

Gut-Liver Axis: A Novel Therapeutic Strategies for Liver Diseases

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Abstract:

The gut–liver axis is a complex bidirectional communication network that links the gastrointestinal tract and the liver through the portal vein, allowing continuous exchange of nutrients, bile components, microbial metabolites, and immune mediators. Alterations in the gut microbiota (gut dysbiosis) disrupt intestinal barrier integrity, increase intestinal permeability, and facilitate the translocation of bacterial endotoxins such as lipopolysaccharide (LPS) into the liver, thereby promoting inflammation, oxidative stress, insulin resistance, and fibrosis. These mechanisms play a important role in the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), hepatitis and Liver Carcinoma. Growing evidence suggests that modulation of the gut microbiota through probiotics, prebiotics, symbiotic, postbiotics, and fecal microbiota transplantation (FMT) may restore gut microbial balance, strengthen intestinal barrier function, reduce hepatic inflammation, and improve metabolic outcomes. In addition, next-generation probiotics and personalized micro biome-based therapies represent promising future strategies for disease management. This review highlights the physiological role of the gut–liver axis, the mechanisms by which gut dysbiosis contributes to MASLD and other Liver diseases pathogenesis, and the emerging therapeutic potential of probiotics and micro biota-targeted interventions in preventing disease progression and improving liver health.

Keywords: MSLD, gut micro biota, fecal micro biota transplantations (FMT), dysbiosis, through probiotics, prebiotics, synbiotics, postbiotics,

Introduction

The gut-liver axis is the close, bidirectional communication network that connects the gastrointestinal tract and the liver. This system relies on a direct physical link: the hepatic portal vein, which drains blood from the intestines straight to the liver. It allows the liver to process nutrients and environmental antigens, while simultaneously exposing it to toxins and microbial components coming from the gut. Chronic disruptions in the gut-liver axis are primary drivers for several major liver diseases [1,2].

The gut micro biota consists of trillions of microorganisms (*i.e.*, approximately 10^{14} bacteria and archaea) from more than 1000 species, with a total weight of approximately 1-2 kg [3]. Dysbiosis of the gut micro biota refers to an imbalance in the microbial community in terms of qualitative and quantitative changes, metabolic activity, and topographic distribution [4, 5, and 6]. The human gut micro biota is mainly composed of Bacteroidetes and Firmicutes. *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria* are present in minor proportions. Physiologically, they contribute 5%-15% of the dietary energy harvest by fermenting undigested alimentary residues. The macrobiotic of obese subjects have a higher capacity to harvest energy from the diet, thereby providing substrates that can activate the lipogenic pathways.[28].

Bidirectional crosstalk along the gut-liver axis controls gastrointestinal health and disease and exploits environmental and host mediators. Nutrients, microbial antigens, metabolites, and bile acids regulate metabolism and immune responses in the gut and liver, which reciprocally shape microbial community structure and function. Perturbation of such host-microbe interactions is observed in a variety of experimental liver diseases and is facilitated by an impaired intestinal barrier, which is fueling hepatic inflammation and disease

progression. Clinical evidence describes perturbation of the gut-liver crosstalk in non-alcoholic fatty liver disease, alcoholic liver disease, and primary sclerosing cholangitis. In liver cirrhosis, a common sequela of these diseases, the intestinal micro biota and microbial pathogen-associated molecular patterns constitute liver inflammation and clinical complications, such as encephalopathy. Because of this strong connection, modern treatments are shifting toward targeting the gut to cure the liver. This includes using specialized probiotics, prebiotics, and fecal micro biota transplantations (FMT) to rebuild the gut micro biome and protect liver function. . Understanding the intricate metabolic interplay between the gut and liver in health and disease opens an avenue for future therapies [7]

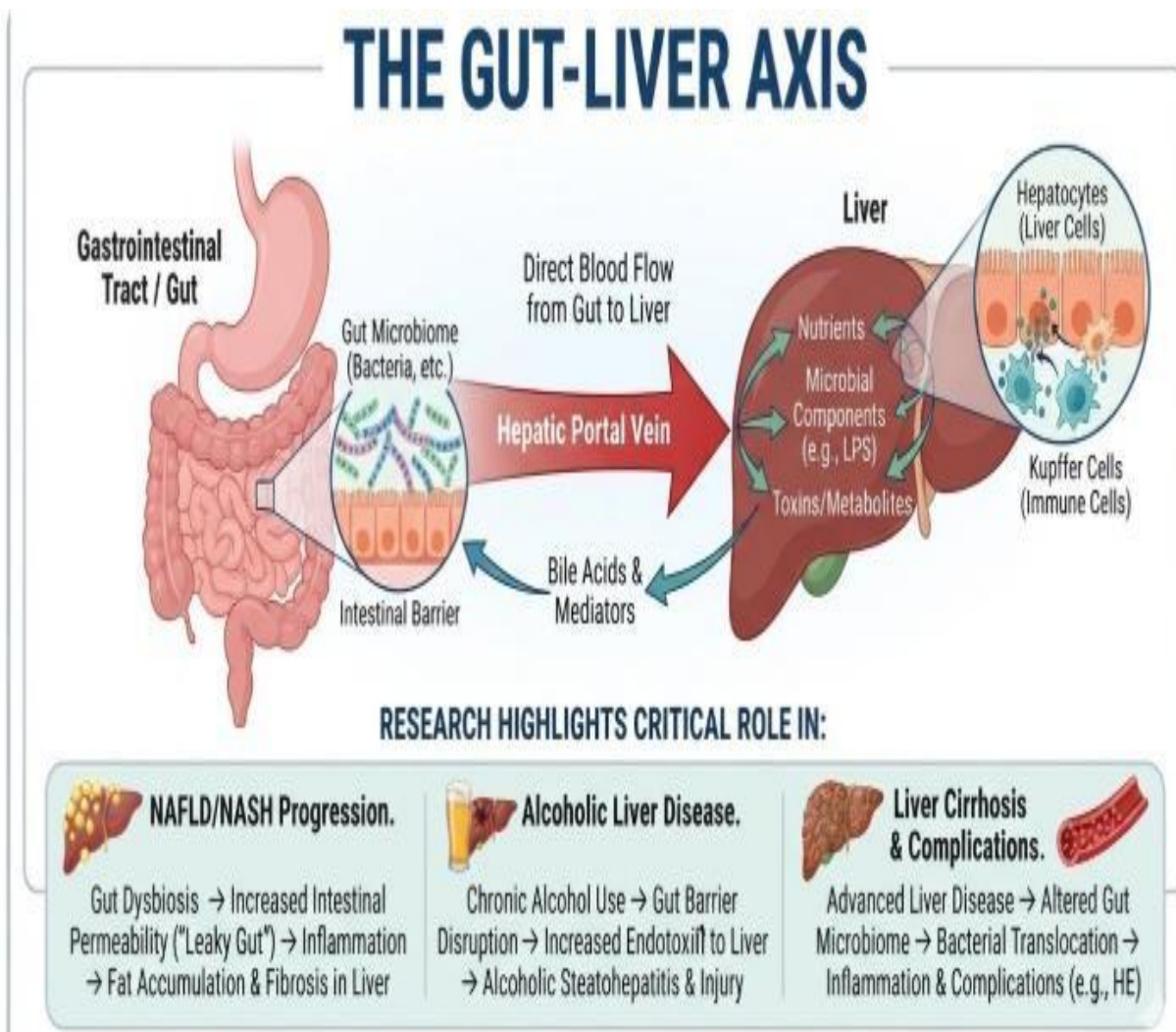


Figure 1: The gut-liver axis

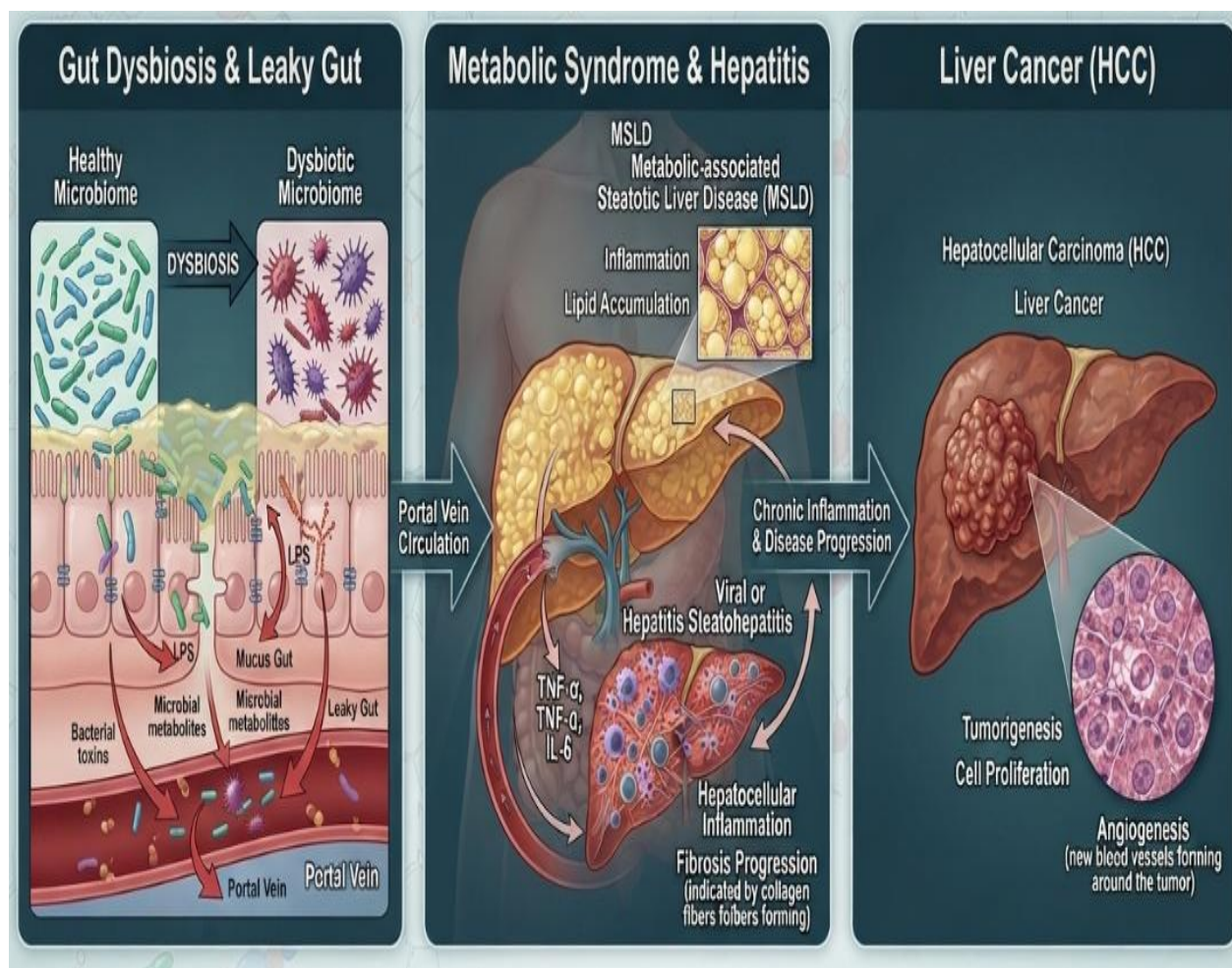


Figure 2: Gut-Liver Axis in Liver Disease Progression

Role of micro biota in metabolic dysfunction-associated steatotic liver disease

The liver and intestine are closely connected through the gut–liver axis, where the portal vein transports nutrients, microbial metabolites, and bacterial products directly from the intestine to the liver. Therefore, alterations in gut microbiota significantly influence liver health and contribute to the pathogenesis of MASLD. Role of Gut Microbiota in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD).[29]

1. Maintenance of Intestinal Barrier
2. Production of Short-Chain Fatty Acids (SCFAs)
3. Regulation of Lipid and Glucose Metabolism
4. Bile Acid Metabolism
5. Endotoxin Translocation and Inflammation
6. Immune Regulation
7. Choline and Ethanol Metabolism
8. Activation of Hepatic Stellate Cells

Mechanism of Gut Microbiota in the Pathogenesis of MASLD

Gut dysbiosis is a key driver in the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). The gut and liver are connected through the portal vein, allowing gut-derived microbial products to directly influence liver function. The mechanism involves the following sequential events:

1. Gut Dysbiosis

Unhealthy diets, obesity, insulin resistance, antibiotics, and other environmental factors alter the normal gut micro biota by reducing beneficial bacteria (*Lactobacillus*, *Bifid bacterium*, *Akkerman Sia*) and increasing pathogenic bacteria (*Escherichia coli*, *Klebsiella*, *Enterobacter*).

2. Increased Intestinal Permeability (“Leaky Gut”)

Gut dysbiosis disrupts the intestinal epithelial barrier by decreasing tight junction proteins such as occludin, claudins, and zonula occludens-1 (ZO-1). This results in increased intestinal permeability, allowing bacterial products to enter the bloodstream. Beneficial bacteria such as *Akkermansiamuciniphila*, *Bifidobacterium*, and *Lactobacillus* strengthen the intestinal barrier by promoting mucus secretion and tight junction proteins (occludin, claudins, and ZO-1). In MASLD, gut dysbiosis disrupts this barrier, increasing intestinal permeability (“leaky gut”) and allowing bacterial endotoxins to enter the portal circulation.

3. Translocation of Microbial Products

Bacterial components such as lipopolysaccharide (LPS), peptidoglycans, bacterial DNA, and microbial metabolites pass through the damaged intestinal barrier into the portal vein and are transported directly to the liver.

4. Activation of Hepatic Immune Cells

In the liver, LPS binds to Toll-like receptor 4 (TLR4) on Kupffer cells, hepatocytes, and hepatic stellate cells. This activates intracellular signalling pathways, particularly the nuclear factor-kappa B (NF- κ B) pathway. The gut micro biota maintains immune homeostasis by promoting regulatory T cells and anti-inflammatory cytokines. Dysbiosis activates innate immune cells and enhances chronic hepatic inflammation, facilitating the progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH).

5. Release of Pro-inflammatory Cytokines

Activation of NF- κ B stimulates the production of inflammatory mediators, including: Tumour necrosis factor- α (TNF- α), Interleukin-1 β (IL-1 β), Interleukin-6 (IL-6)

These cytokines promote hepatocyte injury, inflammation, and insulin resistance. Gut dysbiosis increases the abundance of Gram-negative bacteria that produce lipopolysaccharide (LPS). Increased intestinal permeability allows LPS to reach the liver, where it activates Toll-like receptor 4 (TLR4) on Kupffer cells. This stimulates the NF-signalling pathway, leading to the release of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which promote hepatocyte injury, inflammation, and fibrosis. Intestinal bacteria convert primary bile acids into secondary bile acids, which activate foresaid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5). These receptors regulate glucose metabolism, lipid metabolism, and inflammation. Gut dysbiosis disrupts bile acid signalling, contributing to hepatic steatosis and inflammation.

6. Oxidative Stress and Lipid Accumulation

Inflammation increases the production of reactive oxygen species (ROS), leading to mitochondrial dysfunction, lipid peroxidation, and hepatocyte apoptosis. At the same time, insulin resistance enhances de novo lipogenesis and free fatty acid accumulation, resulting in hepatic steatosis. Gut bacteria ferment dietary fiber to produce acetate, propionate, and butyrate. SCFAs provide energy to colonocytes, improve insulin sensitivity, reduce inflammation, maintain gut barrier integrity, and regulate lipid metabolism. Reduced SCFA-producing bacteria in MASLD contribute to insulin resistance and hepatic fat accumulation. The gut micro biota regulates lipid absorption, fatty acid oxidation, cholesterol metabolism, and glucose homeostasis. It also stimulates the release of gut hormones such as GLP-1 and PYY, which improve insulin sensitivity and energy balance. Dysbiosis promotes de novo lipogenesis, hepatic triglyceride accumulation, and insulin resistance, accelerating MASLD progression. Certain gut bacteria convert dietary choline into trimethylamine (TMA), reducing choline

availability for very-low-density lipoprotein (VLDL) synthesis. This impairs hepatic triglyceride export and promotes steatosis. Some bacteria, such as *Klebsiella pneumoniae*, also produce endogenous ethanol, which increases oxidative stress and hepatocyte damage.

7. Activation of Hepatic Stellate Cells and Fibrosis

Persistent inflammation and oxidative stress activate hepatic stellate cells, which differentiate into collagen-producing myofibroblasts. This causes extracellular matrix deposition, fibrosis, and eventually cirrhosis if left untreated. [Gut Dysbiosis] [Leaky Gut Barrier] (Toxins Escape)[Portal Vein Transit][Hepatic TLR4Activation]

[Inflammation & Fat Steatosis (MASH)] $\Rightarrow$ $\Rightarrow$

Clinical Evidence for the Role of Gut Micro biota in MASLD

Several clinical studies have demonstrated that alterations in gut micro biota are associated with the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD). Compared with healthy individuals, patients with MASLD exhibit reduced microbial diversity and an increased abundance of potentially pathogenic bacteria such as *Escherichia*, *Klebsiella*, *Enterobacter*, and *Proteobacteria*, along with a reduction in beneficial bacteria including *Akkermansia muciniphila*, *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium prausnitzii*. These microbial changes correlate with disease severity, insulin resistance, hepatic steatosis, inflammation, and fibrosis.

Clinical studies have also shown that increased intestinal permeability (“leaky gut”) and elevated circulating lipopolysaccharide (LPS) levels are common in patients with MASLD. The translocation of bacterial endotoxins from the gut to the liver activates inflammatory pathways, promoting progression from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH).

Several randomized controlled trials have evaluated micro biota-targeted therapies, including probiotics, prebiotics, and synbiotics. These interventions have demonstrated improvements in liver enzymes (ALT and AST), insulin resistance, inflammatory markers, lipid profile, and hepatic steatosis in many patients. However, variations in study design, treatment duration, and microbial strains have produced inconsistent results, limiting firm clinical recommendations.

Fecal micro biota transplantation (FMT) has also emerged as a promising therapeutic approach. Early clinical studies suggest that FMT can improve gut microbial diversity, intestinal barrier function, and certain metabolic parameters in MASLD patients. Nevertheless, current evidence is based on small clinical trials, and larger, well-designed studies are needed to establish its long-term efficacy and safety. Overall, available clinical evidence supports a significant role of the gut micro biota in MASLD pathogenesis and indicates that microbiota-targeted therapies may provide clinical benefits. However, further large-scale randomized controlled trials are required before these interventions can be routinely incorporated into clinical practice.

Hepatitis:

Introduction to Hepatitis

Hepatitis refers to inflammation of the liver, a vital organ responsible for numerous metabolic, synthetic, detoxification, and immunological functions. The liver regulates carbohydrate, lipid, and protein metabolism, synthesizes plasma proteins and coagulation factors, stores vitamins and minerals, detoxifies endogenous and exogenous substances, and produces bile essential for fat digestion. Inflammation of the liver disrupts these functions and may result in a spectrum of disease ranging from mild, self-limiting illness to chronic liver disease, cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

Hepatitis is a major global public health problem, affecting millions of people worldwide. It may occur as an acute condition lasting less than six months or progress to chronic hepatitis, in which inflammation persists for more than six months. Chronic hepatitis is particularly concerning because prolonged hepatic inflammation promotes fibrosis, cirrhosis, portal hypertension, liver failure, and liver cancer. According to the World Health Organization (WHO), viral hepatitis alone causes approximately 1.3 million deaths annually, making it one of the leading causes of infectious disease-related mortality worldwide. Chronic hepatitis B virus (HBV) and

hepatitis C virus (HCV) infections account for the majority of these deaths due to complications such as cirrhosis and HCC.

Although viral infections remain the most recognized cause of hepatitis, liver inflammation can also result from excessive alcohol consumption, autoimmune disorders, metabolic dysfunction, drug-induced liver injury, toxins, and genetic diseases.

Traditionally, hepatitis has been viewed primarily as a liver-specific disease. However, recent advances in microbiome research have demonstrated that hepatic inflammation is strongly influenced by the gut–liver axis. The human gastrointestinal tract harbours approximately 10^{13} – 10^{14} microorganisms, collectively known as the gut microbiota. These microorganisms include bacteria, viruses, fungi, archaea, and bacteriophages that maintain intestinal homeostasis by regulating digestion, vitamin synthesis, bile acid metabolism, immune maturation, and production of beneficial metabolites such as short-chain fatty acids (SCFAs). Under healthy conditions, the intestinal epithelial barrier and tight junction proteins prevent harmful bacteria and endotoxins from entering the circulation while allowing selective absorption of nutrients.

In hepatitis, however, multiple factors—including viral infection, alcohol consumption, chronic inflammation, oxidative stress, and medications—can disturb the composition and diversity of the gut microbiota a condition referred to as gut dysbiosis.

Loss of intestinal barrier integrity allows bacterial products such as lipopolysaccharide (LPS), peptidoglycans, flagellin, bacterial DNA, and other pathogen-associated molecular patterns (PAMPs) to translocate into the portal circulation and reach the liver. Within the liver, these microbial components activate resident macrophages (Kupffer cells), dendritic cells, hepatic stellate cells, and infiltrating immune cells through pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs). Activation of these signalling pathways stimulates production of pro-inflammatory cytokines including tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-17 (IL-17), and interferon- γ (IFN- γ), thereby amplifying hepatic inflammation and accelerating hepatocellular injury.

Persistent activation of inflammatory pathways contributes to oxidative stress, hepatocyte apoptosis, extracellular matrix deposition, and activation of hepatic stellate cells, ultimately leading to fibrosis, cirrhosis, and hepatocellular carcinoma. In addition to promoting inflammation, gut dysbiosis alters microbial metabolism, resulting in reduced production of beneficial SCFAs and dysregulated bile acid metabolism. These changes impair immune regulation, weaken intestinal barrier function, and perpetuate a vicious cycle of gut-derived inflammation and liver injury.

Accumulating evidence from preclinical animal studies and clinical investigations has confirmed that alterations in the gut microbiome are closely associated with disease severity in various forms of hepatitis. Patients with chronic HBV and HCV infections exhibit reduced microbial diversity, increased circulating endotoxin levels, and distinct microbial signatures that correlate with fibrosis progression and clinical outcomes. Experimental studies have demonstrated that modulation of the gut microbiota through probiotics, prebiotics, symbiotic, fecal microbiota transplantation (FMT), dietary interventions, and bile acid targeted therapies can attenuate hepatic inflammation and improve liver function, highlighting the therapeutic potential of targeting the gut–liver axis.

Therefore, the gut–liver axis has emerged as a critical determinant of hepatitis pathogenesis and progression. Understanding the complex interactions between intestinal microbiota, the immune system, and hepatic metabolism provides new insights into disease mechanisms and offers promising opportunities for developing microbiome-based diagnostic biomarkers and novel therapeutic strategies. [8,9,10,11]

Gut–liver axis in different types of hepatitis

Hepatitis comprises a diverse group of inflammatory liver diseases caused by viral infections, alcohol abuse, autoimmune disorders, drugs, and toxins. Although these diseases differ in their etiologic, accumulating evidence suggests that disruption of the gut–liver axis is a common pathogenic mechanism contributing to hepatic inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Under physiological conditions, a balanced gut microbiota, intact intestinal barrier, and regulated immune responses maintain liver homeostasis. In hepatitis, however, gut dysbiosis, increased intestinal permeability, altered bile acid metabolism, and bacterial translocation activate hepatic innate immunity and amplify liver injury. While the specific microbial changes

differ among various forms of hepatitis, the underlying mechanisms involving microbial translocation, Toll-like receptor (TLR) signalling, inflammatory cytokinin production, an hepatic stellate cell activation is largely shared.

1. Gut–Liver Axis in Hepatitis (HBV):

Chronic hepatitis B virus (HBV) infection is one of the most important causes of chronic liver disease worldwide and remains a leading cause of cirrhosis and hepatocellular carcinoma. Recent studies have demonstrated that chronic HBV infection is associated with significant alterations in gut microbial composition. Patients commonly exhibit decreased abundance of beneficial bacteria such as *Bifidobacterium*, *Lactobacillus*, *Faecal bacteriumprausnitzii*, and *Rose Buria*, accompanied by increased levels of potentially pathogenic bacteria including *Enterobacteriaceae*, *Enterococcus*, *Escherichia coli*, and *Streptococcus*. The reduction in beneficial bacteria leads to decreased production of short-chain fatty acids (SCFAs), particularly butyrate, which is essential for maintaining intestinal epithelial integrity and immune tolerance.

Gut dysbiosis in HBV infection disrupts tight junction proteins such as occludin, claudins, and zonula occludens-1 (ZO-1), resulting in increased intestinal permeability. Consequently, bacterial endotoxins, particularly lipopolysaccharide (LPS), enter the portal circulation and activate Toll-like receptor 4 (TLR4) on Kupffer cells. Activation of the TLR4/MyD88/NF-signalling pathway induces the release of pro-inflammatory cytokines including TNF- α , IL-1 β , IL-6, and TGF- β , promoting hepatocyte injury and activation of hepatic stellate cells. Continuous extracellular matrix deposition eventually leads to fibrosis and cirrhosis. Clinical studies have demonstrated a strong correlation between gut dysbiosis, endotoxemia, viral persistence, fibrosis severity, and poor clinical outcomes in chronic HBV infection.

2. Gut–Liver Axis in Hepatitis C (HCV)

Hepatitis C virus (HCV) infection is another major cause of chronic hepatitis and hepatocellular carcinoma. Chronic HCV infection is associated with significant alterations in gut microbial diversity characterized by depletion of beneficial SCFA-producing bacteria such as *Faecal bacterium*, *Bifidobacterium*, and *Ruminococcin*, together with increased abundance of *Streptococcus*, *Veillonella*, and *Enterococcus*. These alterations impair intestinal barrier function and reduce production of anti-inflammatory microbial metabolites.

Compromised intestinal integrity facilitates bacterial translocation into the portal circulation, leading to activation of hepatic pattern-recognition receptors including TLR4 and NOD-like receptors. Subsequent activation of the MyD88/NF- κ B pathway and the NLRP3 inflammasome stimulates excessive production of inflammatory cytokines and reactive oxygen species, thereby promoting hepatocyte apoptosis, chronic inflammation, and progressive fibrosis. Although direct-acting antiviral (DAA) therapy effectively eradicates HCV infection, several studies have shown that gut microbial dysbiosis may persist after viral clearance, suggesting that restoration of microbial homeostasis may require additional microbiota-targeted interventions.

3. Gut–Liver Axis in Alcoholic Hepatitis

Chronic alcohol consumption alters the gut microbiota by depleting beneficial bacteria, like *Lactobacillus*, and promoting harmful Gram-negative species. Alcohol and acetaldehyde directly destroy the intestinal barrier by disrupting tight junctions and increasing permeability. This allows large amounts of lipopolysaccharides (LPS) to leak into portal circulation, activating liver Kupffer cells via TLR4 signalling. Once activated, these cells release pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and reactive oxygen species, causing severe hepatocyte injury. This persistent inflammation stimulates hepatic stellate cells to deposit collagen, ultimately leading to fibrosis, cirrhosis, and liver failure. Consequently, microbiota-targeted therapies like probiotics, prebiotics, and fecal microbiota transplantation (FMT) serve as promising treatments.

4. Gut–Liver Axis in Autoimmune Hepatitis (AIH)

Autoimmune hepatitis (AIH) involves a loss of immune tolerance toward hepatocytes, heavily influenced by gut microbiota alterations. Patients with AIH exhibit reduced microbial diversity, characterized by a depletion of beneficial bacteria (*Bifidobacterium*, *Faecal bacterium*) and an enrichment of pathogenic genera (*Enterococcus*, *Veillonella*, *Streptococcus*). This dysbiosis increases intestinal permeability, allowing microbial antigens and endotoxins to leak into the liver. These bacterial products activate innate immunity and induce molecular mimicry, where microbial antigens resemble hepatic self-antigens. This resemblance activates autoreactive T

lymphocytes, triggering a persistent release of inflammatory mediators (IL-17, TNF- α , IFN- γ) that perpetuates autoimmune liver injury. Consequently, restoring gut microbial balance represents a promising strategy to enhance conventional immunosuppressive therapies.

5. Gut–Liver Axis in Drug-Induced Hepatitis (Drug-Induced Liver Injury)

Drug-induced liver injury (DILI) results from direct hepatotoxic effects or immune-mediated reactions caused by medications, herbal preparations, and environmental toxins. Increasing evidence indicates that the gut microbiota influences drug metabolism, bioavailability, and host susceptibility to hepatotoxicity. Dysbiosis alters microbial enzymatic activity, leading to formation of toxic metabolites or impaired detoxification pathways. Furthermore, increased intestinal permeability permits bacterial endotoxins to enter the portal circulation, thereby enhancing inflammatory responses induced by hepatotoxic drugs. Oxidative stress, mitochondrial dysfunction, cytokine production, and bacterial translocation collectively aggravate hepatocyte injury and contribute to disease severity. [26,27]

6. Gut–Liver Axis in Acute Viral Hepatitis (HAV and HEV)

Unlike chronic HBV and HCV infections, hepatitis A virus (HAV) and hepatitis E virus (HEV) usually cause acute self-limiting hepatitis. Nevertheless, acute infection induces temporary alterations in gut microbial composition, bile acid metabolism, and intestinal barrier integrity. Transient intestinal permeability allows limited bacterial translocation and activation of hepatic innate immunity. Because viral clearance generally occurs rapidly, intestinal barrier function and microbial diversity are restored during recovery, preventing progression to chronic liver disease in most individuals. However, severe HEV infection, particularly in immunocompromised patients and pregnant women, may involve more pronounced disturbances of the gut–liver axis. [50, 51, 52, 53].

Molecular Mechanisms of the Gut–Liver Axis in Hepatitis

The progression of hepatitis from acute inflammation to chronic liver disease is driven by a complex interplay between gut dysbiosis, intestinal barrier dysfunction, microbial translocation, and immune activation. When the intestinal barrier is compromised, microbial products such as lipopolysaccharide (LPS), peptidoglycan, flagellin, bacterial DNA, and fungal β -glucans enter the portal circulation and are transported directly to the liver. These molecules are recognized by pattern recognition receptors (PRRs) expressed on hepatic immune and non-immune cells, initiating intracellular signalling cascades that promote inflammation, oxidative stress, hepatocyte injury, fibrosis, and eventually cirrhosis or hepatocellular carcinoma (HCC).

The major molecular pathways involved include TLR4–MyD88–NF-signalling, inflammasome activation, cytokine production, oxidative stress pathways, hepatic stellate cell activation, and deregulated bile acid signalling.[28].

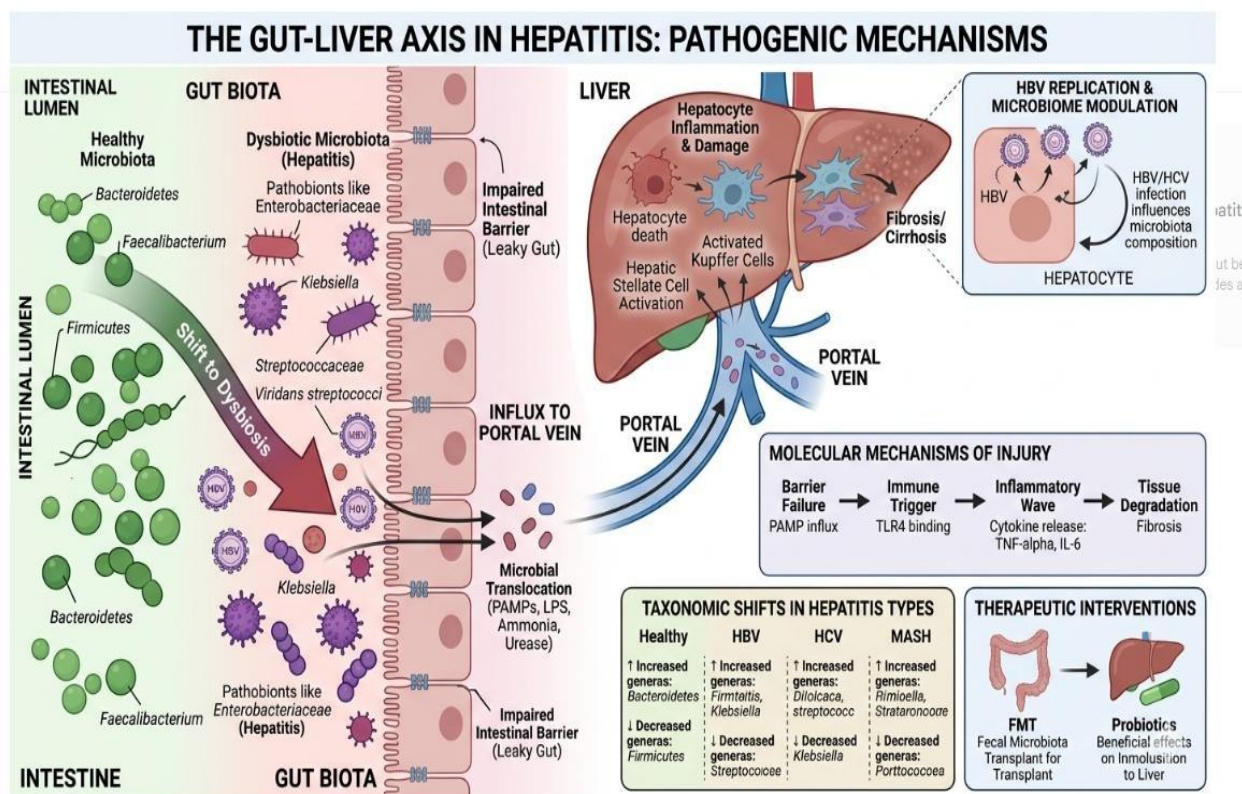


Figure 3: THE GUT-LIVER AXIS IN HEPATITIS: PATHOGENIC MECHANISMS

1. Microbial Recognition & Receptor Activation

- **PAMP Translocation:** Increased gut permeability allows pathogen-associated molecular patterns (PAMPs)—including Gram-negative LPS, peptidoglycan, flagellin, bacterial DNA, and fungal β -glucans—to reach the liver via the portal vein.
- **Cellular Detection:** These PAMPs are recognized by Pattern Recognition Receptors (PRRs) like TLRs, NLRs, and RLRs expressed across Kupffer cells, hepatic stellate cells (HSCs), hepatocytes, dendritic cells, and liver sinusoidal endothelial cells.

2. The LPS–TLR4 Signalling Cascade

- **LPS Delivery:** Circulating LPS binds to LPS-Binding Protein (LBP). This complex transfers LPS to CD14, which then presents it to the TLR4–MD2 receptor complex on Kupffer cells.
- **Intracellular Kinases:** TLR4 activation initiates the MyD88-dependent pathway (the primary driver in hepatitis), recruiting a cascade of intracellular kinases: IRAK4 → IRAK1 → TRAF6 → TAK1.

3. Transcription Factor Activation (NF- κ B & MAPK)

- **NF- κ B Translocation:** TAK1 activates the I κ B kinase (IKK) complex, which phosphorylates and degrades I κ B. This releases NF- κ B, allowing it to enter the nucleus and transcribe pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), chemokines (MCP-1, IL-8), adhesion molecules, and enzymes (iNOS, COX-2).
- **MAPK Pathways:** TLR activation simultaneously triggers MAPK signaling (ERK, JNK, p38), which regulates cytokine synthesis, cell proliferation, oxidative stress, and hepatocyte apoptosis.

4. Downstream Inflammatory Amplification

- **NLRP3 Inflammasome:** Operates via a two-stage process. Priming (via NF- κ B) increases the synthesis of NLRP3, pro-IL-1 β , and pro-IL-18. Activation (via ROS, extracellular ATP, or toxins) triggers caspase-1 to cleave these precursors into mature, inflammatory IL-1 β and IL-18.
- **Kupffer Cell Response:** As the liver's resident macrophages, activated Kupffer cells generate ROS and nitric oxide while secreting TNF- α , IL-1 β , IL-6, and TGF- β to recruit neutrophils and amplify liver injury.
- **Oxidative Stress:** Driven by mitochondria and NADPH oxidases, excessive ROS/RNS cause lipid peroxidation, DNA damage, protein oxidation, and hepatocyte apoptosis, while further feeding back to activate the NLRP3 inflammasome and HSCs.

5. Fibrogenesis & Tissue Remodelling

- **Stellate Cell Transformation:** Quiescent vitamin A-storing hepatic stellate cells (HSCs) are stimulated by inflammatory signals—primarily TGF- β , PDGF, and TNF- α —to transform into proliferative, contractile myofibroblasts.
- **Matrix Accumulation:** Activated HSCs produce collagen types I and III, secrete extracellular matrix proteins, and increase Tissue Inhibitors of Metalloproteinases (TIMPs), preventing matrix degradation and building fibrous scars.
- **Bile Acid Deregulatory Loop:** Gut dysbiosis simultaneously reduces secondary bile acids and impairs FXR and TGR5 signalling, which worsens intestinal permeability and metabolic dysfunction, accelerating tissue damage. [17,18,19,20,21]

Chronic Hepatitis Progresses to Liver Cancer (HCC):

- **The Vicious Cycle:** Persistent hepatitis means the liver is under constant inflammatory stress (flooded with destructive cytokines like TNF- α and IL-6).
- **The Scarring:** To protect itself, the liver develops continuous scar tissue (Fibrosis and Cirrhosis).
- **The Endpoint:** Years of rapid cellular damage, constant tissue repair, and genetic mutation in this highly inflamed environment culminate in uncontrolled cell proliferation—causing Hepatocellular Carcinoma (HCC).[22]

Therapeutic strategies targeting the gut–liver axis in MSLD, hepatitis.

Introduction

The development of therapeutic strategies aimed at restoring gut microbial homeostasis, strengthening the intestinal barrier, reducing bacterial translocation, and modulating immune responses. Unlike conventional antiviral or immunosuppressive therapies that primarily target the underlying cause of hepatitis, MSLD, liver cancer, gut–liver axis-directed therapies seek to interrupt the pathogenic cycle of gut dysbiosis, endotoxemia, chronic inflammation, and fibrosis. Current approaches include dietary interventions, probiotics, prebiotics, synbiotics, postbiotics, fecal microbiota transplantation (FMT), antibiotics, bile acid receptor agonists, and emerging microbiome-based therapies. Although many of these strategies are still under investigation, growing preclinical and clinical evidence suggests that modulation of the gut microbiota may complement standard hepatitis treatment and improve liver outcomes. [23]

1. Dietary and Lifestyle Interventions

Diet is one of the most effective methods for modifying the gut microbiota. A diet rich in dietary fiber, fruits, vegetables, whole grains, and fermented foods promotes the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, increasing the production of short-chain fatty acids (SCFAs). SCFAs strengthen intestinal barrier integrity, suppress inflammatory cytokine production, and reduce bacterial

translocation. Conversely, excessive alcohol intake, high-fat diets, and processed foods promote gut dysbiosis and intestinal permeability. In patients with alcoholic hepatitis, complete alcohol abstinence remains a cornerstone of therapy because it partially restores microbial diversity and reduces endotoxemia. Nutritional optimization also supports immune function and liver regeneration. [24].

2. Probiotics

Probiotics are live microorganisms that confer health benefits when administered in adequate amounts. **Common** probiotic strains include *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*, and multi-strain formulations such as VSL#3. Probiotics improve gut–liver communication by: Restoring microbial diversity, Increasing SCFA production, strengthening intestinal tight junctions, reducing intestinal permeability, decreasing endotoxin (LPS) translocation, Suppressing TLR4/NF- κ B-mediated inflammation, Enhancing regulatory T-cell responses.

Clinical studies have demonstrated improvements in inflammatory markers, endotoxemia, liver function tests, and gut microbial composition in chronic liver diseases, particularly alcoholic hepatitis and cirrhosis. However, evidence in viral hepatitis is still limited, and larger randomized trials are needed.

3. Prebiotics

Prebiotics are non-digestible dietary substrates that selectively stimulate the growth of beneficial gut bacteria. Common prebiotics include Inulin, Fructose-oligosaccharides (FOS), Galacto-oligosaccharides (GOS), Resistant starch

Fermentation of prebiotics increases SCFA production, particularly butyrate, which enhances epithelial barrier integrity, stimulates mucin production, and suppresses inflammation. In experimental liver disease models, prebiotics reduce endotoxemia, oxidative stress, and hepatic fibrosis. Although clinical evidence in hepatitis remains limited, prebiotics are considered promising adjunctive therapies.

4. Symbiotic

Symbiotic combine probiotics with prebiotics to enhance probiotic survival and activity. This combination improves colonization of beneficial bacteria, increases SCFA production, restores microbial diversity, and reduces intestinal inflammation more effectively than either intervention alone.

Clinical studies in chronic liver diseases have demonstrated improvements in intestinal permeability, endotoxin levels, inflammatory cytokines, and liver biochemical parameters. Symbiotic may represent an attractive supportive therapy for chronic hepatitis, although further disease-specific clinical trials are required.

5. Postbiotics

Postbiotics are bioactive compounds produced by probiotic microorganisms, including Short-chain fatty acids, Bacteriocins, Cell wall components, Extracellular polysaccharides. Unlike probiotics, postbiotics do not contain live bacteria, reducing concerns regarding infection in immunocompromised patients. Postbiotics exert beneficial effects by Improving epithelial barrier function, reducing oxidative stress, modulating immune responses, Suppressing inflammatory cytokine production. Although clinical evidence in hepatitis remains limited, postbiotics represent an emerging therapeutic strategy.

6. Fecal Microbiota Transplantation (FMT)

Definition

Fecal microbiota transplantation (FMT) is the transfer of processed stool from a healthy donor into the gastrointestinal tract of a patient to restore a healthy gut microbial community.

Procedure:

1. Careful screening of healthy donors for infectious diseases and gastrointestinal disorders.
2. Collection and processing of donor stool under sterile conditions.

3. Administration of the stool suspension through: Colonoscopy, Naso jejunal or nasogastric tube, Enema, Oral capsules (freeze-dried microbiota)

Mechanism of Action

FMT restores microbial diversity and reverses dysbiosis by: Replacing pathogenic bacteria with beneficial microorganisms, Increasing SCFA-producing bacteria, restoring intestinal barrier integrity, reducing intestinal permeability, Decreasing LPS translocation, improving bile acid metabolism, reducing hepatic inflammation and oxidative stress, Improving insulin sensitivity and metabolic homeostasis.[25]

Clinical Evidence: Early clinical studies have shown that FMT:

- * Improves gut micro biota diversity.
- * Enhances intestinal barrier function.
- * Reduces liver inflammation.
- * Improves insulin sensitivity.
- * Reduces hepatic fat accumulation in some patients.

Although promising, the available evidence is limited by small sample sizes and short follow-up periods. Large randomized clinical trials are still required before FMT can be routinely recommended for MASLD.

7. Antibiotic Therapy

Selective intestinal antibiotics reduce bacterial overgrowth and bacterial translocation. Rifaximin is the most widely studied agent because it is minimally absorbed and primarily acts within the intestinal lumen. Its benefits include: Reduction of pathogenic bacteria, Lower LPS production., Improved intestinal barrier function, Decreased systemic inflammation. Rifaximin is widely used in cirrhosis and hepatic encephalopathy, but its long-term role in hepatitis without cirrhosis remains uncertain due to concerns regarding antimicrobial resistance and micro biome alterations.

8. Bile Acid Receptor Modulators:

Gut micro biota regulates bile acid metabolism, making bile acid signalling an attractive therapeutic target.

Foresaid X Receptor (FXR) Agonists: Agents such as Obet cholic acid activate FXR, resulting in Reduced hepatic inflammation, Improved intestinal barrier integrity, Suppression of bacterial overgrowth, Reduced bile acid toxicity, Inhibition of hepatic fibrosis.

TGR5 Agonists: Activation of TGR5 promotes Anti-inflammatory signalling, Improved glucose metabolism, Reduced macrophage activation, Enhanced intestinal barrier function. Although most studies have focused on metabolic liver disease, these pathways may also be relevant in chronic hepatitis.

9. Microbial Metabolite-Based Therapy:

Therapeutic approaches aimed at restoring beneficial microbial metabolites include: Butyrate supplementation, SCFA-producing probiotics, Tryptophan-derived indole supplementation, Secondary bile acid modulation. These interventions improve epithelial integrity, reduce inflammation, and regulate immune homeostasis. Most evidence currently comes from experimental models, but translation into clinical practice is actively being explored.

10. Emerging Microbiome-Based Therapies: Novel approaches under investigation include: Next-generation probiotics (e.g., Akkermansiamuciniphila, Faecalibacteriumprausnitzii), Engineered probiotic bacteria, Bacteriophage therapy targeting pathogenic microorganisms, Precision microbiome medicine, multi-omics-guided personalized microbiota therapy, Artificial intelligence-assisted microbiome profiling. These strategies aim to provide individualized treatment based on each patient's microbial composition and metabolic profile. Enhances intestinal barrier function, reduces liver inflammation, Improves insulin sensitivity. Reduces hepatic fat accumulation in some patients.[30].

Although promising, the available evidence is limited by small sample sizes and short follow-up periods. Large randomized clinical trials are still required before FMT can be routinely recommended for MASLD.

Table 1: Therapeutic Strategies Targeting the Axis

Strategy	Target	Operational Mechanism
Probiotics	Gut Dysbiosis	Supplies beneficial strains like <i>Lactobacillus</i> and <i>Bifidobacterium</i> to lower toxic bacterial levels.
Prebiotics	Mucosal Barrier	Provides non-digestible fibers that bacteria convert into Short-Chain Fatty Acids (SCFAs) like butyrate to repair tight junctions.
Antibiotics (e.g., Rifaximin)	SIBO	Reduces bacterial overgrowth in the small intestine, stopping the production of harmful endotoxins.
FXR Agonists (e.g., Obet cholic Acid)	Bile Acid Pathways	Activates bile receptors to lower fat production in the liver and improve insulin sensitivity.

Future perspectives:

Advances in understanding the gut–liver axis have identified the gut micro biota as a promising therapeutic target for liver diseases. Although current approaches such as lifestyle modification, prebiotics, probiotics, synbiotics, and fecal micro biota transplantation (FMT) have shown encouraging results, further research is needed to establish their long-term efficacy, safety, and standardized clinical use.

1. Personalized Microbiome-Based Therapy

Future treatment strategies are expected to focus on personalized medicine, where therapies are tailored according to an individual's gut micro biota composition, genetic profile, dietary habits, and metabolic status. Personalized interventions may improve treatment efficacy and reduce disease progression.

2. Development of Next-Generation Probiotics

Research is shifting toward next-generation probiotics, including beneficial bacteria such as *Akkermansiamuciniphila* and *Faecalibacteriumprausnitzii*. These microorganisms have shown strong anti-inflammatory and gut barrier–protective effects and may offer greater therapeutic benefits than conventional probiotics.

3. Microbiome-Derived Therapeutics

The use of postbiotics (bioactive microbial metabolites) and engineered bacterial products is an emerging area of research. These therapies aim to deliver the beneficial effects of the gut micro biota without administering live microorganisms, potentially improving safety and stability.

4. Optimization of Faecal Microbiota Transplantation (FMT)

Future studies should focus on optimizing donor selection, stool preparation, dosing, route of administration, and treatment frequency to improve the efficacy and safety of FMT. Large, multicenter randomized controlled trials are required before FMT can become a standard treatment for MASLD.

5. Novel Drug Targets

Targeting microbial metabolites and signalling pathways, such as bile acid receptors (FXR and TGR5), short-chain fatty acids (SCFAs), and inflammatory pathways (TLR4/NF- κ B), may provide new therapeutic options for preventing liver inflammation and fibrosis.

6. Artificial Intelligence and Multi-Omics Approaches

Emerging technologies, including metagenomics, metabolomics, transcriptomics, proteomics, and artificial intelligence (AI), are expected to improve understanding of host–micro biome interactions. These tools may help identify novel biomarkers for early diagnosis, predict disease progression, and guide individualized treatment strategies. [13,14,15,16,17]

conclusion: The gut-liver axis facilitates bidirectional communication through the portal vein, where intestinal barrier dysfunction allows bacterial products like LPS to induce liver inflammation and fibrosis. Prebiotics, probiotics, and fecal micro biota transplantation (FMT) are promising micro biota-targeted therapies for MASLD, hepatitis, liver cancer. Prebiotics promote the growth of beneficial bacteria, probiotics directly restore microbial balance, and FMT replaces the dysbiotic micro biota with a healthy microbial community. These therapies improve intestinal barrier function, reduce endotoxin translocation, suppress inflammation, enhance insulin sensitivity, and decrease hepatic steatosis. While current evidence supports their beneficial role as adjunctive treatments, lifestyle modification remains the cornerstone of liver diseases management, and further large-scale clinical trials are needed to establish standardized treatment protocols.

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