REVIEW ARTICLE

# Probiotics and Liver Disease

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## Abstract

Intestinal microbiota play an important role in health and disease. The gut-liver axis provides for an interaction between bacterial components like lipopolysaccharide and hepatic receptors (Toll-like receptors). Dysbiosis and altered intestinal permeability may modulate this interaction and therefore result in hepatic disorders or worsening of hepatic disorders. Administration of health-promoting microbial strains may help ameliorate these harmful interactions and hepatic disorders. This review focuses on changes in gut microbiota in the context of liver disease and possible roles of probiotics, prebiotics, and synbiotics in liver disease.

## Introduction

Humans coexist with an enormous quantity of microbial organisms collectively termed microbiota. This very old relationship is a subject of active research. Since the mid-1990s there has been a steady increase in the interest in and understanding of microbiota and their functions.[1] This is partly because of new tools that have lifted the veil off organisms that cannot be cultured by standard microbiologic techniques. The approach to the study of microbiota has now become multidimensional and involves methods to identify not only the organisms but also their genes (metagenomics) and metabolic products.[2] In fact, along the lines of the Human Genome Project, the Human Microbiome Project attempted to evaluate the entire collection of genomes that the microbiota harbor. Human microbiota exist at various sites on and inside the human body, including the skin, nares, oral cavity, urogenital tract, and gut. Of course, the human gastrointestinal tract is the most heavily colonized site, and the colon contains more than two-thirds of the microbial load. On the whole, our gut has approximately 100 trillion ($10^{14}$) microbes, which make up approximately 1 to 2 kilograms of our weight.[1,3] The number of microbial species estimated to exist in a human gut is more than 1800. In the human gut the bacterial density gradient progressively increases from the stomach to the colon. The vastness of the human microbiota is evident given that the bacterial cells in the human gut outnumber human cells by a factor of 10 and microbial genes outnumber human genes by a factor of 100.[1] There are variations in the predominant bacterial species not only along the length of the gastrointestinal tract but also from the lumen to the epithelium.[1]

## Functions of Gut Microbiota in Health and Disease

Gut microbiota perform diverse immunologic, digestive, and metabolic functions. They are capable of producing energy by means of specialized digestion of complex polysaccharides that cannot otherwise be digested by humans. Colonic microbes can produce short-chain fatty acids like acetate, butyrate, and propionate by metabolizing these polysaccharides. Although acetate is the dominant short-chain fatty acid, butyrate is the primary source of energy for colonocytes.[4] This microbial activity is put to clinical use in management of short bowel syndrome—the loss of small intestinal absorptive surface can be compensated to some extent by utilizing production of short-chain fatty acid by colonic bacteria. This can account for energy production of up to 1000 kcal. Even in healthy adults, microbiota can produce varying amounts of energy (50 kcal to 200 kcal).[5] This energy harvesting is believed to vary with variations in gut microbiota. Excessive energy harvesting has been implicated in the causation of obesity.

Gut microbiota also have an extremely important immune function. Our gastrointestinal tracts are exposed daily to a large number of microorganisms. However, we are able to handle this immense microbial load without any adverse consequences. This is predominantly a result of the colonization resistance afforded by the flora in our intestines.[6] The mechanisms involved are complex and include the epithelium's recognition of microbiota as nonpathogenic and a contained, inflammatory response to these commensals.[7] This interaction occurs via the recognition of bacterial antigens (commensalism-associated molecular patterns) to the pattern-recognition receptors of the host (Toll-like receptors [TLRs]). This interaction mediates the further cascade of inflammatory activation. The intracellular cytosolic pattern recognition is mediated by the nucleotide oligomerization domains. A number of factors prevent unwarranted activation of the inflammatory cascade. These include the intracytoplasmic location of some of the pattern-recognition receptors, limited expression of TLRs, inhibitory cytokines, etc. All in all, the commensal bacteria do not incite an uncontrolled immune response and therefore continue to exist in a delicate equilibrium in the human gut.

The barrier function of the human gut includes physical, chemical, and immunologic components. Antimicrobial peptides (eg, defensins, mucins, and angiogenin 4) and secretory immunoglobulin A contribute to luminal chemical and immunologic mechanisms to maintain the gut's barrier function.[8] However,

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this barrier is disrupted in stressful situations like pathogen-enterocyte interaction, the presence of certain drugs, inflammation, hypoxia, etc. Disruption of this barrier is an opportunity for the previously excluded antigens and lipopolysaccharides to enter the enterocytes and systemic circulation.[8] This situation has been described as a leaky gut and the resulting phenomenon as metabolic endotoxemia. Metabolic endotoxemia is different from the endotoxemia associated with septicemia, because plasma lipopolysaccharide levels are elevated by a factor of 2 to 3 compared with the much larger increases in septicemia.[9] Beyond their digestive, immune, and barrier functions, gut microbiota are also involved in metabolism, including synthesis of vitamins (folate, vitamin K, and biotin), biotransformation of drugs and xenobiotics, and metabolism of bile acids.[1]

### Microbiota and Liver Disease

The close interaction of the gastrointestinal tract and the liver and the fact that the nutrients absorbed by the gut first reach the liver have fostered use of the term gut-liver axis. Cirrhosis patients have colonic microbiota that are different from that of healthy control subjects.[10,11] Increases in *Enterobacteriaceae* and *Enterococcus* with a reduction in *Bifidobacterium* species were noted in one report. Whether these changes are a cause or a consequence of cirrhosis is not clear.[10] An earlier report had indicated a reduced proportion of bacteroidetes and an increase in proteobacteria and fusobacteria.[11] In fact, a positive correlation was observed between Child-Turcotte-Pugh score and streptococcaceae.[11] Another report contradicted these findings vis-à-vis the diversity in intestinal microbiota amongst subjects with hepatitis B virus-related cirrhosis, subjects with chronic hepatitis B, and controls. However, there were changes in the composition of intestinal *Bifidobacterium* species, indicating dysbiosis in cirrhosis.[12] Another report indicated a progressive decrease in the ratio of *Bifidobacterium* to *Enterobacteriaceae* accompanying progression of liver disease in a range of subjects, from healthy controls to subjects with decompensated hepatitis B virus cirrhosis to asymptomatic carriers and subjects with chronic hepatitis B.[13] This indicates that changes in gut microbiota seem to mirror changes in severity of disease. The TLR 4/lipopolysaccharide interaction may be the link modulating this relationship; the role of this interaction in fibrogenesis is increasingly recognized.[14]

Changes in microbiota have also been reported in nonalcoholic fatty liver disease (NAFLD), hepatic encephalopathy, alcohol-related liver disease, and hepatocellular carcinoma. Gut microbiota may cause NAFLD by luminal ethanol production, causing a leaky gut and metabolic endotoxemia, or by metabolizing choline, which is no longer available for the liver.[15] Also, those who suffer from NAFLD may have a microbiota phenotype with a better energy-harvesting capacity that increases the calorie load to the liver. Indeed, the microbiota of obese individuals includes a reduced level of bacteroidetes and an increased level of firmicutes.[16] The role of the inflammasome-mediated (intracytoplasmic protein complexes to sense pathogen-associated molecular patterns) microbiota-host interaction may have a role in the transition from NAFLD to nonalcoholic steatohepatitis.[17]

Regarding alcohol-related liver disease, there is evidence from animal studies that chronic alcohol intake does lead to changes in microbiota.[18] A study in human subjects confirmed these findings and also indicated a correlation between alcohol-induced dysbiosis and endotoxemia.[19] Recent animal studies have shown that microbial translocation begins early in the course of alcoholic liver disease, leading to increased inflammation and eventually cirrhosis.[20] In rat models of hepatocarcinogenesis, induction of gut dysbiosis significantly promoted carcinogenesis.[21] Another report indicates that microbiota may not be involved in initiation of hepatocellular carcinoma but in promotion and proliferation of hepatocellular carcinoma.[22] Changes in microbiota have also been implicated in causation of hepatic encephalopathy, but the reports are conflicting.[23-25] However, the weight of evidence suggests some relationship between changes in microbiota and cognition. Changes in gut microbiota may also have a role in the pathogenesis of other complications of cirrhosis (eg, spontaneous bacterial peritonitis, hepatorenal syndrome, and cirrhotic

**Table 1. Common preparations of probiotics and synbiotics**

| Strain | Comment | Benefits[1] |
|---|---|---|
| Probiotics | | |
| *E coli* Nissle | One of the earliest strains to be used | Possible benefit in ulcerative colitis |
| *Lactobacillus* (many strains) | *L rhamnosus* GG is most commonly used, as it can survive gastric and biliary secretions | Prevention and treatment of acute childhood diarrhea, prevention of antibiotic-associated diarrhea |
| *Bifidobacterium* spp | Immense contemporary interest for possible anti-obesity effects | Childhood diarrhea, ulcerative colitis |
| *Sacchromyces boulardii* | Nonpathogenic yeast inherently resistant to all antibiotics | Prevention of antibiotic-associated diarrhea |
| VSL#3[a] | Multistrain probiotic with 300 billion per gram of bacteria | Ulcerative colitis, prevention of pouchitis |
| Synbiotic | | |
| Synbiotic 2000Forte[b2] | Mixture of 4 *Lactobacillus* strains and biofibers (inulin, pectin, resistant starch, and β-glucan) | Critically ill patients |

[a] Sigma-tau: VSL Pharmaceuticals Inc; Gaithersburg, MD.

[b] Synbiotic 2000Forte, Medipharm, Sweden.

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hyperdynamic circulation). It has also been suggested that microbiota are involved in the pathogenesis of cholestatic disorders like primary sclerosing cholangitis and primary biliary cirrhosis. The expression of TLRs is elevated in both of these conditions, and therefore TLR tolerance declines.[26] It is, therefore, apparent that changes in microbiota coexist with many hepatic disorders and may play a role in their causation. If this is indeed true, modulation of colonic microbiota may be an effective strategy for managing these diseases.

## Probiotics and Related Compounds

Clinicians have traditionally modulated the microbial environment of the gut with nonabsorbable disaccharides to manage hepatic encephalopathy related to cirrhosis. Lactulose acts not just by lowering pH in the colonic lumen and thereby improving excretion of ammonia but also by exerting a prebiotic effect and promoting the growth of certain bacteria, like *Bifidobacterium* and *Lactobacillus*.[27] This approach is often termed selective gut decontamination. Another approach is use of prebiotics, probiotics, and synbiotics. Probiotics are live microorganisms supplied from outside the human body, usually in the form of spores in a dosage believed to have beneficial effects.[28,29] However before a microbial strain can exert any beneficial effect in the intestine, it must be able to tolerate the acidic gastric and the alkaline bile juices and survive the journey from the mouth to the intestine. Prebiotics are, on the other hand, substrates that are fermented by the microbiota. By virtue of their promicrobiota properties, they are believed to increase microbial diversity and increase colonization resistance against pathogens.[29] These are usually plant fibers and consist of nondigestible carbohydrates. Synbiotics are combinations of prebiotics and probiotics. A synbiotic composition should ideally include a probiotic strain with evidence of health benefits along with a prebiotic that promotes growth of the coadministered probiotic strain.[28]

Numerous commercial preparations have flooded the market, creating confusion about probiotics (Table 1). Probiotics cannot be recommended as a panacea. An ideal probiotic preparation would comprise species with a human origin, as these are likely to be safe. Probiotics should be used only in those clinical situations where benefits have irrevocably been proven in adequate clinical trials, and the strain and dosage should be those shown to be beneficial. Although probiotics are generally regarded as safe, some complications have been noted. Occasional cases of bacteremia, endocarditis, and fungemia have been reported.[30]

## Probiotics in Liver Disease

### Hepatic Encephalopathy

Hepatic encephalopathy encompasses a broad range of neuropsychiatric disturbances that may accompany portosystemic shunting, acute liver failure, and cirrhosis. Cirrhotic encephalopathy is

**Table 2. Trials of probiotics and synbiotics in minimal hepatic encephalopathy**

| Reference | Setting | Intervention | Outcome |
|---|---|---|---|
| Saji et al[1] | RCT; 43 children with A and B cirrhosis and MHE | *Lactobacillus acidophilus, L rhamnosus, Bifidobacterium longum, and Saccharomyces boulardi*; 1.25 billion spores 3 times daily for 4 weeks versus placebo | No change in ammonia, evoked responses, and NCT |
| Mittal et al[2] | RCT; 160 subjects with cirrhosis and MHE | Lactulose versus L-ornithine L-aspartate versus probiotics[a] 110 billion colony-forming units twice daily for 3 months | All improved MHE and QOL |
| Sharma et al[3] | Open label; 105 subjects with Cirrhosis and MHE | Probiotics (*Streptococcus faecalis, Clostridium butyricum, Bacillus mesentricus,* LAB) 1 capsule 3 times daily for 1 month versus lactulose versus both | All were equally effective in treating MHE |
| Bajaj et al[4] | Nonblinded randomized trial; 25 subjects with nonalcoholic cirrhosis and MHE | Probiotic yogurt for 2 months versus no drug | Improvement NCT-A, BDT, and DST; reduction in overt HE |
| Liu et al[5] | 55 subjects with cirrhosis and MHE | Synbiotic preparation (Cocktail 2000; Medipharm, Kagerod, Sweden) for 30 days versus fermentable fiber versus placebo | Increase in nonurease producers, reduced ammonia levels, MHE, and endotoxemia |
| Malaguarnera et al[6] | RCT; 60 subjects with cirrhosis and MHE | *Bifidobacterium longum* with fructo-oligosaccharide versus placebo for 90 days | Reduced ammonia, improved symbol digit test; reduced performance on trail making tests |

[a] Nature of probiotics unknown.

BDT = block design test; DST = digital symbol test; HE = hepatic encephalopathy; LAB = lactic acid bacteria; MHE = minimal hepatic encephalopathy; NCT = number connection test; QOL = quality of life; RCT randomized controlled trial.

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broadly classified as overt and minimal hepatic encephalopathy (MHE). MHE refers to the condition of that subset of patients with cirrhosis who do not have any clinically detectable neurologic abnormality but have abnormal neuropsychometric or neurophysiologic test results.[31] Specifically, these patients have abnormal results for 2 of 4 tests: number connection test A and B, block design test, and digital symbol test. The traditional therapy for hepatic encephalopathy has been antibiotics or nonabsorbable polysaccharides. There is, however, emerging evidence that various probiotic preparations have a role in various stages of hepatic encephalopathy, especially MHE. Table 2 summarizes the various trials that have evaluated the roles of prebiotics, probiotics, and synbiotics in MHE. The effect is believed to be modulated by changes in gut microbiota: an increase in non-urease-producing bacteria like lactobacilli and a concomitant reduction in urease producers like *Escherichia coli* and *Staphylococcus aureus*.

As these trials suggest, the bulk of evidence favors the use of probiotics for MHE. A meta-analysis of 9 eligible reports indicated a beneficial effect of prebiotics, probiotics, and synbiotics in patients with hepatic encephalopathy.[32] In fact, a guideline by the Indian National Association for Study of the Liver recommends use of probiotics in MHE.[31] The situation is less clear with regards to probiotic preparations for overt hepatic encephalopathy. A Cochrane review of probiotics for hepatic encephalopathy could not determine any evidence of improvement in clinically significant outcomes, although probiotics reduced plasma ammonia levels. However, some reports indicate that probiotics are beneficial for overt hepatic encephalopathy; this issue needs to be addressed in further trials before any clear recommendations can be made regarding use of probiotics for treatment or secondary prevention of overt hepatic encephalopathy.[33]

### Nonalcoholic Fatty Liver Disease

Many data from animal experiments have indicated that modulating gut microbiota with prebiotics, probiotics, and synbiotic preparations has a beneficial effect on NAFLD. Loguercio et al first postulated the role of a gut-liver axis in causation of liver disease and its related complications.[34] They reported benefits of a complex preparation of probiotics, prebiotics, vitamins, and minerals in reducing aminotransferase levels in patients with nonalcoholic steatohepatitis. The same group reported a reduction in parameters of lipid peroxidation in NAFLD patients with use of VSL#3 (Sigma-tau: VSL Pharmaceuticals, Inc; Gaithersburg, MD).[35] Another small report, on the contrary, indicated an increase in hepatic fat with probiotic use. Some human studies have further evaluated the role of probiotics in NAFLD (Table 3); this includes 1 study in a pediatric sample.[36]

Therefore, it is premature to recommend probiotics for treatment of NAFLD. Ongoing research may shed more light in the future. The recent guidelines by the American Association for Study of Liver Diseases do not recommend probiotics for NAFLD.[37]

### Other Liver Diseases

Probiotic use has been evaluated in patients with compensated cirrhosis with at least one major complication. A multistrain probiotic had no benefit in these patients except for a nonsignificant trend toward reduction in serum ammonia levels in those with elevated ammonia.[38] Preoperative and postoperative use of probiotics in cirrhosis and hepatocellular carcinoma patients who underwent tumor resection was associated with a lower serum TNF-α level and quicker recovery of hepatic function.[39] Use of VSL#3 for 2 months in cirrhosis patients with an elevated hepatic venous pressure gradient (>10 mm of Hg) did not reduce hepatic venous pressure gradient, although reductions in plasma endotoxemia and cytokines (TNF-α, interleukin 6, and interleukin 8) were noted.[40] Use of *E Coli* Nissle strain was reported to result in improvement in liver function, as measured by Child-Pugh score, and reduction in endotoxin levels.[41] Those results, however, have not been replicated. These reports indicate the need for large prospective trials to evaluate clinical outcomes of patients with cirrhosis and liver disease treated with probiotics. In a recent study, probiotic strains were used with norfloxacin for prophylaxis of spontaneous bacterial peritonitis in patients

**Table 3. Reports of probiotic use in humans with nonalcoholic fatty liver disease**

| Reference | Setting | Interventions | Outcomes |
|---|---|---|---|
| Aller et al[1] | Open label, randomized; 30 subjects with NAFLD | 500 million *Lactobacillus bulgaricus* and *Streptococcus thermophilus* for 3 months versus placebo | Improvement in transaminases |
| Loguercio et al[2] | Open label; NAFLD, alcoholic cirrhosis, HCV, HCV cirrhosis | VSL#3[a] for 3 months | Reduction in plasma levels, malondialdehyde, and 4-hydroxynonenal |
| Solga et al[3] | Open label; 4 subjects with NAFLD | VSL#3, 1 sachet for 4 months | Increased hepatic fat |
| Vajro et al[4] | RCT; pediatric NAFLD | *Lactobacillus rhamnosus*, 12 billion CFU/day for 8 weeks | Improved transaminases, reduced lipopolysaccharide levels |

[a] Sigma-tau: VSL Pharmaceuticals, Inc; Gaithersburg, MD.

CFU = colony-forming unit; HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease; RCT = randomized controlled trial.

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with cirrhosis. However, the authors observed no accrual benefits of the combination compared with norfloxacin alone.[42]

Probiotics have also been evaluated in primary sclerosing cholangitis. Primary sclerosing cholangitis is a cholestatic liver disease characterized by relentless fibro-inflammatory involvement of the extrahepatic and intrahepatic biliary system. It is often seen in association with inflammatory bowel disease. Inflammatory bowel disease is known to be associated with dysbiosis, and use of probiotics has been shown to be beneficial. However, the use of a multistrain probiotic in patients with primary sclerosing cholangitis for three months had no benefit for pruritus or liver functions.[43] Another interesting report from China evaluated a multistrain probiotic *(Lactobacillus* and *Propionobacterium* species) in healthy individuals and noted a decrease in urinary excretion of aflatoxin metabolite, suggesting that probiotics may reduce exposure to aflatoxin and may have a chemopreventive role in hepatocellular carcinoma.[44] Also, the use of synbiotics seems to decrease bacterial infections after liver transplantation.[45] In a recent randomized study, preoperative and postoperative use of a synbiotic preparation significantly reduced infectious complications after elective living-donor liver transplantation.[46]

To summarize, with the growing recognition of the roles that changes in gut microbiota have in the causation of various liver diseases and their complications, there is an increasing interest in probiotics and related products for preventing and treating hepatic disorders. For now, probiotics cannot be recommended for treatment of most hepatic disorders—apart from minimal hepatic encephalopathy—in clinical settings. With accumulating evidence, however, probiotics may be used more widely to treat other liver diseases. ❖

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**Liver, noun**

A large red organ thoughtfully provided by nature to be bilious with … .
It was at one time considered the seat of life; hence its name—liver,
the thing we live with.

— *The Devil's Dictionary,* Ambrose Bierce, 1842-1913,
American editorialist, journalist, satirist, and author