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The Impact of Diet and Nutrition on the Gut-Liver Axis in Cirrhosis and Hepatic Encephalopathy

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Abstract

Background & Objective: Cirrhosis, the end stage of chronic liver disease, is associated with high morbidity and mortality worldwide. Central to its progression is the gut-liver axis, a bidirectional communication system between the gut microbiota and the liver. Disruption of this axis, including gut barrier dysfunction, small intestinal bacterial overgrowth (SIBO), and microbial dysbiosis, contributes to liver injury, systemic inflammation, and complications such as hepatic encephalopathy (HE). This review synthesizes current evidence on the impact of diet and nutrition on the gut-liver axis, focusing on dietary interventions, probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT). **Methods:** A structured narrative review was conducted using PubMed, Embase, Cochrane Library, and Web of Science to identify relevant human studies published between 2000 and 2025. Search terms included "cirrhosis," "hepatic encephalopathy," "diet," "nutrition," "gut microbiota," "SIBO," "prebiotics," "probiotics," and "FMT." We prioritized randomized controlled trials, systematic reviews, and meta-analyses, along with high-quality observational studies. **Results:** Cirrhosis is linked to gut dysbiosis, increased intestinal permeability, and SIBO, all contributing to inflammation and HE. Dietary interventions—particularly high-fiber, plant-based diets and supplementation with prebiotics, probiotics, or synbiotics—show promise in restoring microbial balance, reducing ammonia levels, and improving HE outcomes. Current guidelines support adequate protein intake, especially from plant or casein sources,

while evidence on BCAA supplementation and FMT remains emerging. **Conclusion:** Optimizing diet and nutrition offers a promising adjunctive approach in cirrhosis management. Future research should focus on personalized, microbiome-based dietary strategies to improve clinical outcomes and quality of life.

Keywords

Cirrhosis, Hepatic Encephalopathy, Gut-Liver Axis, Gut Microbiota, Diet, Nutrition, Gut Barrier, SIBO, Probiotics, Prebiotics, Synbiotics, Fecal Microbiota Transplantation, Branched-Chain Amino Acids

1. Introduction: The Gut-Liver Axis in Cirrhosis

Cirrhosis is a chronic liver disease marked by the replacement of healthy hepatic tissue with fibrotic tissue and regenerative nodules, ultimately distorting the liver's architecture and impairing its function [1]. This condition represents a significant global health burden, with an estimated worldwide prevalence of 1.3% [2]. Beyond prevalence, cirrhosis is a major contributor to global morbidity and mortality, adversely affecting quality of life and accounting for a substantial number of disability-adjusted life years (DALYs) [3].

The etiology of cirrhosis is multifactorial. Chronic alcohol abuse remains the most common cause, although viral hepatitis—particularly hepatitis B and C—has historically played a large role. Encouragingly, the global prevalence of viral hepatitis is decreasing due to advancements in screening and antiviral therapies. In contrast, the incidence of non-alcoholic fatty liver disease (NAFLD)-related cirrhosis is rising, largely driven by the global epidemics of obesity and metabolic syndrome [4]. Other, less common causes include autoimmune hepatitis, genetic disorders such as Wilson's disease and hemochromatosis, and cholestatic liver diseases like primary biliary cirrhosis [5].

On a pathophysiological level, cirrhosis results from chronic liver injury that triggers ongoing inflammation and fibrosis. Hepatic stellate cells are central to this process, producing extracellular matrix components that accumulate over time. As fibrosis progresses, the liver's regenerative capacity leads to the formation of nodules, further contributing to architectural distortion and compromised hepatic function. Over time, this pathological remodeling can give rise to severe complications, including portal hypertension, hepatic encephalopathy, and an increased risk of hepatocellular carcinoma [6].

The gut microbiota plays a crucial role in maintaining liver health and contributes significantly to the development of liver disease. Central to this relationship is the gut-liver axis, a bidirectional communication network through which microbial metabolites and components travel from the gut to the liver via the portal vein. Disruption of this axis—commonly due to dysbiosis, or an imbalance in gut microbial composition—can increase intestinal permeability. This allows harmful

substances such as lipopolysaccharides (LPS) to translocate to the liver, where they trigger inflammatory responses and contribute to liver damage [7]. Distinct gut microbiota patterns have been associated with a range of liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and cirrhosis [8].

The mechanisms underlying this gut-liver interaction are multifaceted, involving microbial metabolites, immune modulation, and bile acid metabolism. Microbial metabolites such as short-chain fatty acids (SCFAs)—including acetate, propionate, and butyrate—are produced by gut bacteria and play key roles in regulating hepatic immune responses and metabolic processes [9]. In parallel, immune modulation occurs as gut-derived microbial components like LPS and peptidoglycan activate liver-resident immune cells, inducing inflammation. This immune activation is central to the pathogenesis of several liver diseases. Additionally, the gut microbiota influences hepatic immune signaling by modulating the expression of Toll-like receptors (TLRs) and related pathways [10]. Lastly, the gut microbiota affects bile acid metabolism, which in turn impacts liver function and inflammation. Bile acids, modulated by microbial activity, interact with hepatic receptors such as farnesoid X receptor (FXR) and TGR5, influencing lipid metabolism, glucose homeostasis, and fibrogenesis [11].

In the setting of cirrhosis, the gut-liver axis becomes profoundly disrupted. Increased intestinal permeability facilitates the translocation of bacteria and their products into the liver, exacerbating inflammation and accelerating hepatic injury. This process also contributes to systemic inflammation, which is associated with complications such as hepatic encephalopathy and spontaneous bacterial peritonitis. Furthermore, cirrhotic patients commonly exhibit microbial dysbiosis, characterized by a reduction in beneficial bacteria and an overgrowth of pathogenic species, further aggravating liver disease progression [12].

The objective of this review is to provide a comprehensive overview of the gut-liver axis in the context of cirrhosis. Specifically, it aims to examine gut barrier dysfunction and alterations in gut microbiota associated with cirrhosis, discuss the impact of small intestinal bacterial overgrowth (SIBO) and the potential role of dietary interventions in modulating gut-liver interactions, and explore emerging therapeutic strategies—including dietary modifications, probiotic supplementation, and fecal microbiota transplantation (FMT)—that target the gut microbiota to improve liver outcomes.

2. Methodology

To conduct this literature review, we carried out a comprehensive and structured search of the existing scientific literature to explore how diet and nutrition impact the gut-liver axis in cirrhosis and hepatic encephalopathy (HE). We searched several major biomedical databases, including PubMed, Embase, the Cochrane Library, and Web of Science, covering studies published between January 2000 and April 2025. We used combinations of keywords and MeSH terms such as "gut-

liver axis," "cirrhosis," "hepatic encephalopathy," "dietary intervention," "gut microbiota," "probiotics," "prebiotics," "synbiotics," "small intestinal bacterial overgrowth," and "fecal microbiota transplantation." We also reviewed the reference lists of relevant articles to identify additional studies that might have been missed in the database searches.

We included articles that were published in English, focused on human adult populations with cirrhosis or HE, and specifically examined the effects of diet, nutrition, or gut-targeted therapies on the gut-liver connection. Eligible study designs included randomized controlled trials, meta-analyses, systematic reviews, observational studies, and high-quality narrative reviews. We excluded animal studies, pediatric-focused research, case reports, editorials, conference abstracts, and opinion pieces without primary data or strong clinical relevance.

The study selection process was done in two stages. First, we screened titles and abstracts to filter out irrelevant publications. Next, we conducted a full-text review of the remaining articles to ensure they met our inclusion criteria. Data extraction was performed systematically, focusing on key details such as the type of intervention, population characteristics, outcomes related to gut microbiota, gut barrier function, ammonia levels, inflammation, and clinical measures like HE episodes or hospitalizations.

Given the wide range of interventions and study designs, we chose a narrative synthesis approach rather than a formal meta-analysis. We grouped the findings into thematic areas, including gut barrier dysfunction, small intestinal bacterial overgrowth, the effects of dietary macronutrients, the role of probiotics and prebiotics in HE, and the emerging role of fecal microbiota transplantation. Throughout the synthesis, we prioritized evidence from higher-quality studies, such as randomized controlled trials and meta-analyses, but we also included mechanistic studies and expert reviews where clinical data were limited. Finally, we critically assessed the strengths and limitations of the available evidence and identified gaps that need to be addressed in future research.

3. Gut Barrier Dysfunction and Small Intestinal Bacterial Overgrowth (SIBO) in Cirrhosis

Components of the gut barrier are essential in maintaining what is permeable into our bloodstream from our digestive tract. This barrier is formed by epithelial cells, which maintain tight cell-to-cell connections that physically separate the intestinal lumen from deeper underlying tissue, called tight junctions. The barrier can adapt in response to signals delivered to the gut immune system and secrete mediators as needed. The epithelial cells have a protective mucus layer, which is a trapping mechanism that prevents the binding of infectious agents from food agents to the cell surface [13]. Dysfunction in the gut barrier ecosystem, also known as dysbiosis, can lead to altered microbial composition and the pathogenesis of several disease factors. An increase in the permeability of the gut barrier is a common finding in cases of cirrhosis, which can promote translocation of bacteria, endotoxin, and

pathogens. There are four major mechanisms in which bacterial translocation can take place, including dysbiosis, bacterial overgrowth, increased permeability, and abnormalities in the immune system [14]. Furthermore, it is critical to consider the impact of bacterial translocation, as the pathogenesis of this mechanism is strongly linked to Cirrhosis.

Increased intestinal permeability introduces the potential for unfavorable Gram-negative bacteria to enter the gut. Endotoxemia is a common characteristic of Cirrhosis, which is measured by the presence of Lipopolysaccharides(LPS), a component of the cell wall of Gram-negative bacteria [15]. The concern with increased levels of LPS is that it can trigger an immune response, such as sepsis, due to the role it plays in stimulating the immune system at a systemic level. Inflammatory markers, such as IL-8, are increased, which is implicated in directly damaging the epithelial barrier. LPS is involved with the innate components of the immune system. TLR-4 triggers the expression of NF-κB, which stimulates several inflammatory processes downstream, such as the release of IFN-β and triggers the differentiation of CD4+ subtypes, all of which increase the inflammatory response and lead to further dysregulation [16]. Gut dysbiosis and systemic inflammation can coexist and lead to the end stages of Cirrhosis complications. Inflammation leads to changes in the liver, such as sinusoidal fibrosis, which leads to less clearance of bacteria, and the impact of inflammatory marker disruption reduces the bactericidal capacity that typically takes place in a healthy liver. Systemic inflammation gives rise to cytopenia, enlarged spleen from portal hypertension, and deranged phagocytic activity, all of which lead to long-term activation and exhaustion of the immune cells, leading to less responsiveness to bacteria [17]. The acute precipitating effect of the bacterial infection can lead to systemic inflammation and diminish liver function, resulting in associated complications such as ascites, SBP, and HE [18]. Moreover, bacterial infection due to increased intestinal permeability leads to challenges in maintaining systemic inflammation and can cause downstream effects in cirrhosis and related complications.

In a systematic review and meta-analysis of 21 studies (including 1264 cirrhotics and 306 controls), the prevalence of Small Intestinal Bacterial Overgrowth (SIBO) was found to be 40.8%, while the control group was 10.7% [19]. A few risk factors for SIBO include: diabetes, autonomic neuropathy, portal hypertension, and alcohol use. SIBO often occurs due to impaired intestinal motility, decreased gastric acid, ileocecal valve reflux or delayed transit time, posing a challenge to the exacerbating effects of liver disease. Patients often present with symptoms related to abdominal discomfort and bloating, and this is due to small bowel function issues as well as intestinal lining disruption, leading to atrophy of the intestinal villi. The gold standard for diagnosis of SIBO is via cultures of small bowel aspirates, which is performed using endoscopy. Another option is a positive breath test, which is non-invasive and inexpensive. Treatment for SIBO is reserved for patients with classically presenting symptoms and clinically high suspicion due to antibiotic risk. Compared to other Metronidazole and neomycin, Rifaximin had

superior efficacy and the most favorable side effect profile. Rifaximin was observed to have improved eradication rates when combined with an insoluble dietary fiber supplement. Probiotics have been explored as a potential treatment due to competition with intestinal pathogens; however, there was no significant difference between Lactobacillus fermentum and a control group, and there was also no added benefit with rifaximin. Correcting the underlying cause of SIBO, such as prokinetic medications for dysmotility, is of greatest therapeutic impact [20]. There are several considerable antibiotics and treatments available, but determining the underlying condition is of utmost importance when choosing an appropriate treatment plan for SIBO.

4. Dietary Interventions and Their Impact on Gut-Liver Health

Diet directly influences gut microbiota, which connects with the liver via the gut-liver axis unit. When our eating choices damage the digestive system and balance, it grows into an unhealthy mix of leaky intestines, triggering body-wide inflammation. Changes in gut microbiota caused by these factors help the liver move toward cirrhosis and NAFLD. Dietary strategies toward specific dietary changes show great promise in fixing gut microbiota balance and protecting the liver from harm.

Consuming Western diets with high fat and sugar content changes the types of gut bacteria in ways that damage liver functions. Endotoxins can leak through an impaired intestinal barrier when gut health imbalance happens, since the gut barrier becomes weak. The liver damage gradually worsens, which makes patients more likely to get NAFLD or cirrhosis. Research shows that Firmicutes and Bacteroidetes bacteria populations change in response to specific diets and worsen liver disease [21].

Research shows that patients with cirrhosis gain better health benefits from following a Mediterranean diet with its supportive nutritional components. The diet maintains many different types of gut bacteria while decreasing inflammation and improving liver scarring [22]. Olive oil helps manage liver inflammation while maintaining digestion through its polyphenol content. Medical research has proven that Mediterranean food antioxidants protect liver cells against day-to-day harm caused by free radicals [23]. Although large-scale trials directly evaluating the Mediterranean diet in decompensated cirrhosis are limited, evidence from related liver conditions supports its benefits on the gut-liver axis. In a randomized controlled trial, the DIRECT-PLUS study, a green-Mediterranean diet enriched with polyphenols and reduced red meat significantly decreased intrahepatic fat and modified gut microbiota composition, especially increasing Ruminococcaceae_UCG-014 and Fournierella, which correlated with hepatic improvements [24]. A 2024 systematic review further confirmed that adherence to the Mediterranean diet enhances gut microbial diversity, increases anti-inflammatory short-chain fatty acid (SCFA)-producing bacteria (Faecalibacterium, Bacteroides, Prevotella), and reduces systemic

inflammation; all key contributors to liver disease progression [25]. While direct studies in cirrhosis are still ongoing, these findings highlight the Mediterranean diet's therapeutic potential via gut-liver axis modulation.

The consumption of processed foods with emulsifiers and additives can harm the gut lining by creating "a leaky gut." This increases the chance of bacteria passing into the bloodstream and hurting the liver tissue. Reducing the consumption of processed foods provides an effective solution to protect the liver and slow fibrosis development [26].

Dietary fiber strengthens the gut lining and promotes the creation of anti-inflammatory SCFAs, with butyrate as its main variety. Research shows that plenty of fiber in the diet keeps liver inflammation at bay and builds better gut bacteria in patients with cirrhosis [27].

Inulin and fructooligosaccharides act as prebiotics, nourishing valuable Bifidobacteria and Lactobacilli to improve gut health while lowering overall body inflammation [23].

Probiotic supplements demonstrate positive effects in the treatment of cirrhosis. The gut bacteria strains Lactobacillus and Bifidobacterium lower ammonia levels while enhancing brain functions and reshaping the gut microbiome profile in liver health [22].

Eating plants and fiber acts as an effective anti-inflammatory diet. The diets increase Short Chain Fatty Acid production, which feeds the digestive system and blocks inflammatory chemicals. Researchers discovered that mainly eating plant foods with their high antioxidant content can lower body-wide inflammation, which drives liver conditions to get worse [27]. These eating plans manage immune reactions, lowering liver scars and improving liver performance.

Dietary macronutrients directly influence how much inflammation our bodies develop. Extreme intake of saturated fats causes a rise in inflammation-promoting cytokines that worsen liver problems. Dietary plans that combine all macronutrients plus healthy fat from fish and flaxseeds reduce inflammation. The liver of patients with the disease experiences less inflammation, while omega-3 fatty acids aid in how the body handles lipids [21].

Diets have a direct impact on hepatic fibrosis levels, which show the extent of liver damage. Research shows that diet altering the gut microbiome can reduce fibrosis pathogen activity within the liver. Eating more fibrous foods and antioxidants with less processed fat and sugar helps decrease fibrosis growth in the liver. The first research shows that diet modifications to modify the gut microbiome could help reverse liver fibrosis [23].

Nutritional changes based on fiber, prebiotic, and probiotic consumption help protect gut-liver health without medicine. Dietary methods protect and repair the gut lining system while decreasing inflammation signals to slow liver disease advance. Doctors should include special diets in their treatments to help patients with liver diseases achieve better results and feel healthier. Research findings may make dietary changes essential for completely managing liver diseases.

5. Protein Intake and Hepatic Encephalopathy (HE)

The production of ammonia by gut microbiota is crucial in the development of hepatic encephalopathy (HE). Research indicates a significant relationship between dysbiosis, neuroinflammation, and cognitive decline, particularly involving the bacterial families Alcaligenaceae, Porphyromonadaceae, and Enterobacteriaceae. Notably, Alcaligenaceae can degrade urea into ammonia, which leads to hyperammonemia, a defining characteristic of hepatic encephalopathy. This capability, along with their involvement in opportunistic infections, renders them especially hazardous for individuals with cirrhosis. Similarly, Enterobacteriaceae are linked to severe infections in cirrhotic patients, contributing to heightened inflammation and elevated MELD scores [28]. Conversely, members of the order Bifidobacteriales have been observed to provide a protective effect against the risk of developing HE [29]. These findings imply that HE could be a metabolic pathway influenced by gut health. Improved outcomes may be achievable through treatment strategies aimed at effectively modulating gut microbiota, highlighting the significance of prebiotics and probiotics. Additionally, this evidence raises the question of whether gut microbiota screening for patients with or at risk for HE could enhance prognosis.

In the 20th century, low-protein diets were regularly recommended for cirrhotic patients to reduce intestinal ammonia production and prevent hepatic encephalopathy (HE). Before 2004, the European Society for Clinical Nutrition and Metabolism (ESPEN) Consensus Group advised a restrictive protein diet, suggesting an intake of 1 g/kg/day for patients with compensated cirrhosis and 0.5 g/kg/day for those with severe cirrhosis [30]. However, a groundbreaking study by Córdoba *et al*. in 2004 suggested that there was no difference in the severity of HE between cirrhotics who received a low protein diet versus a normal protein diet. Their parameters of measurement included ammonia levels, albumin, bilirubin, and prothrombin time, all of which showed no statistical differences between the groups [31]. This randomized prospective study significantly challenged prior recommendations, demonstrating that a normal protein diet does not worsen HE. Current recommendations have built on these findings, with numerous organizations in the USA and Europe, such as ESPEN, the American Association for the Study of Liver Diseases (AASLD), and the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), now recommending a protein intake of 1.2 - 1.5 g/kg/day [32]. The modern emphasis on higher protein intake highlights the need for evidence-based, individualized interventions to support overall patient health.

There is much debate on the source of protein intake for cirrhotics, and as a result, there is an extensive amount of data. A significant area of discussion is the benefits of branched–chain amino acids (BCAAs) (leucine, isoleucine, and valine) as they are compounds that the body cannot produce itself. A meta-analysis by Gluud *et al*. demonstrated improvements in HE signs and symptoms among cirrhotic patients given BCAAs; however, these patients were not treated with lactu-

lose or neomycin. Those who were receiving these treatments but did not reveal benefits after BCAA administration [33]. This meta-analysis encompassed trials through 2014. Additional large-scale studies are needed to further elucidate the effect of BCAAs. Likewise, additional studies are essential to assess the therapeutic advantages of a vegetarian diet compared to an omnivorous one. However, a randomized clinical trial by Badal *et al*. found that meat-based protein resulted in higher serum ammonia levels than non-meat protein [34]. This discovery, alongside the association of elevated ammonia levels with HE symptoms, supports the idea that plant-based diets might be more beneficial for cirrhotic patients; however, additional large-scale studies are still needed to make a definitive conclusion.

6. Therapeutic Potential of Dietary Modulation in Cirrhosis

6.1. Vegetarian vs. Omnivorous Diets and Ammonia Levels

Hepatic encephalopathy (HE) is a common and debilitating neuropsychiatric complication of cirrhosis, contributing to increased mortality, hospitalization, and diminished quality of life. Central to its pathogenesis is hyperammonemia—elevated levels of circulating ammonia—which, when combined with systemic inflammation, impairs cognitive function [35] [36]. While pharmacologic interventions like lactulose remain first-line for reducing ammonia production [36], there is growing recognition of the significant role that nutrition plays in modifying ammonia production in the long-term management of HE.

Historically, patients with cirrhosis were advised to restrict protein intake due to concerns that dietary protein could exacerbate HE. However, this belief has shifted significantly [37]. Current guidelines recommend a daily protein intake of 1.2 - 1.5 g/kg/day, given the high prevalence of protein-calorie malnutrition (PCM) in this population. As a serious complication of cirrhosis, PCM is linked to poor outcomes, including infections, ascites, and spontaneous bacterial peritonitis [38]. Studies now emphasize the importance of maintaining a positive nitrogen balance and protein intake to support hepatic function in these patients [38].

Emerging clinical evidence indicates that many patients can tolerate normal to even high-protein diets without significant or sustained elevations in ammonia, particularly when the source of protein is considered. In fact, recent studies suggest that not all proteins are equal in their impact on ammonia levels or cognitive outcomes in cirrhosis. Plant-based and casein-based proteins appear to offer distinct advantages over meat-based proteins.

In fact, casein- and vegetable-based proteins, rich in fiber and low in sulfur-containing amino acids, produce less ammonia in the colon and favorably modulate postprandial metabolism. Two randomized studies reported superior psychometric performance and fewer hospital admissions on vegetable-protein diets versus meat-based diets [33] [39]. In a small crossover trial (n = 10), a vegan diet yielded better mental status outcomes than an omnivorous regimen [40].

Most notably, a 2024 randomized study by Badal *et al*. compared the acute effects of a single meal containing meat, vegetarian, or vegan protein in 30 outpa-

tients with cirrhosis. The meat meal caused a significant rise in ammonia levels and adverse changes in branched-chain amino acids (BCAAs) and lipid markers, whereas plant-based meals did not [34]. These findings support the potential of even a single plant-based meal to mitigate the ammonia burden and improve metabolic parameters.

In summary, rather than restricting protein universally, patients with cirrhosis should be encouraged to meet protein goals using high-quality sources—particularly plant-based and casein-rich options. This approach not only addresses malnutrition but also reduces ammonia production, supports pharmacologic therapy, and improves cognitive function and overall quality of life.

6.2. Fermented Foods and Their Role in Liver Health

Fermented foods such as yogurt, kefir, kimchi, and other probiotic-rich staples have gained increasing attention in recent years for their potential to improve liver health, particularly in patients with cirrhosis and HE. Their clinical value largely stems from their ability to modulate a critical therapeutic target in HE—the gut microbiome.

Mechanistically, probiotics in fermented foods help reduce gut lumen pH, limiting the growth of urease-producing bacteria that contribute to ammonia production. They also enhance intestinal microbial diversity, strengthen gut barrier function, and thus, reduce the translocation of bacterial endotoxins that lead to systemic inflammation. Considering HE pathogenesis arises in large part from gut-derived neurotoxins entering systemic circulation and affecting the brain, probiotic-rich fermented foods have multiple benefits: decreasing hepatic inflammation, lowering blood ammonia levels, and improving cognitive outcomes.

A 2023 meta-analysis of nine randomized controlled trials involving 776 participants found that probiotic supplementation significantly improved minimal hepatic encephalopathy (MHE) compared to placebo or no treatment, with an odds ratio of 3.95 (95% CI: 2.05 - 7.60, $p < 0.0001$) [41]. Additionally, probiotics were also associated with a significant reduction in serum ammonia levels (mean difference (MD): −25.94 μmol/L; 95% CI: −50.21 to −1.66; $p = 0.04$) [41]. Although probiotics did not outperform standard treatments like lactulose or L-ornithine L-aspartate (LOLA) in these outcomes, these findings underscore their supportive value.

Additional support comes from a 2017 Cochrane review, which concluded that probiotics reduce the risk of overt HE episodes and improve cognitive performance by decreasing systemic ammonia burden and inflammation [42]. Further, a 2024 meta-analysis by Zhou *et al.* systematically reviewed 18 RCTs (n = 1274) and reported that probiotic supplementation significantly reduced blood ammonia levels (MD = −2.68 μmol/L; 95% CI: −3.90 to −1.46; $p < 0.0001$) and increased the remission rate of MHE (RR = 2.79; 95% CI: 1.23–6.35; $p = 0.01$) [43]. The study also demonstrated improvements in liver injury markers—reducing alanine aminotransferase (ALT) (MD = −11.10 U/L; 95% CI: −16.17 to −6.03; $p < 0.0001$)

and lowering Model for End-Stage Liver Disease (MELD) scores (MD = −2.55; 95% CI: −3.56 to −1.54; $p < 0.00001$)—and a striking decrease in MHE incidence (RR = 0.18; 95% CI: 0.09 - 0.34; $p < 0.00001$) [43]. Most recently, a 2024 meta-analysis by Zhang *et al.* reported reversal of MHE (RR: 1.54; 95% CI: 1.03 - 2.32) and improvement in overall HE outcomes (RR: 1.94; 95% CI: 1.24 - 3.06), alongside enhanced quality of life [44]. Collectively, these robust findings reinforce the therapeutic utility of fermented foods and probiotic supplementation in managing cirrhosis-related complications.

Note: The meta-analyses above largely derive from trials in which probiotics were administered via fermented dairy products (e.g., probiotic yogurt).

6.3. Synbiotics in Cirrhosis Management

Building on the benefits of probiotics alone, synbiotics pair live beneficial bacteria with the prebiotic fibers they need to thrive. This targeted combination ensures both direct introduction of beneficial microbes and sustained support for their proliferation. Thus, this nutritional strategy can more reliably rebalance the gut microbiome in patients with cirrhosis and hepatic encephalopathy (HE).

Mechanistically, prebiotics like inulin or fructo-oligosaccharides act as fertilizer for supplemented probiotics like Lactobacillus and Bifidobacterium—helping them establish and outcompete the urease-producing bacteria. Synbiotics further exert their therapeutic effects by helping acidify the gut lumen, inhibiting urease-producing species responsible for ammonia generation, thereby lowering systemic ammonia levels. They also strengthen the intestinal barrier by enhancing mucus layer production and tightening epithelial junctions, preventing translocation of bacterial endotoxins that fuel systemic inflammation and hepatic injury. Additionally, by modulating immune responses, synbiotics help reduce the chronic inflammatory state that exacerbates both liver dysfunction and neurotoxicity.

The clinical promise of synbiotics is supported by several key studies. A randomized controlled trial of 55 cirrhotic patients with minimal HE received either a synbiotic mixture (probiotics plus fermentable fiber), fiber alone, or placebo for 30 days; half of those in the synbiotic arm experienced reversal of HE, with significant drops in blood ammonia, reduced endotoxemia, and improvements in Child-Turcotte-Pugh scores [45]. A meta-analysis confirmed these findings, demonstrating a 45% - 60% reversal rate of minimal HE with improvements in ammonia levels and psychometric performance [46]. One hypothesis paper has proposed that pairing lactulose with targeted probiotics could act synergistically to further reduce ammonia and endotoxin burden [47]. This is reinforced by a Cochrane systematic review, which concluded that probiotics likely improve recovery from minimal HE and may reduce overt HE episodes, although the certainty of the evidence was low [48]. More recently, a pilot randomized trial of synbiotics combined with branched-chain amino acids demonstrated significant cognitive improvements after eight weeks, even in the absence of major ammonia changes, highlighting neurologic benefits that extend beyond nitrogen lowering [49]. Ultimately, while synbiotics

are not a replacement for first-line pharmacologic treatments like lactulose or rifaximin, their complementary mechanisms—targeting the gut-liver-brain axis—offer a low-risk, evidence-based tool to improve hepatic and neurologic outcomes and support quality of life in patients with cirrhosis and HE.

7. Fecal Microbiota Transplantation (FMT) as a Novel Therapy

While previously-mentioned interventions in cirrhosis target the gut microbiome through dietary modulation, fecal microbiota transplantation (FMT) is a new therapy that aims to directly restore microbial balance. FMT involves the infusion of stool from a healthy donor into the gastrointestinal tract of a recipient. In cirrhosis, gut dysbiosis is a pathophysiologic feature that contributes to disease progression. Patients often exhibit reduced microbial diversity and an overgrowth of opportunistic organisms [50]. These microbial shifts include increases in *Fusobacteria*, *Proteobacteria*, *Enterococcaceae*, and *Streptococcaceae*, alongside reductions in beneficial taxa such as *Bacteroidetes*, *Ruminococcus*, *Roseburia*, *Veillonellaceae*, and *Lachnospiraceae* [51]. FMT works by introducing a diverse community of gut microbes to recreate a eubiotic state. Therefore, this mechanism is relevant in cirrhosis where the gut-liver axis plays a central role in disease outcomes. Pathogenic bacteria in cirrhosis may also produce ammonia, contributing to the development of HE, while weakened gut barriers allow harmful microbes to perpetuate liver injury [52]. FMT has the potential to improve gut barrier integrity and control these immune responses.

Recent clinical studies have explored the broader impact of FMT on gut microbiota. Vaughn *et al*. conducted a prospective study involving patients with active Crohn's disease who underwent a single colonoscopic FMT. The results showed a significant increase in microbial diversity after 8 weeks ($p = 0.02$) among clinical responders [53]. A shift toward a healthy donor's profile would target the root cause of cirrhosis-associated complications: dysbiosis and endotoxemia. In a pilot study of another irritable bowel disease, FMT led to significant reductions in inflammatory markers IL-6, IL-1Ra, IP-10, and ENA-78 after the second FMT ($p < 0.05$) [54]. These cytokines correlated with a downward trend in CRP and ESR, suggesting immune modulation. With the gut-liver axis in mind, these results may extend to the systemic inflammation seen in cirrhosis as a means to improve symptoms. The 2017 study by Bajaj *et al*. demonstrated that among men with recurrent cirrhosis and hepatic encephalopathy, FMT administered alongside lactulose and rifaximin led to fewer hospitalizations compared to standard of care alone [55]. Reducing systemic ammonia underscores how critical normalizing the gut microbiome is to easing the burden of HE. The FMT group also showed significant QoL and cognitive improvements by day 20 in PHES scores ($p = 0.003$) and EncephalApp Stroop performance ($p = 0.01$) [55]. Importantly, no major widespread events were observed, so these studies reinforce the safety and tolerability of FMT in selected patients.

Although the literature for FMT in cirrhosis has been steadily growing, there is an urgent need to standardize protocols across the board. Many questions remain unanswered, and the full management has yet to be realized. Current studies vary widely in donor screening processes, dosage, frequency, and delivery methods (from colonoscopy to oral capsules), limiting comparability and reproducibility across trials. Early reports by Mehta *et al*., for example, indicated sustained clinical benefits for 6 out of 10 patients who received a single FMT treatment at 20 weeks [56], but larger, multicenter randomized controlled trials with long-term follow-up are lacking. Establishing uniform protocols is essential to confirm efficacy and guide future patient selection. FMT has generally been shown to be safe in the most complex cirrhotic populations, from those with HE to *Clostridium difficile* co-infection, but adverse events such as ESBL-producing *E. coli* bacteremia have occurred [57]. Careful donor screening and safety measures are needed in immunocompromised hosts post-COVID. Recent trends are shifting away from the traditional "one stool fits all" approach toward more personalized microbiome therapeutics. Clinicians can now assess a patient's baseline gut metabolic profile and match them with an optimal donor or tailored synthetic microbial consortia [58]. This microbiome-based precision medicine approach has the potential to enhance the efficacy and consistency of FMT outcomes.

8. Clinical Implications, Future Directions, and Conclusions

Understanding the gut-liver axis via the lens of advanced microbiome research brings us closer to precision medicine approaches in cirrhosis care. Microbiome sequencing allows individuals to look at the unique profile of their gut microbiome. The gut microbiome is greatly shaped by the foods we eat, offering a new path in guiding personalized dietary interventions [59]. The microbial shifts that occur in response to certain nutrients create signatures of dysbiosis that can be used to adjust dietary strategies that have the potential to enhance the balance within the gut-liver axis. Proinflammatory pathways highlighted by Juanola *et al*. are the result of a cascade of cytokines in response to gut dysbiosis, bacterial overgrowth, and barrier dysfunction in cirrhotic patients [60]. Furthermore, data on microbiome and associations with clinical phenotype can help identify patients who are more likely to respond to and benefit from dietary therapeutics such as probiotics, BCAA supplementation, and fecal microbiota transplantation compared to those who need more aggressive medical therapy.

Dietary interventions tailored to gut microbiota offer a non-invasive adjunct to treatment when there are limited options for cirrhosis patients or the availability of liver donors in end-stage liver disease. Utilizing the gut-liver axis can help to stabilize disease progression by reducing systemic inflammation and preserving the epithelial barrier meant to protect organs from damage [61].

Nutritional therapy impacts transplant-free survival in patients by correcting the nutrient deficiencies and muscle loss that is inherent to liver disease. Having optimal nutrition therapy also reduces the risk of infections. In a living donor trans-

plant, having a nutrition plan in place helps build muscle preoperatively. Nutritional therapy can likewise stabilize clinical status for candidates of deceased donor transplant while awaiting surgery [62].

To fully elucidate the therapeutic potential of gut microbiome-based interventions in cirrhosis, there are gaps in current research that should be addressed. First, large-scale, randomized controlled trials are essential to evaluate the impact of diet and microbiome-friendly supplementation on clinical outcomes, including cirrhotic decompensation, hepatic encephalopathy, and transplant-free survival. Second, a future direction could include differentiating microbiome-targeted therapies for specific cirrhotic disease phenotypes, such as alcoholic cirrhosis, NASH, or cholestatic disease, to determine different responses to therapy. Finally, the benefit to patients of developing a standardized, evidence-based nutritional guideline with the integration of microbiome-related dietary approaches cannot be understated. This will allow for practical options for cirrhosis patients and avoid harm.

In summary, the gut-liver axis plays a key role in the pathophysiology of cirrhosis. Malnutrition is a driver of morbidity and mortality in cirrhosis patients and is impacted by factors like poor intake due to appetite changes, malabsorption due to inflammatory processes, and increased protein catabolism [63]. By understanding the interplay of microbial homeostasis and how these shifts in signals are communicated via this connection, there is potential for the gut-liver axis to be a valuable target for therapeutic intervention. The gut microbiome is a dynamic hub of signals determined by the balance of microbes, put out in response to stimuli such as metabolites, endotoxins, and immune modulators. Emerging evidence supports the use of diet, probiotics, and fecal microbiota transplantation (FMT) as promising adjunctive strategies to conventional medical management. FMT has been shown to improve dysbiosis and reduce hospitalizations in cirrhosis with recurrent hepatic encephalopathy [55]. Microbiome sequencing may help inform personalized nutrition in cirrhosis care, expanding the current therapeutic landscape. Optimization of the implementation of microbiome-directed dietary therapeutics requires continued investment in translational and clinical research.

Conflicts of Interest

The authors of this manuscript declare that they have no conflicts of interest that are directly or indirectly related to the work submitted for publication. Specifically: 1) Financial Interests: None of the authors has received any financial compensation, funding, grants, or other monetary support that could be perceived as influencing the research, analysis, or conclusions presented in this work. 2) Professional Relationships: The authors have no employment, consultancy, board membership, or other professional relationships with organizations that could be perceived as influencing the work presented here. 3) Intellectual Property: The authors declare no patents, copyrights, or other intellectual property rights that could be affected by or affect the publication of this work. 4) Personal Relationships: The

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