

## Gut microbiota and liver diseases

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previous findings, trials using probiotics have been performed for the prevention or treatment of liver diseases. In this review, we summarize the current understanding of the changes in gut microbiota associated with various liver diseases, and we describe the therapeutic trials of probiotics for those diseases.

**Key words:** Gut microbiota; Immune system; Liver disease; Metabolites; Non-alcoholic fatty liver disease; Hepatic encephalopathy

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**Core tip:** Gut microbiota are associated with various human diseases (*e.g.*, metabolic, gastroenterological and liver diseases, and allergies). Genomic analyses of gut microbiota have enabled the comprehensive identification of the population of gut bacteria and revealed that changes in these populations are involved in various diseases' pathophysiology. The liver is affected by changes in the intestinal milieu due to the entry of gut bacteria or their metabolites into the liver through the portal vein. Here we summarize the current understanding of changes in gut microbiota associated with various liver diseases. We also summarize the recent therapeutic trials of probiotics in liver diseases.

### Abstract

Several studies revealed that gut microbiota are associated with various human diseases, *e.g.*, metabolic diseases, allergies, gastroenterological diseases, and liver diseases. The liver can be greatly affected by changes in gut microbiota due to the entry of gut bacteria or their metabolites into the liver through the portal vein, and the liver-gut axis is important to understand the pathophysiology of several liver diseases, especially non-alcoholic fatty liver disease and hepatic encephalopathy. Moreover, gut microbiota play a significant role in the development of alcoholic liver disease and hepatocarcinogenesis. Based on these

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### INTRODUCTION

More than  $10^{14}$  microorganisms live in the human gastroenterological tract, including  $> 10^4$  bacterial species. Most of the bacteria are anaerobic, and the numbers and composition of the bacteria differ according to the site of the gut (Table 1<sup>[1]</sup>). The

**Table 1** Composition of gut microbiota<sup>[11]</sup>

Microorganism	Stomach	Jejunum	Ileum	Colon
Total count	0-10 <sup>4</sup>	0-10 <sup>5</sup>	10 <sup>4</sup> -10 <sup>8</sup>	10 <sup>10</sup> -10 <sup>12</sup>
Aerobic microorganisms				
<i>Streptococcus</i>	0-10 <sup>3</sup>	0-10 <sup>4</sup>	10 <sup>2</sup> -10 <sup>4</sup>	10 <sup>3</sup> -10 <sup>5</sup>
<i>Enterococcus</i>	rare	0-10 <sup>2</sup>	10 <sup>2</sup> -10 <sup>4</sup>	10 <sup>5</sup> -10 <sup>10</sup>
<i>Staphylococcus</i>	0-10 <sup>3</sup>	0-10 <sup>3</sup>	10 <sup>2</sup> -10 <sup>5</sup>	10 <sup>4</sup> -10 <sup>6</sup>
<i>Enterobacteria</i>	0-10 <sup>2</sup>	0-10 <sup>3</sup>	10 <sup>2</sup> -10 <sup>7</sup>	10 <sup>4</sup> -10 <sup>10</sup>
Anaerobic microorganisms				
<i>Peptostreptococcus</i>	0-10 <sup>3</sup>	0-10 <sup>3</sup>	10 <sup>2</sup> -10 <sup>6</sup>	10 <sup>10</sup> -10 <sup>12</sup>
<i>Bifidobacterium</i>	0-10 <sup>2</sup>	0-10 <sup>4</sup>	10 <sup>3</sup> -10 <sup>9</sup>	10 <sup>8</sup> -10 <sup>11</sup>
<i>Lactobacillus</i>	0-10 <sup>3</sup>	0-10 <sup>4</sup>	10 <sup>2</sup> -10 <sup>5</sup>	10 <sup>6</sup> -10 <sup>8</sup>
<i>Clostridium</i>	rare	rare	10 <sup>2</sup> -10 <sup>4</sup>	10 <sup>6</sup> -10 <sup>9</sup>
<i>Eubacterium</i>	rare	rare	rare	10 <sup>9</sup> -10 <sup>12</sup>
<i>Veillonella</i>	0-10 <sup>2</sup>	0-10 <sup>3</sup>	10 <sup>2</sup> -10 <sup>4</sup>	10 <sup>3</sup> -10 <sup>6</sup>
<i>Fusobacterium</i>	0-10 <sup>2</sup>	0-10 <sup>3</sup>	10 <sup>3</sup> -10 <sup>4</sup>	10 <sup>6</sup> -10 <sup>8</sup>
<i>Bacteroides fragilis</i>	rare	0-10 <sup>3</sup>	10 <sup>3</sup> -10 <sup>7</sup>	10 <sup>10</sup> -10 <sup>12</sup>
<i>Prevotella</i>	0-10 <sup>2</sup>	10 <sup>2</sup> -10 <sup>4</sup>	10 <sup>3</sup> -10 <sup>4</sup>	10 <sup>4</sup> -10 <sup>5</sup>

numbers of bacteria increase from the stomach, to the jejunum, ileum and colon. The composition of the bacterial flora also changes according to age and diet<sup>[2,3]</sup>. It has been clarified that gut microbiota play a critical role in the formation of the gut immune system<sup>[4,5]</sup> and that they also affect the systemic immune system<sup>[6,7]</sup>. Moreover, interactions between gut microbiota and the liver<sup>[8-12]</sup> or brain<sup>[13-15]</sup> have been analyzed. The composition of the microbiota is also associated with various diseases. In this review, we summarize the current understanding of the role of gut microbiota, especially in relation to liver diseases, and we describe relevant clinical trials of the treatment of liver diseases by probiotics.

## COMPOSITION OF GUT MICROBIOTA

### Methods for analyzing gut microbiota

Since most of the gut bacteria cannot be cultured, comprehensive analyses of them have been difficult<sup>[16]</sup>. Advances in molecular biological techniques have enabled the analyses of the whole genomes of gut microbiota, and real-time PCR, microarray, and pyrosequencing have been applied to improve the resolution of the microbial biodiversity and quantification of microbial species<sup>[17]</sup>. Among those gene-based methods, DNA pyrosequencing based on 16S rRNA genes<sup>[18]</sup> is currently the most useful method for comprehensive analysis of gut microbiota with high resolution and accurate quantification.

### Composition of gut microbiota and its change according to age

Claesson *et al.*<sup>[19]</sup> analyzed the composition of intestinal microbiota by pyrosequencing of over 40000 16S rRNA gene V4 region amplicons. They found that the phylum *Bacteroides* was the most predominant species of bacteria in 68% of the individuals studied, with an average proportion of 57%, followed by the phylum *Firmicutes* with an average proportion of

40%. Other detected species were *Proteobacteria*, *Actinobacteria*, and *Faecalibacteria*. The composition differed dramatically among individuals, and was also different according to the individuals' ages. Elderly individuals were reported to show increased *Bacteroides* species diversity whereas *bifidobacteria* were reduced<sup>[20]</sup>, although contrasting results have been obtained<sup>[21,22]</sup>.

## FUNCTIONS OF GUT MICROBIOTA

### Digestion and metabolism

Human enzymes are known to be unable to digest complex carbohydrates and plant polysaccharides. Instead, gut microbiota ferment the non-digestible carbohydrates, including cellulose, resistant starch and inulin in the colon to yield energy for microbial growth and end products such as short-chain fatty acids (SCFAs)<sup>[23]</sup>. The SCFAs formed are organic fatty acids, and the major SCFAs consist of acetate, propionate and butyrate. Butyrate is an energy substrate for the colonic epithelium, and acetate and propionate are energy substrates for peripheral tissues<sup>[23]</sup>. Propionic and butyric acids were shown to regulate cell proliferation and differentiation, and to induce hormone release<sup>[24]</sup>, the hepatic control of lipids, and carbohydrate metabolism<sup>[25]</sup>. Moreover, several SCFAs have been shown to exert anti-inflammatory and immunomodulatory effects<sup>[26,27]</sup>.

### Immune response to gut microbiota

Although we harbor more than 10<sup>4</sup> bacterial species in the gut and the composition is relatively stable in each person without causing inflammation<sup>[28]</sup>, the mechanisms responsible for maintaining the flora over the long term are not yet clearly understood. The maintenance of the gut flora may be based on immune tolerance to microbiota because of the formation of the repertoire of microbiota during early life after birth, when the immune system is too immature to eradicate intestinal micro-organisms.

Round *et al.*<sup>[29]</sup> showed that *Bacteroides fragilis* could induce immune tolerance to gut microbiota by developing and promoting functions of Foxp3+ regulatory T cells (Tregs) through polysaccharide A produced by the bacteria. In another study, certain *Clostridium* species, especially phylogenetic clusters IV and XIV (but not *Lactobacillus* or *Bacteroides* species) were the most effective in inducing the differentiation of Tregs<sup>[30]</sup>. Natural killer T (NKT) cells, a subgroup of T cells that recognize self-antigens and microbial lipid antigens presented by CD1d, have an important role in the development and the composition of gut microbiota through the CD1d molecule. Conversely, the development and maturation of mucosal and systemic NKT cells are controlled by commensal gut microbiota<sup>[31]</sup>. Moreover, CD1d presents self-antigens and microbial lipid antigens to NKT cells, which are

**Table 2** Changes in gut microbiota in human diseases<sup>[35]</sup>

Diseases	Change in microbiota
Allergies	<i>Lactobacillus</i> spp. ↓ <i>Bifidobacterium adolescentis</i> ↓ <i>Clostridium difficile</i> ↓ <i>Helicobacter pylori</i> ↓
Autism	<i>Bacteroidetes</i> ↑ <i>Proteobacteria</i> ↑ <i>Actinobacteria</i> ↓ <i>Firmicutes</i> ↓
Obesity	<i>Bacteroidetes</i> ↓ <i>Lactobacillus</i> ↑ <i>Firmicutes/Bacteroidetes</i> ratio ↓
Type 2 Diabetes	<i>Firmicutes</i> ↓ <i>Clostridia</i> ↓ <i>Betaproteobacteria</i> ↓ <i>Bacteroidetes/Firmicutes</i> ratio ↑
Celiac disease	<i>Bacteroides vulgatus</i> ↑ <i>Escherichia coli</i> ↓ <i>Clostridium coccoides</i> ↓

involved in the pathogenesis of human inflammatory bowel disease<sup>[32]</sup>. Thus, cross-talk between the microbiota and CD1d-restricted NKT cells plays an important role in microbial homeostasis and intestinal inflammation.

These overall data suggest that the immune tolerance is important not only for the maintenance of gut microbiota, but also for suppressing harmful immune responses to microbiota in the gut. Inflammatory bowel diseases are now thought to be caused by an uncontrolled immune response to gut microbiota<sup>[33]</sup>.

### Role of gut microbiota in the maturation of the immune system

The role of gut microbiota in gut immune maturation, including the numbers of intestinal CD4+ and CD8+ T cells and dendritic cells, has been demonstrated in mice<sup>[5]</sup>. The effect of early gut colonization on systemic immune responses was also shown by Hansen *et al.*<sup>[34]</sup>, who reported that a single oral inoculation of a bacteria suspension made from caecal content of specific pathogen-free mice to germ-free mice at 3 wk of age, but not at 1 wk of age, permanently changed the gut microbiota composition, and the delayed colonization caused permanent changes in the immune systems of the mice. The mechanisms responsible for the influence of commensal bacteria on host immunity are thought to be nutrient- and metabolite-dependent.

Collectively, these data indicate an interplay between gut microbiota and the host's immune system.

## GUT MICROBIOTA AND HUMAN DISEASES

Several specific changes in the composition of gut microbiota in a number of human diseases have been reported (Table 2<sup>[35]</sup>). It would be reasonable to speculate that not a single disease-causing microbe

but rather microbial dysbiosis causes those diseases.

## GUT MICROBIOTA AND THE LIVER

Since 70% of the liver's blood is supplied from the portal vein, gut-derived toxins and microbial products constantly enter the liver. The liver could thus be greatly influenced by the composition and function of gut microbes, mainly by receiving metabolites derived from the microbes.

In normal conditions, small amounts of bacteria or bacterial metabolites enter the liver, and most of them are eliminated by Kupffer cells with little activation. However, when the gut-mucosal barrier is damaged by intestinal inflammation or portal hypertension, large amounts of bacteria enter the liver and activate Kupffer cells and hepatic stellate cells. One of the pathogenic bacteria-derived factors is lipopolysaccharide (LPS), and LPS activates those cells *via* its binding to Toll-like receptor 4 on their surface. Upon the activation of those cells, pro-inflammatory cytokines are produced and are involved in liver damage. It is of note that alcohol was shown to disrupt the intestinal epithelial cell tight junctions and impair the functioning of the gut barrier, leading to bacterial translocation and enhanced entry of bacteria metabolites into the portal vein<sup>[36]</sup>.

Moreover, the impaired motility of the intestines, increased epithelial permeability, and increased release of pro-inflammatory cytokines in the intestines found in cases of liver cirrhosis with portal hypertension may affect the liver<sup>[37]</sup>.

## GUT MICROBIOTA AND LIVER DISEASES

There are several reports on the changes in gut microbiota in liver diseases, and the representative data are summarized in Table 3.

### Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a common disease all over the world, following the increasing prevalence of obesity and metabolic syndrome. About 10% of patients with NAFLD are now thought to progress to non-alcoholic steatohepatitis (NASH) with the potential to develop liver cirrhosis and even hepatocellular carcinoma (HCC). Since it is now evident that the gut microbiota play an important role in energy storage and the subsequent development of obesity<sup>[38]</sup>, the role of gut microbiota in the development and progression of NAFLD has become a focus of research.

Indeed, the compositions of microbiota have been shown to differ in obese and lean individuals, with increased *Firmicutes* and decreased *Bacteroidetes* levels in the obese under the intake of the same amount of food<sup>[39]</sup>. Extensive analyses of gut microbiota in patients with NAFLD have been performed recently,

**Table 3** Changes in gut microbiota in liver diseases

Diseases	Change in microbiota	Ref.
NAFLD	<i>Bacteroidetes</i> ↓ <i>Prevotella</i> ↑	[41]
Cirrhosis	<i>Porphyromonas</i> ↑ <i>Enterobacteriaceae</i> ↑ <i>Streptococcaceae</i> ↑ <i>Bifidobacteria</i> ↓ <i>Lachnospiraceae</i> ↓ <i>Bacteroidetes</i> ↓ <i>Firmicutes</i> ↓ <i>Streptococcus</i> spp. ↑ <i>Veillonella</i> spp. ↑	[45,46] [47]
Alcoholics	<i>Bacteroidaceae</i> ↓ <i>Prevotellaceae</i> ↑	[50,51]
Alcoholic liver cirrhosis	<i>Enterobacteriaceae</i> ↑	[53]
Cirrhosis with encephalopathy	<i>Porphyromonadaceae</i> ↑ <i>Alcaligenaceae</i> ↑	[55]

NAFLD: Nonalcoholic fatty liver disease.

and individuals with NAFLD were found to show a lower percentage of *Bacteroidetes* and higher levels of *Prevotella* and *Porphyromonas* species compared to healthy controls. Moreover, the predisposition to develop to NAFLD was dependent on the expression of Toll-like receptors (TLR) 4 or 9, or tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) receptor<sup>[40]</sup>.

The mechanisms underlying the progression from simple fatty liver to NASH are not fully understood, but a study suggested that NASH harbors modified microbiota that produce endogenous ethanol, leading to the development of NASH<sup>[39]</sup>.

A bacteria-mediated mechanism for the progression of NASH was recently proposed by Imajo *et al.*<sup>[41]</sup>. They found that obesity-induced leptin upregulates CD14 via STAT3 signaling, resulting in hyper-responsibility to low-dose LPSs, leading to the liver inflammation and fibrosis of NASH.

### Liver cirrhosis

In liver cirrhosis, the decreased secretions of bile acid<sup>[42,43]</sup> and portal hypertension<sup>[44]</sup> could affect the composition and the growth of gut microbiota. Previous studies<sup>[45,46]</sup> revealed that the gut microbiota in patients with liver cirrhosis showed a higher prevalence of pathogenic bacteria such as *Enterobacteriaceae* and *Streptococcaceae* and a lower prevalence of beneficial bacteria such as *Bifidobacteria* and *Lachnospiraceae* compared to healthy controls. The gut microbial communities were the same irrespective of their etiologies, indicating that the composition characteristics in the liver cirrhosis patients were due mostly to the liver cirrhosis. Interestingly, a positive correlation was observed between the patients' Child-Turcotte-Pugh (CTP) scores and *Streptococcaceae*, whereas *Lachnospiraceae* was significantly decreased in the cirrhosis patients and negatively correlated with the CTP scores, suggesting a contribution of

gut microbiota to the prognosis of patients with liver cirrhosis<sup>[45,46]</sup>.

Qin *et al.*<sup>[47]</sup> analyzed the gut microbiomes in liver cirrhosis patients by quantitative metagenomics, and they found that the gut microbiota in the patients contained less *Bacteroidetes* and *Firmicutes* and more *Streptococcus* spp. and *Veillonella* spp. compared to healthy controls. Both *Streptococcus* spp. and *Veillonella* spp. are bacteria of oral origin and might be associated with the pathophysiology of liver cirrhosis. Although the functions and the contribution of these bacteria in the pathogenesis and complications of liver cirrhosis remain to be clarified, these findings could help develop a new therapeutic strategy against liver cirrhosis by focusing on the gut microbiota.

### Alcoholic liver disease

Chronic alcohol consumption is related to fatty liver, liver fibrosis and liver cirrhosis, and both alcohol and acetaldehyde have been suspected to be pathogenic for liver injury. However, the importance of gut microbiota in the pathogenesis of alcoholic liver injury has been revealed. In alcohol-fed mice, *Akkermansia* and *Bacteroides* were increased, and *Lactobacillus* was decreased<sup>[48]</sup>. In human alcoholics, a decrease in *Bacteroidaceae* and an increase in *Prevotellaceae* were found<sup>[49]</sup>. Besides gut dysbiosis, increased gut permeability-due to the disruption of tight junctions caused by ethanol and acetaldehyde-leads to the increased entry of LPS, endotoxin and bacterial DNA into the liver<sup>[50,51]</sup>. These activate Kupffer cells via TLR4 or TLR 9 on the cell surface, and induce pro-inflammatory cytokines from Kupffer cells<sup>[52]</sup>.

Tuomisto *et al.*<sup>[53]</sup> analyzed bacterial DNA in the feces of patients with alcoholic liver cirrhosis, and they found that the feces contained more bacterial DNA of *Enterobacteriaceae* compared to those of healthy volunteers. They also analyzed ascites, and found that 50% of the ascites from the alcoholic liver cirrhosis patients contained *Enterobacteriaceae*, a *Clostridium leptum* group or *Lactobacillus* spp.<sup>[53]</sup>.

### Hepatic encephalopathy

Hepatic encephalopathy (HE) is a complication often found in patients with advanced liver cirrhosis. It greatly affects the quality of life in those patients. HE is characterized by reversible cognitive impairment which is caused not by organic organ damage but by toxic substances produced by microbiota in the intestine. Although ammonia is thought to be the main factor causing HE, other factors such as mercaptans, phenols, short- and medium-chain fatty acids and benzodiazepine-like compounds could contribute to the development of HE. Since most of these factors are derived from gut microbiota, analyses of the composition of the microbes will be important for both the understanding and management of HE.

A report from Bajaj *et al.*<sup>[54]</sup> found that fecal



microbiota in cirrhotic patients contained significantly higher levels of *Enterobacteriaceae*, *Alcaligenaceae*, and *Fusobacteriaceae* and lower levels of *Ruminococcaceae* and *Lachnospiraceae* compared to those in controls. Moreover, in cirrhotic patients with HE, the correlation between *Porphyromonadaceae* and *Alcaligenaceae* with poor performance on cognitive tests was observed. However, Bajaj *et al.*<sup>[55]</sup> later reported that sigmoid colon mucosal microbiomes are different from stool microbiomes in patients with liver cirrhosis and HE, and they found that in patients with HE the mucosal microbiome, but not the stool microbiome, showed less *Roseburia* and more *Enterococcus*, *Veillonella*, *Megasphaera*, and *Burkholderia* compared to non-HE subjects. These data suggest that a stool microbiota analysis might not be enough to understand the pathogenesis of HE, and that changes in the colonic mucosal microbiota could contribute to the development of HE.

### HCC

Eighty percent of HCCs develop in fibrotic or cirrhotic livers, and the main etiologies include hepatitis B, hepatitis C, and alcohol intake. However, as obesity has become more prevalent in most developed countries, the development of HCC in patients with NAFLD has been increasing. In viral hepatitis, chronic inflammation of the liver is thought to be associated with hepatocarcinogenesis, but the mechanism underlying the development of HCC in NAFLD patients has not been clarified.

Yoshimoto *et al.*<sup>[56]</sup> reported that obese mice show alterations of gut microbiota, leading to an increased production of a gut bacterial metabolite, deoxycholic acid (DCA), which is known to cause DNA damage. Increased levels of DCA in the enterohepatic circulation induce a senescence-associated secretory phenotype in the hepatic stellate cells, which secrete inflammatory and tumor-promoting factors in the liver. The obese mice showed HCC development after exposure to a chemical carcinogen. These data indicate that gut bacterial metabolites promote obesity-induced HCC development in mice. Yoshimoto *et al.*<sup>[56]</sup> also found that a similar pathway may contribute to NASH-associated HCC development in humans.

Dapito *et al.*<sup>[57]</sup> demonstrated in a mouse model that TLR4 activation by LPS from the intestinal microbiota was closely associated with injury- and inflammation-driven tumor promotion but not with the tumor initiation of hepatocarcinogenesis induced by a combination of diethylnitrosamine and the hepatotoxin carbon tetrachloride. The contribution of intestinal microbiota was confirmed by a decrease in hepatocarcinogenesis in germ-free mice compared to specific pathogen-free mice. On the other hand, a metabolite from gut microbiota, propionate, was shown to inhibit the cancer cell proliferation of liver cancer cells in the liver in a mouse model<sup>[58]</sup>.

Intratumoral interleukin-17-producing T helper cells (Th17) were found to be associated with poor prognoses of patients with HCC<sup>[59]</sup>, possibly due to the promotion of angiogenesis and tumor growth<sup>[60]</sup>, and most of these Th17 cells are generated in the gut by an interaction with gut microbiota<sup>[61]</sup>. Therefore, there could be close associations among HCC progression, the generation of Th17 cells, and gut microbiota. Taken together, the above-described findings indicate that the development of liver cancer can be modulated by gut microbiota, suggesting the possibility of therapeutic intervention.

## UTILIZATION OF PROBIOTICS IN LIVER DISEASES

Bacterial translocation and endotoxemia, which can be caused by increased permeability of the intestinal mucosa<sup>[62]</sup>, are thought to contribute to the pathogenesis of various complications in liver cirrhosis such as hepatic encephalopathy<sup>[63,64]</sup> and spontaneous bacterial peritonitis<sup>[65,66]</sup>. The changes of intestinal microflora might also be associated with the pathogenesis of NASH<sup>[67]</sup>. Beneficial effects of probiotics have been reported in not only gastrointestinal but also liver diseases. Here we describe therapeutic trials using probiotics and their indications in liver diseases.

### HE

HE is a common complication of liver cirrhosis<sup>[63]</sup>. Gut flora are associated with the pathogenesis of HE<sup>[64]</sup>, because urease-producing gut bacteria such as *Klebsiella* and *Proteus* species can increase the production of ammonia and endotoxins. It was reported in several studies that the alteration of gut flora using probiotics and/or prebiotics could improve HE. The probiotics include strains of lactic acid bacilli (e.g., *Lactobacillus* and *Bifidobacterium*), a nonpathogenic strain of *Escherichia coli* (e.g., *E. coli* Nissle 1917), *Clostridium butyricum*, *Streptococcus salivarius*, and *Saccharomyces boulardii* (a nonpathogenic strain of yeast), and VSL#3. The most-studied probiotic, VSL#3, consists of a mixture of eight probiotic strains (*Streptococcus thermophilus*, *Bifidobacterium breve*, *B. longum*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, and *L. bulgaricus*)<sup>[68]</sup>.

As of 2011, nine randomized controlled trials (RCTs) had been reported comparing probiotics and synbiotics with no intervention or placebo in patients with HE (Table 4)<sup>[69-77]</sup>. Some of these studies included cases using lactulose for prebiotics or as control arms; lactulose acts by altering the colonic pH and improving gastrointestinal transit. McGee *et al.*<sup>[78]</sup> and Holte *et al.*<sup>[79]</sup> independently reported a systematic review and a meta-analysis of these randomized trials on probiotics for HE, respectively. Both groups found that patients treated with probiotics appeared to have reduced plasma ammonia concentrations compared

**Table 4 Randomized controlled trials for hepatic encephalopathy**

Ref.	Year	Sample size (treatment/ placebo)	Treatment regimens	Duration	Favorable effects
<sup>1,2</sup> Loguercio <i>et al</i> <sup>[69]</sup>	1987	40 (20/20)	<i>Enterococcus Lactic Acid bacteria</i> strain SF68 <i>vs</i> lactulose	10 d	NH <sub>3</sub> ↓ Performance status: improved
<sup>2</sup> Loguercio <i>et al</i> <sup>[70]</sup>	1995	40 (21/19)	<i>Enterococcus Lactic Acid bacteria</i> strain SF68 <i>vs</i> lactulose	3 x 4 wk	NH <sub>3</sub> ↓ Psychometric test: improved
<sup>1,2</sup> Liu <i>et al</i> <sup>[71]</sup>	2004	55 (20/35)	<i>Pediococcus pentoseceus</i> , <i>Leuconostoc mesenteroides</i> , <i>Lactobacillus paracasei</i> , and <i>Lactobacillus plantarum</i> with fermentable fibers <i>vs</i> fermentable fibers only or non-fermentable fiber	30 d	Endotoxemia ↓ Child-Turcotte-Pugh classification: improved
<sup>2</sup> Malaguarnera <i>et al</i> <sup>[72]</sup>	2007	60 (30/30)	<i>Bifidobacterium</i> (subtype not available) with fructo-oligosaccharide (FOS) <i>vs</i> mix of vitamins	90 d	NH <sub>3</sub> ↓ Psychometric test: improved
<sup>1,2</sup> Bajaj <i>et al</i> <sup>[73]</sup>	2008	25 (17/8)	<i>Streptococcus thermophilus</i> , <i>Lactobacillus bulgaricus</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , and <i>Bifidobacteria</i> <i>vs</i> none	60 d	Psychometric test: improved
<sup>1,2</sup> Sharma <i>et al</i> <sup>[74]</sup>	2008	105 (70/35)	<i>Streptococcus faecalis</i> , <i>Clostridium butyricum</i> , <i>Bacillus mesentericus</i> , and <i>Lactic acid bacillus</i> with lactulose <i>vs</i> lactulose	30 d	NH <sub>3</sub> ↓ Psychometric test: improved
<sup>1,2</sup> Mittal <i>et al</i> <sup>[75]</sup>	2011 (2009)	160 (120/40)	VSL#3 (containing <i>Streptococcus thermophilus</i> , <i>Bifidobacterium breve</i> , <i>Bifidobacterium longum</i> , <i>Bifidobacterium infantis</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Lactobacillus paracasei</i> , <i>Lactobacillus bulgaricus</i> ) <i>vs</i> lactulose or placebo	3 mo	NH <sub>3</sub> (arterial) ↓
<sup>1</sup> Malaguarnera <i>et al</i> <sup>[76]</sup>	2010	125 (63/62)	<i>Bifidobacterium</i> (subtype not available) and FOS <i>vs</i> lactulose	60 d	NH <sub>3</sub> ↓ Psychometric test: improved
<sup>1</sup> Pereg <i>et al</i> <sup>[77]</sup>	2011	40 (20/20)	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus bulgaricus</i> , <i>Bifidobacterium bifidum</i> , and <i>Streptococcus thermophiles</i> (Bio-plus, Supherb, Israel) <i>vs</i> placebo	6 mo	NH <sub>3</sub> ↓
Agrawal <i>et al</i> <sup>[80]</sup>	2012	235 (157/78)	VSL#3 <i>vs</i> lactulose or none	> 3 mo	NH <sub>3</sub> (arterial) ↓ Psychometric test: improved Secondary prophylaxis of HE
Lunia <i>et al</i> <sup>[81]</sup>	2014	160 (86/74)	VSL#3 <i>vs</i> placebo	> 6 mo	NH <sub>3</sub> (arterial) ↓ Prevention of HE

<sup>1</sup>RCTs included in meta-analysis by McGee *et al*<sup>[78]</sup>; <sup>2</sup>RCTs included in meta-analysis by Holte *et al*<sup>[79]</sup>.

to patients treated with placebo or no intervention, but treatment with neither probiotics nor synbiotics did not significantly alter the clinically relevant outcomes (*i.e.*, mortality and quality of life). The trials had high risks of systematic and random errors, because each sample size was small and the dosing periods and quantities of the probiotics were different among the trials.

After those meta-analyses, Agrawal *et al*<sup>[80]</sup> reported a randomized trial examining the use of probiotics for the secondary prophylaxis of HE. The study assigned 235 patients who had suffered from HE previously, and the results showed that recurrent HE occurred in fewer patients who received probiotics or lactulose compared with no treatment (34% and 27%, respectively, *vs* 57%). There was no significant difference in recurrence rates between the patients who received probiotics and those who received lactulose. Lunia *et al*<sup>[81]</sup> reported preventive effects of probiotics on the development of HE in patients with liver cirrhosis who had not experienced overt HE. Patients who received the probiotics were less likely to develop overt HE compared to controls (1.2% *vs* 19%; HR = 2.1). These prospective trials indicate

that probiotics could be effective in preventing overt HE.

On the other hand, *Lactobacillus* GG AT strain 53103 (LGG), which is a well-studied probiotic with a published history of safety and efficacy in humans, was examined to evaluate its safety and tolerability in patients with minimal HE<sup>[82]</sup>. The trial showed that LGG was safe and well-tolerated in patients with cirrhosis and could cause reductions of the endotoxemia and TNF- $\alpha$  production seen in these patients<sup>[82]</sup>.

Among the various probiotics, the most efficacious species for HE appeared to be *Lactobacilli* and *Bifidobacteria*. However, additional prospective and randomized controlled trials are needed before these probiotics can be routinely recommended.

### Non-alcoholic steatohepatitis

NAFLD is characterized by the accumulation of triglyceride in hepatocytes in non-alcohol users. NAFLD can progress to more severe liver diseases, such as NASH<sup>[83,84]</sup>. It has been reported the NAFLD/NASH was associated with increased intestinal permeability and small bowel bacterial overgrowth, which could increase the production of proinflammatory cytokines

**Table 5 Randomized controlled trials for non-alcoholic steatohepatitis**

Ref.	Year	Sample size (treatment/placebo)	Treatment regimens	Duration	Favorable effects	Other information
<sup>1</sup> Aller <i>et al</i> <sup>[90]</sup>	2011	28 (14/14)	<i>Lactobacillus bulgaricus</i> and <i>Streptococcus thermophilus</i> vs placebo	3 mo	ALT ↓	Cardiovascular risk factors: NS
<sup>1</sup> Vajro <i>et al</i> <sup>[91]</sup>	2011	20 (10/10)	<i>Lactobacillus rhamnosus</i> strain GG vs placebo	8 wk	ALT ↓ PG-PS IgA ↓	Hepatorenal US ratio: NS
<sup>1</sup> Malaguamera <i>et al</i> <sup>[92]</sup>	2012	66 (34/32)	<i>Bifidobacterium longum</i> with fructo-oligosaccharides vs placebo	24 wk	ALT ↓ CRP ↓ TNF-α ↓ LDL-cholesterol ↓ Serum endotoxin ↓ HOMA-IR ↓ Steatosis ↓ NASH activity index ↓	
<sup>1</sup> Wong <i>et al</i> <sup>[93]</sup>	2013	20 (10/10)	<i>Lactobacillus plantarum</i> , <i>Lactobacillus deslbrueckii</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium bifidum</i> (The Lepicol probiotic formula) vs usual care	6 mo	AST ↓ Liver fat (IHTG) ↓	

<sup>1</sup>RCTs included in meta-analysis by Ma *et al*<sup>[94]</sup>. PG-PS: Peptidoglycan-polysaccharide; IHTG: Intrahepatic triglyceride content; NASH: Non-alcoholic steatohepatitis; NS: Not significant.

and contribute to the pathogenesis of NASH<sup>[85]</sup>. Several pharmacologic treatments for NAFLD/NASH have been reported, including insulin-sensitizers (*e.g.*, pioglitazone), antioxidants (*e.g.*, N-acetylcysteine, vitamin E), ursodeoxycholic acid, and anti-TNF-α agents, but a standard treatment has not been established<sup>[86]</sup>.

In animal models of NASH, treatments with probiotics such as VSL#3 improved the histological findings including reduced fat deposits and damage to the liver parenchyma, with decreasing serum alanine aminotransferase (ALT) levels<sup>[87,88]</sup>. VSL#3 also reduced oxidative and inflammatory liver damage in mouse NASH models<sup>[89]</sup>.

Several clinical trials of probiotics administered to patients with NAFLD have been reported. Loguercio *et al*<sup>[70]</sup> found that the administration of VSL#3 might reduce liver injury and improve liver function in NAFLD patients. Four relatively high-quality RCTs that evaluated the effects of probiotics in NAFLD patients were reported (Table 5)<sup>[90-93]</sup>. All four trials showed that probiotic therapy significantly decreased the serum levels of ALT, but only two of the trials revealed an improvement of liver steatosis, which was evaluated by repeated liver biopsies<sup>[92]</sup> or proton-magnetic resonance<sup>[93]</sup>. Ma *et al*<sup>[94]</sup> performed a meta-analysis of these four RCTs to assess the efficacy of probiotic therapies, and they found that the probiotic therapy significantly decreased the levels of aminotransferases, total-cholesterol, high-density lipoprotein (HDL) and TNF-α in the serum, and the homeostasis model assessment of insulin resistance. The lower levels of HDL in the probiotic-treated groups compared to the placebo groups was unexpected, and the mechanism is unclear. In two of the RCTs, probiotics were used with prebiotics in NAFLD patients, and the combination significantly reduced the patients' serum aminotransferase levels and liver steatosis.

*Lactobacillus*, *bifidobacterium*, and *streptococcus* are used as probiotics for patients with NASH, and prebiotics such as fructo-oligosaccharides (FOS) are frequently used with these probiotics because they can be fermented by *bifidobacteria* and *lactobacilli*<sup>[95]</sup>. FOS could contribute to *bifidobacteria* growth as the dominant species in the large bowel and reduce the growth of harmful bacteria<sup>[96]</sup>.

Although the above-described studies have several limitations including small sample sizes and a lack of data about the patients' diets and exercise, the treatments with probiotics and prebiotics for patients with NAFLD are promising.

### Alcoholic liver disease

The chronic consumption of alcohol induces various biological abnormalities including liver injury (ranging from fatty liver, liver fibrosis, and alcoholic hepatitis to liver cirrhosis), pancreatitis, impaired neutrophil functions, endotoxemia, and increased oxidative stress in the gut. Most of these abnormalities could be associated with altered gut microbiota, raising the possibility that probiotics would be effective for the improvement of these conditions.

In an open-label study with *Lactobacillus casei* Shirota<sup>[97]</sup>, patients with alcoholic cirrhosis who received the probiotic for 4 wk showed a restoration of neutrophil phagocytic capacity, possibly due to the decreased expression of TLR4 on the surface of these cells. In a mouse model fed an ethanol-containing diet, heat-killed *Lactobacillus brevis* (*L. brevis*) SBC8803 significantly decreased the serum levels of ALT and AST and the hepatic content of triglyceride and total cholesterol in the liver caused by ethanol, which may be associated with the up-regulation of TNF-α and sterol regulatory element-binding proteins in the liver<sup>[98]</sup>.

In a pilot study reported by Kirpich *et al*<sup>[99]</sup>, alcoholic patients who received *bifidobacteria* and

*Lactobacilli* for 5 d showed increased numbers of those bacteria in the gut, and they showed significantly lower AST and ALT activity in the serum, indicating that a short-term administration of probiotics can change the gut microbiota, leading to the amelioration of liver injury induced by chronic alcohol consumption. The therapeutic effect of probiotics could be due to a reduction in oxidative stress and inflammation in the intestine and liver and the preservation of gut barrier function<sup>[100]</sup>. *L. plantarum* was recently microencapsulated and administered to rats chronically fed alcohol<sup>[101]</sup>. The rats showed reductions in the levels of endotoxemia, serum aminotransferase, NF- $\kappa$ B, cytokines such as TNF- $\alpha$ , and IL12/p40, and they also showed improvements in the histology of the intestine and liver. Considering the greater survival of probiotics under gastric acidic conditions, this approach might be efficacious. However, the bacteria-free culture supernatant of *Lactobacillus rhamnosus* GG was proven to suppress the alcohol-induced intestinal permeability, endotoxemia and subsequent liver injury<sup>[102]</sup>. It thus remains uncertain whether the survival of probiotics is necessary for obtaining the optimal effect of treatment with probiotics.

## HCC

Most HCCs develop in the liver chronically infected by Hepatitis B or C virus. However, with the increasing prevalence of metabolic syndrome, the incidence of HCC from NASH has been increasing<sup>[103]</sup>. Although the mechanism of HCC development from NASH in association with dysbiosis of gut microbiota has been proposed as mentioned above, no therapeutic trials for the prevention of HCC in patients with NASH have been reported, to our knowledge. Reports of the therapeutic prevention of HCC using probiotics are limited to aflatoxin-induced HCC. In a clinical study, healthy but aflatoxin-exposed subjects were randomly assigned to two groups; one group received a mixture of *Lactobacillus rhamnosus* LC705 and *Propionibacterium freudenreichii* subsp. *shermanii* strains and the other received a placebo, and the groups' urinary excretions of aflatoxin-DNA adduct (aflatoxin B(1)-N(7)-guanine) were compared<sup>[104]</sup>. The results showed that the elevated urinary excretion of aflatoxin B(1)-N(7)-guanine was significantly decreased in the probiotics group but not in the controls, suggesting the inhibition of the intestinal absorption of aflatoxin B(1) by probiotics<sup>[104]</sup>. These data may also indicate that probiotics therapy could contribute to the inhibition of aflatoxin B-induced hepatocarcinogenesis. In a rat study examining the effects of probiotic fermented milk and chlorophyllin on the prevention of aflatoxin-induced hepatocarcinogenesis, the probiotics treatment reduced the expressions of c-myc, bcl-2, cyclin D1 and rasp-21, suggesting the protective potential of the probiotics in aflatoxin-induced hepatocarcinogenesis<sup>[105]</sup>.

## Surgical procedures

Probiotic and symbiotic therapies have been attempted to maintain liver function or prevent post-surgical infections in patients undergoing liver resection or liver transplantation.

Rayes reported a randomized double-blind study with a composition of four lactic acid bacteria (*Pediacoccus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 77:1, *Lactobacillus paracasei* ssp. *paracasei* F19, and *L. plantarum* 2362) and four fibers<sup>[106]</sup>. The treated group received probiotics for 15 d, and the control group received fibers only. The treated group showed less post-operative infections (3% in the treated group vs 48% in the control group) and needed shorter antibiotic therapy compared to the control group. Similar results were obtained in a study conducted in Japan<sup>[107]</sup> in which probiotics treatment reduced the perioperative infections in liver transplantation recipients from 24% to 4%. In another study, treatment with probiotics 3 d preoperatively and 7 d postoperatively was found to be efficacious for the better and faster recovery of liver functions<sup>[108]</sup>. These data suggest that perioperative probiotics or synbiotics may have significant benefits by reducing infections and by maintaining liver functions in patients undergoing liver resection or liver transplantation.

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