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Review

Influence of Gut–Liver Axis on Portal Hypertension in Advanced Chronic Liver Disease: The Gut Microbiome as a New Protagonist in Therapeutic Management

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Abstract: Clinically significant portal hypertension is associated with most complications of advanced chronic liver disease (ACLD), including variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy. Gut dysbiosis is a hallmark of ACLD with portal hypertension and consists of the overgrowth of potentially pathogenic bacteria and a decrease in autochthonous bacteria; additionally, congestion makes the intestinal barrier more permeable to bacteria and their products, which contributes to the development of complications through inflammatory mechanisms. This review summarizes current knowledge on the role of the gut–liver axis in the pathogenesis of portal hypertension, with a focus on therapies targeting portal hypertension and the gut microbiota. The modulation of the gut microbiota on several levels represents a major challenge in the upcoming years; in-depth characterization of the molecular and microbiological mechanisms linking the gut–liver axis to portal hypertension in a bidirectional relationship could pave the way to the identification of new therapeutic targets for innovative therapies in the management of ACLD.

Keywords: gut microbiome; portal hypertension; cirrhosis; hepatic encephalopathy; HVPG; CSPH; ACLD; inflammation; FMT; NSBBs

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1. Introduction

Humans live in cooperation with their gut microbiome, as an integrated superorganism [1,2]. More than 100 trillion microorganisms, including over 1000 species of bacteria, archaea, viruses, fungi, and protozoa, are hosted in our gastrointestinal tract and are now recognized as the variable part of our genome [3,4]. The composition of the gut microbiome is the final result of the interplay between a complex network of factors, including the genetic landscape and environmental agents, immune response, and dietary habits [5]. Beyond its critical role in many metabolic pathways [6], the gut microbiome is involved in the maintenance of the intestinal barrier's integrity, the protection of the host against pathogens, and the regulation of both innate and adaptive host immunity [7]. A perturbation of this balance results in dysbiosis, a condition that can contribute to the pathogenesis and the further evolution of different disorders, including liver diseases [8].

The gut–liver axis is an entity that stems from the close anatomical and functional relationship between the gastrointestinal tract and the liver [9]. Under physiological conditions, this system allows only a small amount of bacteria and their products to reach the liver through portal circulation, where they are readily eliminated. In this way, the hepatic firewall prevents the dissemination of potential inflammatory triggers

into the systemic bloodstream, maintaining a balanced immune response [10]. With the development and progression of liver disease, the gut–liver axis undergoes a gradual and profound change, characterized by a breakdown of the intestinal barrier, dysbiosis, bacterial overgrowth, and excessive bacterial translocation. This causes a dysfunctional immune response perpetuating hepatic and systemic inflammation, which worsens liver damage into a vicious cycle [11].

It is, therefore, not surprising that pathological changes in the gut microbiome have been associated with advanced chronic liver disease (ACLD) and its complications, such as hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatocellular carcinoma [12]. In recent years, increasing attention has been paid to the role that portal hypertension plays in shaping the gut–liver axis [13,14]. Since portal hypertension represents the primary driver of hepatic decompensation, which, in turn, is associated with increased mortality and morbidity in cirrhotic patients, a proper understanding of its link with the gut microbiome is of paramount importance for diagnostic, prognostic, and therapeutic approaches [15]. Indeed, the last Baveno VII consensus in portal hypertension underlined the importance of the gut microbiome as one of the fields that needs to be explored in the future in order to improve the management of portal hypertension in patients with ACLD [16].

This review aims to summarize current knowledge on the effects of portal hypertension on gut–liver axis remodeling. In addition, we provide a reinterpretation of currently available therapeutic approaches, emphasizing their impact on the gut–liver axis.

2. Pathogenesis of Portal Hypertension in Liver Disease

Portal hypertension represents one of the major consequences of ACLD; it is defined as an increase in the hepatic venous pressure gradient (HVPG) of >5 mmHg [16]. Clinically significant portal hypertension (CSPH) develops in the case of HVPG > 10 mmHg and is related to all of the complications of ACLD, such as gastroesophageal variceal bleeding, hepatic encephalopathy, and ascites. These complications represent the first cause of death and the main indication for liver transplantation in these patients [17].

The development of portal hypertension in ACLD results from both an increased inflow and an obstructed outflow in the hepatic venous system. Indeed, structural modifications of hepatic sinusoids due to fibrosis and regenerative nodules, together with vasoconstriction in the intrahepatic circulation due to decreased production of vasodilators from sinusoidal endothelial cells, are responsible for the rise in intrahepatic vascular resistance [18,19]. On the other hand, splanchnic vasodilation, as a consequence of the huge amount of nitric oxide (NO) released by hyperactive vascular endothelial cells, causes an increase in portal venous inflow [20].

The pathophysiology of portal hypertension has also been linked to intrahepatic microvascular thrombosis. While, in the past, cirrhosis was considered a pro-hemorrhagic condition, it is now accepted that cirrhosis is rather characterized by a delicate hemostatic balance [21]. Parenchymal extinction, which results from the death of the hepatocytes and their replacement with fibrotic tissue following the thrombotic occlusion of intrahepatic veins and sinusoids, is involved in the progression of cirrhosis and in worsening portal hypertension [22–24]. Several studies have demonstrated that anticoagulation therapy can reduce hepatic fibrosis and portal hypertension, and delay hepatic decompensation [25,26].

3. Gut–Liver Axis Composition and Function

Everything that connects the intestine to the liver contributes to the realization of the gut–liver axis.

The intestinal barrier is the most exposed part to the external environment; it is composed of the mucus layer, produced by intestinal goblet cells [27], the enterocytes connected by intercellular tight junctional complexes [28], Paneth cells, the gut-associated lymphoid tissue (GALT) [29–31], and the gut vascular barrier [32]. The gut microbiome resides on top of the intestinal barrier, in the intestinal lumen and the outer mucus layer,

along with many substances that serve as host defense and regulate the gut ecosystem, such as antimicrobial peptides (AMPs), IgA, and bile acids [33–37].

Under normal conditions, a limited amount of gut microbiome-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs), which include lipopolysaccharide (LPS) and other components of the bacterial cell membrane, flagellin, and bacterial DNA [38], can cross the epithelial barrier. These molecules activate pattern-recognition receptors (PRRs) on antigen-presenting cells and on B and T cells located in the GALT and the mesenteric lymph nodes (MLNs) [29–31,39], which is crucial for modeling the immune system and avoiding a systemic immune response [40].

On the inner side of the gut–liver axis, the hepatic sinusoids act as the final filter of the substances collected by the splanchnic vessels. This functional unit is composed of fenestrated sinusoidal endothelial cells (SECs), resident macrophages named Kupffer cells, and hepatic stellate cells (HSCs); the latter are located in the space of Disse, between the endothelium and the hepatocytes, and are involved in tissue repair and fibrogenesis [41,42].

In summary, the gut–liver axis is an extremely dynamic system, regulated by several host cytokines, vasoactive mediators, and microbial metabolites, in a constant balance between pro-inflammatory and tolerance factors [43–45]. The disruption of its homeostasis participates in the development of portal hypertension, which leads to the dysfunction of the gut–liver axis at several points, not only causing liver damage and systemic inflammation, but also worsening liver hemodynamics in a vicious cycle (Figure 1).

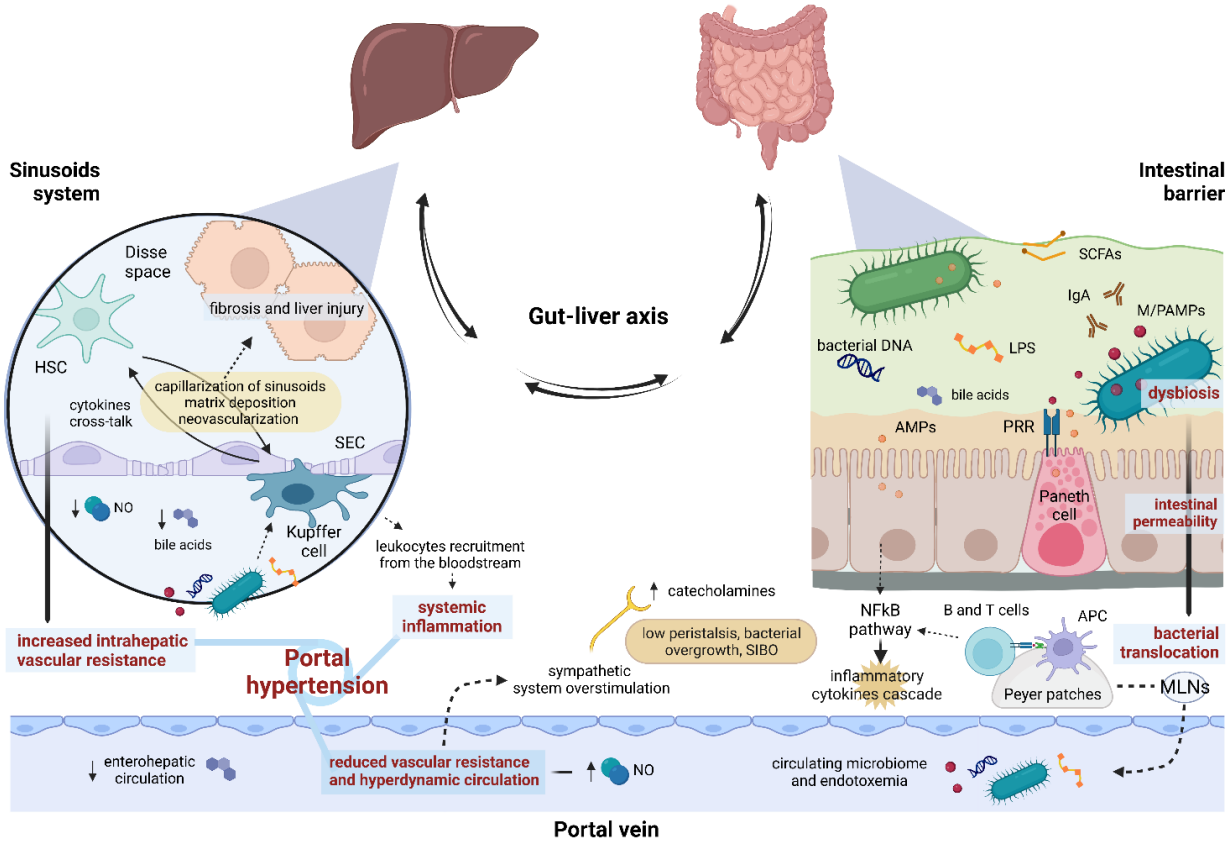

Figure 1. Gut–liver axis and portal hypertension. The intestinal barrier and the hepatic sinusoid system represent the two hinges of the firewall involved in containing bacterial translocation within the gut–liver axis. Impairment of continuous, bi-univocal communication between all these elements at several points gives rise to a vicious cycle leading to portal hypertension. AMPs, antimicrobial peptides; APC, antigen-presenting cell; HSC, hepatic stellate cell; LPS, lipopolysaccharide; M/PAMPs, microbiome/pathogen-associated molecular patterns; MLNs, mesenteric lymph nodes; NO, nitric oxide; PRR, pattern-recognition receptor; SCFAs, Short-chain fatty acids; SEC, sinusoidal endothelial cell; SIBO, small intestinal bacterial overgrowth.

4. Gut–Liver Axis Impairment and Portal Hypertension: A Two-Way Street

The gut microbiome shows qualitative and quantitative alterations in cirrhotic patients, and portal hypertension plays a central role in this process through intestinal mucosal congestion and atrophy, which reduce gastric acid production and peristalsis, impairing bacterial clearance [10,40,46]. This mechanism results in a reduced ratio between autochthonous and potentially pathogenic taxa [47], with a decrease in *Lactobacillus, Bifidobacterium*, *Ruminococcaceae*, *Lachnospiraceae*, *Clostridium* cluster IV, and *Bacteroides*, and an increase in *Streptococcus*, *Veillonella*, *Fusobacterium, Enterococcaceae,* and *Proteobacteria* (in particular *Enterobacteriaceae*) [13,48,49]. Small intestinal bacterial overgrowth (SIBO) is also a frequent finding in patients with cirrhosis, which can be explained by the impaired intestinal motility associated with the high sympathetic tone in portal hypertension [50,51].

Bacterial translocation has been recognized as a key pathological mechanism triggering the onset and the progression of portal hypertension. In cirrhotic patients, the abnormal bacterial translocation overcomes MLNs' defense capacity, consequently engaging the sinusoid system [19,52–56]. Kupffer cells are overstimulated in producing pro-inflammatory mediators, such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and chemokines, through a series of pathways, including toll-like receptor 4 (TLR-4), Myeloid differentiation primary response 88 (MyD88), and nuclear factor kappa B (NFκB), in a cross-talk with SECs and HSCs, which acquire an activated, fibrinogenic phenotype [10,42,45,57–60]. All of this results in a series of maladaptive consequences: capillarization of liver sinusoids, extracellular matrix deposition and fibrosis, liver damage, and neovascularization [61,62]. Nevertheless, the inflammatory response extends beyond the liver; inflammatory mediators overflow into the systemic circulation, causing the recruitment of leukocytes from the bloodstream [63,64] and the release of vasoactive mediators. Among others [65,66], NO, produced by endothelial and inducible NO synthases (eNOS and iNOS), plays a key role in steering the hemodynamic changes in liver disease. While NO is reduced in the intrahepatic microcirculation, causing vascular hypertonus and increasing microvascular resistance, in the splanchnic and systemic bed, both iNOS and eNOS are upregulated, resulting in arterial vasodilation, reduced vascular resistance, and hyperdynamic circulation [40,67–69].

Therefore, gut–liver axis disruption plays a crucial role in the development and progression of portal hypertension [70]. Although it is difficult to determine whether the chicken or the egg comes first and, in particular, at what point of liver disease, growing attention has been paid to identifying the mechanisms through which the gut microbiome can modulate portal hypertension.

5. Influence of the Gut Microbiome on Portal Hypertension

Recently, various studies have suggested a strong interplay between the gut microbiota and the development and progression of portal hypertension (Table 1) [13,14].

A recent study comparing conventional and germ-free mice showed that the presence of the gut microbiota stimulates the proliferation of vessels and lymphatic collectors in the intestinal wall, which depends, at least in part, on the production by Paneth cells of Angiogenin-4 (Ang-4), a ribonuclease with angiogenic and antimicrobial properties [77,78]. This was paralleled by the increase in portal pressure, outlining the hypothesis that gut microbiota may per se drive portal hypertension, irrespective of bacterial translocation, systemic inflammation, and the development of ACLD [79].

Microbial metabolites represent an additional pathophysiological link between portal hypertension and the gut–liver axis. Hydrogen sulfite (H2S) [14] is produced by sulfur-reducing gut bacteria (i.e., *Bilophila* and *Desulfovibrio* genera, both belonging to the *Proteobacteria* phylum) and by the host via H2S-catalyzing enzymes variably expressed in many organs [80]. H2S induces vasodilation when interacting with endothelial and smooth muscle cells, and suppresses the contraction of HSCs in experimental cirrhosis [81,82]. Furthermore, it reduces gastrointestinal motility, favoring bacterial overgrowth and the development of SIBO [83].

Table 1. Features of the gut microbiome associated with portal hypertension in animal models and human studies.

Study	Endpoint	Patients	Analysis	Microbiota Profile
Gedgaudas R et al., 2022 [71]	Circulating bacterial DNA signatures of PH severity	58 cirrhotic pts 46 healthy controls	16S rRNA	Circulating microbiome profile could not predict CSPH or severe PH
Virseda-Berdices A et al., 2022 [72]	Association between baseline-specific bacterial taxa and HVPG decrease in pts with HCV-related cirrhosis after successful DAA therapy	32 cirrhotic pts (21 HIV-positive) with CSPH (HVPG $\geq$ 10 mmHg)	16S rRNA	↑ in *Corynebacteriales* and *Diplorickettsiales* orders, *Diplorickettsiaceae* family, *Corynebacterium* and *Aquicella* genera, and *Undibacterium parvum* species ↓ in *Oceanospirillales* and *Rhodospirillales* orders, *Halomonadaceae* family, and *Massilia* genus
Yokoyama K et al., 2020 [73]	To find gut microbiota changes associated with PH in cirrhotic pts	12 pts with cirrhosis and PH 24 controls	16S rRNA	↑ in *Lactobacillales* order, ↓ in *Clostridium* cluster IV and cluster IX in pts with cirrhosis and PH compared to controls
Gómez-Hurtado I et al., 2019 [74]	To explore portal hemodynamics changes in experimental portal hypertensive cirrhosis/BDL rats after *B. pseudocatenulatum* CECT 7765 administration	6 sham-operated, 6 BDL, and 8 BDL rats previously treated with *B. pseudocatenulatum*	16S rRNA	↑ in *Clostridiales* and *Bacteroidales* orders was independently associated with variations in portal vein area and portal flow, while changes in the *Proteobacteria* phylum were independently associated with congestion. *B. pseudocatenulatum* significantly decreased *Proteobacteria* and increased *Bacteroidetes*
Huang HC et al., 2021 [75]	Outcomes of FMT in BDL cirrhotic rats	BDL rats received either vehicle, fecal, or gut (terminal ileum) microbiota transplantation	16S rRNA	Both microbiota transplants increased *Bifidobacteria*. Microbiota transplantation in cirrhotic rats was associated with reduced PP
Garcıa-Lezana T et al., 2018 [76]	Role of intestinal microbiota in PH onset in NASH	23 control rats (13 receiving FMT from HFGFD rats) and 27 HFGFD rats (14 receiving FMT from control rats)	16S rRNA	*Clostridium* and *Adlercreutzia* abundance was inversely related to PP

BDL, bile duct ligation; DAA, direct-acting antiviral; FMT, fecal microbiota transplant; HFGFD, high-fat high-glucose–fructose diet; HVPG, hepatic venous pressure gradient; NASH, non-alcoholic steatohepatitis; PH, portal hypertension; PP, portal pressure.

Short-chain fatty acids (SCFAs) (acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, and isovaleric acid) result from the gut microbiome fermentation of non-absorbable carbohydrates; they regulate the function of the intestinal barrier both directly, providing energy to enterocytes, and indirectly, exerting anti-inflammatory effects on the innate and adaptive immune system [84–86]. SCFAs have been found in the portal and peripheral blood, participating in several processes, including the modulation of liver hemodynamics [87]. A study enrolling 62 patients with cirrhosis showed how the level of circulating SCFAs was inversely associated with the severity of liver disease and the model for end-stage liver disease (MELD) score; above them, butyric acid was inversely correlated with the HVPG values, inflammatory markers, such as TNF-alpha and IL-6, and NO in hepatic, peripheral, and portal blood [88]. Nevertheless, SCFAs were related

to hemodynamic changes, not only at a portal level, but also at a systemic level, being directly correlated with systemic vascular resistance and inversely correlated with the cardiac index.

Bile acids are key protagonists of intestinal functions and act as signaling molecules, regulating several metabolic and physiological processes. Bile acids have anti-microbial and immune-modulating properties in the gut [89,90] while participating in the regulation of intrahepatic vascular resistance by interacting with the sinusoid system via farnesoid x receptor (FXR) signaling [91,92]. In advanced cirrhosis, both primary and particularly secondary bile acid production is reduced [93], thus contributing to dysbiosis, SIBO, and bacterial translocation [13], as well as altered sinusoidal vasoregulation, consequently affecting the progression and the severity of portal hypertension.

Antimicrobial peptides (AMPs) are a wide and diverse group of small proteins implied in the host–microbiome interplay [94–96]. Defensins, cathelicidins, and lectins are the most common AMPs in the gut, mainly derived from Paneth cells and enterocytes; they operate in a complex and synergistic dynamic in the regulation of the gut microbiome, both directly by damaging microbes and indirectly by interacting with the host intracellular signaling pathways and stimulating the immune response [95]. Many intestinal bacterial strains also produce specific AMPs, i.e., the bacteriocins, involved in the mechanisms of bacterial competition and communication, as well as biodiversity and environmental niche formation [97–99]. There is some evidence of the relevance of the AMPs network in liver disease. In mice models of ethanol-induced liver injury, a deficiency of the regenerating islet-derived 3 beta and gamma (REG3B and REG3G), two gut lectins with bactericidal properties against Gram-negative bacteria, was associated with an increase in mucosa-associated bacteria and in bacterial translocation, together with worsening disease progression [100]. Of interest, in experimental cirrhosis, increased bacterial translocation was associated with a depletion of Paneth cells and a reduced expression of AMPs [101]; however, in the same study, this association was not observed in mice with acute portal hypertension without cirrhosis. While a considerable amount of data is already available on the gut microbiota composition associated with liver cirrhosis, the detailed analysis of which is beyond the scope of this paper, evidence on microbiota signatures associated with portal hypertension and its severity is still lacking. Some attempts have been made to demonstrate the value of the gut microbiota profile as a noninvasive diagnostic marker of portal hypertension. In particular, the circulating microbiome has been identified as a possible target in this context, reasonably mirroring bacterial translocation from the gut [49,102,103]. A recent study aimed to find microbial signatures of portal hypertension in blood compartments of patients with cirrhosis, particularly in peripheral circulation and hepatic veins [71]. While there were significant differences in the circulating microbial composition compared with controls and in association with MELD or biomarkers of inflammation, no predictive value regarding portal hypertension severity could be demonstrated. It has also recently been shown that specific components of the microbiome in the peripheral blood flow at baseline can predict the reduction in HVPG after direct-acting antiviral (DAA) therapy in HCV-related cirrhosis [72]. However, the study enrolled only 32 patients, including people with HIV and HCV coinfection, making it difficult to draw strong conclusions. Another study analyzed the gut microbiome of 12 inpatients with esophageal and gastric varices compared with 24 healthy controls, showing a higher relative abundance of *Lactobacillales* and a reduction in *Clostridium* cluster IV and cluster IX [73]; in this setting, no distinction was made concerning the severity of portal hypertension or in comparison with cirrhotic patients without CSPH.

6. Effects of Gut-Microbiota Modulation on Portal Hypertension

6.1. Rifaximin

Rifaximin is a derivative of rifamycin, an oral broad-spectrum antibiotic; it shows negligible absorption, with a low risk of inducing bacterial resistance, and has known eubiotic properties [104,105]. Rifaximin administration is recommended for the prophylaxis

and treatment of hepatic encephalopathy; notwithstanding, there is growing evidence for a broader benefit of rifaximin in patients with liver disease.

A case–control study evaluated the cumulative incidence and frequency of complications in 200 patients with decompensated cirrhosis, randomized at a ratio of 1:1 to receive or not receive rifaximin 400 mg twice daily for 6 months [106]. In addition to the significantly lower overall complication rate in the treatment group, a reduction in the incidence of esophageal and gastric variceal bleeding was observed. Another study including 30 patients with alcoholic cirrhosis confirmed that receiving rifaximin at 1200 mg/day can reduce HVPG and endotoxemia after 29 days of treatment [107]. A total of 23 out of the 30 patients included in this study who responded with improved HVPG were enrolled to continue rifaximin treatment. After a 5-year follow-up, the treatment arm showed a significantly lower risk of variceal bleeding (35% vs 59.5%, P=0.011) compared with the controls. In addition, rifaximin was found to be independently associated with a lower rate of hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome [108]. Furthermore, the combination therapy with propranolol plus rifaximin seemed to be more effective than propranolol alone, not only in lowering HVPG, but also in reducing markers of bacterial translocation (e.g., LPS, LPS-binding protein, IL-6, and TNF-alpha) [109].

The exact mechanisms leading to the effects of rifaximin on the gut–liver axis and liver hemodynamics are being widely investigated. Most of the studies have been focused on hepatic encephalopathy. Rifaximin administration results in the functional modulation of the gut microbiome, rather than its composition [110]. Bajaj et al. evaluated the impact of rifaximin on patients with mild hepatic encephalopathy; notably, the metabolomic analysis revealed an increase in serum saturated and unsaturated fatty acids, as well as a positive modulation of the bacterial metabolic network, with only a slight change in the microbiota composition itself [111]. Based on recent findings, rifaximin may affect certain components of the gut microbiome that metabolically contribute to hepatic encephalopathy, and the effectiveness or failure of therapy may depend on this [112]. Instead, the TLR4/LPS pathway could be the key to understanding the effect of rifaximin on portal hypertension. In bile duct-ligated TLR4-mutant mice, rifaximin did not reduce portal hypertension, angiogenesis, and liver fibrosis as it did in wild-type mice, suggesting that the attenuation of portal hypertension induced by rifaximin is mediated by TLR4, and that acting on this pathway can influence the fibrogenic activity of HSCs and endothelial cells [113]. Moreover, rifaximin upregulates pregnane X receptor (PXR) target genes, which contribute to the integrity of the intestinal barrier and further prevent the activation of NFκB, along with the following pro-inflammatory cascade in the gut [114–116].

Rifaximin is undoubtedly the best-studied molecule in the modulation of portal hypertension. Little evidence is available regarding other antibiotics; in the early 2000s, norfloxacin's effects were evaluated in small cohorts, with absent or weak results in ameliorating portal hypertension [117,118].

6.2. Probiotics

Probiotics administration, providing the gut ecosystem with beneficial bacteria, is extensively used in intestinal and extra-intestinal diseases, with often unclear evidence for the wide variety of products on the market and the heterogeneous experimental settings.

In animal models of cirrhosis, the administration of *Bifidobacterium pseudocatenulatum* CECT 7765, which upregulates anti-inflammatory markers and molecules associated with intestinal barrier integrity in experimental cirrhosis, was associated with a reduction in portal flow and the portal vein area and an increase in serum NO [74,119]. This was paralleled by the improvement in the gut microbiota profile, with a reduction in the relative abundance of *Proteobacteria* and an increase in that of *Bacteroidetes*, and the amelioration of liver function. The action of *B. pseudocatenulatum CECT* 7765 seems to be dose-dependent, as the increase in the dose is inversely related to the endotoxin serum levels and markers of intestinal permeability [120].

There is limited evidence on the effect of probiotics on portal hypertension from human studies; the most relevant data on this topic concern VSL3, a widely known probiotic mixture associated with inflammatory bowel disease and other gastrointestinal conditions. Jayakumar et al. sought to demonstrate the impact of a high dose of VSL3 (4 sachets/day for two months) on portal hypertension compared with a placebo in 17 patients with decompensated cirrhosis. They observed a decrease in HVPG not reaching statistical significance, either with respect to the gut microbiota composition or to endotoxins and inflammatory cytokines, probably due to the small sample size [121]. Similarly, another study analyzed the administration of VSL3 in preventing portal hypertension-related complications in 94 cirrhotic patients with large esophageal varices, showing that the combination of propranolol plus VSL3 was able to achieve a reduction in HVPG of up to 58% compared with 31% in the control group receiving propranolol alone [122]. Another study reported the beneficial effect of VSL3 (two sachets/day) in a small group of 12 cirrhotic patients with ascites, resulting in a widespread improvement in systemic and portal hemodynamics, as suggested by the reduction in the HVPG, cardiac index, and heart rate, as well as the increase in systemic vascular resistance and mean arterial pressure [123].

6.3. Fecal Microbiota Transplantation and Other Agents

Fecal microbiota transplantation (FMT) can deeply modify the natural history of liver disease, especially acting on complications such as hepatic encephalopathy, being a unique tool able to completely reset the gut microbiome.

Although data on the effect on portal hypertension are limited, evidence exists regarding the effects of FMT on portal hypertension in mouse models. Fecal and terminal ileum microbiota transplantation in bile duct-ligated rats significantly reduced splanchnic flow, portosystemic shunt flow, and portal pressure in association with a decrease in splanchnic eNOS activity and an increase in *Bifidobacteria* [75]. In another study, FMT from rats on a control diet to rats with early steatohepatitis was associated with the restoration of intrahepatic vascular resistance through the normalization of endothelial dysfunction pathways, mainly involving phosphorylated protein kinase B and phosphorylated eNOS [76]. However, FMT from the steatohepatitis rat model in healthy animals did not cause a rise in portal pressure within the study time of 14 days. As suggested by the authors, the beneficial effects of FMT are likely to be fleeting, and therefore hardly usable in a clinical setting if not sustained over time. Perhaps prolonged treatment may achieve superior benefits, but further studies are needed to prove this effect.

Finally, recent data have demonstrated that obeticholic acid, an FXR-agonist, can decrease portal hypertension and improve the intestinal barrier, acting on mucus production and on the gut–vascular barrier, both in animal models of NASH and in a preliminary study involving patients with alcoholic cirrhosis [124–126]. Other FXR agonists have been investigated in liver disease [127,128], with promising effects on the modulation of liver fibrosis progression and of intrahepatic vascular resistance.

7. Effects of Portal Hypertension Lowering Agents on the Gut Microbiome

7.1. Non-Selective Beta-Blockers

Non-selective beta-blockers (NSBBs) are currently indicated in the primary and secondary prophylaxis of variceal bleeding, given their effects on the portal venous system, splanchnic blood flow, and heart rate [16,129,130]. In addition to the effects on hemodynamics, there is emerging evidence regarding the effects of NSBBs on the gut and the microbiota itself. Reinberger et al. [131] showed that the long-term response to NSBBs improved markers of intestinal permeability, bacterial translocation, and IL-6 serum levels in 50 patients with ACLD. Although this improvement was not exclusively observed in HVPG responders, but also in non-responders, patients with baseline HVPG >20 mmHg showed a poor improvement, likely suggesting that there also is a point of no return in the modulation of the gut–liver axis. In this regard, Reverter et al. identified several biomarkers predicting the acute HVPG response to NSBBs through metabolomic serum

analysis. Sixty-six patients with cirrhosis and HVPG> = 10 mmHg underwent intravenous administration of propranolol during HVPG measurement; among the 177 metabolites analyzed, the serum levels of a phosphatidylcholine and a free fatty acid, combined in a two-cutoff system, were able to predict the acute response to NSBBs, with a positive predictive value of 84% and a negative predictive value of 82%.

A meta-analysis reported a reduced risk of SBP in NSBBs-treated patients both in hemodynamic responders and non-responders [132]. One possible explanation concerns the function of the sympathetic nervous system in this context, through the regulation of the enteric nerve plexus activity, but also of the intestinal mucosa and the GALT [133]. ACLD, among the above-mentioned mechanisms, is associated with the increased release of catecholamines in an attempt to counteract the vasodilation of the splanchnic venous system [51]. There is strong evidence suggesting that a high sympathetic tone in the gut is associated with a series of sustained alterations, starting with the reduction in intestinal peristalsis and impairing bacterial clearance. In addition, the increased sympathetic tone in the gut may be associated with SIBO and the overgrowth of specific bacteria, including *Escherichia coli* or other virulent strains [134–136], and also participates in interfering with phagocytosis and diapedesis, which are critical for gut immune homeostasis [137–139]. All these alterations seem to be, at least partially, counteracted by NSBBs [140,141].

Taken together, these data suggest that NSBBs, beyond their established effect on portal hemodynamics, may also act on the gut–liver axis through the modulation of the sympathetic nervous system, thereby improving the gut microbiome profile and restoring the integrity of the intestinal barrier [136].

7.2. Statins

In addition to their lipid-lowering property, statins are molecules with multiple pleiotropic effects, including anti-inflammatory and anti-fibrotic effects [142]. In particular, simvastatin and atorvastatin have been shown to exert a beneficial role in ACLD, reducing portal pressure and fibrosis, and improving liver sinusoidal and microvascular dysfunction [143].

A recent study in mice with NASH demonstrated statins' ability to decrease portal pressure by reverting SECs' transition to capillarization and HSCs' abnormal activation [144]. The effects of statins have also been studied in patients with cirrhosis and portal hypertension.

A randomized controlled trial including 59 patients with portal hypertension evaluated the effect of simvastatin administration, initially at a dose of 20 mg/day that then increased to 40 mg/day on day 15, compared with a placebo for one month. Simvastatin significantly decreased HVPG and improved liver perfusion without inducing arterial hypotension [145]. Another study with a similar design enrolled 158 patients with variceal bleeding who were followed over 2 years [146]. The addition of simvastatin to NSBBs and band ligation was not associated with a significant reduction in the re-bleeding rate, but it achieved a significant survival benefit.

Currently, there are no published studies linking the effect of statins on portal hypertension to the modulation of the gut microbiome. However, some evidence showed that statins can influence the composition of the gut microbiome, especially in patients with cardiovascular disorders [147,148]. Indeed, a study including patients with acute coronary syndrome demonstrated that statins could reduce potentially pathogenic bacteria and increase beneficial bacteria, shifting the gut microbiome toward a healthier condition [149]. This might result in an improved profile of circulating metabolites and reduced metabolic risk.

Based on these findings, the LIVERHOPE project is trying to assess if the combination of simvastatin plus rifaximin can prevent the progression to ACLF in patients with decompensated cirrhosis, with the analysis of the gut microbiome planned as a secondary endpoint (NCT03780673).

8. Conclusions

Our understanding of the role of the gut microbiota in human diseases has rapidly advanced in recent years. The increasing accessibility of complex methods of integrated metagenomics and metabolomics analysis provides a broader perspective, aiding in the identification of new molecular targets that can change the disease story from diagnosis to treatment. Metabolomics shed light on the importance of functional diversity in gut microbiome enzymatic activities, distancing from a point of view based solely on compositional analysis. However, there is still much to learn about the role of the gut–liver axis in the development and progression of ACLD and portal hypertension. There is growing evidence that the disruption of the gut–liver axis leads to the development of CSPH, especially through dysbiosis, damage to the intestinal barrier resulting in increased permeability, and alterations in the enterohepatic circulation of bile acids. The analysis of the microbial components crossing the intestinal barrier could be a shortcut to stratify patients according to the systemic inflammatory and hemodynamic conditions. The identification of the gut–liver-axis-related metabolic and molecular pathways that can be involved in this process is an unmet need that may serve to not only clarify pathogenesis and to define prognosis, but also as a target for new therapeutic strategies. The modulation of the intestinal environment with FMT is a very promising tool for the treatment of portal hypertension, with interesting results in animal models; however, randomized controlled trials in humans are needed to demonstrate its efficacy and to elucidate its mechanisms of action. Finally, the interaction between the gut microbiome and the different available pharmacological treatments could be a useful tool to monitor treatment efficacy as a noninvasive predictor of the hemodynamic response, shifting to a personalized therapy approach and thus having a considerable impact on the prognosis and survival of these patients.

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