Review

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Research Progress in Understanding the Role of the Intestinal Barrier in Liver Diseases via the Gut-Liver Axis: A Comprehensive Review

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The gut-liver axis has emerged as a fundamental concept in elucidating liver diseases. Central to this axis is the intestinal barrier, which exerts a significant influence on the progression of various liver conditions, including non-alcoholic fatty liver disease, alcoholic liver disease, viral liver diseases, autoimmune liver diseases, and cirrhosis. This review synthesizes domestic and international literature to explore the intricate association between the intestinal barrier and liver diseases. Mechanistic insights into how the intestinal barrier modulates liver pathology are elucidated, emphasizing its role in mediating the systemic effects of intestinal contents on liver health. Additionally, this paper sheds light on the potential clinical and scientific implications of targeting the intestinal barrier in liver disease management. The review highlights the imperative for continued research efforts to unravel the intricate connections between the intestinal barrier and liver diseases to unveil novel therapeutic strategies to alleviate the burden of these conditions.

Keywords: intestinal-liver axis; intestinal barrier; liver disease; research progress

Introduction

The intestine and liver are anatomically adjacent, interconnected by bile ducts. This physical and functional linkage forms the basis of the "gut-liver axis", a concept first proposed by Marshall in 1998 [1]. The enterohepatic axis, central to this relationship, facilitates bidirectional metabolic, neuroendocrine, and immune interactions through the integration of portal and enterohepatic circulation of bile. The portal circulation transports substances absorbed from food, microbial factors from the intestinal microflora, and immune response products into hepatic tissue. Concurrently, hepatocytes synthesize bile acids, which combine with glycine or taurine to form bile salts, which are stored in the gallbladder and later released into the small intestine, modulating the intestinal microflora [2].

The intestinal barrier is a critical component of the gut-liver axis. It comprises structural and functional elements of the intestine that prevent harmful substances in the intestinal lumen, such as bacteria and endotoxins, from crossing through the intestinal mucosa into blood circulation and other organs. This barrier ensures that most microorganisms and toxic metabolites remain confined in the intestinal tract. Disruption of this barrier may lead to the systemic spread of microorganisms, triggering severe endotoxemia.

The liver and intestines interact closely at the greater papilla of the duodenum. Blood vessels from the intestinal mucosa converge into the hepatic portal vein, channeling blood from the intestines through the liver for detoxification before returning it to the heart and lungs. Consequently, the liver is often the first organ to encounter toxins in portal blood [3]. This specialized anatomical and functional relationship facilitates a significant interaction: when intestinal flora is disrupted, the enterotoxins secreted by pathogenic bacteria can increase intestinal mucosa permeability. This condition and small intestinal bacteria overgrowth can lead to bacterial translocation. Consequently, harmful bacterial metabolites, such as endotoxin, may enter the liver through the hepatic portal system, inducing endotoxemia, damaging liver cells, and potentially contributing to the progression of chronic liver diseases [4] (Fig. 1, Ref. [1,5–12]).

Gut Barrier Components

The gut barrier is essential for maintaining homeostasis between the internal and external environments of the body, preventing the entry of harmful substances into the bloodstream from the gastrointestinal tract. The barrier comprises several crucial components, including the mechanical barrier, the immune barrier, the chemical barrier, and the biological barrier. Recent research has provided

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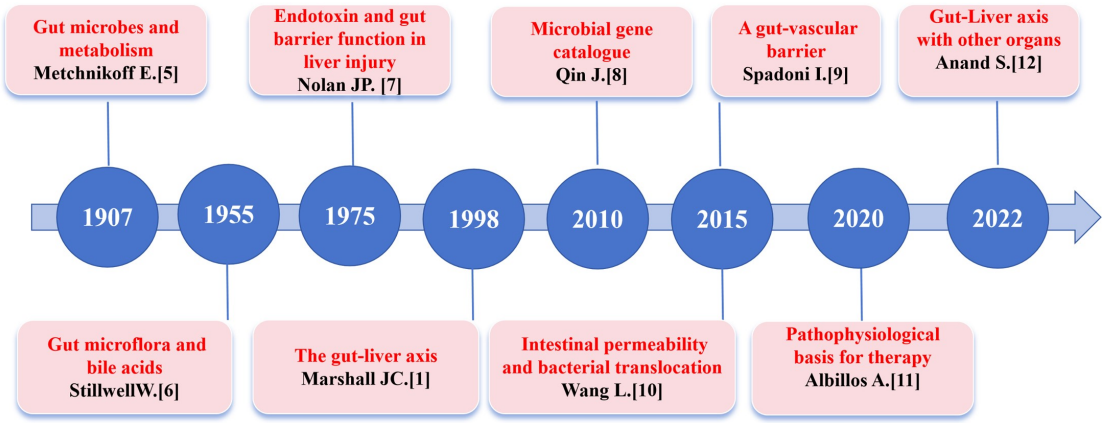

Fig. 1. Timeline of key developments in gut-liver axis research. 1907: Initial studies identified a connection between gut microbiota and liver function, especially in metabolic processes [5]. 1955: Exploration of microbial metabolites, such as bile acids, and their impacts on liver health through the enterohepatic cycle began [6]. 1975: Research on endotoxemia highlighted the association between gut barrier integrity and liver disease [7]. 1998: Introduction of the gut-liver axis concept [1]. 2010: Advancements in high-throughput sequencing technologies facilitated detailed analyses of gut microbial community structures [8]. 2015: Proposal of the intestinal vascular barrier concept, focusing research on intestinal permeability and its role in bacterial translocation in liver diseases [9,10]. 2020: Following the establishment of the enterohepatic axis theory, its implications in liver disease pathophysiology emerged as a focal research area [11]. 2022: Expansion of gut-liver axis studies to encompass interactions with other associated organs and the impact on non-hepatic disorders, including cardiovascular diseases, obesity, diabetes, and neurodegenerative diseases [12]. This figure was created using Adobe Illustrator (version 22.0, Adobe, San Jose, CA, USA).

new insights into the structure and function of these barriers. This section provides an overview of each barrier and summarizes the latest advances in the field.

Mechanical Barrier

The mechanical barrier predominantly comprises intestinal epithelial cells linked by intercellular tight junctions. Recent studies have indicated that the expression and distribution of tight junction proteins, such as claudin and occludin, are regulated by various internal and external environmental factors, including nutritional status, gastrointestinal hormones, and inflammatory mediators [13]. Additionally, emerging research underscores the pivotal role of stem cells and associated signaling pathways in maintaining and repairing the intestinal epithelial barrier [14].

Immune Barrier

Composed of immune cells and molecular mediators within the gut, the immune barrier is primarily responsible for defending against pathogens and foreign substances. Recent research emphasizes the critical interaction between the gut microbiota and the host immune system in sustaining intestinal immune balance [15]. For instance, short-chain fatty acids (SCFAs), which are metabolites produced by gut microbiota, have been found to regulate the function of the intestinal immune barrier, enhance the differentiation of regulatory T cells (Tregs), and mitigate inflammatory responses [16].

Chemical Barrier

The chemical barrier primarily refers to the mucus layer covering the surface of the intestinal lumen. This layer is stratified into a loose outer layer, where the intestinal flora predominantly resides, and a dense inner layer that acts as a physical barrier and a lubricant, providing a source of nutrients for commensal bacteria [17]. The cup cells secrete mucus rich in glycoproteins and glycolipids, analogues of bacterial adhesion receptors. These glycoproteins help modulate bacterial adhesion sites, facilitating their removal from the body via feces [18]. Additionally, pan cells produce significant quantities of antimicrobial peptides and growth factors, while plasma cells in the lamina propria secrete immunoglobulin A (IgA). Other components of the chemical barrier include gastric acid, bile, various digestive enzymes, and lysozyme, all of which are secreted by the digestive tract and contribute to its defensive mechanisms.

Microbiological Barrier

The microbiological barrier, or intestinal bio-barrier, comprises a dynamic and stable community of commensal bacteria that interact symbiotically with the host in the gut. This includes dominant groups such as the Thick-walled bacteria and the *Mycobacterium* phyla, which together create a bacterial membrane barrier [19]. The intestinal microbiota is crucial in metabolic and structural functions within the gut ecosystem, aiding in the digestion of food and supplying essential nutrients to intestinal

cells. Moreover, these bacteria produce short-chain fatty acids (SCFAs) that serve as an energy substrate for intestinal epithelial cells and have a regulatory function [20]. Typically, there is a stable equilibrium among the microbiota, the host, and the external environment. Symbiotic flora provides colonization resistance, thereby preventing the establishment of pathogenic microorganisms [21]. Additionally, gut microbiota influences the development of the host immune system through the production of metabolites, microbe-associated molecular patterns (MAMPs), and antigens [22]. Toll-like receptors (TLRs) initiate immune responses via activation of the nuclear transcription factor-kappa B (NF-κB) pathway when stimulated by pathogens, yet they are also engaged by commensal bacteria [23], fostering a protective role in maintaining intestinal homeostasis.

Gut-Vascular Barrier

The gut-vascular barrier (GVB) represents an emergent concept in biomedical research that is critical for preventing the translocation of gut-derived toxins and pathogens into the bloodstream [24]. Composed of intestinal vascular endothelial cells, GVB possesses unique biological properties similar yet distinct from those of the blood-brain barrier. Recent studies indicate that inflammatory conditions and certain diseases can impair the integrity of the GVB, increasing the risk of systemic exposure to gastrointestinal pathogens and endotoxins, which significantly impact the health of the liver and other vital organs [25].

Liver-Related Diseases

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a chronic inflammatory condition characterized by aberrant lipid accumulation, including simple steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and hepatocellular carcinoma. Chronic consumption of diets rich in saturated fats and fructose has been implicated in perturbations of the gut microflora, increased permeability of the intestinal barrier, and disruption of tight junctions, leading to bacterial translocation and the influx of bacterial metabolites into the liver through the portal vein, ultimately inducing hepatic injury. Notably, in NAFLD patients, a high-fat diet emerges as a significant contributor to intestinal barrier dysfunction, with early evidence of disruption of the intestinal epithelial barrier and GVB observed in models of high-fat-induced NAFLD. For example, reduced Zonula occludens-1 (ZO-1) levels and up-regulation of plasmalemma vesicle-associated protein-1 (PV-1) correlate with elevated GVB permeability and increased intestinal permeability, fostering endotoxemia and hepatitis [19]. Moreover, a high-fat diet leads to intestinal dysbiosis, amplifies the production of intestinal metabolites such as trimethylamine, trimethylamine-N-oxide, and endogenous ethanol, and disrupts bile acid metabolism signaling, contributing to intestinal barrier dysfunction [26]. At the same time, NAFLD patients often exhibit co-morbid metabolic syndrome, wherein insulin resistance, reduced aryl hydrocarbon receptor (AhR) ligands, and lipid peroxidation further compromise intestinal barrier function [27,28]. Emerging studies suggest that interventions aimed at improving the mechanical integrity of the intestinal barrier, targeting GVB, and modulating *E. coli* may hold therapeutic promise for NAFLD management [29].

Alcoholic Liver Disease

Alcoholic liver disease (ALD) is a prominent form of chronic liver disease primarily induced by excessive alcohol consumption. Global data from 2010 indicate that approximately 500,000 individuals succumbed to alcoholic cirrhosis, accounting for 47.9% of cirrhosis-related deaths [30]. In ALD patients, increased intestinal permeability emerges as a well-recognized feature evident in mouse models of alcohol exposure and pre-cirrhotic ALD patients. Studies underscore the direct deleterious effects of ethanol on the intestinal mucosa, exacerbating intestinal epithelial barrier permeability in a dose- and time-dependent manner through alterations in the expression of tight junction-associated proteins, notably ZO-1 and claudin-1 [31].

Prolonged alcohol abuse may induce intestinal apoptosis and degradation of intestinal tight junction and adhesion junction proteins, fostering a “leaky gut” phenomenon characterized by endotoxemia and heightened hepatic inflammation [32]. Ethanol further exacerbates these effects through a dose-dependent upregulation of TLR4 expression, amplifying intercellular permeability [33]. Notably, chronic alcohol consumption in humans or alcohol-fed rodent models induces subclinical intestinal inflammation, augmenting the recruitment of monocytes and macrophages in the intestinal lamina propria, where they produce pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α).

Moreover, alcohol impairs specific components of the intestinal barrier, such as proteins involved in innate antimicrobial defenses and, inhibits intestinal epithelial regeneration [34]. The altered state of the lamina propria and heightened intestinal permeability foster bacterial and endotoxin translocation, activating toll-like receptors on hepatic immune cells, further contributing to hepatic immune-mediated injury.

Viral Hepatitis Disease

Viral hepatitis disease encompasses infectious conditions induced by various hepatitis viruses, primarily affecting liver function. Presently, five hepatitis virus types are recognized: hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E. Among these, chronic hepatitis B infection poses a significant threat to human health, leading to liver conditions such as liver fibrosis, liver failure, cirrho-

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sis, and hepatocellular carcinoma (HCC). Despite extensive research on ALD and NAFLD, our understanding of intestinal barrier function and related mechanisms in Hepatitis B virus (HBV)-associated liver disease remains limited.

Studies investigating intestinal mucosal permeability in severe chronic hepatitis B (CHB) have revealed significantly elevated intestinal mucosal permeability and plasma endotoxin levels [35]. Furthermore, investigations into post-hepatitis B cirrhosis patients have demonstrated compromised intestinal barrier function in both compensated and decompensated stages of cirrhosis [36]. Plasma diamine oxidase (DAO) levels have emerged as a widely used molecular indicator of intestinal barrier function and permeability. Li *et al*. [37] showed that DAO was significantly elevated in chronic CHB infection and was an independent risk factor for 6-month readmission in decompensated cirrhosis. Additionally, reduced serum levels of connexin and skin pigment in CHB patients further underscore intestinal barrier dysfunction [38]. Collectively, these studies have shown that intestinal barrier function is reduced in patients with HBV-related liver disease. Mechanistically, inflammation and oxidative stress are believed to underlie this phenomenon [39,40]. Viral infection and liver injury lead to elevated blood levels of inflammatory mediators such as tumor necrosis factor, interleukins, -interferon, and nitric oxide (NO), contributing to intestinal inflammation and epithelial barrier dysfunction. NO, in particular, regulates intestinal permeability by regulating tight junction function through cyclic guanosine monophosphate (cGMP) signaling pathways.

As HBV infection progresses to severe hepatitis, hepatic encephalopathy, acute-on-chronic liver failure, and cirrhosis, the etiology of intestinal barrier dysfunction may encompass factors such as intestinal wall edema induced by portal hypertension and hypoproteinemia [41].

Autoimmune Liver Disease

Autoimmune liver disease comprises a group of non-infectious liver diseases characterized by hepatic pathology and abnormalities in liver function, the precise etiology remains incompletely elucidated. Major subtypes include autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). Manifesting as a lifelong chronic ailment, autoimmune liver disease follows a protracted natural course, progressing from hepatitis to liver fibrosis, cirrhosis, and eventual liver failure.

Currently, the pathogenesis of autoimmune liver disease remains elusive, with most studies implicating environmental factors, such as pathogens or xenobiotics, in triggering immune dysregulation among genetically predisposed individuals, leading to disease onset [42]. Increasingly, research has highlighted the pivotal role of gut microbes as key contributors to the pathogenesis of various autoimmune diseases, including autoimmune liver disease [43,44]. For instance, scholar [45] has demonstrated that dysbiosis induced by vancomycin aggravates immune-mediated liver injury in mice, which can be attributed to decreased levels of short-chain fatty acids and consequent disruption of intestinal barrier function, leading to heightened intestinal permeability and increased hepatic antigen influx. Mechanistically, this exacerbation is associated with elevated interleukin-6 (IL-6) and interferon-gamma (IFN-γ) levels.

Comparative analyses between the healthy group and AIH mice revealed decreased intestinal microbial diversity, elevated abundance of *Aspergillus* and *Mycobacterium* phyla, intensified intestinal permeability, and heightened infiltration of peripheral origin macrophages in the liver. Moreover, distinctive bacterial strains have been cultured and identified in the liver, spleen, and lymph nodes of mice in the AIH group, with *Lactococcus formosanus* and other strains found to be unique to this group. Furthermore, the other study [46] has reported that AIH patients exhibit reduced expression of intestinal epithelial tight junction proteins, elevated plasma lipopolysaccharide levels, and reduced abundance of intestinal anaerobic bacteria (*Bifidobacteria* and *Lactobacillus*) compared to healthy individuals. Moreover, it has been demonstrated that the translocation of specific intestinal bacteria affects T helper cell differentiation and may also directly impact liver function, inducing the production of autoantibodies, cytokines, and other autoimmune chemokines, driving possible autoimmune pathological responses, as exemplified by *Enterococcus quinquefasciatus* [47]. Collectively, these observations suggest that the pathogenesis of autoimmune liver disease is associated with gut microbial dysbiosis, increased intestinal mucosal barrier permeability, and the subsequent entry of gut microbes or their metabolites into the systemic immune circulation.

Cirrhosis

Cirrhosis is a progressive chronic liver disease originating from one or more causes, histologically characterized by diffuse liver tissue fibrosis, pseudo follicles, and regenerative nodules. It represents a prevalent disease and ranks among the leading causes of death in China [48].

During cirrhosis, intestinal barrier damage emerges as a notable feature [49]. Cirrhotic patients and experimental models commonly exhibit heightened intestinal permeability, which is symptomatic of intestinal barrier disruption, especially when accompanied by ascites and intestinal bacterial translocation [50]. This phenomenon leads to increased passage of macromolecules, including bacterial components such as lipopolysaccharide or bacterial DNA, into the systematic circulation [51]. The primary mechanism underlying this phenomenon is the elevated pressure within the portal vein, leading to systemic blood volume alterations disrupting the intestinal mucosa microcirculation. This disruption manifests as dilation of interstitial spaces within intestinal epithelial cells, intestinal walls

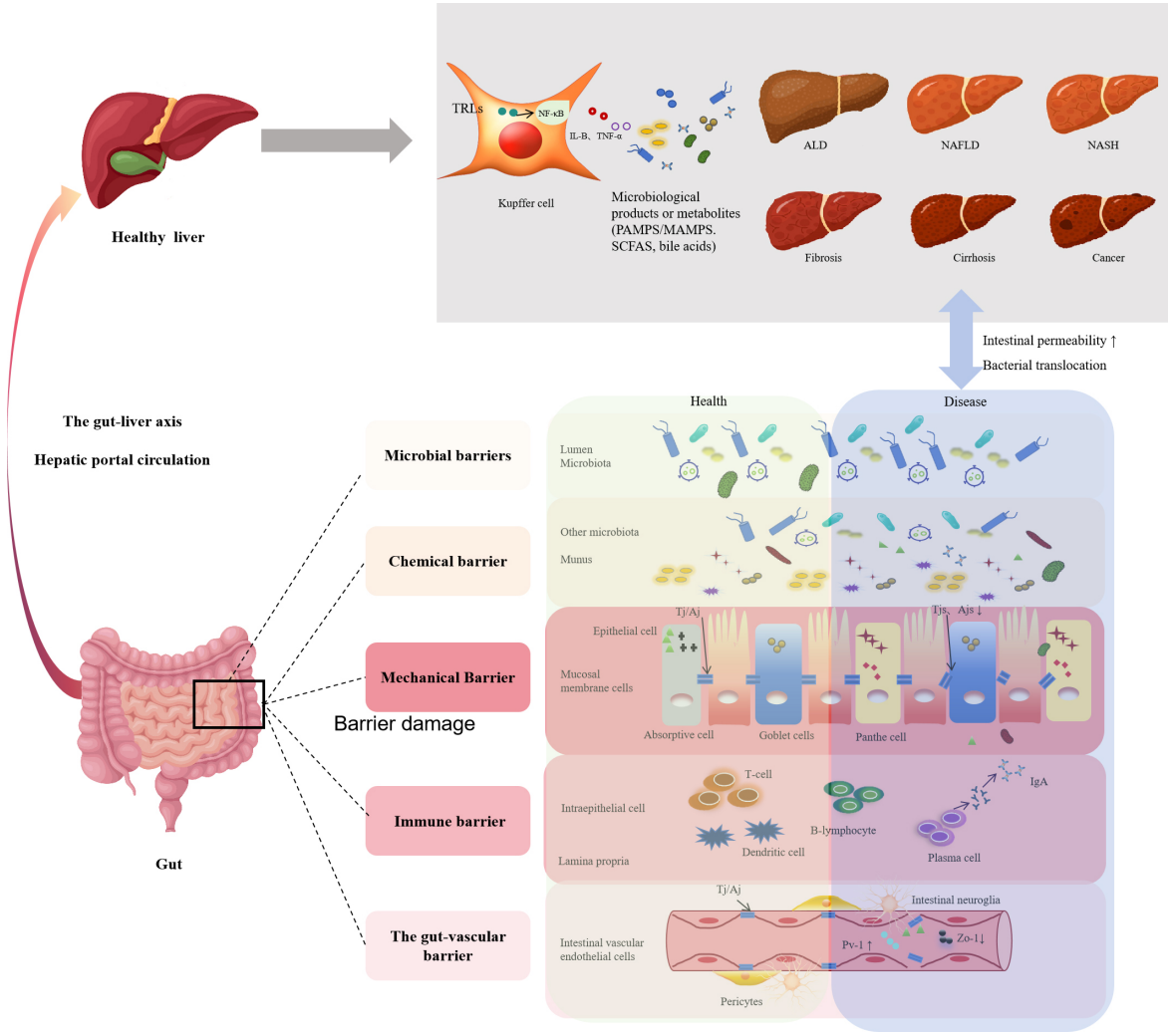

Fig. 2. Overview of the gut-liver axis and its fundamental components. The gut-liver axis is a vital communication link between the intestine and liver, facilitated by the intricate interplay of portal and enterohepatic circulation of bile. Central to this axis is the intestinal barrier, comprised of five fundamental components: (1) Microbial barrier: A dynamic, stable ecosystem of commensal microorganisms, including bacteria, viruses, fungi, and protozoa, coexisting harmoniously with the host. This symbiotic relationship supports food digestion, vitamin synthesis, immune regulation, and defense against pathogenic invaders. (2) Chemical barrier: Encompassed by the mucosal layer lining the intestinal lumen, housing intestinal flora and numerous cellular secretions and chemicals, including gastric acid, bile, various digestive enzymes, and lysozyme produced by the gastrointestinal tract. (3) Mechanical barrier: Formed by intestinal epithelial cells and their intricate intercellular connections, including absorptive cells, goblet cells, and Paneth cells, among others. The integrity and permeability of these interconnected cells are pivotal in defining the overall barrier function of the intestinal epithelium. (4) Immune barrier: An elaborate network of innate and adaptive immune cells and molecules, predominantly orchestrated by mucosal lymphoid tissues, regulatory T cells in the lamina propria, and immunoglobulin-producing plasma cells. This system combats pathogenic microorganisms while preserving tolerance towards beneficial commensals and dietary components. (5) Intestinal vascular barrier: Comprised of vascular endothelial cells expressing connexins and close associations with intestinal neuroglia and pericytes, forming a cohesive intestinal-vascular unit. In pathological conditions, disruptions in the intestinal barrier or microbiota imbalance can trigger or exacerbate hepatic inflammation through mechanisms yet to be fully elucidated. The "↑" symbol represents activation or upregulation; the "↓" symbol represents inhibition or downregulation. The figure was drawn by Adobe Illustrator (version 22.0, Adobe, San Jose, CA, USA). Aj, adhesive junction; ALD, alcoholic liver disease; IL, interleukin; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear transcription factor-kappa B; MAMPs, microbe-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PV-1, plasmalemma vesicle-associated protein-1; SCFAs, short-chain fatty acids; Tj, tight junction; TLRs, toll-like receptors; TNF-α, tumor necrosis factor alpha; ZO-1, Zonula occludens-1.

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with edema, and compromised integrity of connective proteins, collectively affecting intestinal permeability. Notably, interventions such as transjugular intrahepatic portal vein shunt surgery [52], or treatment with non-selective beta-agonists [53], have demonstrated significant improvements in intestinal permeability and bacterial translocation, further underscoring the influence of portal hypertension on intestinal barrier function [54].

In terms of the immune barrier, cirrhosis is marked by heightened expression of pro-inflammatory cytokines such as TNF-α and TNF-γ in the lamina propria, along with depletion of Th17 cells and upregulation of Th1 cells [55]. Impaired microbial barriers play a pivotal role in cirrhosis, leading to microbiota composition and overgrowth alterations. Disruption of the gut barrier facilitates bacterial translocation, exacerbating the pathological manifestation of cirrhosis [56].

Furthermore, the impaired liver function in cirrhosis contributes to reduced bile flow in the intestinal lumen, reduced mucosal thickness, and synthesis of antimicrobial proteins, thereby compromising the GVB. Additionally, bile acids influence the composition of the intestinal flora, which further affects bile acid metabolism. Impaired intestinal motility and prolonged transit time further exacerbate intestinal barrier dysfunction and promote intestinal bacterial overgrowth [57,58] (Table 1, Ref. [59–67]).

The Intertwined Relationship between the Intestinal Barrier and Liver Diseases

The intricate relationship between the intestinal barrier and liver diseases exemplifies how distant organ systems interact through complex networks of biochemical signals and metabolic products. This gut-liver axis serves as a critical conduit, where the integrity of the intestinal barrier plays a pivotal role in maintaining liver health and influencing the pathogenesis of liver diseases.

Recent research highlights a direct link between intestinal barrier dysfunction and the onset and progression of NAFLD. A compromised intestinal barrier allows for the translocation of bacteria and their metabolic byproducts, such as lipopolysaccharide (LPS), into the portal circulation, triggering hepatic inflammation and insulin resistance, thereby exacerbating NAFLD progression towards non-alcoholic steatohepatitis (NASH) [68,69]. Similarly, alcohol consumption exacerbates intestinal permeability by directly impairing the tight junctions of the intestinal epithelium. This heightened permeability facilitates the influx of endotoxins such as LPS from the gut into the liver, activating hepatic stellate cells and Kupffer cells, leading to the inflammation and fibrosis characteristic of ALD [70].

In chronic viral hepatitis, compromised intestinal barrier function facilitates the translocation of microbial products into the liver, promoting inflammation and fibrogenesis. In cirrhosis, portal hypertension exacerbates intestinal permeability, leading to bacterial translocation and systemic endotoxemia, further compromising liver function and contributing to complications such as hepatic encephalopathy [71]. Autoimmune liver diseases such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are also impacted by altered gut barrier function. The migration of gut-derived antigens into the liver may trigger autoimmune responses in genetically predisposed individuals, thereby triggering or exacerbating liver inflammation [72].

The gut-liver axis underscores the significance of the intestinal barrier in gastrointestinal health and systemic physiology and pathology (Fig. 2). To effectively modulate liver disease outcomes, therapeutic strategies to restore or maintain intestinal barrier integrity are being explored. These strategies encompass probiotics, prebiotics, and synbiotics to normalize gut microbiota and pharmacological agents targeting specific pathways implicated in barrier function and inflammation.

Discussion

The progression of liver disease entails constant inflammatory stimulation, leading to conditions such as hepatitis progressing to hepatocellular carcinoma within 30–50 years. During the progression of liver disease, various factors contribute to hepatocyte damage, including the activation of inflammatory cells, proliferation of extracellular matrix, impaired hepatic clearance capacity, deposition of toxic lipids, oxidative stress in hepatocytes, aberrant bile acids metabolism, autoimmune system dysfunction, nutritional deficiencies, tissue ischemia, and hypoxia. This cascade of events not only facilitates the evolution of hepatitis to hepatocellular carcinoma but also compromises the mucosal barrier of the intestinal tract, intimately linking the progression of liver disease with intestinal barrier dysfunction.

The intestinal mucosal barrier, when compromised, serves as a critical factor in the pathogenesis of liver diseases. Damage to the intestinal barrier facilitates the migration of bacteria and endotoxins into the portal vein system, triggering immune-mediated damage and inflammatory responses within the liver. At the same time, the interplay between different cytokines and inflammatory mediators induces further damage to the intestinal mucosa and distant organs. Hence, disruption of intestinal barrier function emerges as a significant contributing factor across various liver diseases. Even the slightest disruption within any layer of the intestinal barrier can facilitate the entry of microorganisms into the bloodstream, resulting in a sustained response that exacerbates liver injury, fibrosis, and the progression from cirrhosis to hepatocellular carcinoma.

Table 1. Studies on the intestinal barrier and liver-related diseases.

Disease	References	Study sample	Conclusion
NAFLD/MAFLD	Cornejo-Pareja I, *et al*. (2024) [59]	110 morbidly obese patients	The study revealed associations between specific gut bacteria, such as Enterobacteriaceae, and metabolic pathways, including ethanol and succinate production, with liver damage. The findings suggest that alterations in gut microbiota contribute to the pathogenesis of MAFLD and may offer novel therapeutic targets.
NAFLD/NASH	Mouries J, *et al*. (2019) [60]	C57BL/6J mice	GVB disruption is an early stage in NASH pathogenesis, facilitating bacterial translocation into the liver. Treatment with obeticholic acid, a bile acid analogue aimed at restoring β-catenin activation in endothelial cells, protected against GVB damage and the progression of NAFLD/NASH, suggesting a potential therapeutic strategy.
ALD	Chen P, *et al*. (2015) [61]	A Lieber-DeCarli model induced intestinal dysbiosis, increased intestinal permeability, and liver disease in mice	Dysbiosis-induced intestinal inflammation and TNFRI signaling in intestinal epithelial cells contribute to the disruption of the intestinal barrier. Thus, intestinal TNFRI is a crucial mediator of ALD.
CHB	Ren YD, *et al*. (2017) [62]	5 patients with CHB in the FMT and 13 CHB in the control	FMT regulates gut flora, enhances the intestinal barrier, suppresses pathogens, and modulates immunity, offering promising prospects for treating extra-intestinal diseases associated with gut dysbiosis. The study revealed that FMT induces HBe Ag clearance in chronic hepatitis B patients who are unresponsive to prolonged antiviral therapy.
CHC	Inoue T, *et al*. (2018) [63]	166 CHC and 23 HCs	HCV infection is associated with gut dysbiosis, even in the early stages of the disease. HCV-infected individuals exhibited reduced bacterial diversity, characterized by a decline in Clostridiales and elevations in Streptococcus and Lactobacillus. Metagenomic analysis revealed increased urease genes encoded by viridans streptococci, potentially contributing to hyperammonemia in CHC patients. The findings suggest that targeting alterations in gut microbiota could offer a therapeutic approach to mitigate complications associated with chronic liver disease.
AIH	Liwinski T, *et al*. (2020) [64]	72 AIH, 95 HCs, 99 PBC, and 81 UC patients	Specific alterations in fecal microbiota were identified in AIH patients. Intestinal dysbiosis in AIH was characterized by a decline in Bifidobacterium, which correlated with increased disease activity. These findings underscore the contribution of intestinal microbiota to AIH pathogenesis and highlight potential novel therapeutic targets.
PBC	Zhao J, *et al*. (2011) [65]	162 PBC patients, 325 patients with other liver diseases, and 80 HC patients	PBC patients exhibited elevated levels of serum LPS, hypersensitivity of monocytes and BECs to LPS, and enhanced production of pro-inflammatory cytokines. LPS altered the expression of TLR4, CD14, and NF-κB on monocytes and BECs, potentially contributing to the pathogenesis and progression of PBC.
PSC	Kummen M, *et al*. (2021) [66]	136 PSC patients (58% with IBD), 158 HC patients, and 93 patients with IBD without PSC	The gut microbiome in PSC patients exhibits significant functional differences compared to HCs, including microbial metabolism of essential nutrients. Alterations in circulating metabolites associated with the disease course suggest that microbial functions may be relevant in PSC pathogenesis.
Cirrhosis	Lou T, *et al*. (2022) [67]	54 hepatitis, 61 cirrhosis, 52 HCC, and 61 HC patients	Intestinal barrier damage and inflammation increased with disease severity, particularly in cirrhosis and cancer. TLR4 and NF-κB expression correlated positively with levels of D-lactic acid and endotoxin. These findings suggest a positive association between intestinal barrier dysfunction and inflammation in liver diseases. Thus, improving gut microbiota and barrier function could mitigate inflammation and offer novel therapeutic strategies.

ALD, alcoholic liver disease; AIH, autoimmune hepatitis; BECs, biliary epithelial cells; UC, ulcerative colitis; CHB, chronic hepatitis B; CHC, chronic hepatitis C; FMT, fecal microbiota transplantation; GVB, gut-vascular barrier; LPS, lipopolysaccharide; HCs, healthy controls; IBD, inflammatory bowel disease; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TLRs, toll-like receptors.

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Consequently, recognizing the importance of intestinal mucosal barrier damage alongside host factors in liver disease pathogenesis is imperative. While the relationship between the intestinal barrier and liver diseases has been increasingly recognized, significant gaps persist in understanding the precise mechanisms and potential therapeutic targets within this complex interaction. To advance our knowledge and clinical management of liver diseases, several key areas require further exploration:

Emerging Mechanisms and Signaling Pathways

In-depth investigations are warranted to elucidate the precise molecular mechanisms underlying the contribution of the intestinal barrier disruptions to liver pathology. This includes uncovering novel signaling pathways that mediate the cross-talk between the gut microbiota, the intestinal barrier, and the liver. For instance, elucidating the role of microbial metabolites, such as bile acids, short-chain fatty acids (SCFAs), and peptidoglycans, in modulating liver disease progression through the intestinal barrier represents a promising avenue for future research.

Microbiome Diversity and Disease Modulation

The gut microbiome is crucial in maintaining the integrity of the intestinal barrier. Future research should focus on identifying specific microbial communities or keystone species that confer protective effects on the intestinal barrier and, consequently, liver health. Advanced metagenomics and metabolomics approaches could shed light on the composition and functional capabilities of the microbiome, facilitating the development of microbiome-based therapeutic strategies for liver diseases.

Personalized and Precision Medicine

The diversity in the etiology and progression of liver diseases necessitates personalized treatment approaches. Tailoring these approaches to individual gut microbiome profiles and barrier function assessments could significantly improve patient outcomes. Developing non-invasive biomarkers to assess intestinal barrier integrity and function is crucial for enabling precise and customized interventions.

Nutritional Interventions and Lifestyle Modification

Diet directly influences gut microbiota composition and intestinal barrier function. Investigating specific dietary components that promote a healthy microbiome and enhance the intestinal barrier could offer accessible, non-pharmacological methods for preventing or managing liver diseases. Clinical trials investigating the impact of dietary interventions, probiotics, and prebiotics on liver health through the gut-liver axis are highly anticipated.

Therapeutic Targeting of the Gut-Liver Axis

The gut-liver axis presents numerous potential therapeutic targets, ranging from modulating the gut microbiota and strengthening the intestinal barrier to inhibiting pro-inflammatory pathways that link gut-derived microbial products to liver inflammation and damage. Research is intensely focused on novel therapeutic agents that can selectively influence these pathways, including next-generation probiotics, engineered bacterial strains, and compounds that protect the barrier. The development of such therapies requires a concerted effort to translate basic research findings into clinical applications.

Conclusion

This review highlights the critical role of the intestinal barrier across a spectrum of liver diseases, emphasizing the intricate interplay involving gut microbiota, intestinal permeability, and liver health. It underscores the imperative for further mechanistic investigations and the exploration of novel therapeutic strategies targeting the gut-liver axis. As we advance our understanding of this complex relationship, it promises to revolutionize the landscape of liver disease prevention, diagnosis, and management, ushering in a personalized and effective treatment strategies.

Abbreviations

ALD, alcoholic liver disease; AIH, autoimmune hepatitis; cGMP, cyclic guanosine monophosphate; CHB, chronic hepatitis B; DAO, diamine oxidase; GVB, gut-vascular barrier; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear transcription factor-kappa B; NO, nitric oxide; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; PV-1, plasmalemma vesicle-associated protein-1; TLRs, toll-like receptors; TNF-α, tumor necrosis factor alpha; ZO-1, Zonula occludens-1.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding authors if needed.

Author Contributions

QYC designed the research study. QYC performed the research. XZ, WLL, YNB and JML analyzed the data. QYC, XZ, and JML drafted this manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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