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Review Article

The Gut-Liver Axis and Gut Dysbiosis: Implications for Liver Health and Disease

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Abstract

Background: The gut-liver axis is a vital bidirectional communication network connecting the gastrointestinal tract and the liver through the portal vein, bile acids, and systemic circulation. This interaction regulates metabolic, immunological, and barrier functions essential for systemic homeostasis. Dysbiosis, or imbalance in gut microbiota, disrupts this axis, contributing to liver diseases via mechanisms like increased intestinal permeability, microbial translocation, and altered metabolite production.

Purpose: This review explores the mechanistic links between gut dysbiosis and liver diseases, focusing on bacterial translocation, pathogenic bacteria, microbiota-derived metabolites, and immune-mediated liver injury. It also highlights emerging microbiome-targeted therapeutic strategies and their potential to restore gut-liver homeostasis.

Main Body: Gut dysbiosis compromises intestinal barrier integrity, allowing microbial products like lipopolysaccharides (LPS) to translocate to the liver, triggering inflammation and fibrosis. Pathogenic bacteria (*Enterococcus faecalis, Escherichia coli*, and *Klebsiella pneumoniae*) exacerbate liver diseases through cytolysin production, endotoxin release, and ethanol metabolism. Altered gut metabolites, such as bile acids and short-chain fatty acids (SCFAs), further impair liver metabolism and immunity. Dysbiosis is implicated in metabolic dysfunction-associated steatotic liver disease (MASLD), alcoholic liver disease (ALD), cirrhosis, and hepatocellular carcinoma (HCC). Emerging therapies like probiotics, fecal microbiota transplantation (FMT), and bacteriophage therapy show promise in restoring gut-liver axis balance, though challenges related to safety, efficacy, and individual variability persist.

Conclusion: Understanding the gut-liver axis and its dysregulation is critical for the development of targeted microbiome-based interventions. Future research must focus on personalized therapies, long-term efficacy, and scaling interventions to address the global burden of liver diseases.

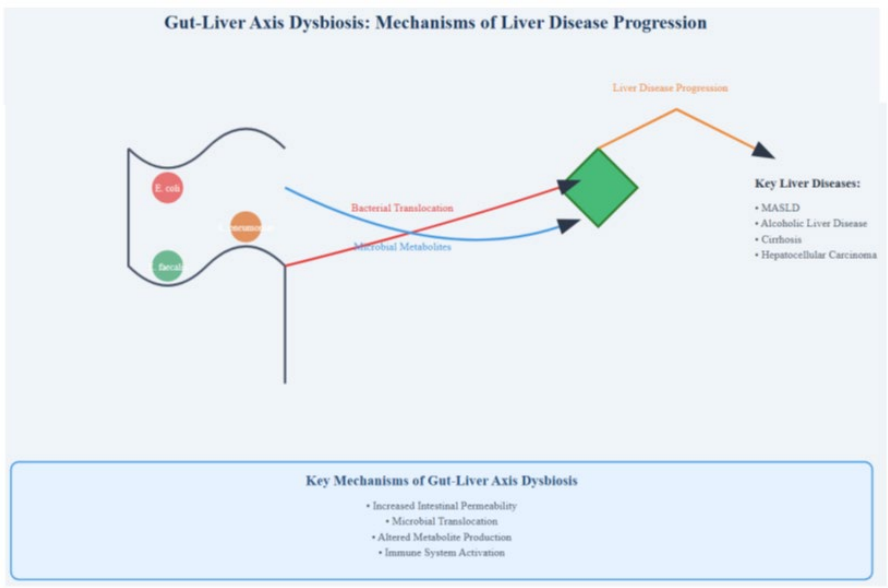
Keywords: *Gut-Liver Axis; Dysbiosis; Liver Diseases; Microbiota-Derived Metabolites; Microbiome-Targeted Therapies*

Abbreviations

ALD: Alcoholic Liver Disease; AH: Alcoholic Hepatitis; FMT: Fecal Microbiota Transplantation; HCC: Hepatocellular Carcinoma; HSCs: Hepatic Stellate Cells; LPS: Lipopolysaccharides; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; MASH: Metabolic Dysfunction-Associated Steatohepatitis; PAMPs: Pathogen-Associated Molecular Patterns; DAMPs: Damage-Associated Molecular Patterns; SBP: Spontaneous Bacterial Peritonitis; SCFAs: Short-Chain Fatty Acids; SIBO: Small Intestinal Bacterial Overgrowth; TLRs: Toll-Like Receptors

Article Highlights

- Gut dysbiosis disrupts the gut-liver axis, driving liver inflammation, fibrosis, and metabolic dysfunction.
- Pathogenic bacteria and altered microbial metabolites are key factors in liver disease progression.
- Emerging therapies like probiotics and bacteriophage therapy offer new avenues for restoring liver health.



Figure

Background

Gut-liver axis: A bidirectional communication network

The gut-liver axis is a complex, bidirectional communication network that links the gastrointestinal tract and the liver via the portal vein, bile ducts, and systemic circulation. This physiological interaction plays a critical role in maintaining hepatic and systemic homeostasis. The liver, as a central metabolic organ, processes nutrients, hormones, and microbial-derived metabolites that are absorbed from the gut. In return, the liver regulates gut function through bile acids and immunological signals. This dynamic relationship ensures the maintenance of intestinal barrier integrity, bile acid metabolism, and immune surveillance [1,2]. Gut-derived metabolites, microbial components, and immune signals significantly influence liver health. These include short-chain fatty acids (SCFAs), bile acids, and

lipopolysaccharides (LPS), which modulate inflammation, liver metabolism, and immune activation. Microbial antigens, such as pathogen-associated molecular patterns (PAMPs), are vital in signaling pathways that affect both gut and liver function. The gut-liver axis is thus a cornerstone of metabolic and immune regulation, making it pivotal in understanding liver diseases [3,4].

Dysbiosis and liver dysfunction

Dysbiosis refers to an imbalance in the composition and function of the gut microbiota. This disruption is implicated in liver dysfunction through mechanisms such as increased intestinal permeability, microbial translocation, and altered microbial metabolite production. Dysbiosis disrupts the critical balance of pro-inflammatory and anti-inflammatory signals within the gut-liver axis, leading to systemic inflammation and hepatic injury [5,6]. Liver diseases associated with gut microbiota alterations include Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), Metabolic Dysfunction-Associated Steatohepatitis (MASH), alcoholic liver disease (ALD), cirrhosis, and hepatocellular carcinoma (HCC). MASLD and MASH are characterized by fat accumulation and inflammation, often linked to gut microbial metabolites like ethanol and LPS. ALD results from alcohol-driven gut barrier damage and dysbiosis, while cirrhosis and HCC are associated with chronic inflammation, microbial translocation, and oncogenesis. These diseases exemplify the critical role of gut-liver interactions in disease progression [7-16].

Rationale for targeting specific bacteria

Emerging studies emphasize the significance of specific bacterial strains in liver inflammation and fibrosis. Pathogenic bacteria, such as *Enterococcus faecalis, Escherichia coli*, and *Klebsiella pneumoniae*, have been implicated in liver disease progression through mechanisms including endotoxin release, ethanol production, and immune activation. Identifying these bacterial culprits offers therapeutic potential for disease prevention and intervention [17-19]. Targeting bacterial strains involved in liver disease represents a promising avenue for therapy. Modifying the gut microbiota composition through probiotics, prebiotics, and other microbiome-targeted interventions can potentially restore gut-liver axis homeostasis. This approach highlights the importance of understanding microbiota-liver interactions to develop effective treatments [20].

Mechanisms linking gut dysbiosis to liver diseases

Bacterial translocation and increased intestinal permeability

The intestinal barrier serves as a critical defense in the gut-liver axis, preventing the entry of harmful bacteria and toxins into the systemic circulation as depicted in table 1. Dysbiosis compromises this barrier, leading to increased intestinal permeability. Mechanisms such as tight junction disruption, small intestinal bacterial overgrowth (SIBO), and immune evasion facilitate bacterial translocation. Bacterial translocation introduces microbial DNA and endotoxins, such as LPS, into the portal circulation. These components promote liver inflammation and injury by activating toll-like receptors (TLRs) on hepatic immune cells. Clinical studies reveal elevated levels of bacterial DNA and endotoxins in patients with liver diseases, underscoring the link between gut permeability and hepatic dysfunction [20-22].

Pathogenic bacteria and liver disease pathogenesis

Enterococcus faecalis

Enterococcus faecalis is a significant contributor to alcoholic hepatitis (AH). Cytolysin-producing strains of this bacterium induce hepatocyte apoptosis and inflammation, exacerbating liver injury. Cytolysin is a bacterial toxin that triggers oxidative stress and immune activation, leading to severe liver damage [23].

Mechanism	Key Processes	Effects on Liver Health	Examples of Supporting Evidence
Bacterial Translocation	- Increased intestinal permeability - Tight junction disruption - Small intestinal bacterial overgrowth (SIBO)	- Introduction of bacterial DNA and endotoxins (e.g., LPS) into the portal circulation - Activation of hepatic toll-like receptors (TLRs)	- Elevated bacterial DNA and LPS levels in patients with cirrhosis and MASLD - Clinical studies linking TLR activation to fibrosis
Pathogenic Bacteria	- Overgrowth of harmful bacteria such as *Enterococcus faecalis*, *Escherichia coli*, and *Klebsiella pneumoniae*	- Cytolysin production by *E. faecalis* induces hepatocyte apoptosis - LPS from *E. coli* exacerbates inflammation and fibrosis	- Studies linking *E. coli* LPS to portal hypertension - *K. pneumoniae* ethanol production linked to steatosis and inflammation
Altered Microbial Metabolites	- Dysregulation of SCFAs (e.g., butyrate) - Altered bile acid metabolism- Elevated ammonia levels	- Impaired hepatic metabolism and immunity - DNA damage from secondary bile acids - Exacerbation of hepatic encephalopathy	- Evidence of altered bile acid profiles in MASLD patients - SCFA dysregulation linked to inflammation and metabolic dysfunction
Immune-Mediated Mechanisms	- Activation of Kupffer cells and hepatic stellate cells (HSCs) - PAMP and DAMP signaling	- Chronic liver inflammation - Fibrosis and systemic immune activation	- Increased immune activation in ALD and cirrhosis - PAMP/DAMP signaling driving fibrogenesis in HCC

Table 1: *Mechanisms linking gut dysbiosis to liver diseases.*

Escherichia coli

Escherichia coli is implicated in cirrhosis and portal hypertension. The bacterium's endotoxin, LPS, activates hepatic toll-like receptor 4 (TLR4), promoting inflammation and fibrosis. Elevated LPS levels in cirrhosis patients highlight its role in disease progression [24].

Klebsiella pneumoniae

Klebsiella pneumoniae contributes to MASLD and fibrosis through ethanol production and metabolic disruption. This bacterium's ability to metabolize ethanol exacerbates hepatic steatosis and inflammation, linking it to metabolic liver diseases [25].

Microbiota-derived metabolites and liver damage

Gut microbiota-derived metabolites significantly influence liver health. SCFAs, such as butyrate, have dual roles, being protective at physiological levels but harmful when dysregulated. Bile acids modulate hepatic metabolism and inflammation, while altered bile acid profiles due to dysbiosis contribute to liver injury. Ammonia and nitrogenous compounds produced by gut bacteria exacerbate hepatic encephalopathy, highlighting the metabolic impact of dysbiosis [26].

Immune-mediated mechanisms

Dysbiosis activates hepatic immune cells, including Kupffer cells and hepatic stellate cells (HSCs). Microbial products such as PAMPs and damage-associated molecular patterns (DAMPs) drive liver inflammation and fibrosis. This immune activation perpetuates a cycle of liver injury and systemic inflammation, emphasizing the gut-liver axis's immunological dimension [27].

Gut microbial dysbiosis in specific liver diseases

Metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH

MASLD and MASH are linked to decreased microbial diversity and shifts in bacterial abundance. *Klebsiella pneumoniae* plays a pivotal role in promoting hepatic steatosis and inflammation through ethanol production and immune activation. Dysbiosis exacerbates insulin resistance, further driving disease progression [28].

Alcoholic liver disease (ALD)

Alcohol consumption disrupts gut barrier integrity and alters microbiota composition. Alcohol-induced dysbiosis promotes the overgrowth of Enterococcus faecalis, whose cytolysin toxin exacerbates alcoholic hepatitis. Ethanol-derived metabolites further impair gut-liver communication, perpetuating liver damage [29].

Cirrhosis

Cirrhosis is characterized by systemic inflammation and portal hypertension. Dysbiosis increases bacterial translocation, introducing microbial DNA into ascitic fluid. This promotes complications such as spontaneous bacterial peritonitis (SBP). *Escherichia coli* and other *Enterobacteriaceae* are prevalent in advanced liver disease, reflecting the gut's role in driving systemic inflammation [30].

Hepatocellular carcinoma (HCC)

Chronic dysbiosis and inflammation are key drivers of HCC. Gut microbiota-derived metabolites, such as secondary bile acids, contribute to DNA damage and oncogenesis. Dysregulated gut-liver interactions create a pro-tumorigenic environment, linking chronic liver disease to cancer development [31].

Therapeutic strategies targeting gut dysbiosis

Probiotics

Probiotics restore gut-liver axis homeostasis by enhancing SCFA production, modulating bile acid metabolism, and reducing inflammation. Evidence supports their efficacy in MASLD, ALD, and cirrhosis, although strain-specific benefits remain a challenge [32].

Fecal microbiota transplantation (FMT)

FMT restores microbial diversity and has shown promise in liver diseases such as MASLD and hepatic encephalopathy. Clinical trials highlight its potential, but risks such as pathogen transmission and ethical concerns require consideration [33].

Bacteriophage therapy

Bacteriophage therapy offers targeted elimination of pathogenic bacteria like *Enterococcus faecalis, Escherichia coli*, and *Klebsiella pneumoniae*. Preclinical studies demonstrate its efficacy, but limitations such as resistance development warrant further research [34].

Other emerging therapies

Postbiotics, prebiotics, and synthetic microbiome engineering represent novel strategies for addressing dysbiosis as depicted in table 2. These approaches focus on leveraging microbial metabolites, promoting beneficial bacteria, and designing therapeutic microbes for liver health [35].

Therapy	Mechanism of Action	Targeted Liver Diseases	Benefits	Challenges
Probiotics	- Restores gut microbiota balance- Enhances SCFA production - Modulates bile acid metabolism	- MASLD - ALD - Cirrhosis	- Reduces inflammation - Improves intestinal barrier integrity - Decreases LPS levels	- Variability in strain-specific effects - Long-term efficacy and safety unclear
Fecal Microbiota Transplantation (FMT)	- Restores microbial diversity - Reintroduces beneficial bacteria	- MASLD - Hepatic encephalopathy	- Effective in restoring gut-liver homeostasis - Promising results in clinical trials	- Risk of pathogen transmission - Ethical concerns
Bacteriophage Therapy	- Targets specific pathogenic bacteria (e.g. *E. faecalis*, *E. coli*, *K. pneumoniae*)	- ALD - Cirrhosis	- Specific elimination of harmful bacteria - Reduces inflammation and fibrosis	- Potential for bacterial resistance - Limited research on long-term effects
Postbiotics	- Utilizes microbial metabolites (e.g., SCFAs) to modulate gut-liver axis	- MASLD - MASH	- Non-living microbial products avoid colonization risks - Anti-inflammatory properties	- Research in liver diseases still nascent
Prebiotics	- Promotes the growth of beneficial bacteria (e.g., *Lactobacillus*, *Bifidobacterium*)	- MASLD- Cirrhosis	- Enhances SCFA production - Improves gut barrier integrity	- Efficacy depends on baseline microbiota composition
Synthetic Microbiome Engineering	- Genetically designed bacteria to deliver therapeutic molecules	- HCC - MASLD	- Targeted modulation of gut-liver axis - Reduces microbial dysbiosis	- Technological and regulatory hurdles

Table 2: *Therapeutic strategies for gut dysbiosis in liver diseases.*

Challenges and Future Directions

Individualized therapeutics

Interindividual variability in gut microbiota composition necessitates personalized approaches to therapy. Multi-omics technologies, such as metagenomics and metabolomics, are crucial for precision medicine in liver diseases [36].

Long-term efficacy and safety

The long-term impact of probiotics, FMT, and bacteriophage therapy remains uncertain. Risks such as unintended colonization and immune reactions highlight the need for cautious implementation [37].

Advancing research

Longitudinal studies are essential to establish causal relationships between dysbiosis and liver diseases. Biomarkers for dysbiosis and therapeutic response are needed to guide clinical interventions [38].

Translational applications

Integrating microbiome-targeted therapies into clinical practice requires cost-effective strategies. Scaling interventions for global accessibility will be critical for addressing the burden of liver diseases worldwide [39].

Conclusion

The article underscores the pivotal role of gut-liver axis dysbiosis in the pathogenesis and progression of liver diseases, identifying mechanisms such as microbial translocation, altered metabolite production, and immune activation as key contributors to hepatic inflammation, fibrosis, and oncogenesis. Pathogenic bacteria (*Enterococcus faecalis, Escherichia coli*, and *Klebsiella pneumoniae*) and dysregulated microbial metabolites (e.g. lipopolysaccharides, bile acids, and short-chain fatty acids) are central to this disruption, linking dysbiosis to conditions such as MASLD, ALD, cirrhosis, and HCC. Emerging microbiome-targeted therapies, like probiotics, fecal microbiota transplantation (FMT), and bacteriophage therapy, offer promising avenues to restore gut-liver homeostasis and mitigate disease progression. However, the long-term safety, efficacy, and scalability of these interventions remain significant challenges, necessitating further research into personalized approaches and precision medicine. These findings are crucial for advancing academic understanding of the gut-liver axis, identifying biomarkers for disease prediction, and developing innovative treatments. Future work must address the limitations of current therapeutic strategies, including interindividual variability in gut microbiota and the ethical, logistical, and economic barriers to widespread clinical application.

Recommendations

To address the challenges posed by gut-liver axis dysbiosis in liver diseases, future research should focus on developing individualized, microbiome-targeted interventions informed by multi-omics technologies such as metagenomics, metabolomics, and transcriptomics. Clinical trials should prioritize the long-term efficacy and safety of emerging therapies like FMT, bacteriophage therapy, and synthetic microbiome engineering, while also exploring the use of postbiotics and prebiotics as complementary strategies. Efforts to scale these therapies globally should include cost-effective innovations and equitable access to address the growing burden of liver diseases worldwide. Additionally, the identification and validation of biomarkers for dysbiosis and therapeutic response are essential to guide precision medicine approaches. A multidisciplinary focus on the interactions between microbial metabolites, immune responses, and hepatic metabolism will be critical for advancing both the prevention and treatment of liver diseases. Finally, ethical considerations, such as pathogen safety in FMT and unintended consequences of microbiome modulation, must remain central to translational research efforts.

Ethical Approval and Consent to Participate

Not Applicable.

Clinical Trial Number

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data are available and sharing is available as well as publication.

Competing Interests

The author hereby that they have no competing interests.

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Authors' Contributions

The corresponding author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy.

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