Title
The role of gut microbiota in liver disease development and treatment.

Permalink
https://escholarship.org/uc/item/5f88v56j

Journal
Liver research, 3(1)

ISSN
2096-2878

Authors
Wang, Lijun
Wan, Yu-Jui Yvonne

Publication Date
2019-03-01

DOI
10.1016/j.livres.2019.02.001

Peer reviewed
The role of gut microbiota in liver disease development and treatment☆

Lijun Wanga,b, Yu-Jui Yvonne Wan a,*

aDepartment of Medical Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA

bThe College of Life Science, Yangtze University, Jingzhou, Hubei, China

Abstract

Liver cancer is the sixth most common cancer worldwide, and the third most common cause of cancer-related death. Hepatocellular carcinoma (HCC), which accounts for more than 90% of primary liver cancers, is an important public health problem. In addition to cirrhosis caused by hepatitis B viral (HBV) or hepatitis C viral (HCV) infection, non-alcoholic fatty liver disease (NAFLD) is becoming a major risk factor for liver cancer because of the prevalence of obesity. Non-alcoholic steatohepatitis (NASH) will likely become the leading indication for liver transplantation in the future. It is well recognized that gut microbiota is a key environmental factor in the pathogenesis of liver disease and cancer. The interplay between gut microbiota and liver disease has been investigated in animal and clinical studies. In this article, we summarize the roles of gut microbiota in the development of liver disease as well as gut microbiota-targeted therapies.

Keywords

Microorganism; Hepatocellular carcinoma (HCC); Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); Cirrhosis; Probiotics; Prebiotics; Synbiotics

1. Introduction

There are about 100 trillion (10^{14}) microorganisms and approximately 2000 different bacterial species in the human digestive tract.¹ The gut microbiota colonizes immediately after birth and plays an essential role in keeping the host healthy by assisting digestion, producing vitamins, generating bile acids, and modulating local and systemic immunity.²–⁵ Many factors, including diet, age, medication, illness, stress, and lifestyle, influence the gut microbiota community structure, which has an impact on disease development.⁶ It is

☆Edited by Peiling Zhu and Genshu Wang.

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Corresponding author. Department of medical Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA. yyjwan@ucdavis.edu (Y.-J.Y. Wan).

Authors’ contributions

L. Wang drafted the manuscript. Y.-J. Y. Wan edited and approved the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.
important to note that genetic factors only contribute to 5–15% of most cancers. About 80% of cancers are caused by the environment or lifestyle. Emerging evidence reveals that the gut microbiota is a major environmental and etiological factor for liver disease development. In this review, we summarize publications on the topics of gut microbiota in liver disease development, as well as treatment, focusing on non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC).

We performed a literature search in PubMed for papers published within the past 10 years, using the keywords: microorganism, microbiota, bacteria, liver, liver disease, HCC, hepatocellular carcinogenesis, NAFLD, NASH, cirrhosis, probiotics, prebiotics, synbiotics, and their combinations.

2. Role of gut microbiota in liver diseases

2.1. Gut microbiota and NAFLD as well as NASH

NAFLD is a global public health problem because of the prevalence of obesity. NAFLD is a spectrum of chronic liver diseases, including simple steatosis, NASH, advanced fibrosis, cirrhosis, and HCC. Dysbiosis refers to unfavorable alteration of the microbiota. It is commonly characterized with a decreased ratio of autochthonous to nonautochthonous taxa. Increasing evidence indicates that gut dysbiosis has an important role in the development of NASH via regulation of inflammation, insulin resistance, bile acids, and choline metabolism.

Data generated from human studies have established the relationship between gut microbiota and NAFLD (Table 1). In 2013, Mouzaki et al. reported that NASH patients have significantly lower levels of Bacteroidetes compared to healthy individuals. Shen et al. showed similar findings. However, Wang et al. found that non-obese patients with NAFLD have significantly higher levels of Bacteroidetes and lower abundance of Firmicutes in addition to reduced diversity. In these non-obese patients with NAFLD, the depletion of Firmicutes included Lachnospiraceae, Ruminococcaceae, and Lactobacillaceae, which generated short-chain fatty acids (SCFAs). Additionally, a different Bacteroidetes abundance pattern in adolescents was revealed in a study conducted by Stanislawski et al. The abundance of Bacteroides showed a U-shaped pattern based on hepatic fat; both low and high abundances were associated with elevated hepatic fat, while a moderate level was associated with reduced hepatic fat. In addition, Bacteroides is associated with a high-fat diet (HFD). However, certain species of Bacteroides have protective roles in obesity. Stanislawski et al. also found that Bilophila, Paraprevotella, Suturella, and RF32 have a positive relationship with hepatic fat, while Oscillospira and Varibaculum correlate negatively. The positive association between hepatic fat and Bilophila is accompanied by reduced Oscillospira. These results suggest that Bilophila might contribute to fatty liver, while Oscillospira might counteract its effects. The abundance of Bilophila wadworthia increases in response to a western diet or HFD. Bilophila wadworthia is also associated with T helper 1 (Th1)-mediated intestinal inflammation. Oscillospira is reduced in pediatric NAFLD and NASH. Reduced Oscillospira accompanied by increased 2-butanone has
been identified as a gut microbiota signature of NAFLD onset. Increases in *Ruminococcus* and *Dorea* have been identified as gut microbiota signatures of NAFLD and NASH progression.\(^\text{21}\) *Oscillospira* is generally linked to leanness and health.\(^\text{23}\) *Bilophila*, *Oscillospira*, and *Bacteroides* are associated with diets high in animal products.\(^\text{29–31}\) In addition, increased levels of *Lactobacillus* and selected members of the Firmicutes (Lachnospiraceae; genera, *Dorea*, *Robinsoniella*, and *Roseburia*) have been observed in NAFLD patients.\(^\text{24}\) NAFLD patients and healthy subjects have a distinct intestinal microbiota community structure.

Further evidence shows that gut dysbiosis and altered metabolic function are linked with the severity of NAFLD. A study by Boursier *et al.*\(^\text{14}\) demonstrated that *Bacteroides* and *Ruminococcus* are associated with NASH and the severity of fibrosis. Patients with NASH and fibrosis severity F ≥2 have higher abundance of *Bacteroides* and lower abundance of *Prevotella* compared to those without NASH. Patients with F ≥2 fibrosis have higher abundance of *Bacteroides* and *Ruminococcus* and lower abundance of *Prevotella* compared to those with F0/F1 fibrosis.\(^\text{14}\) Patients with mild/moderate NAFLD have a higher abundance of Proteobacteria. Patients with advanced fibrosis have lower abundance of *Ruminococcus obeum* CAG: 39, *Ruminococcus obeum*, and *Eubacterium rectale* compared to those with mild/moderate NAFLD.\(^\text{32}\)

Small intestinal bacterial overgrowth (SIBO) is defined as bacterial culture >10\(^5\) CFU/ml in upper jejunal aspirate.\(^\text{33,34}\) SIBO has a direct relationship with the severity of liver disease. Many patients with chronic liver disease have dysbiosis with SIBO.\(^\text{3,35}\) SIBO in patients with NAFLD/NASH has an estimated prevalence of 39–85%.\(^\text{36–41}\) As a consequence of reduced intestinal motility and decreased bile acid production, SIBO has a role in NAFLD progression.\(^\text{42}\) Miele *et al.*\(^\text{37}\) have reported that SIBO is implicated in increased intestinal permeability and development of fatty liver. SIBO increases lipopolysaccharide (LPS) secretion and inflammation. Hepatic expression of Toll-like receptor 4 (TLR4), together with release of interleukin-8 (IL-8) induced by SIBO, promotes inflammation.\(^\text{4}\) SIBO increases endogenous ethanol and intestinal permeability, favoring LPS production and increased inflammation via TLR4 signaling.\(^\text{43,44}\) SIBO is considered as an independent risk factor for the severity of NAFLD and is essential for NAFLD to progress into NASH, followed by development of cirrhosis.\(^\text{15,19,38,45,46}\)

Enteric dysbiosis or intestinal inflammation induced by HFD and dextran sulfate sodium significantly promotes liver fibrosis in mice with NASH.\(^\text{47}\) The inflammasome-mediated dysbiosis, including increased Prevotellaceae and Porphyromonadaceae families as well as the TM7 taxa, promote NAFLD progression in mouse models.\(^\text{6}\) Apart from providing bacterial byproducts and increasing intestinal permeability, the gut microbiota might also inhibit small intestinal secretion of fasting-induced adipocyte factor, resulting in increased hepatic triglyceride deposition.\(^\text{48}\) Antibiotic treatment or surgical removal of the bypassed section of the intestine can reverse SIBO and steatohepatitis.\(^\text{36,42}\) SIBO might be an important target for using antibiotics in treating NAFLD as well as NASH.\(^\text{49,50}\)
Patients with liver cirrhosis and liver or colon cancer have reduced bile acid receptor farnesoid X receptor (FXR).\textsuperscript{51–53} Wan’s group has shown that the sex of an animal can affect the gut microbiota, which is implicated in the dissimilar development of steatosis in both western-diet-fed mice and FXR knockout (KO) mouse models according to sex.\textsuperscript{54} Decreased S24–7, in parallel with increased Bacteroidiaceae, Rikenellaceae, Lactobacillaceae, and Verrucomicrobiaceae, has been observed in wild-type female mice compared to their male counterparts. However, these sex differences are abolished in FXR KO mice, indicating that sex difference in steatosis is FXR dependent.\textsuperscript{54} Western-diet-fed male FXR KO mice develop advanced NASH with massive hepatic lymphocyte infiltration, and have decreased Firmicutes and increased Proteo-bacteria.\textsuperscript{55} Broad-spectrum as well as a Gram-negative coverage antibiotics are useful in treating NASH in male FXR KO mice, but are relatively ineffective when FXR KO male mice are on a western diet.\textsuperscript{55} In the Proteobacteria, the relative abundance of Heli-cobacterae and Desulfovibrionaceae substantially increases because of FXR inactivation. Consistently, antibiotic-reduced hepatic inflammation is accompanied by their reduction. In contrast, \textit{Lactococcus}, \textit{Lactobacillus}, and \textit{Coprococcus} have a protective effect in hepatic inflammation.\textsuperscript{55} The basic mechanisms of dysbiosis affecting liver disease are summarized in Fig. 1.

2.2. Gut microbiota and liver cirrhosis as well as cirrhosis-associated complications

2.2.1. Gut microbiota and liver cirrhosis—Liver cirrhosis is the end stage of chronic liver diseases and is characterized by fibrosis, abnormal hepatic architecture, and portal hypertension. Liver cirrhosis may lead to progressive hepatic failure and cancer. It has been shown that dysbiosis can affect clinical outcomes, including 90-day-hospitalization, organ failure, and death.\textsuperscript{56–58}

Cirrhosis-associated gut dysbiosis is accompanied by reduced Bacteroidetes, increased Proteobacteria at the phylum level, and reduced Lachnospiraceae as well as increased Enterobacteriaceae and Veillonelaceae at the family level\textsuperscript{5}. Potentially pathogenic overgrowth of Enterobacteriaceae is linked to the severity of cirrhosis and its complications, such as hepatic encephalopathy.\textsuperscript{5} Chen \textit{et al.}\textsuperscript{59} demonstrated an increase in Proteobacteria and Fusobacteria, along with a decrease in Bacteroidetes and change in Firmicutes at the phylum level in fecal samples from cirrhotic patients. In addition, cirrhotic patients have increased fecal Enterobacteria, Veillonelaceae, and Streptococcaceae, and reduced Lachnospiraceae.\textsuperscript{59} Moreover, several commensal genera, such as, \textit{Coprococcus}, \textit{Pseudobutyrivibrio}, and \textit{Roseburia} in the Lachnospiraceae family, are beneficial to the host via production of SCFAs.\textsuperscript{59}

In 2014, Bajaj \textit{et al.}\textsuperscript{56} compared fecal microbiota analysis in cirrhotic patients and healthy controls. They reported that the reduction of autochthonous taxa, including Lachnospiraceae, Ruminococcaceae, and Clostridiales XIV, and increase of non-autochthonous taxa including Staphylococcaceae, Enter-ococcaceae, and Enterobacteriaceae, are linked to liver failure and plasma LPS levels in cirrhosis patients. In addition, Enterobacteriaceae and endotoxemia are enriched in patients with alcoholic compared with non-alcoholic cirrhosis.\textsuperscript{56} Enterobacteriaceae are also frequently found in spontaneous bacterial peritonitis; an infection in decompensated cirrhosis.\textsuperscript{60} Enterobacteriaceae are more abundant in patients
with decompensated cirrhosis compared to patients with compensated cirrhosis and healthy controls.\textsuperscript{51} The mucosal microbiota in the duodenum also differs markedly between cirrhotic patients and healthy controls.\textsuperscript{34} Based on the predicted metagenomes analyzed, pathways related to nutrient absorption are enriched in the duodenal microbiota of patients with cirrhosis, while bacterial proliferation and colonization, including bacterial motility proteins and secretory systems, are over-represented in control subjects.\textsuperscript{34}

Bile acid pool size and composition are major regulators of microbiome structure.\textsuperscript{61,62} Increased primary bile acid, cholic acid (CA) can cause dysbiosis with a dramatic shift toward the Firmicutes, particularly \textit{Clostridium} cluster XIVa and can increase production of deoxycholic acid (DCA).\textsuperscript{61,62} Cirrhosis-associated dysbiosis increases inflammation via metabolism, LPS, and translocation. Inflammation can suppress synthesis of bile acids in the liver.\textsuperscript{61,62} Secondary bile acids, which are generated by the Clostridiales cluster, are reduced in cirrhotic patients.\textsuperscript{63,64} Bile acids have an important role in the pathogenesis of cirrhosis.\textsuperscript{54,55,65} Reduced bile acid secretion facilitates oral microbiota migration to the distal gut and boosts SIBO. In contrast, activation of FXR stimulates bile acid excretion and induces production of antimicrobial peptides.\textsuperscript{66,67} The interaction between bile acids and microbiota plays an important role in cirrhosis.\textsuperscript{61,62} The data related to alteration of gut microbiota in cirrhotic patients are summarized in Table \ref{tab:2}.\textsuperscript{34,56,57,59,64}

2.2.2. Gut microbiota and complications associated with liver cirrhosis—

Bacterial translocation (BT) plays a crucial role in the development of complications associated with hepatic cirrhosis.\textsuperscript{68} By inoculating an equal amount of \textit{Escherichia coli} (\textit{E. coli}) into small and large intestines, it was found that BT predominantly occurs in the small intestine.\textsuperscript{69} Consistently, the small intestine is a preferred site for BT in cirrhotic patients.\textsuperscript{70} In addition, BT is closely associated with SIBO as well as intestinal barrier injury in cirrhotic rats.\textsuperscript{71}

Spontaneous bacterial peritonitis is a common complication of liver cirrhosis because bacterial infections occur in cirrhotic patients with ascites.\textsuperscript{72–74} Most of the bacteria in patients with spontaneous bacterial peritonitis are \textit{E. coli}, \textit{Klebsiella pneumoniae}, coagulase-negative \textit{Staphylococcus}, and \textit{Enterococcus}.\textsuperscript{74} \textit{E. coli} is the predominant pathogen of spontaneous bacterial peritonitis.\textsuperscript{72–74}

Hepatic encephalopathy is a common complication of liver cirrhosis and a result of liver failure.\textsuperscript{75,76} Hepatic encephalopathy affects brain astrocytes, microglia, and neurons.\textsuperscript{75,76} A decrease in autochthonous bacteria and increase in Gram-negative bacteria are observed in cirrhotic patients with hepatic encephalopathy. It has been shown that elevated serum ammonia levels are linked to astrocytic impairment\textsuperscript{77} Moreover, ammonia-associated brain magnetic resonance imaging changes are associated with autochthonous taxa and \textit{Enterobacteriaceae}, while white matter inflammatory changes are associated with oral taxa such as \textit{Porphyromonadaceae}.\textsuperscript{77} Only mucosal and not fecal microbiota is altered significantly in patients with hepatic encephalopathy. The Firmicutes phylum, including \textit{Veillonella}, \textit{Megasphaera}, \textit{Bifidobacterium}, and \textit{Enterococcus}, is highly enriched in hepatic encephalopathy, whereas \textit{Roseburia} is more abundant in the non-hepatic encephalopathy group.\textsuperscript{73}
2.2.3. **Gut microbiota and liver transplantation**—Liver transplantation is one option used to treat cirrhosis or cirrhosis-associated complications.\(^78,79\) Liver transplantation affects the recipient’s microbiota (Table 3).\(^79–81\) Gut microbiota diversity is increased after liver transplantation, but does not reach the levels in healthy controls.\(^80\) Alteration of Proteobacteria and Firmicutes links with improved cognitive level of patients with liver transplantation.\(^80\) In 2016, the Wan laboratory established the relationship between intestinal microbiota and expression of hepatic genes in regenerating the liver, using partial hepatectomy mouse models.\(^82\) Removal of two-thirds of mouse liver led to rapid changes in gut microbiota, with increased Bacteroidetes S24–7 and Rikenellaceae as well as decreased Firmicutes Clostridiales, Lachnospiraceae, and Ruminococcaceae.\(^82\) The abundance of Ruminococcaceae, Lachnospiraceae, and S24–7 was closely linked with liver metabolism and immune functions.\(^82\) Hepatic secondary bile acids are positively correlated with Firmicutes and negatively with Bacteroidetes, while tauro-conjugated bile acids show positive correlations with Bacteroidetes and negative correlations with Firmicutes.\(^82\) Priming mice with all-trans retinoic acid lowers the ratio of Firmicutes to Bacteroidetes and increases hydrophilic bile acids, which is linked with facilitated metabolism and enhanced cell proliferation in regenerating mouse livers.\(^83\) Bajaj *et al.*\(^81\) have reported the effect of liver transplantation on microbial composition and functionality in patients. Successful liver transplantation increases the microbial diversity accompanied by an increase in autochthonous and a decrease in potentially pathogenic taxa.\(^81\) The favorable changes in the gut microbiota also have the benefit of increasing fecal bile acids and urinary phenyl-acetylglutamine, accompanied with a reduction in serum ammonia and endotoxemia.\(^81\)

2.2.4. **Fungal dysbiosis and complications associated with liver cirrhosis**—In addition to bacteria, microbiota includes archaea, protists, fungi, viruses, and bacteriophages.\(^84\) A recent study showed fungal dysbiosis in cirrhotic patients. Bajaj *et al.*\(^85\) have demonstrated a link between fungal and bacterial diversity in patients with liver cirrhosis, and Bacteroidetes/Ascomycota ratio can affect 90-day-hospitalization (Table 4). Moreover, *Candida* overgrowth and reduced intestinal fungal diversity are observed in patients with alcoholic cirrhosis (Table 4).\(^86\)

2.2.5. **Oral microbiota and liver cirrhosis**—Oral microbiota contributes to the progression of liver diseases. Elevated oral *Streptococcus* and *Veillonella* are found in cirrhotic patients.\(^87\) Increased Enterobacteriaceae and Enterococcaceae, as well as reduced autochthonous bacteria, are found in patients with previous episodes of hepatic encephalopathy.\(^87\) Oral microbiota has a significant impact on duodenal microbiota. At the genus level, the most distinctive taxa found in cirrhotic patients and controls include *Veillonella, Prevotella, Neisseria,* and *Haemophilus,* which are commonly found in the oral cavity.\(^88\) Bajaj *et al.*\(^89\) performed a direct comparison of the salivary microbiome between healthy controls and patients with cirrhosis. Relative abundance of potentially pathogenic taxa (*Prevotella* and Fusobacteriaceae) increased whereas autochthonous taxa (Lach-nospiraceae and Ruminococcaceae) decreased in oral microbiota of cirrhotic patients with previous
hepatic encephalopathy. Microbes of oral origin can be present in the duodenum. Duodenal *Prevotella* and *Fusobacterium* are also increased significantly in cirrhotic patients. Proton pump inhibitors increase the microbiota of oral origin in patients with cirrhosis. The removed pH barrier in the gastrointestinal tract allows the microbiota of oral origin to migrate along the gastrointestinal tract and even into feces. Certain oral bacteria can produce high levels of hydrogen sulfide (H₂S) and methyl mercaptan (CH₃SH). Higher proportions of *Neisseria*, *Porphyromonas*, and *SRI* are linked to H₂S production that can damage deoxyribonucleic acid (DNA). *Prevotella*, *Veillonella*, *Atopobium*, *Megasphaera*, and *Selenomonas* are associated with production of CH₃SH, which contributes to development of hepatic encephalopathy. Literature related to oral microbiota and liver disease is summarized in Table 5.

### 2.3. Gut microbiota and HCC

Gut microbes are implicated in liver carcinogenesis. *Helicobacter* species are important pathogens that may be directly involved in the occurrence of liver cancer, and are found in human HCC specimens. A human study has shown that *Helicobacter* is present in the liver of patients with primary liver carcinoma but not in controls without primary liver carcinoma. However, *Helicobacter hepaticus* (*H. hepaticus*) is not present in HCC patients with chronic hepatitis B or C.

*H. hepaticus* infection promotes HCC in chemical and viral transgenic liver cancer models. However, HCV transgene or *H. hepaticus* exposure alone is not sufficient to initiate liver cancer. Moreover, increased risk of HCC is not dependent on translocation of *H. hepaticus* to the liver. Gut *H. hepaticus* colonization induces nuclear factor κ-light-chain-enhancer of activated B cell signaling, which activates innate and Th1-type adaptive immunity. Thus, *H. hepaticus* in the intestinal niche without translocation to the liver can change the immune signaling and play a synergistic role with chemical and viral carcinogenic factors.

Gut dysbiosis is found in patients with liver cirrhosis and HCC as well as animal models using streptozotocin-HFD, diethylnitrosamine (DEN), or carbon tetrachloride (CCl₄). Blooming of *E. coli* is found in cirrhotic patients who have HCC compared to those without HCC. In the C57BL/6J mouse model of NASH and HCC induced by streptozotocin-HFD, a significant increase of *Atopobium* spp., *Bacteroides* spp., *Bacteroides vulgatus*, *Bacteroides acidifaciens*, *Bacteroides uniformis*, *Clostridium cocleatum*, *Clostridium xylanolyticum*, and *Desulfovibrio* spp. is associated with disease progression. A significant reduction of *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* species, along with increased *E. coli* and *Atopobiumcluster*, has been found in rat models of HCC induced by DEN. Moreover, *Clostridium* spp. are reduced in CCl₄-induced liver carcinogenesis models. When DEN is used in combination with CCl₄, gut sterilization or TLR4 deletion reduces tumor number and volume but does not affect tumor incidence, while continuous low-dose LPS administration increases tumor number and size.

Changes in the microbiota of the tongue coating have been noted in patients with HCC. Moreover, enrichment of tongue *Oribacterium* and *Fusobacterium* could be microbial biomarkers of HCC. Microbial genes in the categories related to nickel/iron transport,
amino acid transport, energy-producing systems, and metabolism differ in abundance between HCC patients and healthy controls.\textsuperscript{104}

The steatohepatitis-inducing HFD (STHD-01) is a NASH-inducing HFD, which promotes HCC without chemical carcinogens.\textsuperscript{105} A recent study revealed that gut bacteria associated with secondary bile acid production promote STHD-01-induced HCC development that can be prevented by antibiotics.\textsuperscript{105,106} In addition, \textit{Prevotella} and \textit{Oscillibacter}, producers of anti-inflammatory metabolites, can inhibit carcinogenesis. This anti-cancer effect may result from increased regulatory T (Treg) cells and reduced, migration of Th17 cells to the liver.\textsuperscript{94} The gut microbiota plays a key role in HCC development and can potentially be used to treat HCC. Literature related to microbiota alteration in human HCC and animal model of HCC is summarized in Tables 6 and 7,\textsuperscript{95-97,99-102,104} respectively.

3. Gut microbiota-targeted therapy

Dysbiosis contributes to the development of liver diseases. Thus, restructuring the gut microbiota community to establish eubiosis can be effective in preventing or treating liver diseases.

3.1. Probiotics

Probiotics are live microorganisms that provide health benefits for the host when consumed in adequate amounts.\textsuperscript{107} In addition to the beneficial effects on gastrointestinal diseases, probiotics also exert a beneficial effect in liver diseases.\textsuperscript{108-113} Li \textit{et al.}\textsuperscript{83} reported that using Prohep for feeding reduces the liver tumor size in xenograft mouse models. Prohep consists of \textit{Lactobacillus rhamnosus} (\textit{L. rhamnosus}) GG, \textit{E. coli} Nissle 1917, and heat-inactivated VSL\#3. Prohep feeding increases the abundance of \textit{Prevotella} and \textit{Oscillibacter} and generates anti-inflammatory metabolites, which lead to reduced Th17 polarization and increased differentiation of Treg/Trl cells in the gut. In addition, \textit{L. rhamnosus} GG protects mice from high-fructose-induced NAFLD and reduces cholesterol in HFD-fed mice.\textsuperscript{114,115} \textit{Lactobacillus casei} shirota protects against NAFLD in multiple mouse NAFLD models via improved insulin sensitivity, reduced plasma LPS-binding protein, and inhibition of LPS/TLR4 signaling in the liver.\textsuperscript{116-118} Other probiotics such as \textit{Lactobacillus plantarum} MA2, \textit{Lactobacillus plantarum} NCU116, \textit{Lactobacillus johnsonii} BS15, \textit{Lactobacillus reuteri} GMNL-263, and \textit{Lactobacillus gasseri} BNR17 also have protective roles in improving dyslipidemia and NAFLD.\textsuperscript{119-122} Moreover, \textit{Bifidobacterium} prevents fat accumulation and increases insulin sensitivity in HFD-fed rats.\textsuperscript{123} Probiotics of \textit{Bifidobacterium} are superior to \textit{Lactobacillus acidophilus} in decreasing hepatic fat accumulation.\textsuperscript{124}

Probiotics of \textit{Clostridium butyricum} MIYAIRI 588, a butyrate-producing bacterium, reduce hepatic lipid droplets and improve insulin sensitivity in rats with HFD-induced NAFLD.\textsuperscript{125} This strain also decreases hepatic lipids and LPS in rats with NAFLD induced by choline-deficient/L-amino acid-defined diet.\textsuperscript{126} Kumar \textit{et al.}\textsuperscript{127} have demonstrated that probiotic-fermented milk and chlorophyllin significantly reduce the incidence of aflatoxin B1-associated HCC.
Although the health effects of probiotics are mainly obtained from animal studies, some consistent results have been generated in clinical studies. Administration of *L. rhamnosus* GG and a mixture of *Lactobacillus bulgaricus* and *Streptococcus thermophiles* has beneficial effects on obese children with NAFLD.\textsuperscript{128,129} VSL\#3 im, proves liver function and increases glucagon-like peptide 1 levels in obese children with NASH.\textsuperscript{130} Moreover, *L. rhamnosus* GG alters gut microbiota in patients with cirrhosis.\textsuperscript{131} Compared with placebo, *L. rhamnosus* GG increases the beneficial autochthonous Clostridiales Incertae Sedis XIV and Lachnospiraceae and reduces the abundance of Enterobacteriaceae and Porphyromonadaceae in patients with stable cirrhosis and minimal hepatic encephalopathy.\textsuperscript{131} Combination of *Bifidobacterium longum* and fructooligosaccharides (FOSs, a mixture of fermentable dietary fibers) improved minimal and overt hepatic encephalopathy in clinical studies.\textsuperscript{132,133} In addition, VSL\#3 prevented hepatic encephalopathy in a randomized controlled clinical study.\textsuperscript{134} Compared with baseline, 3 months treatment with VSL\#3 increased psychometric hepatic encephalopathy scores and reduced the levels of arterial ammonia, SIBO, and orocecal transit time.\textsuperscript{134} Over 6 months, VSL\#3 treatment reduced the recurrence of hepatic encephalopathy in cirrhotic patients compared with the placebo-treated controls.\textsuperscript{135} VSL\#3 also decreased the hepatic venous pressure gradient, cardiac index, and heart rate, and increases systemic vascular resistance and mean arterial pressure in patients with cirrhosis and ascites.\textsuperscript{136} This indicates that VSL\#3 improves the hepatic and systemic hemodynamics in patients with cirrhosis.\textsuperscript{136} A probiotics combination of eight strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*, is also effective in preventing secondary hepatic encephalopathy in patients with cirrhosis.\textsuperscript{137} However, in a study conducted by Solga *et al.*\textsuperscript{138} 4 months supplementation with VSL\#3 increased hepatic lipid content in four patients who already had steatosis. Another randomized double-blind study conducted by And reasen *et al.*\textsuperscript{139} revealed that 4 weeks intake of *L. acidophilus* NCFM improved insulin sensitivity but did not affect systemic inflammatory response. Additionally, 6 weeks supplementation with *L. acidophilus* did not change serum lipids in volunteers who had elevated cholesterol.\textsuperscript{140} More well-designed trials are needed to further study the effects of probiotics in preventing liver diseases.

### 3.2. Prebiotics

Prebiotics are food ingredients that selectively stimulate the growth or activity of beneficial microorganisms, such as bacteria and fungi.\textsuperscript{141,142} They can alter the composition and/or activity of gut microbiota. Prebiotics are useful in preventing NAFLD in laboratory animals and clinical studies.\textsuperscript{109,143–145}

Prebiotics of FOSs prevent NAFLD via restoring the gut microbiota composition and intestinal epithelial barrier function, leading to reduced serum LPS, hepatic inflammation, and hepatic cholesterol content in NAFLD mice.\textsuperscript{146–148,157} FOS supplementation significantly reduces serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in NASH patients.\textsuperscript{143} Lactulose increases the growth of lactic acid bacteria and *Bifidobacterium*.\textsuperscript{149} It also decreases serum LPS and hepatic inflammation in rats with NASH.\textsuperscript{150} Chitin-glucan, a prebiotic from a fungal source, reduces hepatic triglyceride, body weight gain, and glucose intolerance via restoring clostridial cluster XIVa in HFD-induced obese mice.\textsuperscript{151} Treatment with isomaltooligosaccharides plus lycopene increases

*Liver Res.* Author manuscript; available in PMC 2020 May 27.
adipose tissue fat mobilization, reduces body weight gain, and improves insulin sensitivity in HFD-induced NAFLD mice. Prebiotics have great potential for prevention of liver disease through improving metabolism and the intestinal barrier, as well as reducing endotoxemia.

### 3.3. Synbiotics

Synbiotics refer to the combination of probiotics and prebiotics in a form of synergism. Synbiotics that consist of *Lactobacillus paracasei* B21060 plus arabinogalactan and FOSs reduce hepatic inflammation in diet-induced NAFLD. Supplementation with seven probiotics consisting of *L. casei*, *L. rhamnosus*, *S. thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *B. longum*, and *L bulgaricus* plus FOSs improves fasting blood glucose, serum triglycerides, and inflammatory cytokines in both lean and obese NAFLD patients. Compared to lifestyle intervention alone, synbiotics of *B. longum* plus FOSs have added benefits for NASH patients. This intervention reduces serum tumor necrosis factor α (TNFa), C-reactive protein, endotoxin, and AST.

Milk oligosaccharides (MOs) selectively increase the growth of *Bifidobacterium infantis* (*B. infantis*). Synbiotics of *B. infantis* and MOs prevent occurrence of cancer-prone NASH in western-diet-fed FXR KO male mice. *B. infantis* and MOs increase G protein-coupled bile acid receptor 1 (also known as Takeda G protein-coupled receptor, TGR5)-regulated signaling, thereby generating beneficial effects. *B. infantis* and/or MO treatment also improves ileal SCFA, signaling in western-diet-fed FXR KO mice. Furthermore, MOs alone and *B. infantis* plus MOs inhibit the growth of genus *Bilophila* and reduce the abundance of bacterial genes including dissimilatory sulfite reductase (*dsrA*) and methyl coenzyme M reductase A (*mcrA*), which are increased in mice with NASH.

### 3.4. Other approaches

#### 3.4.1. Bacterial metabolite butyrate

Butyrate is generated by bacterial fermentation of non-digestible polysaccharides. Sodium butyrate treatment reduces inflammation and fat accumulation in diet-induced NAFLD, potentially via enriching beneficial bacteria *Christensenellaceae*, *Blautia*, and *Lactobacillus*. Additionally, butyrate supplementation reverses NASH via reducing hepatic β-muricholic acid (β-MCA) as well as DCA, which are implicated in the development of NASH in western-diet-fed FXR KO mice. It has been shown that *Lactobacillus* and *Bifidobacterium* reduce adiposity and inflammation in NAFLD rats via butyrate production and butyrate receptor G-protein-coupled receptor 109A-regulated signaling. Butyrate and its synthetic derivative, N-(l-carbamoyl-2-phenyl-ethyl) butyramide, reduce the intracellular lipid accumulation and oxidative stress in diet-induced insulin-resistant obese mice. Furthermore, sodium butyrate has a protective role in NAFLD pathogenesis via increased duodenal melatonin synthesis, as well as decreased hepatic inducible nitric oxide synthase in fructose-induced NAFLD mice.

#### 3.4.2. Fecal microbiota transplantation

A randomized clinical trial in patients with cirrhosis and recurrent hepatic encephalopathy was conducted to compare the safety of fecal microbiota transplantation with no such intervention. Fecal microbiota transplantation reduced hospitalization and improved cognition and dysbiosis in patients with cirrhosis with...
recurrent hepatic encephalopathy, when compared with standard of care (SOC).\textsuperscript{164} Fecal microbiota transplantation has protective effects in rats with CCl\textsubscript{4}-induced hepatic encephalopathy.\textsuperscript{165} Fecal microbiota transplantation reduces intestinal permeability and improves the TLR response of the liver, leading to improved cognitive function and reduced liver function indexes.\textsuperscript{165}

3.4.3. Diet—Diet is a contributing factor to liver diseases. Fructose-enriched diet alters liver metabolism and gut barrier function, increases endotoxemia, decreases \textit{Bifidobacterium} and \textit{Lactobacillus}, and eventually leads to NAFLD.\textsuperscript{166} Long-term fructose consumption increases lipogenic enzymes via activation of sterol regulatory element binding protein-\textit{l}c (SREBP\textit{l}c) and carbohydrate responsive element binding protein (ChREBP).\textsuperscript{167} It promotes lipogenesis, hypertriglyceridemia, hepatic insulin resistance, and hepatic steatosis.\textsuperscript{167} A diet rich in fermented milk, vegetables, cereals, coffee, and tea contributes to a higher microbial diversity in patients with cirrhosis.\textsuperscript{168} Microbial diversity is an independent factor that reduces the risk of 90-day hospitalization.\textsuperscript{168}

4. Conclusions and perspectives

Gut microbiota plays a pivotal role in the pathogenesis of metabolic liver diseases. Re-establishing eubiosis using probiotics, prebiotics, and synbiotics, as well as natural products, is a promising avenue to prevent and treat liver diseases and, potentially, liver cancer. Although bile acid and SCFA-regulated pathways can explain how diet through gut microbiota affects health and disease processes, other molecular links remain to be uncovered. With the advancement of sequencing technology as well as cultural techniques, specific bacterial species and microbial functions can be uncovered to establish a causal relationship. There is no doubt that metabolomics and epigenetic genomics are powerful tools to elucidate the underlying mechanism for disease processes, leading to innovative treatment strategies. The generated information should have an impact on personalized nutrition as well as precision medicine.

Acknowledgments

This work was supported by the USA National Institutes of Health (NIH), USA grants U01CA179582 and R01 CA222490. We also thank Michelle Nguyen (Department of Medical Pathology and Laboratory Medicine, University of California, Davis, Sacramento, CA, USA) and Mindy Huynh (Department of Dermatology, University of California, Davis, Sacramento, CA, USA) for reviewing the manuscript.

References

1. Minemura M, Shimizu Y. Gut microbiota and liver diseases. World J Gastroenterol. 2015;21:1691–1702. [PubMed: 25684933]
2. Pennisi E. Cancer therapies use a little help from microbial friends. Science. 2013;342:921. [PubMed: 24264971]
3. Wan MLY, El-Nezami HT. Targeting gut microbiota in hepatocellular carcinoma: probiotics as a novel therapy. Hepatobiliary Surg Nutr. 2018;7:11–20. [PubMed: 29531939]
4. Ma J, Zhou Q, Li H. Gut microbiota and nonalcoholic fatty liver disease: insights on mechanisms and therapy. Nutrients. 2017-9 10.3390/nu9101124.
5. Sanduzzi Zamparelli M, Rocco A, Compare D, Nardone G. The gut microbiota: a new potential driving force in liver cirrhosis and hepatocellular carcinoma. United European Gastroenterol J. 2017;5:944–953.

6. Henao-Mejia J, Elinav E, Jin C et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012;482:179–185. [PubMed: 22297845]

7. Safe S, Papineni S, Chintharlapalli S. Cancer chemotherapy with indole-3-carbinol, bis(3'-indoly)methane and synthetic analogs. Cancer Lett 2008;269:326–338. [PubMed: 18501502]

8. Wieland A, Frank DN, Hamke B, Bambha K. Systematic review: microbial dysbiosis and nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2015;42:1051–1063. [PubMed: 26304302]

9. Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. Gut. 2016;65: 2035–2044. [PubMed: 27802157]

10. Fukui H. Gut microbiome-based therapeutics in liver cirrhosis: basic consideration for the next step. J Clin Transl Hepatol. 2017;5:249–260. [PubMed: 28936406]

11. Acharya C, Bajaj JS. Gut microbiota and complications of liver disease. Gastroenterol Clin JV Am. 2017:46:155–169.

12. Henao-Mejia J, Elinav E, Thaiss CA, Flavell RA. The intestinal microbiota in chronic liver disease. Adv Immunol. 2013;117:73–97. [PubMed: 23611286]

13. Doulberis M, Kotronis G, Gialamprinou D, Kountouras J, Katsinelos P. Non-alcoholic fatty liver disease: an update with special focus on the role of gut microbiota. Metabolism. 2017;71:182 197. [PubMed: 28521872]

14. Boursier J, Mueller O, Barret M, et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatology. 2016:63:764–775. [PubMed: 26600078]

15. Quigley EM, Monsour HP. The gut microbiota and nonalcoholic fatty liver disease. Semin Liver Dis. 2015;35:262–269. [PubMed: 26378643]

16. Miura K, Ohtsuki H. Role of gut microbiota and Toll-like receptors in nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20:7381–7391. [PubMed: 24966608]

17. Mouzaki M, Comelli EM, Arendt BM, et al. Intestinal microbiota in patients with nonalcoholic fatty liver disease. Hepatology. 2013;58:120–127. [PubMed: 23401313]

18. Shen F, Zheng RD, Sun XQ, Ding WJ, Wang XY, Fan JG. Gut microbiota dysbiosis in patients with non-alcoholic fatty liver disease. Hepatobiliary Pancreat Dis Int. 2017;16:375–381. [PubMed: 28823367]

19. Wang B, Jiang X, Cao M, et al. Altered fecal microbiota correlates with liver biochemistry in nonobese patients with non-alcoholic fatty liver disease. Sri Rep. 2016:6:32002.

20. Stanislawski MA, Lozupone CA, Wagner BD, et al. Gut microbiota in adolescents and the association with fatty liver: the EPOCH study. Pediatr Res. 2018;84:219–227. [PubMed: 29538359]

21. Del Chierico F, Nobili V, Vemocchi P, et al. Gut microbiota profiling of pediatric nonalcoholic fatty liver disease and obese patients unveiled by an integrated meta-omics-based approach. Hepatology. 2017:65:451–464. [PubMed: 27028797]

22. Zhu L, Baker SS, Gill C, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology. 2013;57:601–609. [PubMed: 23055155]

23. Konikoff T, Gophna U. Oscillospira: a central, enigmatic component of the human gut microbiota. Trends Microbiol. 2016;24:523–524. [PubMed: 26996766]

24. Raman M, Ahmed I, Gillevet PM, et al. Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2013;11:868–875 (el-e3). [PubMed: 23454028]

25. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature. 2012;486:222–227. [PubMed: 22696611]

26. Walters WA, Xu Z, Knight R. Meta-analyses of human gut microbes associated with obesity and 1BD. FEBS Lett. 2014;588:4223–4233. [PubMed: 25307765]
27. Devkota S, Wang Y, Musch MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in 1110−/− mice. Nature. 2012;487: 104–108. [PubMed: 22722865]
28. O’Keefe SJ, Li J, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. Nat Commun. 2015;6:6342. [PubMed: 25919227]
29. Ridlon JM, Kang DI, Hylemon PB, Bajaj JS. Bile acids and the gut microbiome. Curr Opin Gastroenterol. 2014;30:332–338. [PubMed: 24625896]
30. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;334:105–108. [PubMed: 21885731]
31. David IAM, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505:559–563. [PubMed: 24336217]
32. Loomba R, Seguritan V, Li W, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metabol. 2017;25:1054–1062 (e5).
33. Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. Science. 2005;308:1635–1638. [PubMed: 15831718]
34. Chen Y, Ji F, Guo J, Shi D, Fang D, Li W, et al. Dysbiosis of small intestinal microbiota in liver cirrhosis and its association with etiology. Sci Rep. 2016;6:34055. [PubMed: 27687977]
35. Compare D, Coccoli P, Rocco A, et al. Gut-liver axis: the impact of gut microbiota on non-alcoholic fatty liver disease. Nutr Metabol Cardiovasc Dis. 2012;22:471–476.
36. Wigg AJ, Roberts-Thomson IC, Dymock RB, McCarthy PJ, Grose RH, Cummins AG. The role of small intestinal bacterial overgrowth, intestinal permeability, endotoxaemia, and tumour necrosis factor alpha in the pathogenesis of non-alcoholic steatohepatitis. Gut. 2001;48:206–211. [PubMed: 11156641]
37. Miele L, Valenza V, La Torre G, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology. 2009;49:1877–1887. [PubMed: 19291785]
38. Sabaté JM, Jouët P, Hamois F, et al. High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: a contributor to severe hepatic steatosis. Obes Surg. 2008;18:371–377. [PubMed: 18286348]
39. Rafiei R, Bermanian M, Rafiei F, et al. Liver disease symptoms in non-alcoholic fatty liver disease and small intestinal bacterial overgrowth. Rom J Intern Med. 2018;56:85–89. [PubMed: 29101772]
40. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010;16:2978–2990. [PubMed: 20572300]
41. Chu H, Williams B, Schnabl B. Gut microbiota, fatty liver disease, and hepatocellular carcinoma. Liver Res. 2018;2:43–51. [PubMed: 30416839]
42. Henao-Mejia J, Elinav E, Thaiss CA, Licona-Limon P, Flavell RA. Role of the intestinal microbiome in liver disease. J Autoimmun. 2013;46:66–73. [PubMed: 24075647]
43. Bibbò S, Ianiro G, Dore MP, Simonelli C, Newton EE, Cammarota G. Gut microbiota as a driver of inflammation in nonalcoholic fatty liver disease. Mediat Inflamm. 2018;2018:9321643.
44. Saltzman ET, Palacios T, Thomsen M, Vitetta L. Intestinal microbiome shifts, dysbiosis, inflammation, and non-alcoholic fatty liver disease. Front Microbiol. 2018;9:61. [PubMed: 29441049]
45. Sajjad A, Mottershead M, Syn WK, Jones R, Smith S, Nwokolo CU. Ciprofloxacin suppresses bacterial overgrowth, increases fasting insulin but does not correct low acylated ghrelin concentration in non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2005;22:291–299. [PubMed: 16097995]
46. Arslan N. Obesity, fatty liver disease and intestinal microbiota. World J Gastroenterol. 2014;20:16452–16463. [PubMed: 25469013]
47. Gäbele E, Dostert K, Hofmann C, et al. DSS induced colitis increases portal LPS levels and enhances hepatic inflammation and fibrogenesis in experimental NASH. J Hepatol. 2011;55:1391–1399. [PubMed: 21703208]
48. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci USA. 2007;104:979–984. [PubMed: 17210919]

49. Ferolla SM, Armiliato GN, Couto CA, Ferrari TC. The role of intestinal bacteria overgrowth in obesity-related nonalcoholic fatty liver disease. Nutrients. 2014;6:5583–5599. [PubMed: 25479248]

50. Fialho A, Thota P, McCullough AJ, Shen B. Small intestinal bacterial overgrowth is associated with non-alcoholic fatty liver disease. J Gastrointestin Liver Dis. 2016;25:159–165. [PubMed: 27308646]

51. Lax S, Schauer G, Prein K, et al. Expression of the nuclear bile acid receptor/ farnesoid X receptor is reduced in human colon carcinoma compared to nonneoplastic mucosa independent from site and may be associated with adverse prognosis. Int J Cancer. 2012;130:2232–2239. [PubMed: 21780109]

52. Liu N, Meng Z, Lou G, et al. Hepatocarcinogenesis in FXR−/− mice mimics human HCC progression that operates through HNF1α regulation of FXR expression. Mol Endocrinol. 2012;26:775–785. [PubMed: 22474109]

53. Su H, Ma C, Liu J, et al. Downregulation of nuclear receptor FXR is associated with multiple malignant clinicopathological characteristics in human hepatocellular carcinoma. Am J Physiol Gastrointest Liver Physiol. 2012;303:G1245–G1253. [PubMed: 23042943]

54. Sheng L, Jena PK, Liu HX, et al. Gender differences in bile acids and microbiota in relationship with gender dissimilarity in steatosis induced by diet and FXR inactivation. Sci Rep. 2017;7:1748. [PubMed: 28496104]

55. Jena PK, Sheng L, Liu HX, et al. Western diet-induced dysbiosis in farnesoid X receptor knockout mice causes persistent hepatic inflammation after anti-biotic treatment. Am J Pathol. 2017;187:1800–1813. [PubMed: 28711544]

56. Bajaj JS, Heuman DM, Hylemon PB, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol. 2014;60:940–947. [PubMed: 24374295]

57. Bajaj JS, Betrapally NS, Hylemon PB, et al. Gut microbiota alterations can predict hospitalizations in cirrhosis independent of diabetes mellitus. Sci Rep. 2015;5:18559. [PubMed: 26692421]

58. Chen Y, Guo J, Qian G, et al. Gut dysbiosis in acute-on-chronic liver failure and its predictive value for mortality. J Gastroenterol Hepatol. 2015;30:1429–1437. [PubMed: 25711972]

59. Chen Y, Yang F, Lu H, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. Hepatology. 2011;54:562–572. [PubMed: 21574172]

60. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis. 2008;28:26–42. [PubMed: 18293275]

61. Ridlon JM, Alves JM, Hylemon PB, Bajaj JS. Cirrhosis, bile acids and gut microbiota: unraveling a complex relationship. Gut Microbiol. 2013;4:382–387.

62. Ridlon JM, Kang DJ, Hylemon PB, Bajaj JS. Gut microbiota, cirrhosis, and alcohol regulate bile acid metabolism in the gut. Dig Dis. 2015;33:338–345. [PubMed: 26045267]

63. Vlahcevic ZR, Buhac I, Bell CC Jr, Swell L. Abnormal metabolism of secondary bile acids in patients with cirrhosis. Gut. 1970;11:420–422. [PubMed: 5428044]

64. Kakiyama G, Pandak WM, Gillevet PM, et al. Modulation of the fecal bile acid profile by gut microbiota in cirrhosis. J Hepatol. 2013;58:949–955. [PubMed: 23333527]

65. Sheng L, Jena PK, Hu Y, et al. Hepatic inflammation caused by dysregulated bile acid synthesis is reversible by butyrate supplementation. J Pathol. 2017;243:431–441. [PubMed: 28892150]

66. Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. J Lipid Res. 2006;47:241–259. [PubMed: 16299351]

67. Inagaki T, Moschetta A, Lee YK, et al. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. Proc Natl Acad Sci USA. 2006;103:3920–3925. [PubMed: 16473946]

68. West R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology. 2005;41:422–433. [PubMed: 15723320]

69. Powell DW. Barrier function of epithelia. Am J Physiol. 1981;241:G275–G288. [PubMed: 7032321]
70. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol. 2014;60:197–209. [PubMed: 23993913]

71. Pardo A, Bartoli R, Lorenzo-Zuniga V, et al. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. Hepatology. 2000;31:858–863. [PubMed: 10733540]

72. Lutz P, Nischalke HD, Strassburg CP, Spengler U. Spontaneous bacterial peritonitis: the clinical challenge of a leaky gut and a cirrhotic liver. World J Hepatol. 2015;7:304–314. [PubMed: 25848460]

73. Bibi S, Ahmed W, Arif A, Khan F, Alam SE. Clinical, laboratory and bacterial profile of spontaneous bacterial peritonitis in chronic liver disease patients. J Coll Physicians Surg Pak. 2015;25:95–99. [PubMed: 25703750]

74. Shi L, Wu D, Wei L, et al. Nosocomial and community-acquired spontaneous bacterial peritonitis in patients with liver cirrhosis in China: comparative microbiology and therapeutic implications. Sci Rep. 2017;7:46025. [PubMed: 28382951]

75. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the study of liver diseases and the European Association for the study of the liver. Hepatology. 2014;60:715–735. [PubMed: 25042402]

76. Kang DJ, Betrapally NS, Ghosh SA, et al. Gut microbiota drive the development of neuroinflammatory response in cirrhosis in mice. Hepatology. 2016;64:1232–1248. [PubMed: 27339732]

77. Ahluwalia V, Betrapally NS, Hylemon PB, et al. Impaired gut-liver-brain axis in patients with cirrhosis. Sci Rep. 2016;6:26800. [PubMed: 27225869]

78. Dunn W, O’Neil M, Zhao J, et al. Donor PNPLA3 rs738409 genotype affects fibrosis progression in liver transplantation for hepatitis C. Hepatology. 2014;59:453–460. [PubMed: 24123231]

79. Sun LY, Yang YS, Qu W, et al. Gut microbiota of liver transplantation recipients. Sci Rep. 2017;7:3762. [PubMed: 28630433]

80. Bajaj JS, Fagan A, Sikaroodi M, et al. Liver transplant modulates gut microbial dysbiosis and cognitive function in cirrhosis. Liver Transplant. 2017;23:907–914.

81. Bajaj JS, Kakiyama G, Cox 1J et al. Alterations in gut microbial function following liver transplant. Liver Transplant. 2018;24:752–761.

82. Liu HX, Rocha CS, Dandekar S, Wan YJ. Functional analysis of the relationship between intestinal microbiota and the expression of hepatic genes and pathways during the course of liver regeneration. J Hepatol. 2016;64:641–650. [PubMed: 26453969]

83. Liu HX, Hu Y, Wan YJ Microbiota and bile acid profiles in retinoic acid-primed mice that exhibit accelerated liver regeneration. Oncotarget. 2016;7:1096–1106.

84. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome Med. 2016;8:51. [PubMed: 27122046]

85. Bajaj JS, Liu EJ Kheradman R, et al. Fungal dysbiosis in cirrhosis. Gut. 2018;67:1146–1154. [PubMed: 28578302]

86. Yang AM, Inamine T, Hochrath K, et al. Intestinal fungi contribute to development of alcoholic liver disease. J Clin Invest. 2017;127:2829–2841. [PubMed: 28530644]

87. Qin N, Yang F, Li A, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014;513:59–64. [PubMed: 25079328]

88. Bik EM, Long CD, Armitage GC, et al. Bacterial diversity in the oral cavity of 10 healthy individuals. ISME J. 2010;4:962–974.

89. Bajaj JS, Betrapally NS, Hylemon PB, et al. Salivary microbiota reflects changes in gut microbiota in cirrhosis with hepatic encephalopathy. Hepatology. 2015;62:1260–1271. [PubMed: 25820757]

90. Bajaj JS, Acharya C, Fagan A, et al. Proton pump inhibitor initiation and withdrawal affects gut microbiota and readmission risk in cirrhosis. Am J Gastroenterol. 2018;113:1177–1186. [PubMed: 29872220]

91. Takeshita T, Suzuki N, Nakano Y, et al. Discrimination of the oral microbiota associated with high hydrogen sulfide and methyl mercaptan production. Sci Rep. 2012;2:215. [PubMed: 22355729]

92. Al Mardini H, Bartlett K, Record CO. Blood and brain concentrations of mercaptans in hepatic and methanethiol induced coma. Gut. 1984;25:284–290. [PubMed: 6998445]
93. Fatima N, Akhtar T, Sheikh N. Prebiotics: a novel approach to treat hepatocellular carcinoma. Chin J Gastroenterol Hepatol. 2017;2017:6238106.

94. Li J, Sung CY, Lee N, et al. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proc Natl Acad Sri USA. 2016;113: E1306–E1315.

95. Nilsson HO, Mulchandani R, Tranberg KG, Stenram li, Wadström T Helicobacter species identified in liver from patients with cholangiocarcinoma and hepatocellular carcinoma. Gastroenterology. 2001;120:323–324. [PubMed: 11246512]

96. Huang Y, Fan XG, Wang ZM, Zhou JH, Tian XF, Li N. Identification of Helicobacter species in human liver samples from patients with primary hepatocellular carcinoma. J Clin Pathol. 2004;57:1273–1277. [PubMed: 15563667]

97. Krüttgen A, Horz HP, Weber-Heynemann J et al. Study on the association of Helicobacter species with viral hepatitis-induced hepatocellular carcinoma. Gut Microb. 2012;3:228–233.

98. Fox JG, Feng Y, Theve EJ, et al. Gut microbes define liver cancer risk in mice exposed to chemical and viral transgenic hepatocarcinogens. Gut. 2010;59: 88–97. [PubMed: 19850960]

99. Grat M, Wronka KM, Krasnodebski M, et al. Profile of gut microbiota associated with the presence of hepatocellular cancer in patients with liver cirrhosis. Transplant Proc. 2016;48:1687–1691. [PubMed: 27496472]

100. Xie G, Wang X, Liu P, et al. Distinctly altered gut microbiota in the progression of liver disease. Oncotarget. 2016;7:19335–19366. [PubMed: 27036035]

101. Zhang HL, Yu LX, Yang W, et al. Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats J Hepatol. 2012;57:803–812. [PubMed: 22727732]

102. Gómez-Hurtado I, Santacruz A, Peiró G, et al. Gut microbiota dysbiosis is associated with inflammation and bacterial translocation in mice with CC14-induced fibrosis. PLoS One. 2011;6, e23037.

103. Dapito DH, Mencin A, Gwak GY, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell. 2012;21:504–516. [PubMed: 22516259]

104. Lu H, Ren Z, Li A, et al. Deep sequencing reveals microbiota dysbiosis of tongue coat in patients with liver carcinoma. Sci Rep. 2016;6:33142. [PubMed: 27605161]

105. Yamada S, Takashina Y, Watanabe M, et al. Bile acid metabolism regulated by the gut microbiota promotes non-alcoholic steatohepatitis-associated hepatocellular carcinoma in mice. Oncotarget. 2018;9:9925–9939. [PubMed: 29515780]

106. Yoshimoto S, Loo TM, Atarashi K, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature. 2013;499:97–101. [PubMed: 23803760]

107. Hill C, Guarner F, Reid G, et al. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11:506–514. [PubMed: 24912386]

108. Brandi G, De Lorenzo S, Candela M, et al. Microbiota, NASH, HCC and the potential role of probiotics. Carcinogenesis. 2017;38:231–240. [PubMed: 28426878]

109. Tarantino G, Finelli C. Systematic review on intervention with prebiotics/probiotics in patients with obesity-related nonalcoholic fatty liver disease. Future Microbiol. 2015;10:889–902. [PubMed: 26000656]

110. Qamar AA. Probiotics in nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and cirrhosis. J Clin Gastroenterol. 2015;49:S28–S32. [PubMed: 26447961]

111. Xue L, He J, Gao N, et al. Probiotics may delay the progression of nonalcoholic fatty liver disease by restoring the gut microbiota structure and improving intestinal endotoxemia. Sci Rep. 2017;7:45176. [PubMed: 28349964]

112. Cesaro C, Tiso A, Del Prete A, et al. Gut microbiota and probiotics in chronic liver diseases. Dig Liver Dis. 2011 ;43:431–438. [PubMed: 21163715]

113. Chen M, Wang MC, Ni R, et al. Role of probiotics in treatment of nonalcoholic fatty liver disease. Zhonghua Gan Zang Bing Za Zhi. 2017;25:77–80. [PubMed: 28297790]

114. Ritzé Y, Bárdos G, Claus A, et al. Lactobacillus rhamnosus GG protects against non-alcoholic fatty liver disease in mice. PLoS One. 2014;9, e80169.
115. Kim B, Park KY, Ji Y, Park S, Holzapfel W, Hyun CK. Protective effects of Lactobacillus rhamnosus GG against dyslipidemia in high-fat diet-induced obese mice. Biochem Biophys Res Commun. 2016;473:530–536. [PubMed: 27018382]
116. Okubo H, Sakoda H, Kushiyama A, et al. Lactobacillus casei strain Shirota protects against nonalcoholic steatohepatitis development in a rodent model. Am J Physiol Gastrointest Liver Physiol. 2013;305:G911–G918. [PubMed: 24113768]
117. Naito E, Yoshida Y, Makino K, et al. Beneficial effect of oral administration of Lactobacillus casei strain Shirota on insulin resistance in diet-induced obesity mice. J Appl Microbiol. 2011;110:650–657. [PubMed: 21281408]
118. Wagnerberger S, Spruss A, Kanuri G, et al. Lactobacillus casei Shirota protects from fructose-induced liver steatosis: a mouse model. J Nutr Biochem. 2013;24:531–538. [PubMed: 22749137]
119. Wang Y, Xu N, Xi A, Ahmed Z, Zhang B, Bai X. Effects of Lactobacillus plantarum MA2 isolated from Tibet kefir on lipid metabolism and intestinal microflora of rats fed on high-cholesterol diet. Appl Microbiol Biotechnol. 2009;84:341–347. [PubMed: 19444443]
120. Li C, Nie SP, Zhu KX, et al. Lactobacillus plantarum NCU116 improves liver function, oxidative stress and lipid metabolism in rats with high fat diet induced non-alcoholic fatty liver disease. Food Funct. 2014;5:3216–3223. [PubMed: 25317840]
121. Xin J Zeng D Wang H, et al. Preventing non-alcoholic fatty liver disease through Lactobacillus johnsonii BS15 by attenuating inflammation and mitochondrial injury and improving gut environment in obese mice. Appl Microbiol Biotechnol. 2014;98:6817–6829. [PubMed: 24811405]
122. Kang JH, Yun SI, Park MH, Park JH, Jeong SY, Park HO. Anti-obesity effect of Lactobacillus gasseri BNR17 in high-sucrose diet-induced obese mice. PLoS One. 2013;8:e54617.
123. Chen J, Wang R, Li XF, Wang RL. Bifidobacterium adolescentis supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. Br J Nutr. 2012;107:1429–1434. [PubMed: 21914236]
124. Xu RY, Wan YP, Fang QY, Lu W, Cai W. Supplementation with probiotics modifies gut flora and attenuates liver fat accumulation in rat nonalcoholic fatty liver disease model. J Clin Biochem Nutr. 2012;50:72–77. [PubMed: 22247604]
125. Seo M, Inoue I Tanaka M, et al. Clostridium butyricum MIYAIR1 588 improves high-fat diet-induced non-alcoholic fatty liver disease in rats. Dig Dis Sci. 2013;58:3534–3544. [PubMed: 24166662]
126. Endo H, Niioka M, Kobayashi N, Tanaka M, Watanabe T. Butyrate-producing probiotics reduce nonalcoholic fatty liver disease progression in rats: new insight into the probiotics for the gut-liver axis. PLoS One. 2013;8:e63388.
127. Kumar M, Verma V, Nagpal R, et al. Effect of probiotic fermented milk and chlorophyllin on gene expressions and genotoxicity during AFB1-induced hepatocellular carcinoma. Gene. 2011;490:54–59. [PubMed: 21963996]
128. Vajro P, Mandato C Licenziati MR, et al. Effects of Lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. J Pediat Gastroenterol Nutr. 2011;52:740–743. [PubMed: 21505361]
129. Aller R, De Luis DA, Izoola O, et al. Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial. Eur Rev Med Pharmacol Sci. 2011; 15:1090–1095. [PubMed: 22013734]
130. Alisi A, Bedogni G, Baviera G, et al. Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2014;39:1276–1285. [PubMed: 24738701]
131. Bajaj JS, Heuman DM, Hylemon PB, et al. Randomised clinical trial: Lactobacillus GG modulates gut microbiome, metabolome and endotoxemia in patients with cirrhosis. Aliment Pharmacol Ther. 2014;39:1113–1125. [PubMed: 24628464]
133. Malaguarnera M, Gargante MP, Malaguarnera G, et al. Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy. Eur J Gastroenterol Hepatol. 2010;22: 199–206. [PubMed: 19730107]

134. Lunia MK, Sharma BC, Sharma P, Sachdeva S, Srivastava S. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. Clin Gastroenterol Hepatol. 2014;12:1003–1008 (el). [PubMed: 24246768]

135. Dhiman RK, Rana B, Agrawal S, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology. 2014;147:1327–1337 (e3). [PubMed: 25450083]

136. Rincón D, Vaquero J, Hernando A, et al. Oral probiotic VSL#3 attenuates the circulatory disturbances of patients with cirrhosis and ascites. Liver Int. 2014;34:1504–1512. [PubMed: 24661740]

137. Agrawal A, Sharma BC. Sharma P, Sarin SK, Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. Am J Gastroenterol. 2012; 107: 1043–1050. [PubMed: 22710579]

138. Solga SF, Buckley G, Clark JM, Horsa A, Diehl AM. The effect of a probiotic on hepatic steatosis. J Clin Gastroenterol. 2008;42:1117–1119. [PubMed: 18936646]

139. Andreasen AS, Larsen N, Pedersen-Skovsgaard T, et al. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr. 2010;104:1831–1838. [PubMed: 20815975]

140. Lewis SJ, Burmeister S. A double-blind placebo-controlled study of the effects of Lactobacillus acidophilus on plasma lipids. Eur J Clin Nutr. 2005;59: 776–780. [PubMed: 15841092]

141. Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14:491–502. [PubMed: 28611480]

142. Hutkins RW, Krumbeck JA, Bindels LB, et al. Prebiotics: why definitions matter. Curr Opin Biotechnol. 2016;37:1–7. [PubMed: 26431716]

143. Daubioul CA, Horsmans Y, Lambert P, Dansie E, Delzenne NM. Effects of oligofructose on glucose and lipid metabolism in patients with nonalcoholic steatohepatitis: results of a pilot study. Eur J Clin Nutr. 2005;59:723–726. [PubMed: 15770222]

144. Parnell JA, Raman M, Rioux KP, Reimer RA. The potential role of prebiotic fibre for treatment and management of non-alcoholic fatty liver disease and associated obesity and insulin resistance. Liver Int. 2012;32:701–711.

145. Sawas T, Al Halabi S, Hemaez R, Carey WD, Cho WK. Patients receiving prebiotics and probiotics before liver transplantation develop fewer infections than controls: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2015;13:1567–1574 (e3). [PubMed: 26044318]

146. Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58:1091–1103. [PubMed: 19240062]

147. Matsumoto K, Ichimura M, Tsukeyama K, et al. Fructo-oligosaccharides and intestinal barrier function in a methionine-choline-deficient mouse model of nonalcoholic steatohepatitis. PLoS One. 2017; 12: e0175406.

148. Pachikian BD, Essaghir A, Demoulin JB, et al. Prebiotic approach alleviates hepatic steatosis: implication of fatty acid oxidative and cholesterol synthesis pathways. Mol Nutr Food Res. 2013;57:347–359. [PubMed: 23203768]

149. Salminen S, Salminen E. Lactulose, lactic acid bacteria, intestinal microecology and mucosal protection. Scand J Gastroenterol Suppl. 1997;222:45–48. [PubMed: 9145446]

150. Fan JG, Xu ZJ, Wang GLEffect of lactulose on establishment of a rat nonalcoholic steatohepatitis model. World J Gastroenterol. 2005;11:5053–5056. [PubMed: 16124065]

151. Neyrinck AM, Possemiers S, Verstraete W, De Backer F, Cani PD, Delzenne NM. Dietary modulation of clostridial cluster XIVa gut bacteria (Roseburia spp.) by chitin-glucan fiber improves host metabolic alterations induced by high-fat diet in mice. J Nutr Biochem. 2012;23:51–59. [PubMed: 21411304]
152. Singh DP, Khare P, Zhu J, et al. A novel cobiotic-based preventive approach against high-fat diet-induced adiposity, nonalcoholic fatty liver and gut derangement in mice. Int J Obes. 2016;40:487–496.

153. Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics—a review. J Food Sci Technol. 2015;52:7577–7587. [PubMed: 26604335]

154. Raso GM, Simeoli R, Iacono A, et al. Effects of a Lactobacillus paracasei B21060 based synbiotic on steatosis, insulin signaling and toll-like receptor expression in rats fed a high-fat diet. J Nutr Biochem. 2014;25:81–90. [PubMed: 24314869]

155. Mofidi F, Poustchi H, Yari Z, et al. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. Br J Nutr. 2017;117:662–668. [PubMed: 28345499]

156. Asgharian A, Askari G, Esmailzade A, Feizi A, Mohammadi V. The effect of synbiotic supplementation on liver enzymes, C-reactive protein and ultrasound findings in patients with non-alcoholic fatty liver disease: a clinical trial. Int J Prev Med. 2016;7:59. [PubMed: 27076897]

157. Malaguarnera M, Vacante M, Antic T, et al. Bifidobacterium longum with fructooligosaccharides in patients with non-alcoholic steatohepatitis. Dig Dis Sci. 2012;57:545–553. [PubMed: 21901256]

158. Jena PK, Sheng L, Nagar N, et al. Synbiotics Bifidobacterium infantis and milk oligosaccharides are effective in reversing cancer-prone non-alcoholic steatohepatitis using Western diet-fed FXR knockout mouse models. J Nutr Biochem. 2018;57:246–254. [PubMed: 29800811]

159. Jena PK, Sheng L, Nagar N, et al. The effect of synbiotics Bifidobacterium Infantis and milk oligosaccharides on shaping gut microbiota community structure and NASH treatment Data. Brief. 2018;19:1025–1029.

160. Liang Y, Lin C, Zhang Y, Deng Y, Liu C, Yang Q. Probiotic mixture of Lactobacillus and Bifidobacterium alleviates systemic adiposity and inflammation in non-alcoholic fatty liver disease rats through Gprl09a and the commensal metabolite butyrate. Inflammopharmacology. 2018;26:1051–1055. [PubMed: 29633106]

161. Zhou D, Pan Q, Xin FZ, et al. Sodium butyrate attenuates high-fat diet-induced steatohepatitis in mice by improving gut microbiota and gastrointestinal barrier. World J Gastroenterol. 2017;23:60–75. [PubMed: 28104981]

162. Mollica MP, Mattace Raso G, Cavaliere G, et al. Butyrate regulates liver mitochondrial function, efficiency, and dynamics in insulin-resistant obese mice. Diabetes. 2017;66:1405–1418. [PubMed: 28223285]

163. Jin CJ, Engstler AJ, Sellmann C. et al. Sodium butyrate protects mice from the development of the early signs of non-alcoholic fatty liver disease: role of melatonin and lipid peroxidation. Br J Nutr. 2016;23:1–12.

164. Bajaj JS, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. Hepatology. 2017;66:1727–1738. [PubMed: 28586116]

165. Wang WW, Huang Y, Huang XB, You N, Zheng L, Li J. Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction. World J Gastroenterol. 2017;23:6983–6994. [PubMed: 29097871]

166. Jegatheesan P, Beuthue S, Ventura G, et al. Effect of specific amino acids on hepatic lipid metabolism in fructose-induced non-alcoholic fatty liver disease. Clin Nutr. 2016;35:175–182. [PubMed: 25736031]

167. Herman MA, Samuel VT. The sweet path to metabolic demise: fructose and lipid synthesis. Trends Endocrinol Metab. 2016;27:719–730. [PubMed: 27387598]

168. Bajaj JS, Idilman R, Mabudian L, et al. Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort. Hepatology. 2018;68:234–247. [PubMed: 29350768]
Under healthy condition, intestinal barrier and integrity prevent the entry of bacterial products, such as endotoxin, from the gut into the portal circulation. Liver immune cells rapidly clear the microbial products and bacteria passing through the gut barrier, thereby establishing immune tolerance without inflammation. Gut microbiota contributes to improving insulin sensitivity, reducing inflammation, and hepatic lipid accumulation via modulating the productions of bile acids, short-chain fatty acids, glucagon-like peptide 1, etc. Factors such as antibiotics, injury, infection, and high-fat diet can cause dysbiosis. Dysbiosis increases endogenous ethanol, endotoxin, and intestinal permeability, thereby leading the translocations of bacteria and bacterial metabolites from the intestine to the liver. Bacteria and their metabolites can activate the innate immune system via toll-like receptors and cause inflammation and subsequent liver damage. Moreover, dysbiosis-associated bile acid dysregulation increases insulin resistance, hepatic lipid accumulation, and inflammatory signaling. Furthermore, dysbiosis converts choline to trimethylamine, which leads to choline deficiency. All these metabolites and factors contribute to liver diseases. Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TLRs, Toll-like receptors.
Table 1

Gut microbiota alteration in NAFLD and NASH patients.

| Authors         | Population                          | N     | Comparison                                      | Implicated microbiota                  | Methodology                          |
|-----------------|-------------------------------------|-------|------------------------------------------------|----------------------------------------|---------------------------------------|
|                  |                                     |       |                                                | Phylum       | Family           | Genus       |                                           |
| Boursier et al.14| F0/F1 fibrosis without NASH         | 20    | NASH vs no NASH                                | Bacteroidetes | Bacteroidaceae   | Bacteroides | 16S rRNA gene sequencing (Stool sample)   |
|                 | F0/F1 fibrosis with NASH            | 10    |                                                | Bacteroidetes | Prevotellaceae   | Prevotella  |                                           |
|                 | F ≥ 2 fibrosis without NASH         | 2     | NASH vs F0/F1 fibrosis                         | Bacteroidetes | Bacteroidaceae   | Bacteroides |                                           |
|                 | F ≥ 2 fibrosis with NASH            | 25    |                                                | Bacteroidetes | Prevotellaceae   | Prevotella  |                                           |
| Mouzaki et al.17| Steatosis patients                  | 11    | NASH vs Healthy                                | Bacteroidetes | N/A              | N/A         | Quantitative real-time PCR (Stool sample) |
|                 | NASH patients                       | 22    | NASH vs Steatosis                              | Bacteroidetes | N/A              | N/A         |                                           |
|                 | Healthy controls                    | 17    |                                                | Bacteroidetes | Lachnospiraceae  | N/A         |                                           |
| Shen et al.18   | NAFLD patients                      | 25    | NAFLD vs Healthy                               | Proteobacteria | Enterobacteriaceae | N/A         | 16S rDNA amplicon sequencing (Stool sample) |
|                 | Healthy controls                    | 22    |                                                | Fusobacteria | N/A              | Lachnospiraceae  |                                           |
|                 |                                     |       |                                                | Firmicutes   | Erysipelotrichaceae | N/A         |                                           |
|                 |                                     |       |                                                | Firmicutes   | Streptococcaceae  | N/A         |                                           |
|                 |                                     |       |                                                | Firmicutes   | Prevotellaceae   | N/A         |                                           |
|                 |                                     |       |                                                | Bacteroidetes | N/A              | N/A         |                                           |
| Wang et al.19   | NAFLD patients                      | 43    | NAFLD vs Healthy                               | Bacteroidetes | N/A              | N/A         | 454 pyrosequencing of the 16S rRNA V3 region (Stool sample) |
|                 | Healthy controls                    | 83    |                                                | Firmicutes   | Lachnospiraceae  | N/A         |                                           |
|                 |                                     |       |                                                | Proteobacteria | Enterobacteriaceae | N/A         |                                           |
|                 |                                     |       |                                                | (Gram-negative bacteria) | | | |                                           |
| Stanislawski et al.20 | Adolescents exposure to gestational diabetes mellitus during singleton pregnancies | 107 | HFF vs non HFF | Proteobacteria | Desulfovibrionaceae | Bikphila | 16S rRNA gene sequencing (Stool sample) |
|                 |                                     |       |                                                | Bacteroidetes | Prevotellaceae   | Paraprevotella  |                                           |
|                 |                                     |       |                                                | Bacteroidetes | RF32             | Suturella   |                                           |
|                 |                                     |       |                                                | Firmicutes   | Bacteroidaceae   | RF32        |                                           |
|                 |                                     |       |                                                |              | Ruminococcaceae  | Bacteroides (U-shaped pattern; ↑ or ↓) |                                           |
| Authors               | Population     | N   | Comparison                      | Implicated microbiota                      | Methodology                          |
|----------------------|----------------|-----|---------------------------------|--------------------------------------------|---------------------------------------|
| Del Chierco et al.   | NAFLD patients | 61  | NAFLD vs Healthy                | Proteobacteria                             | Bradyrhizobiaceae                     |
|                      |                |     |                                 | Bradyrhizobiaceae                          | Bradyrhizobium                        |
|                      |                |     |                                 |                                             | 454 pyrosequencing of the 16S rRNA V1-V3 region (Stool sample) |
|                      | Healthy controls | 54  |                                 | Firmicutes                                  | unassigned                            |
|                      |                |     |                                 | Actinobacteria                              | Lachnospiraceae                       |
|                      |                |     |                                 | Firmicutes                                  | Peptoniphilaceae                      |
|                      |                |     |                                 | Firmicutes                                  | Peptoniphilus                         |
|                      |                |     |                                 | Firmicutes                                  | Propionibacterium acnes               |
|                      |                |     |                                 | Bacteroidetes                               | Rikenellaceae                         |
|                      |                |     |                                 |                                             |                                      |
| Zhu et al.           | NASH patients  | 22  | NASH or Obese vs Healthy        | Actinobacteria                              | Bifidobacteriaceae                    |
|                      |                |     |                                 |                                             | Bifidobacterium                       |
|                      | Obese patients | 25  |                                 | Bacteroidetes                               | Bacteroides (-)                       |
|                      |                |     |                                 |                                             |                                      |
|                      | Healthy controls | 16  |                                 | Bacteroidetes                               | Parabacteroides (-)                   |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Porphyromonadaceae (-)                |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Porphyromonadaceae (-)                |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Prevotellaceae (-)                    |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Alistipes (-)                         |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Clostridiales family XI (-)           |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Peptoniphilaceae                      |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Lachnospiraceae (-)                   |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Clostridiales family XI (-)           |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Bacteroidetes                               | Lachnospiraceae (-)                   |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Eubacteriaceae (-)                    |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Lachnospiraceae (-)                   |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Ruminococcaceae (-)                   |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Clostridiales (-)                     |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Clostridiales (-)                     |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Clostridiales (-)                     |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
|                      |                |     |                                 | Firmicutes (-)                              | Firmicutes (-)                        |
|                      |                |     |                                 |                                             |                                      |
| Authors          | Population                        | N  | Comparison                  | Implicated microbiota | Methodology                                      |
|------------------|-----------------------------------|----|-----------------------------|------------------------|-------------------------------------------------|
|                  |                                    |    |                             | Phylum | Family       | Genus            |                                                 |
| Koniffkoff et al. | Mild/moderate NAFLD (Stage 0–2 fibrosis) | 72 | Stage 0–2 fibrosis vs Stage 3 or 4 fibrosis | Proteobacteria ↑ | N/A          | N/A              | Whole genome shotgun sequencing of DNA (Stool sample) |
|                  | Advanced fibrosis (Stage 3 or 4 fibrosis) | 14 |                             | Firmicutes ↓ | Eubacteriaceae | Eubacterium rectale ↓ |                                                 |
| Roma et al.      | NAFLD                             | 30 | NAFLD vs Healthy            | Proteobacteria ↑ | Kilomeliellaceae ↑ | N/A              | 16S rRNA gene pyrosequencing (Stool sample)     |
|                  | Healthy controls                  | 30 |                             | Firmicutes ↓ | Pasteurellaceae ↑ | N/A              |                                                 |
|                  |                                    |    |                             | Firmicutes ↑ | Lactobacillaceae ↑ | Lactobacillus ↑ |                                                 |
|                  |                                    |    |                             | Firmicutes ↑ | Lachnospiraceae ↑ | Robinsonella ↑ |                                                 |
|                  |                                    |    |                             | Firmicutes ↑ | Ruminococcaceae ↑ | Roseburia ↑, Dorea ↑ |                                                 |
|                  |                                    |    |                             | Bacteroidetes ↑ | Veillonellaceae ↑ | Ocillobacter ↑ | N/A              |                                                 |
|                  |                                    |    |                             | Bacteroidetes ↑ | Porphyromonadaceae ↑ | N/A              |                                                 |

Comparison of condition A vs condition B:

↑ signifies an increase in condition A relative to condition B.
↓ signifies a decrease in condition A relative to condition B.
(−) signifies no changes in condition A relative to condition B.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HFF, hepatic fat fraction; N/A, not applicable.
# Gut microbiota alteration in cirrhotic patients.

| Authors          | Population                              | N    | Comparison          | Implicated microbiota                                      | Methodology                                              |
|------------------|------------------------------------------|------|---------------------|------------------------------------------------------------|----------------------------------------------------------|
| Chen et al.34    | Cirrhotic patients with HBV              | 24   | Cirrhosis vs Healthy| Actinobacteria, Firmicutes                                  | 16S rRNA gene pyrosequencing (Mucosa of the distal duodenum sample) |
|                  | Cirrhotic patients with PBC              | 6    |                     | Actinobacteria                                              |                                                         |
|                  | Healthy controls                         | 28   |                     |                                                            |                                                         |
| Bajaj et al.56   | Patients with liver cirrhosis            | 219  | Cirrhosis vs Healthy| Firmicutes, Lachnospiraceae, Ruminococcaceae, Clostridiales XIV, Enterococcaceae | Multi-tagged pyrosequencing (Stool sample)              |
| Healthy controls | 25                                       |      |                     |                                                            |                                                         |
| Bajaj et al.57   | Patients with liver cirrhosis            | 278  | Hospitalized vs non Hospitalized | Bacteroidetes, Bacteroidaceae, Clostridiales XIV, Lachnospiraceae, Ruminococcaceae | 16S rRNA pyrosequencing (Stool sample) |
| Non hospitalized patients with liver cirrhosis within 90 days | 162 |                | Firmicutes          |                                                            | N/A                                                      |
|                  | Hospitalized patients with liver cirrhosis | 94   |                     | Bacteroidetes                                                 |                                                         |
|                  |                                         |      |                     | Bacteroidetes, Bacteroidaceae                                |                                                         |
| Authors | Population | \(N\) | Comparison | Implicated microbiota | Genus | Methodology |
|---------|------------|-------|------------|----------------------|-------|-------------|
|         |            |       |            | Phylum               | Family |             |
| Wang and Wan | Non DM | 191 | DM vs non DM | Firmicutes | Firmicutes_Lactobacillaceae↑ | N/A |             |
|         |            |       |            | Firmicutes | Firmicutes_Enterococcaceae↑ | N/A |             |
|         |            |       |            | Firmicutes | Firmicutes_Clostridiales_AIV↑ | N/A |             |
|         |            |       |            | Firmicutes | Firmicutes_Lachnospiraceae↓ | N/A |             |
|         |            |       |            | Proteobacteria | Firmicutes_Ruminococcaceae↑ | N/A |             |
|         |            |       |            | Proteobacteria | Proteobacteria_Enterobacteriaceae↑ | N/A |             |
|         |            |       |            | Proteobacteria | Proteobacteria_Pasteurellaceae↑ | N/A |             |
|         | DM         | 87   |            | Bacteroidetes | Bacteroidetes_Bacteroidaceae↑ | N/A |             |
|         |            |       |            | Proteobacteria | Firmicutes_Eubacteriaceae↑ | N/A |             |
|         |            |       |            | Firmicutes | Firmicutes_Ruminococcaceae↑ | N/A |             |
|         |            |       |            | Firmicutes | Firmicutes_Veillonellaceae↑ | N/A |             |
|         |            |       |            | Actinobacteria | Firmicutes_Streptococcaceae↓ | N/A |             |
|         |            |       |            | Fusicobacteria | Actinobacteria_Streptomyctaceae↑ | N/A |             |
| Chen et al.59 | Patients with liver cirrhosis | 36 | Cirrhosis vs Healthy | Bacteroidetes↑ | Enterobacteriaceae↑ | N/A | The 16S rRNA V3 region pyrosequencing; Real-time PCR (Stool sample) |
|         | Healthy controls | 24 |            | Proteobacteria↑ | N/A |             |
|         |            |       |            | Fusicobacteria↑ | Veillonellaceae↑ | N/A |             |
|         |            |       |            | Fircicutes | Streptococcaceae↑ | N/A |             |
|         |            |       |            | Firmicutes | Lachnospiraceae↓ | N/A |             |
| Kakiyama et al.64 | Early cirrhotics | 23 | Cirrhosis vs Healthy | Firmicutes | Lachnospiraceae↑ | N/A | Culture-independent multi-targeted pyrosequencing (Stool sample) |
|         |            |       |            |         | Ruminococcaceae↑ | N/A |             |
|         | Advanced cirrhots | 24 |            | Firmicutes | Lachnospiraceae | N/A |             |
|         | Healthy controls | 14 |            | Bacteroidetes | Rikenellaceae↑ | N/A |             |

Comparison of condition A vs condition B:

\(↑\) signifies an increase in condition A relative to condition B.
signifies a decrease in condition A relative to condition B.
Abbreviations: HBV, hepatitis B virus; PBC, primary biliary cirrhosis; DM, diabetes mellitus; N/A, not applicable.
Table 3

Gut microbiota alteration and liver transplantation.

| Authors | Population | N  | Comparison | Implicated microbiota | Methodology |
|---------|------------|----|------------|------------------------|-------------|
|         |            |    |            | Phylum | Family | Genus |                     |
| Sun et al. | Post-LT patients | 9 15 | Post-LT vs Pre-LT | Proteobacteria | Pasteurellaceae | Actinobacillus |
|          | Healthy controls |    |            | Proteobacteria | Enterobacteriaceae | Escherichia and Shigella |
|          |            |    |            | Actinobacteria | Micromonosporaceae | Desulfobacterales |
|          |            |    |            | Proteobacteria | Eubacteriaceae | the Sarcina genus of Eubacteriaceae |
|          |            |    |            | Verrucomicrobia | Akkermansia | Akkermansia |
| Bajaj et al. | Outpatient patients with cirrhosis on the LT list | 45 45 | Improved cognition post-LT vs Pre-LT | Proteobacteria and Firmicutes | N/A | N/A |
|          | Healthy controls |    |            | N/A | N/A | Multitagged sequencing; 16S rRNA (Stool sample) |
|          |            |    |            | Ruminococaceae and Lachnospiraceae | N/A | N/A |
|          |            |    |            | Bifidobacteriaceae | N/A | N/A |
|          |            |    |            | Bacteroidaceae | N/A | N/A |
|          |            |    |            | Enterobacteriaceae | N/A | N/A |
|          |            |    |            | Shigella | ↓ | N/A |
|          |            |    |            | Escherichia | ↓ | N/A |
|          |            |    |            | Salmonella | ↓ | N/A |
|          |            |    |            | Bilophila | ↑ | N/A |
|          |            |    |            | Bifidobacterium | ↓ | N/A |
|          |            |    |            | Desulfatibacter | ↑ | N/A |
|          |            |    |            | Anaerovorax | ↑ | N/A |
| Bajaj et al. | Patients with cirrhosis | 40 | Post-LT vs Pre-LT | Proteobacteria | Enterobacteriaceae | Shigella and Escherichia |
|          |            |    |            | Proteobacteria | Desulfovibrionales | Salmonella |
|          |            |    |            | Actinobacteria | Bifidobacteriaceae | Suterella |
|          |            |    |            | Firmicutes | Clostridiales Incertae Sedis XI | Bilophila |
|          |            |    |            | Firmicutes | Clostridiales Incertae Sedis XIII | Bifidobacterium |
|          |            |    |            | Firmicutes | Clostridiales | Desulfobacter |
|          |            |    |            | Firmicutes | Streptococcaceae | Sporanaerobacter |
|          |            |    |            | Firmicutes | Clostridiales | ClostridiumV |
|          |            |    |            | Bacteroidetes | Rikenellaceae | Oudiibacteria |
|          |            |    |            | Bacteroidetes | N/A | N/A |
|          |            |    |            | Enterobacteriaceae | N/A | N/A |
|          |            |    |            | Desulfovibrionales | N/A | N/A |
|          |            |    |            | Bifidobacteriaceae | N/A | N/A |
|          |            |    |            | Clostridiales | N/A | N/A |
|          |            |    |            | Rikenellaceae | N/A | N/A |
|          |            |    |            | Shigella | ↓ | N/A |
|          |            |    |            | Escherichia | ↓ | N/A |
|          |            |    |            | Salmonella | ↓ | N/A |
|          |            |    |            | Bilophila | ↑ | N/A |
|          |            |    |            | Bifidobacterium | ↓ | N/A |
|          |            |    |            | Desulfobacter | ↑ | N/A |
|          |            |    |            | Sporanaerobacter | ↑ | N/A |
|          |            |    |            | ClostridiumV | ↓ | N/A |
|          |            |    |            | Oudiibacteria | ↓ | N/A |
|          |            |    |            | Anaerovorax | ↑ | N/A |
Comparison of condition A vs condition B:

\( \uparrow \) signifies an increase in condition A relative to condition B.

\( \downarrow \) signifies a decrease in condition A relative to condition B.

(−) signifies no changes in condition A relative to condition B.

Abbreviations: LT, liver transplantation; N/A, not applicable.

| Authors | Population | N | Comparison | Implicated microbiota | Methodology |
|---------|------------|---|------------|-----------------------|-------------|
|         |            |   |            | Phylum                | Family      | Genus       |
|         |            |   |            | **Anaerostipes**\[^{1}\], **Clostridium XIVb**\[^{1}\], **Blautia**\[^{2}\] **Roseburia**, and **Dorea**\[^{2}\] **Streptococcus**\[^{1}\], **Butyricoccus**\[^{1}\], **Clostridium XIVa**\[^{1}\] **Alistipes**\[^{2}\] |            |             |
Table 4

Fungal dysbiosis in complications associated with liver cirrhosis.

| Authors      | Population                        | N  | Comparison                     | Implicated microbiota                          | Methodology                                           |
|--------------|-----------------------------------|----|-------------------------------|------------------------------------------------|------------------------------------------------------|
| Bajaj et al  | Outpatients cirrhotics            | 77 | Inpatients vs Outpatients     | Basidiomycota† Ascomycota                   | N/A Metagenomics (Stool sample)                      |
|              | Inpatients cirrhotics             | 66 | After antibiotics vs before antibiotics | Ascomycota Saccharomyctaceae     | Candida†                                             |
|              | Controls                          | 26 | Inpatients vs Outpatients     | Ascomycota Saccharomyctaceae   | Candida†                                             |
|              |                                   |    |                               | Proteobacteria Enterobacteriaceae †   | N/A                                                  |
|              |                                   |    |                               | Firmicutes Enterococcaceae †        | N/A                                                  |
|              |                                   |    | Outpatients vs Controls       | Basidiomycota† N/A                  | Candida†                                             |
|              |                                   |    |                               | Ascomycota Saccharomyctaceae     | N/A                                                  |
|              |                                   |    |                               | Proteobacteria Enterobacteriaceae † | N/A                                                  |
|              |                                   |    |                               | Firmicutes Enterococcaceae †       | N/A                                                  |
|              |                                   |    | Outpatients on antibiotics    | Ascomycota Saccharomyctaceae     | Candida†                                             |
|              |                                   |    |                               | Proteobacteria Pasteurellaceae †    | N/A                                                  |
| Yang et al   | Healthy individuals               | 8  | Patients vs Healthy individuals | Ascomycota Saccharomyctaceae     | Candida† Illumina MiSeq platform                     |
|              | Alcohol-dependent                 | 10 |                               |                                          | sequencing of the V4 region of 16S rRNA (Stool sample) |
|              | patients (nonprogressive liver disease) |    |                               |                                          |                                                      |
|              | Patients with alcoholic liver cirrhosis | 4  |                               |                                          |                                                      |

Comparison of condition A vs condition B:
† signifies an increase in condition A relative to condition B.
‡ signifies a decrease in condition A relative to condition B.
Abbreviation: N/A, not applicable.
### Table 5

Oral microbiota alteration in patients with cirrhosis.

| Authors       | Population                        | N     | Comparison                  | Implicated microbiota                          | Methodology                                      |
|---------------|-----------------------------------|-------|-----------------------------|------------------------------------------------|------------------------------------------------|
| Chen et al.34 | Cirrhotic patients                | 30    | Patients vs Controls        | Actinobacteria, Firmicutes, Firmicutes          | 16S rRNA gene pyrosequencing (Mucosal from the distal duodenum sample) |
|               | Healthy controls                  | 28    |                             |sr1 genera incertae sedis, Firmicutes, Firmicutes|                                                 |
| Qin et al.37  | Patients with cirrhosis           | 98    | Patients vs Controls        | Firmicutes, Firmicutes                          | Quantitative metagenomics (Stool sample)         |
|               | Healthy controls                  | 83    |                             |                                                 |                                                 |
| Bajaj et al.99| Patients with cirrhosis without HE| 59    | Patients vs Controls        | Bacteroidetes, Fusobacteria, Firmicutes         | Quantitative metagenomics (Stool or saliva sample) |
|               | Patients with cirrhosis with previous HE | 43 |                             |                                                 |                                                 |
|               | age-matched controls              | 32    |                             |                                                 |                                                 |
| Bajaj et al.90| Cirrhotic outpatients on PPI      | 59    | PPI users vs Patients without PPI and Controls | Firmicutes, Firmicutes                          | Multi-tagged sequencing (Stool sample)           |
|               | Cirrhotic outpatients not on PPI  | 78    |                             |                                                 |                                                 |
|               | Healthy controls                  | 45    |                             |                                                 |                                                 |
| Authors | Population | N  | Comparison | Implicated microbiota | Methodology |
|---------|------------|----|------------|-----------------------|-------------|
|         | Cirrhotic outpatients not on PPI | 15 | After vs Before PPI initiation | Bacteroidetes | N/A |
|         |            |    |            | Porphyromonadaceae↑ | N/A         |
|         |            |    |            | Streptococcaceae↑   | N/A         |
|         | Patients with decompensated cirrhosis on chronic PPI | 15 | PPI withdrawal vs Pre-PPI therapy | Bacteroidetes | N/A |
|         |            |    |            | Porphyromonadaceae↓ | N/A         |
|         |            |    |            | Streptococcaceae↓, and Veillonellaceae↓ | N/A |

Comparison of condition A vs condition B:

↑ signifies an increase in condition A relative to condition B.
↓ signifies a decrease in condition A relative to condition B.

Abbreviations: HE, hepatic encephalopathy; PPI, proton pump inhibitors; N/A, not applicable.
Gut microbiota alteration in human HCC.

| Authors       | Population                                                                 | N  | Comparison                                  | Implicated microbiota       | Methodology                                      |
|---------------|------------------------------------------------------------------------------|----|---------------------------------------------|------------------------------|-------------------------------------------------|
| Nilsson et al. | Liver specimens of patients with cholangiocarcinoma HCC human specimens Controls (liver tissue from patients with resected metastases from colorectal cancers) | 14 | HCC or cholangiocarcinoma specimens vs Controls | Proteobacteria, Helicobacteraceae, *Helicobacter* spp. | PCR and DNA sequencing (HCC human specimens) |
| Huang et al.   | HCC human specimens Controls without HCC                                    | 20 | HCC specimens vs Controls                    | Proteobacteria, Helicobacteraceae, *Helicobacter pylori* | PCR, DNA sequencing, and immunostaining (Liver specimens) |
| Krüttgen et al.| Patients with viral-induced HCC Control patients                            | 14 | Patients with viral-induced HCC vs Control patients | Proteobacteria, Helicobacteraceae, *H. hepaticus* (no exist) | PCR (Stool sample) |
| Grat et al.    | Patients with HCC Non HCC patients                                         | 15 | HCC vs non HCC                               | Proteobacteria, Enterobacteriaceae, *Escherichia coli* | Culturing on enriching and selective agar media (Stool sample) |
| Lu et al.      | Early liver carcinoma patients with cirrhosis Healthy controls              | 35 | HCC vs Healthy                               | Firmicutes, Fusobacteria, Lachnospiraceae, *Oribacterium* changes, *Fusobacterium* changes | 16S rRNA gene sequencing (Tongue coat sample) |

Comparison of condition A vs condition B:

\( \uparrow \) signifies an increase in condition A relative to condition B.
Abbreviation: HCC, hepatocellular carcinoma.
| Authors            | Model                        | Agent | Comparison                          | Implicated microbiota                         | Phylum            | Family          | Genus                | Methodology                             |
|--------------------|------------------------------|-------|-------------------------------------|-----------------------------------------------|-------------------|------------------|----------------------|-----------------------------------------|
| Xie et al.         | NASH-HCC C57BL/6J mouse model | STZ-HFD | NASH-HCC vs Controls                | Actinobacteria, Bacteroidetes, Coriobacteriaceae | Firmicutes, Bacteroidetes, Proteobacteria | Clostridiaceae, Enterococcaceae, Bifidobacteriaceae | Lactobacillus, Enterococcus, Bifidobacterium | 16S rRNA gene pyrosequencing (Stool sample) |
| Zhang et al.       | Male Sprague-Dawley rat model | DEN   | HCC rats vs Controls                | Firmicutes, Actinobacteria, Clostridiaceae     | Firmicutes, Lactobacillaceae, Enterococcaceae, Bifidobacteriaceae | Desulfovibrionaceae, Desulfovibrio | Desulfovibrio, Clostridium cocleatum | Quantitative real-time PCR (Stool sample) |
| Gómez-Hurtado et al | Female Balb/c fibrosis mice  | CCL   | Fibrosis mice vs Controls           | Firmicutes, Actinobacteria                      | Firmicutes, Lactobacillaceae, Enterococcaceae, Bifidobacteriaceae | Desulfovibrionaceae | Desulfovibrio, Clostridium cocleatum | Quantitative real-time PCR (Stool sample) |

Comparison of condition A vs condition B: ↑ signifies an increase in condition A relative to condition B; ↓ signifies a decrease in condition A relative to condition B.

Abbreviations: STZ-HFD, streptozotocin-high fat diet; DEN, diethylnitrosamine; HCC, hepatocellular carcinoma; CCL4, carbon tetrachloride.