote SCFA production, thereby more effectively improving hepatic steatosis and metabolic disorders.³²⁷

Microbiota modulation assisting standard treatment for liver fibrosis and cirrhosis

In the management of liver fibrosis and cirrhosis, microbiota modulation can serve as an effective adjunct to antifibrotic drugs and complication prevention medications, improving disease progression through multi-target actions. Studies show that Biejiajian Pill combined with entecavir treatment for 48 weeks in hepatitis B cirrhosis/fibrosis patients resulted in a significantly higher liver fibrosis improvement rate than the control group using entecavir alone; its mechanism is closely related to regulating gut flora, increasing beneficial bacteria (*Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*) and reducing potential pathogens (*Escherichia*, *Bacteroides*, *Ruminococcus*).³²⁸ For cirrhosis complications, microbial modulation strategies demonstrate unique value. In the prevention and treatment of HE, probiotics, prebiotics, antibiotics, and FMT can all improve hyperammonemia and endotoxemia by regulating the gut microbiome.³²⁹ For instance, a randomized controlled trial showed that combined probiotic and prebiotic treatment for autoimmune hepatitis had effects comparable to prednisone with no adverse effects; its mechanism involved regulating flora composition, enhancing the gut barrier, and inhibiting TLR4/NF- κ B and NLRP3/Caspase-1 inflammatory pathways.³³⁰ Regarding infection prevention in cirrhosis patients, research found that diets rich in grains and yogurt are associated with higher microbial diversity, beneficial flora abundance, and lower 90-day hospitalization risk, suggesting dietary flora modulation as an adjunct strategy for infection prevention.³³¹ Notably, 12 months after splenectomy plus pericardial devascularization in chronic hepatitis B cirrhosis patients, gut flora composition restored to near healthy control levels, and liver function, intestinal permeability, and inflammation levels improved compared to pre-surgery, indicating that the improvement in liver function and intestinal permeability after splenectomy plus pericardial devascularization may be related to gut flora recovery.³³² For portal hypertension, the non-absorbable antibiotic rifaximin is a standard treatment, with partial efficacy derived from gut flora regulation. Studies found that although fructooligosaccharides did not affect portal pressure, they reduced hepatic vascular resistance in cirrhotic rats by improving gut flora dysbiosis and oxidative stress, offering new ideas for dietary intervention assisting blood pressure reduction.³³³ Therefore, integrating microbiota management (including dietary guidance, probiotics/prebiotics, selective intestinal decontamination) into the full-course treatment of liver fibrosis/cirrhosis is expected to synergize with existing therapies from multiple dimensions such as reducing pathogenic signal output, enhancing the gut barrier, and regulating immunity, delaying disease progression and improving patient quality of life.

Construction and future challenges of individualized integrated intervention strategies

Achieving optimal integration of microbiota modulation and exist-

ing liver disease therapies ultimately depends on developing individualized, dynamic intervention strategies, but this faces multiple challenges such as mechanistic complexity, efficacy prediction, and clinical translation. The core lies in establishing a precision stratification system based on multi-omics. By integrating patients' gut metagenomic, metabolomic, immunomic, and clinical data, specific "microbe-host" interaction patterns can be identified, thereby predicting their likely response to different interventions (such as specific probiotic strains, FMT donor types, dietary fiber types). For example, microbial network features centered on Ruminococcaceae and Christensenellaceae at baseline may be associated with future risk of decompensation events; such patients might initiate intensive flora intervention early.¹⁹¹ The timing of intervention is also crucial. For HCC patients planning to receive immunotherapy, flora "pre-conditioning" (such as using specific synbiotics) can be performed before treatment to shape a microenvironment conducive to immune response; for patients receiving antiviral therapy, simultaneous flora modulation can be conducted to alleviate liver inflammation and improve metabolism. However, most current evidence still comes from observational studies or small-scale clinical trials; large-scale, prospective, randomized controlled trials are urgently needed to verify the impact of integrated intervention strategies on hard clinical endpoints (such as liver cancer occurrence, cirrhosis decompensation, overall survival). For example, a randomized double-blind placebo-controlled trial targeting MASH patients aims to evaluate the efficacy of lyophilized fecal microbiota capsules combined with next-generation beneficial bacteria and oligofructose; its results will provide high-level evidence.³³⁴ Standardization issues are also prominent, including FMT donor screening and preparation standards, probiotic/prebiotic strain and dosage specifications, and intervention efficacy evaluation systems all need unification. In the future, with deeper understanding of gut–liver axis mechanisms and the popularization of microbiome testing technologies, liver disease treatment will truly enter a new era of "liver-gut combined therapy." Clinicians are expected to formulate integrated prescriptions containing "traditional liver-targeted drugs" and "personalized intestinal niche management plans" for each patient, thereby maximizing therapeutic benefits and achieving a fundamental shift from disease treatment to healthy ecological niche maintenance.

Limitations

Despite the significant advancements described in this review, several critical limitations in the current field of gut–liver axis research must be acknowledged. First, a vast majority of existing evidence is derived from cross-sectional clinical observations and animal models, which establish strong correlations but often fail to provide definitive proof of causality. Human microbiome studies are highly susceptible to confounding factors such as diet, genetics, and concomitant medications; thus, the complex relationship between microbiome shifts and liver pathology remains a fundamental challenge.²³⁶ Furthermore, the heavy reliance on commercialized cell lines and rodent models creates a significant translational barrier. The inherent discrepancies in immune-metabolic baselines, gastrointestinal anatomy, and foundational gut microbiota composition—exacerbated by behaviors like murine coprophagia—mean that preclinical mechanistic findings frequently fail to translate into consistent clinical efficacies.²³⁵

Second, the lack of universal standardization severely hinders the reproducibility and comparability of results. Variations at every methodological step, including sample collection, DNA extrac-

tion kits, sequencing platforms, and bioinformatic pipelines, can introduce substantial technical bias. Additionally, the current research focus remains predominantly on the bacteriome, frequently neglecting the critical roles of the mycobiome, virome, and their cross-kingdom interactions, which are essential for a holistic understanding of the intestinal ecosystem.¹⁶ Finally, there is a profound individual heterogeneity in response to microbiome-targeted therapies. The efficacy of broad-spectrum interventions is highly dependent on the recipient's baseline mucosal colonization resistance,³³⁵ highlighting the urgent need to transition toward personalized microbiome engineering.

Perspectives

Despite these insights, existing research is largely limited by observational associations, a lack of global standardization in microbiome analysis, and significant individual heterogeneity in response to broad-spectrum interventions like FMT. To advance the field toward "precision hepatology," future research must address several critical frontiers: Future studies should utilize Mendelian randomization, prospective longitudinal cohorts, and multi-omics integration combined with advanced spatiotemporal technologies. This will dynamically resolve the interactive evolution of the microbiome and host networks, identifying key functional modules driving disease turning points. Developing predictive machine-learning models that integrate microbial and metabolite features will be essential to guide precise patient stratification and tailor individualized therapies. Clinical focus should shift from broad interventions to targeted combinations, such as utilizing phage therapy to clear specific pathogens alongside supplementation with engineered beneficial metabolite-producing strains. Large-scale randomized controlled trials (RCTs) are urgently needed to validate these approaches. Establishing a robust, standardized system for microbial therapeutic products—covering donor screening, formulation preparation, and strict efficacy evaluation—is imperative for clinical translation. Ultimately, shifting the clinical paradigm from a singular "liver-targeted" approach to a holistic "liver–gut combined therapy" will pave the way for a new era of fundamental and effective precision management in liver diseases.

Conclusions

This review comprehensively elucidates the common features and etiology-specific patterns of gut microbiota dysbiosis across various liver diseases, ranging from MASLD and ALD to cirrhosis and HCC. The core consensus is that the gut microbiota is not merely a passive companion but a key active regulator of liver disease pathogenesis. Disruption of gut barrier integrity leads to the translocation of microbes and their products, accelerating disease progression. Concurrently, microbial metabolites critically modulate hepatic metabolism and host immunity via the gut–liver axis. Ultimately, these distinct gut microbiome signatures hold great potential as non-invasive biomarkers for diagnosis, prognosis, and therapeutic efficacy assessment, establishing intestinal niche modulation as a viable synergistic strategy with existing hepatology therapies.

Acknowledgments

The authors would like to thank the Organ Transplantation Center and the Key Laboratory of Organ Transplantation of the Affiliated Hospital of Qingdao University for support.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82370666), the Key R&D Program of Shandong Province, China (No. 2025KJHZ016), and the Science Foundation of Qingdao Science and Technology Bureau (No. 24-1-8-smjk-1-nsh).

Conflict of interest

XL has been an Editorial Board Member of *Journal of Translational Gastroenterology* since 2026. The authors declare no other conflicts of interest.

Author contributions

Research design (XL, KZ, FW, JC), literature search and evidence synthesis (XL, RD, PJ, XtW, GG, XW, CX, HL), and writing of the manuscript (XL, RD). All authors contributed to the article and approved the publication of the manuscript.

References

- [1] Manco R, Moliterni C, Neiryck G, Claus R, De Rudder M, Picalausa C, *et al*. Liver Sinusoidal Endothelial Cells and Laminin dictate cholangiocytes' fate in chronic liver disease. *J Hepatol* 2026. doi:10.1016/j.jhep.2026.03.022, PMID:41905508.
- [2] Fan Z, Li X, Jiang P, Teng D, Cai J. Diverse immunological roles of liver-resident immune cells in liver diseases. *Precis Med Sci* 2026;15(1):4–17. doi:10.1002/prm2.70026.
- [3] Wang Y, Li X, Shan J, Ding R, Cai J. Unraveling the role of anoikis in non-alcoholic fatty liver disease progression and immune cell infiltration. *Life Conflux* 2025;1(2):e129. doi:10.71321/p63ws623.
- [4] Sharma SP, Gupta H, Kwon GH, Lee SY, Song SH, Kim JS, *et al*. Gut microbiome and metabolome signatures in liver cirrhosis-related complications. *Clin Mol Hepatol* 2024;30(4):845–862. doi:10.3350/cmh.2024.0349, PMID:39048520.
- [5] Yan F, Zhang Q, Shi K, Zhang Y, Zhu B, Bi Y, *et al*. Gut microbiota dysbiosis with hepatitis B virus liver disease and association with immune response. *Front Cell Infect Microbiol* 2023;13:1152987. doi:10.3389/fcimb.2023.1152987, PMID:37201112.
- [6] Yang X, Wang J, Qi X, Hou M, Liu M, Xiao Y, *et al*. HLF and PPAR α axis regulates metabolic-associated fatty liver disease through extracellular vesicles derived from the intestinal microbiota. *Imeta* 2025;4(2):e70022. doi:10.1002/imt2.70022, PMID:40236774.
- [7] Wu Z, Zhou H, Liu D, Deng F. Alterations in the gut microbiota and the efficacy of adjuvant probiotic therapy in liver cirrhosis. *Front Cell Infect Microbiol* 2023;13:1218552. doi:10.3389/fcimb.2023.1218552, PMID:37483387.
- [8] Ganesan R, Gupta H, Jeong JJ, Sharma SP, Won SM, Oh KK, *et al*. Characteristics of microbiome-derived metabolomics according to the progression of alcoholic liver disease. *Hepatol Int* 2024;18(2):486–499. doi:10.1007/s12072-023-10518-9, PMID:37000389.
- [9] Eom JA, Jeong JJ, Han SH, Kwon GH, Lee KJ, Gupta H, *et al*. Gut-microbiota prompt activation of natural killer cell on alcoholic liver disease. *Gut Microbes* 2023;15(2):2281014. doi:10.1080/19490976.2023.2281014, PMID:37988132.
- [10] Carr RM, Li Y, Chau L, Friedman ES, Lee JJ, Adorini L, *et al*. An integrated analysis of fecal microbiome and metabolomic features distinguish non-cirrhotic NASH from healthy control populations. *Hepatology* 2023;78(6):1843–1857. doi:10.1097/HEP.0000000000000474, PMID:37222264.
- [11] Shen R, Ke L, Li Q, Dang X, Shen S, Shen J, *et al*. Abnormal bile acid-microbiota crosstalk promotes the development of hepatocellular carcinoma. *Hepatol Int* 2022;16(2):396–411. doi:10.1007/s12072-022-10299-7, PMID:35211843.
- [12] Luo M, Du Y, Liu X, Zhang S, Zhu W, Liu K, *et al*. Fecal microbiota

- transplantation alleviates cirrhotic portal hypertension in rats via butyrate-mediated HDAC3 inhibition and PI3K/Akt/eNOS signaling regulation. *Eur J Pharmacol* 2025;1002:177781. doi:10.1016/j.ejphar.2025.177781, PMID:40441587.
- [13] Li B, Liang X, Li Y, Wang R, Wei Y, Liu Q, *et al*. Tryptophan catabolites from microbiota ameliorate immune-mediated hepatitis through activating aryl hydrocarbon receptor of T cells. *Gut Microbes* 2025;17(1):2557979. doi:10.1080/19490976.2025.2557979, PMID:40995824.
 - [14] Groenewegen B, Ruissen MM, Crossette E, Menon R, Prince AL, Norman JM, *et al*. Consecutive fecal microbiota transplantation for metabolic dysfunction-associated steatotic liver disease: a randomized controlled trial. *Gut Microbes* 2025;17(1):2541035. doi:10.1080/19490976.2025.2541035, PMID:40755230.
 - [15] Demir M, Lang S, Hartmann P, Duan Y, Martin A, Miyamoto Y, *et al*. The fecal mycobiome in non-alcoholic fatty liver disease. *J Hepatol* 2022;76(4):788–799. doi:10.1016/j.jhep.2021.11.029, PMID:34896404.
 - [16] Kim H, Nelson P, Nzabarushimana E, Shen J, Jensen J, Bhosle A, *et al*. Multi-omic analysis reveals transkingdom gut dysbiosis in metabolic dysfunction-associated steatotic liver disease. *Nat Metab* 2025;7(7):1476–1492. doi:10.1038/s42255-025-01318-6, PMID:40604156.
 - [17] Kang BE, Park A, Yang H, Jo Y, Oh TG, Jeong SM, *et al*. Machine learning-derived gut microbiome signature predicts fatty liver disease in the presence of insulin resistance. *Sci Rep* 2022;12(1):21842. doi:10.1038/s41598-022-26102-4, PMID:36528695.
 - [18] Yang J, He Q, Lu F, Chen K, Ni Z, Wang H, *et al*. A distinct microbiota signature precedes the clinical diagnosis of hepatocellular carcinoma. *Gut Microbes* 2023;15(1):2201159. doi:10.1080/19490976.2023.2201159, PMID:37089022.
 - [19] Philips CA, Ahamed R, Oommen TT, Nahaz N, Tharakan A, Rajesh S, *et al*. Clinical outcomes and associated bacterial and fungal microbiota changes after high dose probiotic therapy for severe alcohol-associated hepatitis: An observational study. *Medicine (Baltimore)* 2024;103(45):e40429. doi:10.1097/MD.0000000000004029, PMID:39533632.
 - [20] Huang Y, Cao J, Zhu M, Wang Z, Jin Z, Xiong Z. *Bacteroides fragilis* aggravates high-fat diet-induced non-alcoholic fatty liver disease by regulating lipid metabolism and remodeling gut microbiota. *Microbiol Spectr* 2024;12(4):e0339323. doi:10.1128/spectrum.03393-23, PMID:38411057.
 - [21] Effenberger M, Waschina S, Bronowski C, Sturm G, Tassiello O, Sommer F, *et al*. A gut bacterial signature in blood and liver tissue characterizes cirrhosis and hepatocellular carcinoma. *Hepatol Commun* 2023;7(7):e00182. doi:10.1097/HC9.0000000000000182, PMID:37314752.
 - [22] Yang C, Wu J, Yang L, Hu Q, Li L, Yang Y, *et al*. Altered gut microbial profile accompanied by abnormal short chain fatty acid metabolism exacerbates nonalcoholic fatty liver disease progression. *Sci Rep* 2024;14(1):22385. doi:10.1038/s41598-024-72909-8, PMID:39333290.
 - [23] Dinçer S, Ülger Y, Delik A. Mucosal microbiota signatures reveal diagnostic insights in chronic liver disease. *BMC Gastroenterol* 2025;25(1):607. doi:10.1186/s12876-025-04204-3, PMID:40841874.
 - [24] Schneider KM, Mohs A, Gui W, Galvez EJC, Candels LS, Hoenicke L, *et al*. Imbalanced gut microbiota fuels hepatocellular carcinoma development by shaping the hepatic inflammatory microenvironment. *Nat Commun* 2022;13(1):3964. doi:10.1038/s41467-022-31312-5, PMID:35803930.
 - [25] Zhao S, Zhang H, Zhu H, Zhao T, Tu J, Yin X, *et al*. Gut microbiota promotes macrophage M1 polarization in hepatic sinusoidal obstruction syndrome via regulating intestinal barrier function mediated by butyrate. *Gut Microbes* 2024;16(1):2377567. doi:10.1080/19490976.2024.2377567, PMID:39012957.
 - [26] Tashkent Y, Choo JM, Richard A, Wang Z, Calzadilla-Bertot L, Vasil E, *et al*. Steatotic Liver Disease in Younger Adults is Associated With Altered Gut Microbiology. *Liver Int* 2025;45(3):e70032. doi:10.1111/liv.70032, PMID:39999013.
 - [27] Efremova I, Maslennikov R, Poluektova E, Medvedev O, Kudryavtseva A, Krasnov G, *et al*. Gut Microbiota and Biomarkers of Endothelial Dysfunction in Cirrhosis. *Int J Mol Sci* 2024;25(4):1988. doi:10.3390/ijms25041988, PMID:38396668.
 - [28] Zhu X, Cai J, Wang Y, Liu X, Chen X, Wang H, *et al*. A High-Fat Diet Increases the Characteristics of Gut Microbial Composition and the Intestinal Damage Associated with Non-Alcoholic Fatty Liver Disease. *Int J Mol Sci* 2023;24(23):16733. doi:10.3390/ijms242316733, PMID:38069055.
 - [29] Pinanga YD, Pyo KH, Shin EA, Lee H, Lee EH, Kim W, *et al*. Association between hepatocyte TM4SF5 expression and gut microbiome dysbiosis during non-alcoholic fatty liver disease development. *Life Sci* 2024;358:123164. doi:10.1016/j.lfs.2024.123164, PMID:39454995.
 - [30] Yang C, Xu J, Xu X, Xu W, Tong B, Wang S, *et al*. Characteristics of gut microbiota in patients with metabolic associated fatty liver disease. *Sci Rep* 2023;13(1):9988. doi:10.1038/s41598-023-37163-4, PMID:37340081.
 - [31] Chuaypen N, Asumpinawong A, Sawangsri P, Khamjerm J, Iadsee N, Jinato T, *et al*. Gut Microbiota in Patients with Non-Alcoholic Fatty Liver Disease without Type 2 Diabetes: Stratified by Body Mass Index. *Int J Mol Sci* 2024;25(3):1807. doi:10.3390/ijms25031807, PMID:38339096.
 - [32] Zheng R, Xiang X, Shi Y, Xie J, Xing L, Zhang T, *et al*. Gut microbiota and mycobiota change with feeding duration in mice on a high-fat and high-fructose diet. *BMC Microbiol* 2024;24(1):504. doi:10.1186/s12866-024-03663-0, PMID:39609794.
 - [33] Wu W, Kaicen W, Bian X, Yang L, Ding S, Li Y, *et al*. Akkermansia muciniphila alleviates high-fat-diet-related metabolic-associated fatty liver disease by modulating gut microbiota and bile acids. *Microb Biotechnol* 2023;16(10):1924–1939. doi:10.1111/1751-7915.14293, PMID:37377410.
 - [34] Hu Y, Hu X, Jiang L, Luo J, Huang J, Sun Y, *et al*. Microbiome and metabolomics reveal the effect of gut microbiota on liver regeneration of fatty liver disease. *EBioMedicine* 2025;111:105482. doi:10.1016/j.ebiom.2024.105482, PMID:39644773.
 - [35] Wu XQ, Ying F, Chung KPS, Leung CON, Leung RWH, So KKH, *et al*. Intestinal Akkermansia muciniphila complements the efficacy of PD1 therapy in MAFLD-related hepatocellular carcinoma. *Cell Rep Med* 2025;6(1):101900. doi:10.1016/j.xcrm.2024.101900, PMID:39798567.
 - [36] Leung H, Long X, Ni Y, Qian L, Nychas E, Siliceo SL, *et al*. Risk assessment with gut microbiome and metabolite markers in NAFLD development. *Sci Transl Med* 2022;14(648):eabk0855. doi:10.1126/scitranslmed.abk0855, PMID:35675435.
 - [37] Nychas E, Marfil-Sánchez A, Chen X, Mirhakkak M, Li H, Jia W, *et al*. Discovery of robust and highly specific microbiome signatures of non-alcoholic fatty liver disease. *Microbiome* 2025;13(1):10. doi:10.1186/s40168-024-01990-y, PMID:39810263.
 - [38] Mogna-Peláez P, Riezu-Boj JI, Milagro FI, Clemente-Llarramendi I, Esteban Echeverría S, Herrero JI, *et al*. Sex-Dependent Gut Microbiota Features and Functional Signatures in Metabolic Dysfunction-Associated Steatotic Liver Disease. *Nutrients* 2024;16(23):4198. doi:10.3390/nu16234198, PMID:39683591.
 - [39] Liu Y, Méric G, Havulinna AS, Teo SM, Åberg F, Ruuskanen M, *et al*. Early prediction of incident liver disease using conventional risk factors and gut-microbiome-augmented gradient boosting. *Cell Metab* 2022;34(5):719–730.e4. doi:10.1016/j.cmet.2022.03.002, PMID:35354069.
 - [40] Zheng C, Lu F, Chen B, Yang J, Yu H, Wang D, *et al*. Gut microbiome as a biomarker for predicting early recurrence of HBV-related hepatocellular carcinoma. *Cancer Sci* 2023;114(12):4717–4731. doi:10.1111/cas.15983, PMID:37778742.
 - [41] Purohit A, Alam MJ, Kandiyal B, Shalimar, Das B, Banerjee SK. Gut microbiome and non-alcoholic fatty liver disease. *Prog Mol Biol Transl Sci* 2022;191(1):187–206. doi:10.1016/bs.pmbts.2022.07.004, PMID:36270678.
 - [42] Mrdjen M, Huang E, Pathak V, Bellar A, Welch N, Dasarathy J, *et al*. Dysregulated meta-organismal metabolism of aromatic amino acids in alcohol-associated liver disease. *Hepatol Commun* 2023;7(11):e0284. doi:10.1097/HC9.0000000000000284, PMID:37820283.
 - [43] Yang Y, Duan Y, Lang S, Fondevila MF, Schöler D, Harberts A, *et al*. Targeted inhibition of pathobiont virulence factor mitigates alcohol-associated liver disease. *Cell Host Microbe* 2025;33(6):957–972.e6.

- doi:10.1016/j.chom.2025.05.003, PMID:40441146.
- [44] Helsley RN, Miyata T, Kadam A, Varadharajan V, Sangwan N, Huang EC, *et al.* Gut microbial trimethylamine is elevated in alcohol-associated hepatitis and contributes to ethanol-induced liver injury in mice. *Elife* 2022;11:e76554. doi:10.7554/eLife.76554, PMID:35084335.
- [45] Shen H, Zhou L, Yang Y, Shu H, Wu D, Yang S, *et al.* The gut microbiota-produced vitamin B6 mitigates alcohol-associated liver disease by attenuating hepatic oxidative stress damage. *Hepatol Commun* 2025;9(1):e0599. doi:10.1097/HC9.000000000000599, PMID:39670862.
- [46] Ferrell JM, Dilts M, Pokhrel S, Stahl Z, Boehme S, Wang X, *et al.* Fibroblast Growth Factor 19 Alters Bile Acids to Induce Dysbiosis in Mice With Alcohol-Induced Liver Disease. *Cell Mol Gastroenterol Hepatol* 2024;18(1):71–87. doi:10.1016/j.jcmgh.2024.02.015, PMID:38417701.
- [47] Hua X, Feng H. Changes in intestinal microbiota of HBV-associated liver cirrhosis with/without hepatic encephalopathy. *Medicine (Baltimore)* 2022;101(33):e29935. doi:10.1097/MD.00000000000029935, PMID:35984175.
- [48] Wang F, Wu Y, Ni J, Xie Q, Shen J, Chen H, *et al.* Gut microbiota links to histological damage in chronic HBV infection patients and aggravates fibrosis via fecal microbiota transplantation in mice. *Microbiol Spectr* 2025;13(8):e0076425. doi:10.1128/spectrum.00764-25, PMID:40642988.
- [49] Lee S, Arefaine B, Begum N, Stamouli M, Witherden E, Mohamad M, *et al.* Oral-gut microbiome interactions in advanced cirrhosis: characterisation of pathogenic enterotypes and salivatypes, virulence factors and antimicrobial resistance. *J Hepatol* 2025;82(4):622–633. doi:10.1016/j.jhep.2024.09.046, PMID:39447963.
- [50] He X, Hu M, Xu Y, Xia F, Tan Y, Wang Y, *et al.* The gut-brain axis underlying hepatic encephalopathy in liver cirrhosis. *Nat Med* 2025;31(2):627–638. doi:10.1038/s41591-024-03405-9, PMID:39779925.
- [51] Buttler L, Velázquez-Ramírez DA, Tiede A, Conradi AM, Woltemate S, Geffers R, *et al.* Distinct clusters of bacterial and fungal microbiota in end-stage liver cirrhosis correlate with antibiotic treatment, intestinal barrier impairment, and systemic inflammation. *Gut Microbes* 2025;17(1):2487209. doi:10.1080/19490976.2025.2487209, PMID:40255076.
- [52] Gedgaudas R, Bajaj JS, Skieceviciene J, Varkalaite G, Jurkeviciute G, Gelman S, *et al.* Circulating microbiome in patients with portal hypertension. *Gut Microbes* 2022;14(1):2029674. doi:10.1080/19490976.2022.2029674, PMID:35130114.
- [53] Shen Y, Wu SD, Chen Y, Li XY, Zhu Q, Nakayama K, *et al.* Alterations in gut microbiome and metabolomics in chronic hepatitis B infection-associated liver disease and their impact on peripheral immune response. *Gut Microbes* 2023;15(1):2155018. doi:10.1080/19490976.2022.2155018, PMID:36519342.
- [54] Shi K, Sun L, Feng Y, Wang X. Distinct gut microbiota and metabolic profiles in HBV-related liver cirrhosis: insights into disease progression. *Front Cell Infect Microbiol* 2025;15:1560564. doi:10.3389/fcimb.2025.1560564, PMID:40458519.
- [55] Jinato T, Anuntakarun S, Sathawiwat N, Chuaypen N, Tangkijvanich P. Distinct alterations of gut microbiota between viral- and non-viral-related hepatocellular carcinoma. *Appl Microbiol Biotechnol* 2024;108(1):34. doi:10.1007/s00253-023-12845-1, PMID:38183473.
- [56] Huo R, Chen Y, Li J, Xu Q, Guo J, Xu H, *et al.* Altered Gut Microbiota Composition and Its Potential Association in Patients with Advanced Hepatocellular Carcinoma. *Curr Oncol* 2023;30(2):1818–1830. doi:10.3390/curroncol30020141, PMID:36826102.
- [57] Lee PC, Wu CJ, Hung YW, Lee CJ, Chi CT, Lee IC, *et al.* Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. *J Immunother Cancer* 2022;10(6):e004779. doi:10.1136/jitc-2022-004779, PMID:35738801.
- [58] Kang YB, Cai Y. Future prospect of "Gut microbiome composition can predict the response to nivolumab in advanced hepatocellular carcinoma patients". *World J Gastroenterol* 2022;28(20):2248–2250. doi:10.3748/wjg.v28.i20.2248, PMID:35721889.
- [59] Liu B, Zhou Z, Jin Y, Lu J, Feng D, Peng R, *et al.* Hepatic stellate cell activation and senescence induced by intrahepatic microbiota disturbances drive progression of liver cirrhosis toward hepatocellular carcinoma. *J Immunother Cancer* 2022;10(1):e003069. doi:10.1136/jitc-2021-003069, PMID:34996812.
- [60] Sun L, Ke X, Guan A, Jin B, Qu J, Wang Y, *et al.* Intratumoural microbiome can predict the prognosis of hepatocellular carcinoma after surgery. *Clin Transl Med* 2023;13(7):e1331. doi:10.1002/ctm2.1331, PMID:37462602.
- [61] Jiang F, Dang Y, Zhang Z, Yan Y, Wang Y, Chen Y, *et al.* Association of intratumoral microbiome diversity with hepatocellular carcinoma prognosis. *mSystems* 2025;10(1):e0076524. doi:10.1128/msystems.00765-24, PMID:39660866.
- [62] Jo HE, Khom S, Lee S, Cho SH, Park SY, You GR, *et al.* Stage dependent microbial dynamics in hepatocellular carcinoma and adjacent normal liver tissues. *Sci Rep* 2024;14(1):26092. doi:10.1038/s41598-024-77260-6, PMID:39478014.
- [63] Meijnikman AS, Davids M, Herrema H, Aydin O, Tremaroli V, Rios-Morales M, *et al.* Microbiome-derived ethanol in nonalcoholic fatty liver disease. *Nat Med* 2022;28(10):2100–2106. doi:10.1038/s41591-022-02016-6, PMID:36216942.
- [64] Zhu SJ, Ding Z. Association between gut microbiota and seven gastrointestinal diseases: A Mendelian randomized study. *J Gene Med* 2024;26(1):e3623. doi:10.1002/jgm.3623, PMID:37957025.
- [65] Zhai Y, Zhou W, Yan X, Qiao Y, Guan L, Zhang Z, *et al.* Astragaloside IV ameliorates diet-induced hepatic steatosis in obese mice by inhibiting intestinal FXR via intestinal flora remodeling. *Phytomedicine* 2022;107:154444. doi:10.1016/j.phymed.2022.154444, PMID:36155217.
- [66] Li X, Zhao W, Xiao M, Yu L, Chen Q, Hu X, *et al.* *Penthorum chinense* Pursh. extract attenuates non-alcoholic fatty liver disease by regulating gut microbiota and bile acid metabolism in mice. *J Ethnopharmacol* 2022;294:115333. doi:10.1016/j.jep.2022.115333, PMID:35500802.
- [67] Nie Q, Luo X, Wang K, Ding Y, Jia S, Zhao Q, *et al.* Gut symbionts alleviate MASH through a secondary bile acid biosynthetic pathway. *Cell* 2024;187(11):2717–2734.e33. doi:10.1016/j.cell.2024.03.034, PMID:38653239.
- [68] Wang Y, Chen YF, Cong YX, Wang YP, Liu P, Du YP, *et al.* n - 3 polyunsaturated fatty acids mediate hydoxycholeic acid-FXR signaling to ameliorate metabolic dysfunction-associated fatty liver disease. *J Nutr Biochem* 2026;147:110136. doi:10.1016/j.jnutbio.2025.110136, PMID:41045973.
- [69] Huang Y, Chen H, Chen J, Wu Q, Zhang W, Li D, *et al.* Yellow tea polysaccharides protect against non-alcoholic fatty liver disease via regulation of gut microbiota and bile acid metabolism in mice. *Phytomedicine* 2024;133:155919. doi:10.1016/j.phymed.2024.155919, PMID:39153277.
- [70] Inoue T, Funatsu Y, Ohnishi M, Isogawa M, Kawashima K, Tanaka M, *et al.* Bile acid dysmetabolism in the gut-microbiota-liver axis under hepatitis C virus infection. *Liver Int* 2022;42(1):124–134. doi:10.1111/liv.15041, PMID:34411400.
- [71] Song Q, Zhang X, Liu W, Wei H, Liang W, Zhou Y, *et al.* Bifidobacterium pseudolongum-generated acetate suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma. *J Hepatol* 2023;79(6):1352–1365. doi:10.1016/j.jhep.2023.07.005, PMID:37459922.
- [72] Dong H, Yang X, Zhou Y, Yang M, Zhang H, Liu X, *et al.* Kudzu resistant starch effectively ameliorates non-alcoholic fatty liver disease by protecting the gut microbiota intestinal barrier and suppressing inflammatory responses. *J Sci Food Agric* 2025;105(12):6538–6555. doi:10.1002/jsfa.14371, PMID:40557534.
- [73] Honda T, Ishigami M, Ishizu Y, Imai N, Ito T, Yamamoto K, *et al.* Gut microbes associated with functional cure of chronic hepatitis B. *Hepatol Int* 2025;19(3):519–528. doi:10.1007/s12072-025-10776-9, PMID:39869245.
- [74] Yi G, Sun W, Zhang X, Wang Z, Yu X, Zhu C, *et al.* Soybean genistin-driven gut microbiota-derived butyrate synthesis activates the SIRT1 signaling pathway to ameliorate metabolic fatty liver. *Free Radic Biol Med* 2025;239:336–351. doi:10.1016/j.freeradbiomed.2025.07.053, PMID:40752635.
- [75] Dissayabuttra T, Chuaypen N, Somnark P, Boonkaew B, Udomkarnjananon S, Kittiskulnam P, *et al.* Characterization of gut dysbiosis and intestinal barrier dysfunction in patients with metabolic dysfunction-associated steatotic liver disease and chronic kidney disease: a com-

- parative study. *Sci Rep* 2025;15(1):15481. doi:10.1038/s41598-025-00237-6, PMID:40319096.
- [76] Silva RSD, Mendonça IP, Paiva IHR, Souza JRB, Peixoto CA. Fructooligosaccharides and galactooligosaccharides improve hepatic steatosis via gut microbiota-brain axis modulation. *Int J Food Sci Nutr* 2023;74(7):760–780. doi:10.1080/09637486.2023.2262779, PMID:37771001.
- [77] Pandey SP, Bender MJ, McPherson AC, Phelps CM, Sanchez LM, Rana M, *et al*. Tet2 deficiency drives liver microbiome dysbiosis triggering Tc1 cell autoimmune hepatitis. *Cell Host Microbe* 2022;30(7):1003–1019.e10. doi:10.1016/j.chom.2022.05.006, PMID:35658976.
- [78] Chen W, Wen L, Bao Y, Tang Z, Zhao J, Zhang X, *et al*. Gut flora disequilibrium promotes the initiation of liver cancer by modulating tryptophan metabolism and up-regulating SREBP2. *Proc Natl Acad Sci U S A* 2022;119(52):e2203894119. doi:10.1073/pnas.2203894119, PMID:36534812.
- [79] Zhao C, Bao L, Shan R, Zhao Y, Wu K, Shang S, *et al*. Maternal Gut Inflammation Aggravates Acute Liver Failure Through Facilitating Ferroptosis via Altering Gut Microbial Metabolism in Offspring. *Adv Sci (Weinh)* 2025;12(9):e2411985. doi:10.1002/advs.202411985, PMID:39808540.
- [80] Song TY, Yang XF, Wang JY, Yin LH, Zhao XR, Wang N, *et al*. Gut microbiota-based metabolism contributes to the protection of pseudolaric acid B against NAFLD. *Phytomedicine* 2025;147:157235. doi:10.1016/j.phymed.2025.157235, PMID:40929883.
- [81] Ding FF, Zhou NN, Mao YJ, Yang J, Limbu SM, Galindo-Villegas J, *et al*. Lactiplantibacillus plantarum attenuate gossypol-induced hepatic lipotoxicity by altering intestinal microbiota for enriching microbial tryptophan metabolites in Nile tilapia (*Oreochromis niloticus*). *Microbiome* 2025;13(1):180. doi:10.1186/s40168-025-02172-0, PMID:40759977.
- [82] Cheng WT, Pei SY, Wu J, Wang YJ, Yang YW, Xiao MF, *et al*. Cannabinoid-2 receptor depletion promotes non-alcoholic fatty liver disease in mice via disturbing gut microbiota and tryptophan metabolism. *Acta Pharmacol Sin* 2025;46(6):1676–1691. doi:10.1038/s41401-025-01495-w, PMID:39979552.
- [83] Fang H, Anhê FF, Zada DK, Barra NG, E-Lacerda RR, McAlpin BT, *et al*. Gut substrate trap of D-lactate from microbiota improves blood glucose and fatty liver disease in obese mice. *Cell Metab* 2025;37(9):1806–1819.e7. doi:10.1016/j.cmet.2025.07.001, PMID:40738110.
- [84] Li C, Wang F, Mao Y, Ma Y, Guo Y. Multi-omics reveals the mechanism of Trimethylamine N-oxide derived from gut microbiota inducing liver fatty of dairy cows. *BMC Genomics* 2025;26(1):10. doi:10.1186/s12864-024-11067-7, PMID:39762777.
- [85] Nian F, Zhu C, Jin N, Xia Q, Wu L, Lu X. Gut microbiota metabolite TMAO promoted lipid deposition and fibrosis process via KRT17 in fatty liver cells in vitro. *Biochem Biophys Res Commun* 2023;669:134–142. doi:10.1016/j.bbrc.2023.05.041, PMID:37271025.
- [86] Yang M, Qi X, Li N, Kaifi JT, Chen S, Wheeler AA, *et al*. Western diet contributes to the pathogenesis of non-alcoholic steatohepatitis in male mice via remodeling gut microbiota and increasing production of 2-oleoylglycerol. *Nat Commun* 2023;14(1):228. doi:10.1038/s41467-023-35861-1, PMID:36646715.
- [87] Sánchez-Tapia M, Tobón-Cornejo S, Noriega LG, Vázquez-Manjarrez N, Coutiño-Hernández D, Granados-Portillo O, *et al*. Hepatic Steatosis Can Be Partly Generated by the Gut Microbiota-Mitochondria Axis via 2-Oleoyl Glycerol and Reversed by a Combination of Soy Protein, Chia Oil, Curcumin and Nopal. *Nutrients* 2024;16(16):2594. doi:10.3390/nu16162594, PMID:39203731.
- [88] Li D, Wan M, Xue L, Zhang Z, Qiu Y, Mei F, *et al*. Zinc promotes microbial p-coumaric acid production that protects against cholestatic liver injury. *Cell Host Microbe* 2024;32(12):2195–2211.e9. doi:10.1016/j.chom.2024.11.002, PMID:39610253.
- [89] Quesada-Vázquez S, Castells-Nobau A, Latorre J, Oliveras-Cañellas N, Puig-Parnau I, Tejera N, *et al*. Potential therapeutic implications of histidine catabolism by the gut microbiota in NAFLD patients with morbid obesity. *Cell Rep Med* 2023;4(12):101341. doi:10.1016/j.xcrm.2023.101341, PMID:38118419.
- [90] Chen J, Yang H, Qin Y, Zhou X, Ma Q. Tryptophan Ameliorates Metabolic Syndrome by Inhibiting Intestinal Farnesoid X Receptor Signaling: The Role of Gut Microbiota-Bile Acid Crosstalk. *Research (Wash D C)* 2024;7:0515. doi:10.34133/research.0515, PMID:39679283.
- [91] Smirnova E, Muthiah MD, Narayan N, Siddiqui MS, Puri P, Luketic VA, *et al*. Metabolic reprogramming of the intestinal microbiome with functional bile acid changes underlie the development of NAFLD. *Hepatology* 2022;76(6):1811–1824. doi:10.1002/hep.32568, PMID:35561146.
- [92] Jee JJ, Lim J, Park S, Koh H, Lee HW. Gut microbial community differentially characterizes patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol* 2022;37(9):1822–1832. doi:10.1111/jgh.15903, PMID:35624084.
- [93] Qiu H, Wen Y, Luo Y, Lv S, Huang J, Chen B, *et al*. Gut microbiota regulates serum metabolites in mice with nonalcoholic fatty liver disease via gut metabolites: mechanisms involving branched-chain amino acids and unsaturated fatty acids. *Front Endocrinol (Lausanne)* 2025;16:1606669. doi:10.3389/fendo.2025.1606669, PMID:40766290.
- [94] Li Z, Zhang Y, Hong W, Wang B, Chen Y, Yang P, *et al*. Gut microbiota modulate radiotherapy-associated antitumor immune responses against hepatocellular carcinoma Via STING signaling. *Gut Microbes* 2022;14(1):2119055. doi:10.1080/19490976.2022.2119055, PMID:36093568.
- [95] Yao H, Ma S, Huang J, Si X, Yang M, Song W, *et al*. Trojan-Horse Strategy Targeting the Gut-Liver Axis Modulates Gut Microbiome and Reshapes Microenvironment for Orthotopic Hepatocellular Carcinoma Therapy. *Adv Sci (Weinh)* 2024;11(44):e2310002. doi:10.1002/advs.202310002, PMID:39373804.
- [96] Tian P, Tian X, Gao L, Ma C, Liang X. Early-life antibiotic exposure aggravate the metabolic dysfunction-associated steatotic liver disease associated hepatocellular carcinoma. *BMC Cancer* 2024;24(1):1358. doi:10.1186/s12885-024-13136-2, PMID:39506660.
- [97] Bertolini A, Nguyen M, Zehra SA, Taleb SA, Bauer-Pisani T, Palm N, *et al*. Prominent role of gut dysbiosis in the pathogenesis of cystic fibrosis-related liver disease in mice. *J Hepatol* 2024;81(3):429–440. doi:10.1016/j.jhep.2024.03.041, PMID:38554847.
- [98] Huo R, Yang WJ, Liu Y, Liu T, Li T, Wang CY, *et al*. Stigmasterol: Remodeling gut microbiota and suppressing tumor growth through Treg and CD8+ T cells in hepatocellular carcinoma. *Phytomedicine* 2024;129:155225. doi:10.1016/j.phymed.2023.155225, PMID:38678948.
- [99] Yang H, Liu Q, Liu H, Kang X, Tian H, Kang Y, *et al*. Berberine alleviates concanavalin A-induced autoimmune hepatitis in mice by modulating the gut microbiota. *Hepatol Commun* 2024;8(4):e0381. doi:10.1097/HCC.0000000000000381, PMID:38466881.
- [100] Zhong HJ, Zhuang YP, Xie X, Song JY, Wang SQ, Wu L, *et al*. Washed microbiota transplantation promotes homing of group 3 innate lymphoid cells to the liver via the CXCL16/CXCR6 axis: a potential treatment for metabolic-associated fatty liver disease. *Gut Microbes* 2024;16(1):2372881. doi:10.1080/19490976.2024.2372881, PMID:38940400.
- [101] Song J, Dai J, Chen X, Ding F, Ding Y, Ma L, *et al*. Bifidobacterium mitigates autoimmune hepatitis by regulating IL-33-induced Treg/Th17 imbalance via the TLR2/4 signaling pathway. *Histol Histopathol* 2024;39(5):623–632. doi:10.14670/HH-18-669, PMID:37916940.
- [102] Lu Y, Xu L, Chen W, Liu W, Zhang Y, Zhou Q, *et al*. Intrahepatic Microbial Heterogeneity in Multifocal Hepatocellular Carcinoma and Its Association with Host Genomic and Transcriptomic Alterations. *Cancer Discov* 2025;15(8):1630–1648. doi:10.1158/2159-8290.CD-24-1259, PMID:40287964.
- [103] Schwenger KJP, Copeland JK, Ghorbani Y, Chen L, Comelli EM, Guttman DS, *et al*. Characterization of liver, adipose, and fecal microbiome in obese patients with MASLD: links with disease severity and metabolic dysfunction parameters. *Microbiome* 2025;13(1):9. doi:10.1186/s40168-024-02004-7, PMID:39810228.
- [104] Liu Q, Huang B, Zhou Y, Wei Y, Li Y, Li B, *et al*. Gut microbiome pattern impacts treatment response in primary biliary cholangitis. *Med* 2025;6(1):100504. doi:10.1016/j.medj.2024.08.003, PMID:39305900.
- [105] Gao Y, Wu H, Luo Y, Deng X, Chen J, Wu T. Mechanisms of Dihydromyricetin for Improving Hepatic Fibrosis through the Integration of Metabolomics and Gut Microbiota. *Am J Chin Med* 2025;53(3):889–908. doi:10.1142/S0192415X25500338, PMID:40374379.
- [106] Gao H, Bai H, Su Y, Gao Y, Fang H, Li D, *et al*. Fecal microbiota transplantation from *Helicobacter pylori* carriers following bismuth quad-

- rupture therapy exacerbates alcohol-related liver disease in mice via LPS-induced activation of hepatic TLR4/NF- κ B/NLRP3 signaling. *J Transl Med* 2025;23(1):627. doi:10.1186/s12967-025-06573-5, PMID: 40462165.
- [107] Wang ZY, Gao PP, Li L, Chen TT, Li N, Qi M, *et al.* Dextran sulfate sodium-induced gut microbiota dysbiosis aggravates liver injury in mice with S100-induced autoimmune hepatitis. *Immunol Lett* 2023;263:70–77. doi:10.1016/j.imlet.2023.10.001, PMID:37797724.
- [108] Deng S, Cao H, Li T, Wang X, Meng J, Zeng T, *et al.* Lachnospiraceae bacterium alleviates ischemia-reperfusion injury in steatotic donor liver by inhibiting ferroptosis via the Foxo3-Alox15 signaling pathway. *Gut Microbes* 2025;17(1):2460543. doi:10.1080/19490976.2025.2460543, PMID:39882747.
- [109] Sucu S, Basarir KE, Mihaylov P, Balik E, Lee JTC, Fridell JA, *et al.* Impact of gut microbiota on liver transplantation. *Am J Transplant* 2023;23(10):1485–1495. doi:10.1016/j.ajt.2023.05.030, PMID:37277064.
- [110] Zheng W, Wang X, Chen H, He K, Yan X, Zhang Y, *et al.* KYNA Ameliorates Hepatic Ischemia-Reperfusion Injury by Activating the Hippo Signalling Pathway via FTO-Dependent m6A Demethylation of LATS1. *Cell Prolif* 2025;58(10):e70048. doi:10.1111/cpr.70048, PMID:40277037.
- [111] Zhou Y, Sun Y, Yin P, Zuo S, Li H, Cao K. Bacterial extracellular vesicles: emerging mediators of gut-liver axis crosstalk in hepatic diseases. *Front Cell Infect Microbiol* 2025;15:1620829. doi:10.3389/fcimb.2025.1620829, PMID:40621163.
- [112] Qin LN, Yu YF, Ma L, Yu R. Intestinal bacteria-derived extracellular vesicles in metabolic dysfunction-associated steatotic liver disease: From mechanisms to therapeutics. *Mol Cells* 2025;48(6):100216. doi:10.1016/j.mocell.2025.100216, PMID:40239896.
- [113] Qin X, Wang S, Yan Z, Zhao N, Yao J. The role of bacterial outer membrane vesicles in inflammatory response of acute-on-chronic liver failure. *Front Microbiol* 2025;16:1608137. doi:10.3389/fmicb.2025.1608137, PMID:40687857.
- [114] Liang X, Shan T, Zheng X, Zhang Z, Fan Y, Zhang H, *et al.* Study on the Regulatory Mechanism of Niacin Combined with *B. animalis* F1-7 in Alleviating Alcoholic Fatty Liver Disease by Up-Regulating GPR109A. *Nutrients* 2024;16(23):4170. doi:10.3390/nu16234170, PMID:39683563.
- [115] Ding Y, Yanagi K, Yang F, Callaway E, Cheng C, Hensel ME, *et al.* Oral supplementation of gut microbial metabolite indole-3-acetate alleviates diet-induced steatosis and inflammation in mice. *Elife* 2024;12:RP87458. doi:10.7554/eLife.87458, PMID:38412016.
- [116] Wu J, Lyu S, Guo D, Yang N, Liu Y. Protective effects of YCHD on the autoimmune hepatitis mice model induced by Ad-CYP2D6 through modulating the Th1/Treg ratio and intestinal flora. *Front Immunol* 2024;15:1488125. doi:10.3389/fimmu.2024.1488125, PMID:39606230.
- [117] Yan G, Zhang L, Wu D, Jiang S, Wu Q, Dai M. Paeonol attenuates nonalcoholic steatohepatitis by regulating intestinal flora and AhR/NLRP3/Caspase-1 metabolic pathway. *J Ethnopharmacol* 2024;329:118147. doi:10.1016/j.jep.2024.118147, PMID:38574779.
- [118] Zhao Y, Li B, Deng H, Zhang C, Wang Y, Chen L, *et al.* Galangin Alleviates Alcohol-Provoked Liver Injury Associated with Gut Microbiota Disorder and Intestinal Barrier Dysfunction in Mice. *J Agric Food Chem* 2024;72(40):22336–22348. doi:10.1021/acs.jafc.4c05617, PMID:39322623.
- [119] Andrews TS, Atif J, Liu JC, Perciani CT, Ma XZ, Thoeni C, *et al.* Single-Cell, Single-Nucleus, and Spatial RNA Sequencing of the Human Liver Identifies Cholangiocyte and Mesenchymal Heterogeneity. *Hepatol Commun* 2022;6(4):821–840. doi:10.1002/hep4.1854, PMID:34792289.
- [120] Suo Y, Thimme R, Bengsch B. Spatial single-cell omics: new insights into liver diseases. *Gut* 2026;75(6):1248–1263. doi:10.1136/gutjnl-2024-332105, PMID:40764061.
- [121] Williams M, Bonnardel J, Haest B, Vanderborcht B, Wagner C, Remmerie A, *et al.* Spatial proteogenomics reveals distinct and evolutionarily conserved hepatic macrophage niches. *Cell* 2022;185(2):379–396.e38. doi:10.1016/j.cell.2021.12.018, PMID:35021063.
- [122] Fujimoto M, Tanaka T. Advancing liver metabolic zonation with single-cell and spatial omics. *Endocr J* 2025;72(10):1069–1078. doi:10.1507/endocrj.EJ25-0140, PMID:40436799.
- [123] Pande A, Sharma S, Khillan V, Rastogi A, Arora V, Shasthry SM, *et al.* Fecal microbiota transplantation compared with prednisolone in severe alcoholic hepatitis patients: a randomized trial. *Hepatol Int* 2023;17(1):249–261. doi:10.1007/s12072-022-10438-0, PMID:36469298.
- [124] Sharma A, Roy A, Premkumar M, Verma N, Duseja A, Taneja S, *et al.* Fecal microbiota transplantation in alcohol-associated acute-on-chronic liver failure: an open-label clinical trial. *Hepatol Int* 2022;16(2):433–446. doi:10.1007/s12072-022-10312-z, PMID:35349076.
- [125] Liu Q, Yang H, Kang X, Tian H, Kang Y, Li L, *et al.* A Synbiotic Ameliorates Con A-Induced Autoimmune Hepatitis in Mice through Modulation of Gut Microbiota and Immune Imbalance. *Mol Nutr Food Res* 2023;67(7):e2200428. doi:10.1002/mnfr.202200428, PMID:36708241.
- [126] Ma C, Awosika JA, Monge C, Coffman D-Annibale K, Xie C, Skorupan N, *et al.* Altering the gut microbiome and tumor microenvironment in advanced liver cancer: A phase II study of nivolumab, tadalafil and oral vancomycin in patients with refractory primary hepatocellular carcinoma or liver dominant metastatic cancer from colorectal or pancreatic cancers. *Cancer Lett* 2025;632:217975. doi:10.1016/j.canlet.2025.217975, PMID:40789510.
- [127] Zhu Y, Pan Y, Wang X, Wei L, Zhu L, Guo Y, *et al.* Lactobacillus rhamnosus GG Combined with Metformin Alleviates Alcohol-Induced Liver Inflammation in Mice by Maintaining the Intestinal Barrier and Regulating Treg/Th1 Cells. *J Med Food* 2025;28(4):354–365. doi:10.1089/jmf.2024.k.0184, PMID:39854767.
- [128] Vega-Abellana S, Román E, Soler Z, Ortiz MÀ, Rossi G, Biagini L, *et al.* A Metagenomics Approach to Frailty in Patients With Cirrhosis Undergoing a Multifactorial Intervention. *Liver Int* 2025;45(12):e70418. doi:10.1111/liv.70418, PMID:41174950.
- [129] Zhu H, Jiang W, Liu C, Wang C, Hu B, Guo Y, *et al.* Ameliorative effects of chlorogenic acid on alcoholic liver injury in mice via gut microbiota informatics. *Eur J Pharmacol* 2022;928:175096. doi:10.1016/j.ejphar.2022.175096, PMID:35697148.
- [130] Feng J, Liu Y, Chen J, Bai Y, He J, Cao H, *et al.* Marine Chitooligosaccharide Alters Intestinal Flora Structure and Regulates Hepatic Inflammatory Response to Influence Nonalcoholic Fatty Liver Disease. *Mar Drugs* 2022;20(6):383. doi:10.3390/md20060383, PMID:35736186.
- [131] Chen L, Lei Y, Lu C, Liu D, Ma W, Liu H, *et al.* Punicic acid ameliorates obesity-related hyperlipidemia and fatty liver in mice via regulation of intestinal flora and lipopolysaccharide-related signaling pathways. *Food Funct* 2024;15(9):5012–5025. doi:10.1039/d4fo00502c, PMID:38618675.
- [132] Zhang Z, Qin X, Yi T, Li Y, Li C, Zeng M, *et al.* Gubra Amylin-NASH Diet Induced Nonalcoholic Fatty Liver Disease Associated with Histological Damage, Oxidative Stress, Immune Disorders, Gut Microbiota, and Its Metabolic Dysbiosis in Colon. *Mol Nutr Food Res* 2024;68(15):e2300845. doi:10.1002/mnfr.202300845, PMID:38966885.
- [133] Nakamura S, Nakamura K, Yokoi Y, Shimizu Y, Ohira S, Hagiwara M, *et al.* Decreased Paneth cell α -defensins promote fibrosis in a choline-deficient L-amino acid-defined high-fat diet-induced mouse model of nonalcoholic steatohepatitis via disrupting intestinal microbiota. *Sci Rep* 2023;13(1):3953. doi:10.1038/s41598-023-30997-y, PMID:36894646.
- [134] Cabré N, Fondevila MF, Wei W, Yamazaki T, Tonetti FR, Eguileor A, *et al.* Activation of intestinal endogenous retroviruses by alcohol exacerbates liver disease. *J Clin Invest* 2025;135(13):e188541. doi:10.1172/JCI188541, PMID:40359032.
- [135] Ciocan D, Spatz M, Trainel N, Hardonnière K, Domenichini S, Mercier-Nomé F, *et al.* Modulation of the Bile Acid Enterohepatic Cycle by Intestinal Microbiota Alleviates Alcohol Liver Disease. *Cells* 2022;11(6):968. doi:10.3390/cells11060968, PMID:35326419.
- [136] Vega-Abellana S, Dopazo C, Yañez F, Soler Z, Xie Z, Canalda-Baltrons A, *et al.* Microbiome composition recovery after liver transplantation correlates with initial liver disease severity and antibiotics treatment. *Am J Transplant* 2024;24(9):1623–1633. doi:10.1016/j.ajt.2024.03.038, PMID:38556088.
- [137] Gan G, Luo Y, Zeng Y, Lin S, Lu B, Zhang R, *et al.* Gut microbiota dysbiosis links chronic apical periodontitis to liver fibrosis in nonalcoholic fatty liver disease: Insights from a mouse model. *Int Endod J*

- 2024;57(11):1608–1622. doi:10.1111/iej.14119, PMID:38958220.
- [138] Dong L, Luo P, Zhang A. Intestinal microbiota dysbiosis contributes to the liver damage in subchronic arsenic-exposed mice. *Acta Biochim Biophys Sin (Shanghai)* 2024;56(12):1774–1788. doi:10.3724/abbs.2024131, PMID:39394819.
- [139] Bloom PP, Rao K, Bassis CM, Zhou SY, Nojkov B, Owyang C, *et al*. Duodenal Permeability Is Associated With Mucosal Microbiota in Compensated Cirrhosis. *Clin Transl Gastroenterol* 2022;13(10):e00522. doi:10.14309/ctg.0000000000000522, PMID:36000993.
- [140] Jin Y, Shi M, Feng J, Zhang Z, Zhao B, Li Q, *et al*. Splenectomy ameliorates liver cirrhosis by restoring the gut microbiota balance. *Cell Mol Life Sci* 2024;81(1):32. doi:10.1007/s00018-023-05055-5, PMID:38214780.
- [141] Xia S, Yan C, Cai G, Xu Q, Zou H, Gu J, *et al*. Gut dysbiosis exacerbates inflammatory liver injury induced by environmentally relevant concentrations of nanoplastics via the gut-liver axis. *J Environ Sci (China)* 2025;155:250–266. doi:10.1016/j.jes.2024.11.022, PMID:40246463.
- [142] Zhang KK, Liu JL, Chen LJ, Li JH, Yang JZ, Xu LL, *et al*. Gut microbiota mediates methamphetamine-induced hepatic inflammation via the impairment of bile acid homeostasis. *Food Chem Toxicol* 2022;166:113208. doi:10.1016/j.fct.2022.113208, PMID:35688268.
- [143] Niu X, Chang G, Xu N, Li R, Niu B, Mao R, *et al*. Vitamin A-Integrated Cinnamaldehyde Nanoemulsion: A Nanotherapeutic Approach To Counteract Liver Fibrosis via Gut-Liver Axis Modulation. *ACS Nano* 2025;19(10):10433–10451. doi:10.1021/acsnano.5c00136, PMID:40045827.
- [144] Abdelmohcine A, Amine SE, Warda K, Baz SE, Khanouchi M, El-Mansoury B, *et al*. Hyperammonemia induced gut microbiota dysbiosis and motor coordination disturbances in mice: new insight into gut-brain axis involvement in hepatic encephalopathy. *Acta Neurobiol Exp (Wars)* 2023;83(2):203–215. doi:10.55782/ane-2023-018, PMID:37493536.
- [145] He S, Cui S, Song W, Jiang Y, Chen H, Liao D, *et al*. Interleukin-17 Weakens the NAFLD/NASH Process by Facilitating Intestinal Barrier Restoration Depending on the Gut Microbiota. *mBio* 2022;13(2):e0368821. doi:10.1128/mbio.03688-21, PMID:35266816.
- [146] Chen H, Wang Y, Shao Y, Su W, Li S, Liu Y, *et al*. Multi-Omics Analysis Revealed Characterization of Gastric Microbiome and Metabolome in *Helicobacter pylori*-Induced Progression of MASLD. *Helicobacter* 2025;30(5):e70069. doi:10.1111/hel.70069, PMID:40916070.
- [147] Hasegawa Y, Okamura T, Ono Y, Ichikawa T, Saijo Y, Nakanishi N, *et al*. Oral exposure to high concentrations of polystyrene microplastics alters the intestinal environment and metabolic outcomes in mice. *Front Immunol* 2024;15:1407936. doi:10.3389/fimmu.2024.1407936, PMID:39600697.
- [148] Li Z, Lei L, Ling L, Liu Y, Xiong Z, Shao Y. Resveratrol modulates the gut microbiota of cholestasis in pregnant rats. *J Physiol Pharmacol* 2022;73(2):261–268. doi:10.26402/jpp.2022.2.09, PMID:36193965.
- [149] He Z, Liu Y, Li Z, Sun T, Li Z, Manyande A, *et al*. Gut microbiota regulates circadian oscillation in hepatic ischemia-reperfusion injury-induced cognitive impairment by interfering with hippocampal lipid metabolism in mice. *Hepatol Int* 2023;17(6):1645–1658. doi:10.1007/s12072-023-10509-w, PMID:37004699.
- [150] Klag KA, Bell R, Jia X, Seguin A, Maschek JA, Bronner M, *et al*. Low-Iron Diet-Induced Fatty Liver Development Is Microbiota Dependent and Exacerbated by Loss of the Mitochondrial Iron Importer Mitoferrin2. *Nutrients* 2024;16(12):1804. doi:10.3390/nu16121804, PMID:38931165.
- [151] Yu J, Zhu H, Yu X, Liu Y, Zhang J, Jiang L, *et al*. Calcitriol/Vitamin D receptor ameliorates fructose-induced enteritis-hepatitis axis dysregulation in mice. *J Nutr Biochem* 2025;145:110017. doi:10.1016/j.jnutbio.2025.110017, PMID:40614836.
- [152] Shou D, Luo Q, Tang W, Cao C, Huang H, Chen H, *et al*. Hepatobiliary and pancreatic: Multi-donor fecal microbiota transplantation attenuated high-fat diet-induced hepatic steatosis in mice by remodeling the gut microbiota. *J Gastroenterol Hepatol* 2023;38(12):2195–2205. doi:10.1111/jgh.16359, PMID:37787118.
- [153] Horvath A, Traub J, Aliwa B, Bourgeois B, Madl T, Stadlbauer V. Oral Intake of L-Ornithine-L-Aspartate Is Associated with Distinct Microbiome and Metabolome Changes in Cirrhosis. *Nutrients* 2022;14(4):748. doi:10.3390/nu14040748, PMID:35215398.
- [154] Chen L, Xie L, Wang L, Zhan X, Zhuo Z, Jiang S, *et al*. Patchoulene epoxide mitigates colitis and hepatic damage induced by dextran sulfate sodium by regulating the colonic microbiota and purine metabolism. *Front Immunol* 2025;16:1509114. doi:10.3389/fimmu.2025.1509114, PMID:40028318.
- [155] Wang B, Zhang B, Zhou L, Li S, Li Z, Luo H. Multi-omics reveals diet-induced metabolic disorders and liver inflammation via microbiota-gut-liver axis. *J Nutr Biochem* 2023;111:109183. doi:10.1016/j.jnutbio.2022.109183, PMID:36270571.
- [156] Mainz RE, Albers S, Haque M, Sonntag R, Treichel NS, Clavel T, *et al*. NLRP6 Inflammasome Modulates Disease Progression in a Chronic-Plus-Binge Mouse Model of Alcoholic Liver Disease. *Cells* 2022;11(2):182. doi:10.3390/cells11020182, PMID:35053298.
- [157] Yang Y, Eguchi A, Wan X, Mori C, Hashimoto K. Depression-like phenotypes in mice with hepatic ischemia/reperfusion injury: A role of gut-microbiota-liver-brain axis via vagus nerve. *J Affect Disord* 2024;345:157–167. doi:10.1016/j.jad.2023.10.142, PMID:37879416.
- [158] Romualdo GR, Valente LC, Sprocati AC, Bacil GP, de Souza IP, Rodrigues J, *et al*. Western diet-induced mouse model of non-alcoholic fatty liver disease associated with metabolic outcomes: Features of gut microbiome-liver-adipose tissue axis. *Nutrition* 2022;103-104:111836. doi:10.1016/j.nut.2022.111836, PMID:36202025.
- [159] Saha P, Upright M, Bose D, Roy S, Trivedi A, More M, *et al*. Subchronic Oral Cylindrospermopsin Exposure Alters the Host Gut Microbiome and Is Associated with Progressive Hepatic Inflammation, Stellate Cell Activation, and Mild Fibrosis in a Preclinical Study. *Toxins (Basel)* 2022;14(12):835. doi:10.3390/toxins14120835, PMID:36548732.
- [160] Gu C, Zhou Z, Yu Z, He M, He L, Luo Z, *et al*. Corrigendum: The Microbiota and Its Correlation With Metabolites in the Gut of Mice With Nonalcoholic Fatty Liver Disease. *Front Cell Infect Microbiol* 2022;12:972118. doi:10.3389/fcimb.2022.972118, PMID:35865827.
- [161] Zhang B, Lin Q, Dai M, Wu Z, Chen L, Li F. Triptophenolide aggravates triptolide-induced liver injury through disrupting the biological function of intestine. *Toxicol Appl Pharmacol* 2025;500:117354. doi:10.1016/j.taap.2025.117354, PMID:40286878.
- [162] Champion C, Neagoe RM, Efferberger M, Sala DT, Servant F, Christensen JE, *et al*. Human liver microbiota modeling strategy at the early onset of fibrosis. *BMC Microbiol* 2023;23(1):34. doi:10.1186/s12866-023-02774-4, PMID:36717776.
- [163] Gu T, Kong M, Duan M, Chen L, Tian Y, Xu W, *et al*. Cu exposure induces liver inflammation via regulating gut microbiota/LPS/liver TLR4 signaling axis. *Ecotoxicol Environ Saf* 2024;278:116430. doi:10.1016/j.ecoenv.2024.116430, PMID:38718729.
- [164] Driuchina A, Hintikka J, Lehtonen M, Keski-Rahkonen P, O'Connell T, Juvonen R, *et al*. Identification of Gut Microbial Lysine and Histidine Degradation and CYP-Dependent Metabolites as Biomarkers of Fatty Liver Disease. *mBio* 2023;14(1):e0266322. doi:10.1128/mbio.02663-22, PMID:36715540.
- [165] Lu Y, Yi F, Chen W, Tan X, Li K, Yang C, *et al*. Involvement of oxidative stress, lipid dysmetabolism and gut microbial dysbiosis in oxaliplatin-induced fatty liver disease: evidence from a tree shrew model. *Clin Res Hepatol Gastroenterol* 2025;49(7):102645. doi:10.1016/j.clinre.2025.102645, PMID:40617320.
- [166] Han X, Du L, Dou Y, Wang H, Lv M, Wang L, *et al*. Orally ingested nanosilica causes liver-specific accumulation and induces liver senescence and fibrosis via the microbiota-gut-liver axis. *J Nanobiotechnology* 2025;23(1):645. doi:10.1186/s12951-025-03711-5, PMID:41074142.
- [167] Rohani P, Shojai S, Nikparast A, Shaygatabar M, Marvasti FE, Asghari G, *et al*. The association between gut microbiota and metabolic dysfunction-associated steatotic liver disease (MASLD): a case-control study. *BMC Pediatr* 2025;25(1):796. doi:10.1186/s12887-025-06144-z, PMID:41068660.
- [168] Geng R, Guo J, Lao Y, Kang SG, Huang K, Tong T. Chronic UVB exposure induces hepatic injury in mice: Mechanistic insights from integrated multi-omics. *Environ Pollut* 2024;362:124933. doi:10.1016/j.envpol.2024.124933, PMID:39265770.
- [169] Liu Y, Kang W, Liu S, Li J, Liu J, Chen X, *et al*. Gut microbiota-bile acid-intestinal Farnesoid X receptor signaling axis orchestrates cadmium-induced liver injury. *Sci Total Environ* 2022;849:157861. doi:10.1016/j.scitotenv.2022.157861, PMID:35934034.

- [170] Hrnčir T, Trcková E, Hrnčířová L. Synergistic Effects of Fructose and Food Preservatives on Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): From Gut Microbiome Alterations to Hepatic Gene Expression. *Nutrients* 2024;16(21):3722. doi:10.3390/nu16213722, PMID:39519554.
- [171] Cao L, Niu M, Tang X, Wang Y, Hu X, Dai W. Gentiopicroside improves DSS-induced ulcerative colitis and secondary liver injury in mice by enhancing the intestinal barrier and regulating the gut microbiome. *Sci Rep* 2025;15(1):27159. doi:10.1038/s41598-025-12255-5, PMID:40715435.
- [172] Heinzer K, Lang S, Farowski F, Wisplinghoff H, Vehreschild MJGT, Martin A, *et al.* Dietary omega-6/omega-3 ratio is not associated with gut microbiota composition and disease severity in patients with nonalcoholic fatty liver disease. *Nutr Res* 2022;107:12–25. doi:10.1016/j.nutres.2022.07.006, PMID:36162275.
- [173] Wang Q, Wang M, Chen J, Zhang W, Lv X. Ameliorative effects of *Bacillus subtilis* C10 on alcoholic liver injury in mice. *J Food Sci* 2024;89(12):10018–10034. doi:10.1111/1750-3841.17539, PMID:39581583.
- [174] Wang H, Bian Y, Li Y, Yuan Y, Li X, Liu Y, *et al.* Echinacoside: A potential therapeutic approach for alcohol-related liver disease by alleviating intestinal microbial dysbiosis, intestinal barrier dysfunction, and liver inflammation mediated by the endotoxin-TLR4/NF- κ B pathway. *Eur J Pharmacol* 2025;1005:178027. doi:10.1016/j.ejphar.2025.178027, PMID:40749869.
- [175] Wang X, Fang Y, Liang W, Cai Y, Wong CC, Wang J, *et al.* Gut-liver translocation of pathogen *Klebsiella pneumoniae* promotes hepatocellular carcinoma in mice. *Nat Microbiol* 2025;10(1):169–184. doi:10.1038/s41564-024-01890-9, PMID:39747695.
- [176] Li J, Zhai X, Chen C, Zhang R, Huang X, Liu Y. The intrahepatic bacterial metatranscriptomic signature of patients with hepatocellular carcinoma. *Sci Rep* 2024;14(1):29077. doi:10.1038/s41598-024-80246-z, PMID:39580523.
- [177] Peng YC, Xu JX, You XM, Huang YY, Ma L, Li LQ, *et al.* Specific gut microbiome signature predicts hepatitis B virus-related hepatocellular carcinoma patients with microvascular invasion. *Ann Med* 2023;55(2):2283160. doi:10.1080/07853890.2023.2283160, PMID:38112540.
- [178] Ji J, Sun J, Li J, Xie J, Xi B, Zhao M. Altered gut microbiome associated with metabolic-associated fatty liver disease in Chinese children. *Clin Nutr* 2024;43(1):187–196. doi:10.1016/j.clnu.2023.11.001, PMID:38070210.
- [179] Zhang J, Shi M, Zhao C, Liang G, Li C, Ge X, *et al.* Role of intestinal flora in the development of nonalcoholic fatty liver disease in children. *Microbiol Spectr* 2024;12(2):e0100623. doi:10.1128/spectrum.01006-23, PMID:38189294.
- [180] Cho EJ, Kim B, Yu SJ, Hong SK, Choi Y, Yi NJ, *et al.* Urinary microbiome-based metagenomic signature for the noninvasive diagnosis of hepatocellular carcinoma. *Br J Cancer* 2024;130(6):970–975. doi:10.1038/s41416-024-02582-1, PMID:38278977.
- [181] Deng T, Li J, He B, Chen B, Liu F, Chen Z, *et al.* Gut microbiome alteration as a diagnostic tool and associated with inflammatory response marker in primary liver cancer. *Hepatol Int* 2022;16(1):99–111. doi:10.1007/s12072-021-10279-3, PMID:35064546.
- [182] Viebahn G, Hartmann P, Lang S, Demir M, Zhang X, Fouts DE, *et al.* Fungal signature differentiates alcohol-associated liver disease from nonalcoholic fatty liver disease. *Gut Microbes* 2024;16(1):2307586. doi:10.1080/19490976.2024.2307586, PMID:38298161.
- [183] Zhang W, Xu X, Cai L, Cai X. Dysbiosis of the gut microbiome in elderly patients with hepatocellular carcinoma. *Sci Rep* 2023;13(1):7797. doi:10.1038/s41598-023-34765-w, PMID:37179446.
- [184] Hu B, Yang Y, Yao J, Lin G, He Q, Bo Z, *et al.* Gut Microbiota as Mediator and Moderator Between Hepatitis B Virus and Hepatocellular Carcinoma: A Prospective Study. *Cancer Med* 2024;13(24):e70454. doi:10.1002/cam4.70454, PMID:39702929.
- [185] Yang X, Mai H, Zhou J, Li Z, Wang Q, Lan L, *et al.* Alterations of the gut microbiota associated with the occurrence and progression of viral hepatitis. *Front Cell Infect Microbiol* 2023;13:1119875. doi:10.3389/fcimb.2023.1119875, PMID:37342245.
- [186] Zhu Y, Geng SY, Chen Y, Ru QJ, Zheng Y, Jiang N, *et al.* Machine learning algorithms reveal gut microbiota signatures associated with chronic hepatitis B-related hepatic fibrosis. *World J Gastroenterol* 2025;31(16):105985. doi:10.3748/wjg.v31.i16.105985, PMID:40308807.
- [187] Saththawit N, Jinato T, Sutheeworapong S, Tanpowpong N, Chuaypen N, Tangkijvanich P. Distinct Gut Microbial Signature and Host Genetic Variants in Association with Liver Fibrosis Severity in Patients with MASLD. *Nutrients* 2024;16(12):1800. doi:10.3390/nu16121800, PMID:38931155.
- [188] Schwenger KJP, Sharma D, Ghorbani Y, Xu W, Lou W, Comelli EM, *et al.* Links between gut microbiome, metabolome, clinical variables and non-alcoholic fatty liver disease severity in bariatric patients. *Liver Int* 2024;44(5):1176–1188. doi:10.1111/liv.15864, PMID:38353022.
- [189] Rodríguez-Díaz C, Taminiau B, García-García A, Cueto A, Robles-Díaz M, Ortega-Alonso A, *et al.* Microbiota diversity in nonalcoholic fatty liver disease and in drug-induced liver injury. *Pharmacol Res* 2022;182:106348. doi:10.1016/j.phrs.2022.106348, PMID:35817360.
- [190] Sun X, Zhou Z, Chi X, Cheng D, Zhang Y, Xu Y, *et al.* Featured intestinal microbiota associated with hepatocellular carcinoma in various liver disease states. *Front Immunol* 2025;16:1674838. doi:10.3389/fimmu.2025.1674838, PMID:41122171.
- [191] Bajaj JS, Peña-Rodríguez M, La Reau A, Phillips W, Fuchs M, Davis BC, *et al.* Longitudinal transkingdom gut microbial approach towards decolonization in outpatients with cirrhosis. *Gut* 2023;72(4):759–771. doi:10.1136/gutjnl-2022-328403, PMID:36343978.
- [192] Mantovani A, Longo L, Thoen RU, Rampelotto PH, Salinas R, Guerreiro GTS, *et al.* Firmicutes/Bacteroidetes and Firmicutes/Proteobacteria ratios are associated with worse prognosis in a cohort of Latin American patients with cirrhosis. *Clinics (Sao Paulo)* 2024;79:100471. doi:10.1016/j.clinsp.2024.100471, PMID:39098143.
- [193] Zhu C, Zhang C, Wang S, Xun Z, Zhang D, Lan Z, *et al.* Characterizations of multi-kingdom gut microbiota in immune checkpoint inhibitor-treated hepatocellular carcinoma. *J Immunother Cancer* 2024;12(6):e008686. doi:10.1136/jitc-2023-008686, PMID:38844407.
- [194] Wu H, Zheng X, Pan T, Yang X, Chen X, Zhang B, *et al.* Dynamic microbiome and metabolome analyses reveal the interaction between gut microbiota and anti-PD-1 based immunotherapy in hepatocellular carcinoma. *Int J Cancer* 2022;151(8):1321–1334. doi:10.1002/ijc.34118, PMID:35579980.
- [195] Zhang S, Chau HT, Tun HM, Huang FY, Wong DK, Mak LY, *et al.* Virological response to nucleos(t)ide analogues treatment in chronic hepatitis B patients is associated with Bacteroides-dominant gut microbiome. *EBioMedicine* 2024;103:105101. doi:10.1016/j.ebiom.2024.105101, PMID:38583259.
- [196] Lee G, Rosa BA, Fernandez-Baca MV, Martin J, Ore RA, Ortiz P, *et al.* Distinct gut microbiome features characterize Fasciola hepatica infection and predict triclabendazole treatment outcomes in Peruvian patients. *Front Cell Infect Microbiol* 2025;15:1555171. doi:10.3389/fcimb.2025.1555171, PMID:40129931.
- [197] Cheng R, Wang L, Le S, Yang Y, Zhao C, Zhang X, *et al.* A randomized controlled trial for response of microbiome network to exercise and diet intervention in patients with nonalcoholic fatty liver disease. *Nat Commun* 2022;13(1):2555. doi:10.1038/s41467-022-29968-0, PMID:35538056.
- [198] Bajaj JS, O’Leary JG, Jakab SS, Fagan A, Sikaroodi M, Gillevet PM. Gut microbiome profiles to exclude the diagnosis of hepatic encephalopathy in patients with cirrhosis. *Gut Microbes* 2024;16(1):2392880. doi:10.1080/19490976.2024.2392880, PMID:39189586.
- [199] Yukawa-Muto Y, Kamiya T, Fujii H, Mori H, Toyoda A, Sato I, *et al.* Distinct responsiveness to rifaximin in patients with hepatic encephalopathy depends on functional gut microbial species. *Hepatol Commun* 2022;6(8):2090–2104. doi:10.1002/hep4.1954, PMID:35429147.
- [200] Li S, Xu Z, Diao H, Zhou A, Tu D, Wang S, *et al.* Gut microbiome alterations and hepatic encephalopathy post-TIPS in liver cirrhosis patients. *J Transl Med* 2025;23(1):745. doi:10.1186/s12967-025-06774-y, PMID:40615853.
- [201] Jiang QR, Zeng DW. Gut microbiota shifts in hepatitis B-related portal hypertension after transjugular intrahepatic portosystemic shunt: Mechanistic and clinical implications. *World J Gastroenterol* 2025;31(3):100752. doi:10.3748/wjg.v31.i3.100752, PMID:39839897.
- [202] Zhou Z, Lv H, Lv J, Shi Y, Huang H, Chen L, *et al.* Alterations of gut

- microbiota in cirrhotic patients with spontaneous bacterial peritonitis: A distinctive diagnostic feature. *Front Cell Infect Microbiol* 2022;12:999418. doi:10.3389/fcimb.2022.999418, PMID:36147601.
- [203] Bajaj JS, Reddy KR, Tandon P, Garcia-Tsao G, Kamath PS, O’Leary JG, *et al*. Association of serum metabolites and gut microbiota at hospital admission with nosocomial infection development in patients with cirrhosis. *Liver Transpl* 2022;28(12):1831–1840. doi:10.1002/lt.26552, PMID:36017804.
- [204] Chen Y, Lv T, Yan D, Zheng L, Zheng B, Wang J, *et al*. Disordered Intestinal Microbial Communities During Clostridioides difficile Colonization and Subsequent Infection of Hepatic Cirrhosis Patients in a Tertiary Care Hospital in China. *Front Cell Infect Microbiol* 2022;12:825189. doi:10.3389/fcimb.2022.825189, PMID:35433508.
- [205] Yuan M, Hu X, Yao L, Chen P, Wang Z, Liu P, *et al*. Causal Relationship Between Gut Microbiota and Liver Cirrhosis: 16S rRNA Sequencing and Mendelian Randomization Analyses. *J Clin Transl Hepatol* 2024;12(2):123–133. doi:10.14218/JCTH.2023.00259, PMID:38343609.
- [206] Zhang DY, Li D, Chen SJ, Zhang LJ, Zhu XL, Chen FD, *et al*. Bacteroides uniformis-generated hexadecanedioic acid ameliorates metabolic-associated fatty liver disease. *Gut Microbes* 2025;17(1):2508433. doi:10.1080/19490976.2025.2508433, PMID:40413726.
- [207] Zhang D, Wang Q, Li D, Chen S, Chen J, Zhu X, *et al*. Gut microbiome composition and metabolic activity in metabolic-associated fatty liver disease. *Virulence* 2025;16(1):2482158. doi:10.1080/21505594.2025.2482158, PMID:40122128.
- [208] Li X, Yi Y, Wu T, Chen N, Gu X, Xiang L, *et al*. Integrated microbiome and metabolome analysis reveals the interaction between intestinal flora and serum metabolites as potential biomarkers in hepatocellular carcinoma patients. *Front Cell Infect Microbiol* 2023;13:1170748. doi:10.3389/fcimb.2023.1170748, PMID:37260707.
- [209] Stols-Goncalves D, Mak AL, Madsen MS, van der Vossen EWJ, Bruinstroop E, Henneman P, *et al*. Faecal Microbiota transplantation affects liver DNA methylation in Non-alcoholic fatty liver disease: a multi-omics approach. *Gut Microbes* 2023;15(1):2223330. doi:10.1080/19490976.2023.2223330, PMID:37317027.
- [210] Yuan C, Fan J, Jiang L, Ye W, Chen Z, Wu W, *et al*. Integrated Analysis of Gut Microbiome and Liver Metabolome to Evaluate the Effects of Fecal Microbiota Transplantation on Lipopolysaccharide/D-galactosamine-Induced Acute Liver Injury in Mice. *Nutrients* 2023;15(5):1149. doi:10.3390/nu15051149, PMID:36904149.
- [211] Zhang Y, Li P, Chen B, Zheng R. Therapeutic effects of fecal microbial transplantation on alcoholic liver injury in rat models. *Clin Res Hepatol Gastroenterol* 2024;48(9):102478. doi:10.1016/j.clinre.2024.102478, PMID:39396755.
- [212] Mitten EK, Baffy G. Microbiota transplantation in portal hypertension: promises and pitfalls. *Clin Sci (Lond)* 2022;136(6):425–429. doi:10.1042/CS20220029, PMID:35333331.
- [213] Philips CA, Ahamed R, Abduljaleel JK, Rajesh S, Tharakan A, Augustine P. Significant gut microbiota related to patterns of drinking and alcohol relapse in patients with alcoholic hepatitis undergoing stool transplant or corticosteroid therapy. *Indian J Gastroenterol* 2023;42(5):724–730. doi:10.1007/s12664-023-01401-4, PMID:37548864.
- [214] Zeng J, Zhao D, Way G, Fagan A, Fuchs M, Puri P, *et al*. Intestinal mucosal mitochondrial oxidative phosphorylation worsens with cirrhosis progression and is ameliorated with fecal microbiota transplantation. *JCI Insight* 2025;10(4):e186649. doi:10.1172/jci.insight.186649, PMID:39773539.
- [215] Lu Q, Zhu R, Zhou L, Zhang R, Li Z, Xu P, *et al*. Gut dysbiosis contributes to the development of Budd-Chiari syndrome through immune imbalance. *mSystems* 2024;9(9):e0079424. doi:10.1128/msystems.00794-24, PMID:39166878.
- [216] Huang L, Wang S, Zhang H, Feng S, Zhong H, Chen J, *et al*. Clinical efficacy evaluation of washed microbiota transplantation treatment for metabolic related fatty liver disease and its impact on tongue coating microorganisms. *Front Endocrinol (Lausanne)* 2025;16:1684173. doi:10.3389/fendo.2025.1684173, PMID:41234231.
- [217] Ren S, Gao Y, Wang J, Feng J, Li J, Xiang T, *et al*. Yinchenhao decoction and its active compound rhein ameliorate intrahepatic cholestasis of pregnancy in mice via modulation of intestinal flora. *Phytomedicine* 2025;148:157397. doi:10.1016/j.phymed.2025.157397, PMID:41135275.
- [218] Wei Y, Li J, Zhu B, Hu Q, Lan M, Zhou J, *et al*. Metagenomic comparison of intestinal microbiota between normal and liver fibrotic rhesus macaques (Macaca mulatta). *Sci Rep* 2024;14(1):15677. doi:10.1038/s41598-024-64397-7, PMID:38977718.
- [219] Zhong HJ, Liu AQ, Huang DN, Zhou ZH, Xu SP, Wu L, *et al*. Exploring the impact of gut microbiota on liver health in mice and patients with Wilson disease. *Liver Int* 2024;44(10):2700–2713. doi:10.1111/liv.16046, PMID:39037193.
- [220] Deng Z, Mei S, Ouyang Z, Wang R, Wang L, Zou B, *et al*. Dysregulation of gut microbiota stimulates NETs-driven HCC intrahepatic metastasis: therapeutic implications of healthy faecal microbiota transplantation. *Gut Microbes* 2025;17(1):2476561. doi:10.1080/19490976.2025.2476561, PMID:40099491.
- [221] Lin D, Sun Q, Liu Z, Pan J, Zhu J, Wang S, *et al*. Gut microbiota and bile acids partially mediate the improvement of fibroblast growth factor 21 on methionine-choline-deficient diet-induced non-alcoholic fatty liver disease mice. *Free Radic Biol Med* 2023;195:199–218. doi:10.1016/j.freeradbiomed.2022.12.087, PMID:36586452.
- [222] Wang X, Jin Y, Di C, Zeng Y, Zhou Y, Chen Y, *et al*. Supplementation of Silymarin Alone or in Combination with Salvianolic Acids B and Puerarin Regulates Gut Microbiota and Its Metabolism to Improve High-Fat Diet-Induced NAFLD in Mice. *Nutrients* 2024;16(8):1169. doi:10.3390/nu16081169, PMID:38674860.
- [223] Xiao Y, Zhang X, Shao B, Wu Z, Li X, Yi D, *et al*. Hydroxytyrosol Improves Metabolic Dysfunction-Associated Fatty Liver Disease Dependent on the Modulation of Gut Microbiota. *J Agric Food Chem* 2025;73(43):27450–27468. doi:10.1021/acs.jafc.5c07003, PMID:4114530.
- [224] Zhang H, Li C, Han L, Xiao Y, Bian J, Liu C, *et al*. MUP1 mediates urolithin A alleviation of chronic alcohol-related liver disease via gut-microbiota-liver axis. *Gut Microbes* 2024;16(1):2367342. doi:10.1080/19490976.2024.2367342, PMID:38889450.
- [225] Nie C, Lan J, Guo H, Ouyang Q, Zhao Y, Wang P, *et al*. Codonopsis pilosula polysaccharides (CPP) intervention alleviates sterigmatocystin (STC)-induced liver injury and gut microbiota dysbiosis. *Int J Biol Macromol* 2024;275(Pt 2):133190. doi:10.1016/j.ijbiomac.2024.133190, PMID:38897503.
- [226] Xu B, Hao K, Chen X, Wu E, Nie D, Zhang G, *et al*. Broussonetia papyrifera Polysaccharide Alleviated Acetaminophen-Induced Liver Injury by Regulating the Intestinal Flora. *Nutrients* 2022;14(13):2636. doi:10.3390/nu14132636, PMID:35807816.
- [227] Chen L, Pu X, Li L, Zhang M, Liu Y, Hu K, *et al*. Shenling Jianpiwei formula ameliorates metabolic associated fatty liver disease through modulation of the gut microbiota and attenuation of LPS-mediated inflammation. *Fitoterapia* 2025;186:106862. doi:10.1016/j.fitote.2025.106862, PMID:40930188.
- [228] Wang T, Wang D, Ding Y, Xu H, Sun Y, Hou J, *et al*. Targeting Non-Alcoholic Fatty Liver Disease with Hawthorn Ethanol Extract (HEE): A Comprehensive Examination of Hepatic Lipid Reduction and Gut Microbiota Modulation. *Nutrients* 2024;16(9):1335. doi:10.3390/nu16091335, PMID:38732582.
- [229] Yang T, Guan Q, Shi JS, Xu ZH, Geng Y. Metformin alleviates liver fibrosis in mice by enriching Lactobacillus sp. MF-1 in the gut microbiota. *Biochim Biophys Acta Mol Basis Dis* 2023;1869(5):166664. doi:10.1016/j.bbdis.2023.166664, PMID:36893671.
- [230] Shi Y, Chen J, Qu D, Sun Q, Yu Y, Zhang H, *et al*. Ginsenoside Rg(5) Activates the LKB1/AMPK/mTOR Signaling Pathway and Modifies the Gut Microbiota to Alleviate Nonalcoholic Fatty Liver Disease Induced by a High-Fat Diet. *Nutrients* 2024;16(6):842. doi:10.3390/nu16060842, PMID:38542753.
- [231] Wang S, Li X, Zhang B, Li Y, Chen K, Qi H, *et al*. Tangshen formula targets the gut microbiota to treat non-alcoholic fatty liver disease in HFD mice: A 16S rRNA and non-targeted metabolomics analyses. *Biomed Pharmacother* 2024;173:116405. doi:10.1016/j.biopha.2024.116405, PMID:38484559.
- [232] Xu Y, Ni Y, Zhou M, Gou X. Qushi Huayu decoction alleviates NAFLD in mice by regulating gut microbiota homeostasis in the gut-liver axis via the pregnane X receptor. *Eur J Pharmacol* 2025;1008:178366. doi:10.1016/j.ejphar.2025.178366, PMID:41241335.

- [233] Li Y, Hu H, Yang H, Lin A, Xia H, Cheng X, *et al.* Vine Tea (*Ampelopsis grossedentata*) Extract Attenuates CCl₄-Induced Liver Injury by Restoring Gut Microbiota Dysbiosis in Mice. *Mol Nutr Food Res* 2022;66(9):e2100892. doi:10.1002/mnfr.202100892, PMID:35188709.
- [234] Xiao K, Li H, Li Y, Zhan B, Fang X, Zhao B, *et al.* Protective effects and mechanism of Sangyu granule on acetaminophen-induced liver injury in mice. *J Ethnopharmacol* 2024;331:118282. doi:10.1016/j.jep.2024.118282, PMID:38701935.
- [235] Hugenholtz F, de Vos WM. Mouse models for human intestinal microbiota research: a critical evaluation. *Cell Mol Life Sci* 2018;75(1):149–160. doi:10.1007/s00018-017-2693-8, PMID:29124307.
- [236] Walter J, Armet AM, Finlay BB, Shanahan F. Establishing or Exaggerating Causality for the Gut Microbiome: Lessons from Human Microbiota-Associated Rodents. *Cell* 2020;180(2):221–232. doi:10.1016/j.cell.2019.12.025, PMID:31978342.
- [237] Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox JJ, *et al.* Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* 2017;66(6):1727–1738. doi:10.1002/hep.29306, PMID:28586116.
- [238] Bloom PP, Donlan J, Torres Soto M, Daidone M, Hohmann E, Chung RT. Fecal microbiota transplant improves cognition in hepatic encephalopathy and its effect varies by donor and recipient. *Hepatology* 2022;6(8):2079–2089. doi:10.1002/hep4.1950, PMID:35384391.
- [239] Tian Y, Xu Q, Wu Z, Wang H, Hu X, He N, *et al.* Ameliorating Effect of *Bifidobacterium breve* CM02-09T on High-Fat Diet-Induced Non-alcoholic Fatty Liver Disease in Mice. *FASEB J* 2025;39(16):e70957. doi:10.1096/fj.202501250RR, PMID:40832781.
- [240] Wenlin C, Fang L, Yuncheng Z, Jinzhen LV, Daguo Y. Effects of Zhenggan Huayu decoction combined with entecavir on gut microbiota in patients with chronic hepatitis B fibrosis. *J Tradit Chin Med* 2023;43(3):559–567. doi:10.19852/j.cnki.jtcm.20230208.002, PMID:37147758.
- [241] Yang X, Li S, Feng Y, Guo Y, Guo Z, Hu Y. A novel extracellular mannan from *Bacillus velezensis* ameliorates metabolic-associated fatty liver disease by modulating gut microbiota in mice model. *Carbohydr Polym* 2025;368(Pt 1):124150. doi:10.1016/j.carbpol.2025.124150, PMID:40912813.
- [242] Hu YC, Ding XC, Liu HJ, Ma WL, Feng XY, Ma LN. Effects of *Lactobacillus paracasei* N1115 on gut microbial imbalance and liver function in patients with hepatitis B-related cirrhosis. *World J Gastroenterol* 2024;30(11):1556–1571. doi:10.3748/wjg.v30.i11.1556, PMID:38617455.
- [243] Chen S, Han P, Zhang Q, Liu P, Liu J, Zhao L, *et al.* *Lactobacillus brevis* alleviates the progress of hepatocellular carcinoma and type 2 diabetes in mice model via interplay of gut microflora, bile acid and NOTCH 1 signaling. *Front Immunol* 2023;14:1179014. doi:10.3389/fimmu.2023.1179014, PMID:37234174.
- [244] Geng W, Zhang Y, Yang J, Zhang J, Zhao J, Wang J, *et al.* Identification of a novel probiotic and its protective effects on NAFLD via modulating gut microbial community. *J Sci Food Agric* 2022;102(11):4620–4628. doi:10.1002/jsfa.11820, PMID:35174500.
- [245] Lok J, Chen C, Iannone V, Babu AF, Lo EKK, Vazquez-Urbe R, *et al.* Advanced Microbiome Therapeutics Accelerate MASLD Recovery by Restoring Intestinal Microbiota Equilibrium and the Gut–Liver Axis in a Mouse Model. *J Agric Food Chem* 2025;73(24):15199–15214. doi:10.1021/acs.jafc.5c01674, PMID:40480642.
- [246] Song W, Wang T, Cui X, Li L, Chen B, Li Y, *et al.* *Lactobacillus coryniformis* subsp. *torquens* T3 alleviates non-alcoholic fatty liver disease via reconstruction of the gut microbiota and redox system. *J Sci Food Agric* 2023;103(14):6814–6825. doi:10.1002/jsfa.12774, PMID:37300818.
- [247] He Q, Yang C, Kang X, Chen Y, Zhang T, Zhang H, *et al.* Intake of *Bifidobacterium lactis* ProBio-M8 fermented milk protects against alcoholic liver disease. *J Dairy Sci* 2022;105(4):2908–2921. doi:10.3168/jds.2021-21265, PMID:35086715.
- [248] Czarnowski P, Wierzbicka-Rucińska A, Socha P. Relationship of gut microbiota and immunological response in obesity-related non-alcoholic fatty liver disease in children. *Acta Biochim Pol* 2023;70(3):469–474. doi:10.18388/abp.2020_6573, PMID:37672729.
- [249] Ran X, Wang YJ, Li SG, Dai CB. Effects of *Bifidobacterium* and rosuvastatin on metabolic-associated fatty liver disease via the gut–liver axis. *Lipids Health Dis* 2024;23(1):401. doi:10.1186/s12944-024-02391-8, PMID:39696288.
- [250] Zhu W, Yan M, Cao H, Zhou J, Xu Z. Effects of *Clostridium butyricum* Capsules Combined with Rosuvastatin on Intestinal Flora, Lipid Metabolism, Liver Function and Inflammation in NAFLD Patients. *Cell Mol Biol (Noisy-le-grand)* 2022;68(2):64–69. doi:10.14715/cmb/2022.68.2.10, PMID:35869734.
- [251] Duan W, Liu F, Ren Y, Zhang X, Shi JS, Xue Y, *et al.* Differences in the Ability of Lactic Acid Bacteria To Prevent Acute Alcohol-Induced Liver Injury via the Gut Microbiota–Bile Acid–Liver Axis. *J Agric Food Chem* 2024;72(27):15265–15275. doi:10.1021/acs.jafc.4c01353, PMID:38918075.
- [252] Yang J, Gao H, Zhang T, Fan Y, Wu Y, Zhao X, *et al.* In Vitro Lactic Acid Bacteria Anti-Hepatitis B Virus (HBV) Effect and Modulation of the Intestinal Microbiota in Fecal Cultures from HBV-Associated Hepatocellular Carcinoma Patients. *Nutrients* 2024;16(5):600. doi:10.3390/nu16050600, PMID:38474727.
- [253] Li LF, Tan ZW, Wang YR, Mao XR, Jiang JX, Liu RR, *et al.* Genotypic and phenotypic characterization of *Lactobacillus paracasei* HP-B1337 associated with lipotropic effect on high-fat-diet-induced obesity mice. *J Appl Microbiol* 2025;136(11):lxf265. doi:10.1093/jambio/lxf265, PMID:41143740.
- [254] Zhang M, Zhang S, Wu H, Xu L, Gao P, Gao Y, *et al.* *Lactobacillus plantarum* 1-2-3 inhibits ferroptosis by regulating dysregulated fatty acid metabolism to protect mice from high-fat diet-induced MAFLD. *Free Radic Biol Med* 2025;238:137–151. doi:10.1016/j.freeradbiomed.2025.06.042, PMID:40555343.
- [255] Wei B, Peng Z, Xiao M, Huang T, Yang S, Liu K, *et al.* Modulation of the Microbiome–Fat–Liver Axis by Lactic Acid Bacteria: A Potential Alleviated Role in High-Fat-Diet-Induced Obese Mice. *J Agric Food Chem* 2023;71(27):10361–10374. doi:10.1021/acs.jafc.3c03149, PMID:37390401.
- [256] Zhang F, Lo EKK, Chen J, Wang K, Felicianna, Ismaiah MJ, *et al.* Probiotic Mixture Ameliorates a Diet-Induced MASLD/MASH Murine Model through the Regulation of Hepatic Lipid Metabolism and the Gut Microbiome. *J Agric Food Chem* 2024;72(15):8536–8549. doi:10.1021/acs.jafc.3c08910, PMID:38575146.
- [257] Hu W, Gao W, Liu Z, Fang Z, Wang H, Zhao J, *et al.* Specific Strains of *Faecalibacterium prausnitzii* Ameliorate Nonalcoholic Fatty Liver Disease in Mice in Association with Gut Microbiota Regulation. *Nutrients* 2022;14(14):2945. doi:10.3390/nu14142945, PMID:35889903.
- [258] Wei J, Luo J, Yang F, Feng X, Zeng M, Dai W, *et al.* Cultivated *Enterococcus faecium* B6 from children with obesity promotes nonalcoholic fatty liver disease by the bioactive metabolite tyramine. *Gut Microbes* 2024;16(1):2351620. doi:10.1080/19490976.2024.2351620, PMID:38738766.
- [259] Ni Y, Qian L, Siliceo SL, Long X, Nychas E, Liu Y, *et al.* Resistant starch decreases intrahepatic triglycerides in patients with NAFLD via gut microbiome alterations. *Cell Metab* 2023;35(9):1530–1547.e8. doi:10.1016/j.cmet.2023.08.002, PMID:37673036.
- [260] Mantri A, Köhlmoos A, Schelski DS, Seel W, Stoffel-Wagner B, Krawitz P, *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, PMID:38732547.
- [261] Mitrović M, Dobrosavljević A, Odanović O, Knežević-Ivanovski T, Kralj Đ, Erceg S, *et al.* The effects of synbiotics on the liver steatosis, inflammation, and gut microbiome of metabolic dysfunction-associated liver disease patients-randomized trial. *Rom J Intern Med* 2024;62(2):184–193. doi:10.2478/rjim-2024-0004, PMID:38421902.
- [262] Kang Y, Ren P, Shen X, Kuang X, Yang X, Liu H, *et al.* A Newly Synbiotic Combination Alleviates Obesity by Modulating the Gut Microbiota–Fat Axis and Inhibiting the Hepatic TLR4/NF-κB Signaling Pathway. *Mol Nutr Food Res* 2023;67(24):e2300141. doi:10.1002/mnfr.202300141, PMID:37594720.
- [263] Huang X, Chen Q, Fan Y, Yang R, Gong G, Yan C, *et al.* Fructooligosaccharides attenuate non-alcoholic fatty liver disease by remodeling gut microbiota and association with lipid metabolism. *Biomed Pharmacoth*

- er 2023;159:114300. doi:10.1016/j.biopha.2023.114300, PMID:36696803.
- [264] Tian Y, Zhou Y, Liao W, Xia J, Hu Q, Zhao Q, *et al*. Flaxseed powder supplementation in non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Food Funct* 2025;16(4):1389–1406. doi:10.1039/d4fo05847j, PMID:39878023.
- [265] Zhang J, Li C, Duan M, Qu Z, Wang Y, Dong Y, *et al*. The Improvement Effects of Weizmannia coagulans BC99 on Liver Function and Gut Microbiota of Long-Term Alcohol Drinkers: A Randomized Double-Blind Clinical Trial. *Nutrients* 2025;17(2):320. doi:10.3390/nu17020320, PMID:39861457.
- [266] Tian S, Lei Y, Zhao F, Che J, Wu Y, Lei P, *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, PMID:39045769.
- [267] Mitrović M, Stanković Popović V, Erceg S, Perišić Mitrović M, Dobrosavljević A, Stupar A, *et al*. Exploring the Potential of Oral Butyrate Supplementation in Metabolic Dysfunction-Associated Steatotic Liver Disease: Subgroup Insights from an Interventional Study. *Int J Mol Sci* 2025;26(12):5561. doi:10.3390/ijms26125561, PMID:40565024.
- [268] He Y, Chen X, Li Y, Liang Y, Hong T, Yang J, *et al*. Curcumin supplementation alleviates hepatic fat content associated with modulation of gut microbiota-dependent bile acid metabolism in patients with non-alcoholic simple fatty liver disease: a randomized controlled trial. *Am J Clin Nutr* 2024;120(1):66–79. doi:10.1016/j.ajcnut.2024.05.017, PMID:38795741.
- [269] Jiang X, Shi T, Han D, Chen J. Exenatide and Metformin Improve Serum Indices and Intestinal Flora in patients with Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease. *J Pak Med Assoc* 2024;74(1):138–140. doi:10.47391/JPMA.8295, PMID:38219182.
- [270] Calabrese FM, Disciglio V, Franco I, Sorino P, Bonfiglio C, Bianco A, *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, PMID:35565740.
- [271] Xue Y, Zhang J. Association between Dietary Index for Gut Microbiota (DI-GM) and non-alcoholic fatty liver disease (NAFLD): Evidence from NHANES 1999–2018. *Asia Pac J Clin Nutr* 2025;34(4):636–646. doi:10.6133/apjcn.202508_34(4).0015, PMID:40738731.
- [272] Calabrese FM, Aloisio Caruso E, De Nunzio V, Celano G, Pinto G, Cofano M, *et al*. Metatranscriptomics and Metabolomics Profiles in Metabolic Dysfunction-Associated Fatty Liver Disease Patients on a "Navelina" Orange-Enriched Diet. *Nutrients* 2024;16(20):3543. doi:10.3390/nu16203543, PMID:39458536.
- [273] He K, Guo LL, Tang H, Peng X, Li J, Feng S, *et al*. A Freshwater Fish-Based Diet Alleviates Liver Steatosis by Modulating Gut Microbiota and Metabolites: A Clinical Randomized Controlled Trial in Chinese Participants With Nonalcoholic Fatty Liver Disease. *Am J Gastroenterol* 2022;117(10):1621–1631. doi:10.14309/ajg.0000000000001885, PMID:35973188.
- [274] Badal BD, Fagan A, Tate V, Mousel T, Gallagher ML, Puri P, *et al*. Substitution of One Meat-Based Meal With Vegetarian and Vegan Alternatives Generates Lower Ammonia and Alters Metabolites in Cirrhosis: A Randomized Clinical Trial. *Clin Transl Gastroenterol* 2024;15(6):e1. doi:10.14309/ctg.0000000000000707, PMID:38696431.
- [275] Reshef N, Gophna U, Reshef L, Konikoff F, Gabay G, Zornitzki T, *et al*. Prebiotic Treatment in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)—A Randomized Pilot Trial. *Nutrients* 2024;16(11):1571. doi:10.3390/nu16111571, PMID:38892505.
- [276] Li X, Pan C, Ma W, Yang T, Wang C, Han W, *et al*. Effects of dietary supplementation of fish oil plus vitamin D(3) on gut microbiota and fecal metabolites, and their correlation with nonalcoholic fatty liver disease risk factors: a randomized controlled trial. *Food Funct* 2024;15(5):2616–2627. doi:10.1039/d3fo02319b, PMID:38356413.
- [277] Gan L, Feng Y, Du B, Fu H, Tian Z, Xue G, *et al*. Bacteriophage targeting microbiota alleviates non-alcoholic fatty liver disease induced by high alcohol-producing *Klebsiella pneumoniae*. *Nat Commun* 2023;14(1):3215. doi:10.1038/s41467-023-39028-w, PMID:37270557.
- [278] Zhang J, Yang J, Luo J, Wu W, Luo H, Wei W, *et al*. Lactobacillus acidophilus potentiates oncolytic virotherapy through modulating gut microbiota homeostasis in hepatocellular carcinoma. *Nat Commun* 2025;16(1):3315. doi:10.1038/s41467-025-58407-z, PMID:40195307.
- [279] Mascardi MF, Mazzini FN, Suárez B, Ruda VM, Marciano S, Casciato P, *et al*. Integrated analysis of the transcriptome and its interaction with the metabolome in metabolic associated fatty liver disease: Gut microbiome signatures, correlation networks, and effect of PN-PLA3 genotype. *Proteomics* 2023;23(18):e2200414. doi:10.1002/pmic.202200414, PMID:37525333.
- [280] Zheng Y, Chen J, Zhang Y, Guan H, Deng S, Chang D, *et al*. Gut Microbiota and Bile Acid Metabolism in the Mechanism of Ginsenoside Re Against Nonalcoholic Fatty Liver Disease. *Phytother Res* 2025;39(5):2339–2356. doi:10.1002/ptr.8474, PMID:40170504.
- [281] Xu H, Yuan M, Niu K, Yang W, Jiang M, Zhang L, *et al*. Involvement of Bile Acid Metabolism and Gut Microbiota in the Amelioration of Experimental Metabolism-Associated Fatty Liver Disease by Nobiletin. *Molecules* 2024;29(5):976. doi:10.3390/molecules29050976, PMID:38474489.
- [282] Liu J, Sun J, Yu J, Chen H, Zhang D, Zhang T, *et al*. Gut microbiome determines therapeutic effects of OCA on NAFLD by modulating bile acid metabolism. *NPJ Biofilms Microbiomes* 2023;9(1):29. doi:10.1038/s41522-023-00399-z, PMID:37258543.
- [283] Zhang D, Ma Y, Liu J, Wang D, Geng Z, Wen D, *et al*. Fenofibrate improves hepatic steatosis, insulin resistance, and shapes the gut microbiome via TFEB-autophagy in NAFLD mice. *Eur J Pharmacol* 2023;960:176159. doi:10.1016/j.ejphar.2023.176159, PMID:37898287.
- [284] Alqudah S, DeLucia B, Osborn LJ, Markley RL, Bobba V, Preston SM, *et al*. The diet-derived gut microbial metabolite 3-phenylpropionic acid reverses insulin resistance and obesity-associated metabolic dysfunction. *Mol Metab* 2025;102:102272. doi:10.1016/j.molmet.2025.102272, PMID:41110769.
- [285] Pomej K, Frick A, Scheiner B, Balcar L, Pajancic L, Klotz A, *et al*. Study protocol: Fecal Microbiota Transplant combined with Atezolizumab/Bevacizumab in Patients with Hepatocellular Carcinoma who failed to achieve or maintain objective response to Atezolizumab/Bevacizumab - the FAB-HCC pilot study. *PLoS One* 2025;20(4):e0321189. doi:10.1371/journal.pone.0321189, PMID:40233040.
- [286] Zeng Y, Wu R, He Y, Zhang Q, Wang Z, Qin P, *et al*. Cohabitation facilitates microbiome shifts that promote isoflavone transformation to ameliorate liver injury. *Cell Host Microbe* 2025;33(5):688–704.e10. doi:10.1016/j.chom.2025.04.011, PMID:40318624.
- [287] Zhong Y, Sun P, Yu J, Luo X, He Z, Yang S, *et al*. Identification of Core gene expression alterations regulated by gut microbiota in tumor progression and immunotherapy resistance through integrative pan-cancer analysis. *Int J Biol Macromol* 2025;322(Pt 3):146911. doi:10.1016/j.ijbiomac.2025.146911, PMID:40819753.
- [288] Preethy S, Ikewaki N, Levy GA, Raghavan K, Dedeepiya VD, Yamamoto N, *et al*. Two unique biological response-modifier glucans beneficially regulating gut microbiota and faecal metabolome in a non-alcoholic steatohepatitis animal model, with potential applications in human health and disease. *BMJ Open Gastroenterol* 2022;9(1):e000985. doi:10.1136/bmjgast-2022-000985, PMID:36167455.
- [289] Zhang T, Lu G, Zhao Z, Liu Y, Shen Q, Li P, *et al*. Washed microbiota transplantation vs. manual fecal microbiota transplantation: clinical findings, animal studies and in vitro screening. *Protein Cell* 2020;11(4):251–266. doi:10.1007/s13238-019-00684-8, PMID:31919742.
- [290] Fecal Microbiota Transplantation-standardization Study Group. Nanjing consensus on methodology of washed microbiota transplantation. *Chin Med J (Engl)* 2020;133(19):2330–2332. doi:10.1097/CM9.0000000000000954, PMID:32701590.
- [291] Zhou Y, Wang M, Wang Z, Qiu J, Wang Y, Li J, *et al*. Polysaccharides from hawthorn fruit alleviate high-fat diet-induced NAFLD in mice by improving gut microbiota dysbiosis and hepatic metabolic disorder. *Phytomedicine* 2025;139:156458. doi:10.1016/j.phymed.2025.156458, PMID:39919328.
- [292] Yang Y, Li M, Wang Q, Huang H, Zhao Y, Du F, *et al*. Pueraria lobata starch regulates gut microbiota dysbiosis and alleviates high-fat high-cholesterol diet induced non-alcoholic fatty liver disease in mice. *Food Res Int* 2022;157:111401. doi:10.1016/j.foodres.2022.111401, PMID:35761655.

- [293] Zuo G, Li M, Guo X, Wang L, Yao Y, Huang JA, *et al.* Fu brick tea supplementation ameliorates non-alcoholic fatty liver disease and associated endotoxemia via maintaining intestinal homeostasis and remodeling hepatic immune microenvironment. *Food Res Int* 2025;209:116207. doi:10.1016/j.foodres.2025.116207, PMID:40253128.
- [294] Chen L-p, Zhang L-f, Liu S, Hua H, Zhang L, Liu B-c, *et al.* Ling-Gui-Zhu-Gan decoction ameliorates nonalcoholic fatty liver disease via modulating the gut microbiota. *Microbiol Spectr* 2024;12(6):e0197923. doi:10.1128/spectrum.01979-23, PMID:38647315.
- [295] Liu Q, Li X, Pan Y, Liu Q, Li Y, He C, *et al.* Efficacy and safety of Qushi Huayu, a traditional Chinese medicine, in patients with non-alcoholic fatty liver disease in a randomized controlled trial. *Phytotherapy* 2024;130:155398. doi:10.1016/j.phymed.2024.155398, PMID:38788390.
- [296] Zhou M, Zhang Y, Song Z, Tang S, Liu Z, Pang M, *et al.* Enhanced bioactivity of honeysuckle-Cassia seeds extracts through *Lactobacillus acidophilus* and *Bacillus subtilis* co-fermentation: Impact on alcoholic liver disease and gut microbiota. *Food Chem* 2025;486:144463. doi:10.1016/j.foodchem.2025.144463, PMID:40339419.
- [297] Li M, Deng K, Zheng R, Li Y, Xiang L, Cheng J, *et al.* Mechanism of Bao Gan Ning decoction in attenuating hepatic fibrosis via modulation of the gut microbiome and PPAR/CYP7A1-mediated bile acid metabolism. *J Ethnopharmacol* 2025;353(Pt B):120488. doi:10.1016/j.jep.2025.120488, PMID:40865652.
- [298] Feng J, Ma H, Yue Y, Wang L, Hao K, Zhang Y, *et al.* Saikosaponin a ameliorates diet-induced fatty liver via regulating intestinal microbiota and bile acid profile in laying hens. *Poult Sci* 2023;102(12):103155. doi:10.1016/j.psj.2023.103155, PMID:37871490.
- [299] Cheng X, Hu Y, Kuang J, Guo X, Cao H, Wu H, *et al.* Berberine alleviates high-energy and low-protein diet-induced fatty liver hemorrhagic syndrome in laying hens: insights from microbiome and metabolomics. *Poult Sci* 2024;103(8):103968. doi:10.1016/j.psj.2024.103968, PMID:38959643.
- [300] He X, Hao P, Wang Y, Wu C, Yin W, Shahid MA, *et al.* *Swertia bimaculata* moderated liver damage in mice by regulating intestine microbiota. *Ecotoxicol Environ Saf* 2023;263:115223. doi:10.1016/j.ecoenv.2023.115223, PMID:37418941.
- [301] Zhao Z, Wang J, Ren W, Bian Y, Wang Y, Wang L, *et al.* Effect of Jiangnan-Jiangzhi Pill on Gut Microbiota and Chronic Inflammatory Response in Rats with Non-Alcoholic Fatty Liver. *Chem Biodivers* 2022;19(5):e202100987. doi:10.1002/cbdv.202100987, PMID:35324083.
- [302] Wang S, Li XY, Ji HF, Shen L. Modulation of gut microbiota by glycyrrhizic acid may contribute to its anti-NAFLD effect in rats fed a high-fat diet. *Life Sci* 2022;310:121110. doi:10.1016/j.lfs.2022.121110, PMID:36272466.
- [303] Xu F, Li H, Pan Y, Zeng Y, Li J, Li S. Effects of Ganfule capsule on microbial and metabolic profiles in anti-hepatocellular carcinoma. *J Appl Microbiol* 2022;132(3):2280–2292. doi:10.1111/jam.15307, PMID:34564943.
- [304] Zhu Z, Zuo S, Zhu Z, Wang C, Du Y, Chen F. THSWD upregulates the LTF/AMPK/mTOR/Becn1 axis and promotes lysosomal autophagy in hepatocellular carcinoma cells by regulating gut flora and metabolic reprogramming. *Int Immunopharmacol* 2025;148:114091. doi:10.1016/j.intimp.2025.114091, PMID:39826450.
- [305] Xin-Yi Z, Bai-Lu C, Ruo-Yi Z, Shi-Yu H, Ze-Han C, Quan-Xi W, *et al.* Zhi-Zi-chi decoction: A promising remedy for liver inflammation via gut microbiota modulation. *Fitoterapia* 2025;184:106603. doi:10.1016/j.fitote.2025.106603, PMID:40414434.
- [306] Chen LW, Wu IW, Cheng TC, Chang LC, Hsu CK, Yeung L, *et al.* Hepatoprotective Potential of *Bacteroides eggerthii* on Fatty Liver Disease: A Mouse Model Study. *In Vivo* 2025;39(6):3226–3235. doi:10.21873/invivo.14122, PMID:41167668.
- [307] Wang H, Wang Q, Yang C, Guo M, Cui X, Jing Z, *et al.* *Bacteroides acidifaciens* in the gut plays a protective role against CD95-mediated liver injury. *Gut Microbes* 2022;14(1):2027853. doi:10.1080/19490976.2022.2027853, PMID:35129072.
- [308] Li H, Wang XK, Tang M, Lei L, Li JR, Sun H, *et al.* *Bacteroides thetaiotaomicron* ameliorates mouse hepatic steatosis through regulating gut microbial composition, gut-liver folate and unsaturated fatty acids metabolism. *Gut Microbes* 2024;16(1):2304159. doi:10.1080/19490976.2024.2304159, PMID:38277137.
- [309] Sharma SP, Cha MG, Kwon GH, Song SH, Park JH, Kim MJ, *et al.* *Phocaicola plebeius* oral treatment improve fibrosis by reversing cirrhosis-related hepatic gene dysregulation. *Life Sci* 2025;381:123979. doi:10.1016/j.lfs.2025.123979, PMID:40992653.
- [310] Oñate FP, Chamignon C, Burz SD, Lapaque N, Monnoye M, Philippe C, *et al.* *Adlercreutzia equolifaciens* Is an Anti-Inflammatory Commensal Bacterium with Decreased Abundance in Gut Microbiota of Patients with Metabolic Liver Disease. *Int J Mol Sci* 2023;24(15):12232. doi:10.3390/ijms241512232, PMID:37569608.
- [311] Choi J, Choi YR, Jeong MK, Song HH, Yu JS, Song SH, *et al.* *Phocaicola dorei* ameliorates progression of steatotic liver disease by regulating bile acid, lipid, inflammation and proliferation. *Gut Microbes* 2025;17(1):2539448. doi:10.1080/19490976.2025.2539448, PMID:40754863.
- [312] Brödel AK, Charpenay LH, Galtier M, Fuche FJ, Terrasse R, Poquet C, *et al.* In situ targeted base editing of bacteria in the mouse gut. *Nature* 2024;632(8026):877–884. doi:10.1038/s41586-024-07681-w, PMID:38987595.
- [313] Lam KN, Spanogiannopoulos P, Soto-Perez P, Alexander M, Nalley MJ, Bisanz JE, *et al.* Phage-delivered CRISPR-Cas9 for strain-specific depletion and genomic deletions in the gut microbiome. *Cell Rep* 2021;37(5):109930. doi:10.1016/j.celrep.2021.109930, PMID:34731631.
- [314] Pathak P, Helsley RN, Brown AL, Buffa JA, Choucair I, Nemet I, *et al.* Small molecule inhibition of gut microbial choline trimethylamine lyase activity alters host cholesterol and bile acid metabolism. *Am J Physiol Heart Circ Physiol* 2020;318(6):H1474–H1486. doi:10.1152/ajpheart.00584.2019, PMID:32330092.
- [315] Hui D, Liu L, Azami NLB, Song J, Huang Y, Xu W, *et al.* The spleen-strengthening and liver-draining herbal formula treatment of non-alcoholic fatty liver disease by regulation of intestinal flora in clinical trial. *Front Endocrinol (Lausanne)* 2022;13:1107071. doi:10.3389/fendo.2022.1107071, PMID:36743913.
- [316] Long J, Saw M, Zhang P, Wang L, Li L, Ren H, *et al.* Role of tenofovir dipivoxil in gut microbiota recovery from HBV-infection induced dysbiosis. *BMC Microbiol* 2024;24(1):359. doi:10.1186/s12866-024-03457-4, PMID:39304810.
- [317] Pinchera B, Scotto R, Zappulo E, Buonomo AR, Maraolo AE, Schiano Moriello N, *et al.* Impact of oral antiviral therapy against HCV on gut microbiota. A prospective study. *New Microbiol* 2023;46(2):196–201. PMID:37247240.
- [318] Huang PY, Chen CH, Tsai MJ, Yao CC, Wang HM, Kuo YH, *et al.* Effects of direct anti-viral agents on the gut microbiota in patients with chronic hepatitis C. *J Formos Med Assoc* 2023;122(2):157–163. doi:10.1016/j.jfma.2022.08.022, PMID:36155707.
- [319] Midori Y, Nosaka T, Hiramatsu K, Akazawa Y, Tanaka T, Takahashi K, *et al.* Isolation of mucosa-associated microbiota dysbiosis in the ascending colon in hepatitis C virus post-sustained virologic response cirrhotic patients. *Front Cell Infect Microbiol* 2024;14:1371429. doi:10.3389/fcimb.2024.1371429, PMID:38650735.
- [320] Yifu F, Hetong Z, Yani Z, Zifei Y, Juan DU, Changquan L. Effectiveness of Jiedu granule on gut microbiota in patients with advanced hepatocellular carcinoma: a randomized controlled trial. *J Tradit Chin Med* 2022;42(6):988–996. doi:10.19852/j.cnki.jtcm.20220902.002, PMID:36378058.
- [321] Qu D, Wang Y, Xia Q, Chang J, Jiang X, Zhang H. Intratumoral Microbiome of Human Primary Liver Cancer. *Hepatol Commun* 2022;6(7):1741–1752. doi:10.1002/hep4.1908, PMID:35191218.
- [322] Dzutsev AK, Trinchieri G. A New Dimension in Tumor Heterogeneity: Intratumoral Bacteria Impact Multifocal Hepatocellular Carcinoma Development. *Cancer Discov* 2025;15(8):1540–1542. doi:10.1158/2159-8290.CD-25-0899, PMID:40755027.
- [323] Agodi A, Ojeda-Granados C, Maugeri A, Barchitta M, Coco O, Pezzino S, *et al.* Changes in Gut Microbial Composition and DNA Methylation in Obese Patients with NAFLD After Bariatric Surgery. *Int J Mol Sci* 2024;25(21):11510. doi:10.3390/ijms252111510, PMID:39519065.
- [324] Dong TS, Katzka W, Yang JC, Chang C, Arias-Jayo N, Lagishetty V, *et al.* Microbial changes from bariatric surgery alters glucose-dependent insulinotropic polypeptide and prevents fatty liver disease. *Gut Microbes* 2023;15(1):2167170. doi:10.1080/19490976.2023.2167170

- O, PMID:36732495.
- [325] Pérez-Rubio Á, Soluyanov P, Moro E, Quintás G, Rienda I, Periañez MD, *et al*. Gut Microbiota and Plasma Bile Acids Associated with Non-Alcoholic Fatty Liver Disease Resolution in Bariatric Surgery Patients. *Nutrients* 2023;15(14):3187. doi:10.3390/nu15143187, PMID: 37513605.
- [326] Uchida Y, Fujii T, Takahashi H, Nakaoka K, Funasaka K, Ohno E, *et al*. Alterations in the gut microbiota in patients with long-term follow-up after pancreaticoduodenectomy and their association with post-operative fatty liver: A pilot study. *Pancreatol* 2024;24(8):1348–1354. doi:10.1016/j.pan.2024.10.005, PMID:39419749.
- [327] Agrinier AL, Morissette A, Daoust L, Gignac T, Marois J, Varin TV, *et al*. Camu-camu decreases hepatic steatosis and liver injury markers in overweight, hypertriglyceridemic individuals: A randomized crossover trial. *Cell Rep Med* 2024;5(8):101682. doi:10.1016/j.xcrm.2024.101682, PMID:39168095.
- [328] Chi X, Cheng DY, Sun X, Liu SA, Wang RB, Chen Q, *et al*. Efficacy of Biejiajian Pill on Intestinal Microbiota in Patients with Hepatitis B Cirrhosis/Liver Fibrosis: A Randomized Double-Blind Controlled Trial. *Chin J Integr Med* 2023;29(9):771–781. doi:10.1007/s11655-023-3542-2, PMID:37222832.
- [329] Zhu R, Liu L, Zhang G, Dong J, Ren Z, Li Z. The pathogenesis of gut microbiota in hepatic encephalopathy by the gut-liver-brain axis. *Biosci Rep* 2023;43(6):BSR20222524. doi:10.1042/BSR20222524, PMID:37279097.
- [330] Kang Y, Kuang X, Yan H, Ren P, Yang X, Liu H, *et al*. A Novel Synbiotic Alleviates Autoimmune Hepatitis by Modulating the Gut Microbiota-Liver Axis and Inhibiting the Hepatic TLR4/NF-κB/NLRP3 Signaling Pathway. *mSystems* 2023;8(2):e0112722. doi:10.1128/msystems.01127-22, PMID:36794950.
- [331] Álvares-da-Silva MR, Oliveira CP, Fagan A, Longo L, Thoen RU, Yoshimura Zitelli PM, *et al*. Interaction of Microbiome, Diet, and Hospitalizations Between Brazilian and American Patients With Cirrhosis. *Clin Gastroenterol Hepatol* 2022;20(4):930–940. doi:10.1016/j.cgh.2021.03.045, PMID:33813071.
- [332] Zhao Y, Zhou R, Guo Y, Chen X, Zhang A, Wang J, *et al*. Improvement of gut microbiome and intestinal permeability following splenectomy plus pericardial devascularization in hepatitis B virus-related cirrhotic portal hypertension. *Front Immunol* 2022;13:941830. doi:10.3389/fimmu.2022.941830, PMID:36159870.
- [333] Pun CK, Huang HC, Chang CC, Chuang CL, Hsu SJ, Hou MC, *et al*. Fructooligosaccharides reverses hepatic vascular dysfunction and dysbiosis in rats with liver cirrhosis and portal hypertension. *Eur J Clin Invest* 2024;54(11):e14287. doi:10.1111/eci.14287, PMID:39017981.
- [334] Augustijn QJJ, Grefhorst A, de Groen P, Wortelboer K, Seegers JFM, Gül IS, *et al*. Randomised double-blind placebo-controlled trial protocol to evaluate the therapeutic efficacy of lyophilised faecal microbiota capsules amended with next-generation beneficial bacteria in individuals with metabolic dysfunction-associated steatohepatitis. *BMJ Open* 2025;15(1):e088290. doi:10.1136/bmjopen-2024-088290, PMID:39788762.
- [335] Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashariades S, *et al*. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. *Cell* 2018;174(6):1388–1405.e21. doi:10.1016/j.cell.2018.08.041, PMID:30193112.