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**Gut microbiota and host metabolism in liver cirrhosis**

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**Abstract**

The gut microbiota has the capacity to produce a diverse range of compounds that play a major role in regulating

the activity of distal organs and the liver is strategically positioned downstream of the gut. Gut microbiota linked compounds such as short chain fatty acids, bile acids, choline metabolites, indole derivatives, vitamins, polyamines, lipids, neurotransmitters and neuroactive compounds, and hypothalamic-pituitary-adrenal axis hormones have many biological functions. This review focuses on the gut microbiota and host metabolism in liver cirrhosis. Dysbiosis in liver cirrhosis causes serious complications, such as bacteremia and hepatic encephalopathy, accompanied by small intestinal bacterial overgrowth and increased intestinal permeability. Gut dysbiosis in cirrhosis and intervention with probiotics and synbiotics in a clinical setting is reviewed and evaluated. Recent studies have revealed the relationship between gut microbiota and host metabolism in chronic metabolic liver disease, especially, non-alcoholic fatty liver disease, alcoholic liver disease, and with the gut microbiota metabolic interactions in dysbiosis related metabolic diseases such as diabetes and obesity. Recently, our understanding of the relationship between the gut and liver and how this regulates systemic metabolic changes in liver cirrhosis has increased. The serum lipid levels of phospholipids, free fatty acids, polyunsaturated fatty acids, especially, eicosapentaenoic acid, arachidonic acid, and docosahexaenoic acid have significant correlations with specific fecal flora in liver cirrhosis. Many clinical and experimental reports support the relationship between fatty acid metabolism and gut-microbiota. Various blood metabolome such as cytokines, amino acids, and vitamins are correlated with gut microbiota in probiotics-treated liver cirrhosis patients. The future evaluation of the gut-microbiota-liver metabolic network and the intervention of these relationships using probiotics, synbiotics, and prebiotics, with sufficient nutrition could aid the development of treatments and prevention for liver cirrhosis patients.

**Key words:** Liver cirrhosis; Microbiota; Metabolism; Fatty acids; Probiotics

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**Core tip:** The gut microbiota has the capacity to produce a diverse range of compounds that have a major role in regulating the activity of distal organs and the liver is strategically positioned downstream of the gut indicating the importance of the gut-liver axis. This review focuses on gut microbiota and host metabolism in liver cirrhosis. The serum lipid levels of phospholipids, free fatty acids, eicosapentaenoic acid, arachidonic acid, and docosahexaenoic acid have significant correlations with specific fecal flora in liver cirrhosis. Various blood metabolome such as cytokines, amino acids, and vitamins are correlated with gut microbiota in probiotics-treated liver cirrhosis patients.

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## INTRODUCTION

An increasing amount of recent evidence has demonstrated that several diseases, such as irritable bowel syndrome, inflammatory bowel disease, diabetes, allergy, cancer, obesity, autism and liver disease, are related to alterations in intestinal microbiota (known as dysbiosis)<sup>[1-3]</sup>. Gut-derived complications in liver cirrhosis such as small intestinal bacterial overgrowth and increased intestinal permeability (leaky gut), resulting in bacterial or endotoxin translocation-related systemic disorders such as spontaneous bacterial peritonitis, hyperdynamic state, portal hypertension, hepatorenal syndrome, hepatic encephalopathy, and multiple organ failure, have been reported in clinical settings<sup>[2,4-8]</sup>. Different etiologies of liver cirrhosis, including viral hepatitis, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD), have different gut microbiota and mechanisms of developing liver fibrosis. Furthermore, each disease has a different hepatic metabolism, suggesting further development in this research area<sup>[2,7-9]</sup>. However, there have been few reports of correlations between gut microbiota and host metabolism in cirrhotic patients. This review will discuss (1) the relationship between gut microbiota and host metabolism in general; (2) the results of intervention for liver cirrhosis by probiotics; and (3) gut-microbiota and host metabolism in cirrhosis and the use of systems biology as a tool for analysis.

## GUT MICROBIOTA AND HOST METABOLISM

The anatomy of the liver provides its close interaction with the gut<sup>[9,10]</sup>. Gut-derived bacteria and their components and metabolites, as well as nutrients

and other signals are delivered to the liver *via* the portal circulation. Then, the liver plays a crucial role in defense against gut-derived materials, which is defined as the gut-liver axis<sup>[9,10]</sup>. Gut microbiota function as a bioreactor for autonomous metabolic and immunological functions that can mediate responses within the host environment in response to external stimuli<sup>[11]</sup>. The complexity of the gut microbiota suggests that it behaves as an organ. Therefore, the concept of the gut-liver axis must be complemented with the gut-microbiota-liver network because of the high intricacy of the microbiota components and metabolic activities<sup>[11]</sup>.

The host and its gut microbiota coproduce a large array of small molecules during the metabolism of food and xenobiotics (compounds of non-host origin that enter the gut with the diet or are produced by microbiota), many of which play critical roles in communication between host organs and the host's microbial symbionts. The metabolite, gut microbiota, and potential biologic functions are shown in Table 1<sup>[12-40]</sup>.

Short-chain fatty acids (SCFAs), predominantly butyrate, acetate and propionate, are anaerobically produced by gut microbiota in the intestine. SCFAs, particularly butyrate, are a significant source of energy for gut enterocytes, and influence the gastrointestinal barrier function through the stimulation of tight junction and mucous production<sup>[41-43]</sup>. The authors showed that tight junction permeability was decreased by SCFAs in a Caco-2 intestinal monolayer and human umbilical vein endothelial cell monolayer, *via* lipoxygenase activation in *in vitro* studies<sup>[44,45]</sup>. This suggests that SCFAs may have biological effects in other organs as well as the gastrointestinal tract. Furthermore, there is growing evidence to suggest a role for SCFAs in reducing inflammation<sup>[41]</sup>. Our previous reports showed that increased pro-inflammatory cytokine production and nuclear factor kappa B activity induced by lipopolysaccharide (LPS) were downregulated by SCFAs using human peripheral blood mononuclear cells and co-culture of macrophages and adipocytes<sup>[46-48]</sup>. LPS-induced acute liver injury was attenuated by orally administered tributyrin, a prodrug of butyrate and a dairy food component, *via* increased portal vein concentration up to one to two orders of magnitude in rats<sup>[49]</sup>. In humans, two reports by Bloemen *et al.*<sup>[50,51]</sup> measuring portal and hepatic venous SCFA concentrations indicated a porto-systemic shunting effect in liver cirrhosis patients.

SCFAs are also proposed to increase satiety following the consumption of a diet rich in fiber as they act as agonists for free fatty acid receptors 2 and 3 (FFAR2/3 known as G-protein coupled receptor; GPR43/41). Both of these GPRs trigger the production and release of glucagon-like peptide 1 (GLP-1), peptide YY (PYY) and other gut hormones that stimulate satiety in the host<sup>[52]</sup>. Gut intestinal (GI) hormones such as ghrelin and leptin secretion are mediated on enteroendocrine cells by the action of SCFAs<sup>[18,53]</sup>.

Table 1 Metabolite, gut microbiota, and potential biologic functions

Metabolites	Related bacteria	Potential biological functions	Ref.
Short-chain fatty acids	Clostridial clusters IV and XIVa of <i>Firmicutes</i> , including species of <i>Eubacterium</i> , <i>Roseburia</i> , <i>Faecalibacterium</i> , and <i>Coprococcus</i>	Decreased colonic pH, inhibit the growth of pathogens; stimulate water and sodium absorption; participate in cholesterol synthesis; provide energy to the colonic epithelial cells; GI hormones secretion <i>via</i> enteroendocrine cells, implicated in human obesity, insulin resistance and type 2 diabetes, colorectal cancer. Immunological homeostasis in the gut	[14-18]
Bile acids	<i>Lactobacillus</i> , <i>Bifidobacteria</i> , <i>Enterobacter</i> , <i>Bacteroides</i> , <i>Clostridium</i>	Absorb dietary fats and lipid-soluble vitamins, facilitate lipid absorption, maintain intestinal barrier function, signal systemic endocrine functions to regulate triglycerides, cholesterol, glucose and energy homeostasis	[19-21]
Choline metabolites	<i>Faecalibacterium prausnitzii</i> , <i>Bifidobacterium</i>	Modulate lipid metabolism and glucose homeostasis. Involved in nonalcoholic fatty liver disease, dietary induced obesity, diabetes, and cardiovascular disease	[22,23]
Phenolic, benzoyl, and phenyl derivatives	<i>Clostridium difficile</i> , <i>F. prausnitzii</i> , <i>Bifidobacterium</i> , <i>Subdoligranulum</i> , <i>Lactobacillus</i>	Detoxification of xenobiotics; indicate gut microbial composition and activity; utilize polyphenols. Urinary hippuric acid may be a biomarker of hypertension and obesity in humans. Urinary 4-hydroxyphenylacetate, 4-cresol, and phenylacetate are elevated in colorectal cancer. Urinary 4-cresyl sulfate is elevated in children with severe autism	[24,25]
Indole derivatives	<i>Clostridium sporogenes</i> , <i>E. coli</i>	Protect against stress-induced lesions in the GI tract; modulate expression of proinflammatory genes, increase expression of anti-inflammatory genes, strengthen epithelial cell barrier properties. Implicated in GI pathologies, brain-gut axis, and a few neurological conditions	[26-28]
Vitamins	<i>Bifidobacterium</i>	Provide complementary endogenous sources of vitamins, strengthen immune function, exert epigenetic effects to regulate cell proliferation	[29,30]
Polyamines	<i>Campylobacter jejuni</i> , <i>Clostridium saccharolyticum</i>	Exert genotoxic effects on the host, anti-inflammatory and antitumoral effects. Potential tumor markers	[31,32]
Lipids	<i>Bifidobacterium</i> , <i>Roseburia</i> , <i>Lactobacillus</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Citrobacter</i> , <i>Clostridium</i>	Impact intestinal permeability, activate intestine-brain-liver neural axis to regulate glucose homeostasis; LPS induces chronic systemic inflammation; conjugated fatty acids improve hyperinsulinemia, enhance the immune system and alter lipoprotein profiles. Cholesterol is the basis for sterol and bile acid production	[33,34]
Neurotransmitters and neuroactive compounds: serotonin, tryptophan, kynurenine, dopamine, noradrenaline, GABA	<i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Escherichia</i> , <i>Bacillus</i> , <i>Saccharomyces</i> , <i>Candida</i> , <i>Streptococcus</i> , <i>Enterococcus</i>	Neurofunction related as mood, emotion, cognition, reward (CNS), motility/secretion and behavior	[35-39]
HPA hormones: cortisol	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Indirect regulation of HPA. Regulation of stress response, host metabolism, anti-inflammation, wound healing, endocrine abnormalities prominent in stress related psychiatric disorders	[40]

GI: Gastrointestinal; LPS: Lipopolysaccharide; GABA:  $\gamma$ -aminobutyric acid; CNS: Central nervous system; HPA: Hypothalamic-pituitary-adrenal. Adapted from Ref. [12, 13] and revised by the authors.

SCFAs that traffic to distal sites and can be carried by monocarboxylate transporters, which are abundantly expressed at the blood-brain barrier then enter the central nervous system<sup>[54-57]</sup>. However, it remains to be definitively established whether alterations in intestinal microbiota-derived SCFAs are actually reflected at physiologically relevant concentrations in the central nervous system<sup>[13]</sup>.

Bile is composed of individual bile acid moieties, mucous, phospholipids and biliverdin, and their main physiological roles in the small intestine are the emulsification of fats, the release of fat-soluble vitamins and regulation of cholesterol metabolism<sup>[58]</sup>. Specific bile acids differentially act as ligands to activate or repress host receptors, including farnesid X receptor, pregnane X receptor, vitamin D receptor and the GPR, TGR5. These receptors are expressed locally on various intestinal epithelial cells and systematically, within a diverse range of organs including both the liver and adipose tissue<sup>[21]</sup>. Therefore, bile acids function

as systemic signaling molecules and significantly alter host gene-expression profiles<sup>[21,59]</sup>.

Choline synthesized by intestinal biota is important for lipid metabolism and is metabolized to trimethylamine, then further metabolized in the liver to trimethylamine-N-oxide that contributes to the development of cardiovascular disease<sup>[22]</sup>. Reducing the bioavailability of choline can contribute to NAFLD and altered glucose metabolism<sup>[60]</sup>. Phenolic, benzoyl, and phenyl derivatives produced by the detoxification of xenobiotics have various bioactivities, are indicators of microbial composition and activity, and are useful biomarkers for several diseases including liver disease<sup>[25]</sup>.

A significant amount of the neurotransmitter dopamine is produced in the human gut<sup>[61]</sup>. Norepinephrine and dopamine production in the gut is mediated by the expression of  $\beta$ -glucuronidases from commensal gut bacteria through the cleavage of their inactive conjugated forms<sup>[62]</sup>. Nitric oxide produced by gut microbes plays a pivotal role in gastric emptying<sup>[63]</sup>. The

inhibitory transmitter  $\gamma$ -aminobutyric acid is generated by *Lactobacillus brevis* and *Bifidobacterium dentium*, both of which have been isolated from humans<sup>[64,65]</sup>. The precursors to neuroactive compounds, such as tryptophan for serotonin function and the kynurenine pathway, are controlled by gut-microbiota as a bidirectional communication component of the brain-gut axis<sup>[39]</sup>.

The role of gut microbiota in the development of the hypothalamic-pituitary-adrenal (HPA) axis has been extensively analyzed using germ-free mice<sup>[40]</sup>. The concept of Microbial Endocrinology was reported and the importance of controlling gut microbiota in relation with various host functions was discussed by Lyte and colleagues<sup>[13,66]</sup>.

## GUT MICROBIOTA AND ITS MANIPULATION IN LIVER CIRRHOSIS

The gut microbiota plays an important role in the pathophysiology of cirrhosis. Changes in gastrointestinal functions, including malabsorption and small intestinal bacterial overgrowth, is common with concomitant portal hypertension in cirrhosis patients<sup>[67]</sup>. Recent reviews reported the pathophysiologic changes of gut microbiota in cirrhotic patients, gut-bacterial interactions, "leaky gut", translocation of bacteria and gut-derived LPS in infectious complications, spontaneous bacterial peritonitis, and hepatic encephalopathy<sup>[2,5,68,69]</sup>. Hyperdynamic circulation, portal hypertension, hepatic encephalopathy, renal disturbance including hepatorenal syndrome, and cirrhotic cardiomyopathy in cirrhosis are correlated with endotoxemia<sup>[6]</sup>.

ALD is a spectrum of alcoholic diseases including steatosis, steatohepatitis, acute alcoholic steatohepatitis, alcoholic fibrosis, and cirrhosis (Laennec's Cirrhosis) caused by excessive alcohol use over a prolonged period of time<sup>[9]</sup>. Multiple pathogenic factors are involved in the development of ALD. Alcohol and its metabolites induce reactive oxygen species and hepatocyte injury through mitochondrial damage and endoplasmic reticulum stress<sup>[70,71]</sup>. The activation of Kupffer cells has been identified as a central element in the pathogenesis of ALD. Kupffer cells and recruited macrophages in the liver are activated by LPS through Toll-like receptor (TLR) 4, and LPS levels increase in the portal and systemic circulation after excessive alcohol intake<sup>[72]</sup>. Fibrosis is a dynamic and progressive process governed by stellate cell activation by LPS, TLR4 and inflammatory cytokines such as transforming growth factor- $\beta$  signaling<sup>[73]</sup>.

NAFLD is the most common cause of chronic liver disease worldwide as a result of the increasing prevalence of obesity, characterized by a spectrum of liver diseases ranging from simple fatty liver (NAFL) to steatohepatitis (NASH) with a possible progression to fibrosis<sup>[11]</sup>. The concept of the gut-liver

axis may be complemented with the gut-microbiota-liver network because of the high intricacy of the microbiota components and metabolic activities; these activities form the active diet-driven power plant of the host<sup>[11,74]</sup>. However, there have been few descriptive studies on gut-microbiota composition under NASH and NAFLD conditions; therefore, the type and role of gut microbes in human liver damage are poorly understood<sup>[11]</sup>. The use of meta-omic platforms to assist the understanding of NAFLD gut-microbiota alteration as a tool and its application in patients has been proposed<sup>[11]</sup>. A detailed explanation of the meta-omic platform is described later.

As for the therapeutic approach to control dysbiosis, selective digestive decontamination (SDD), probiotics, prebiotics, and synbiotics have been performed. SDD is a method to treat bacterial translocation-related complications caused by poorly absorbed antibiotics such as quinolone. SDD was effective in some studies but a major concern of long-term antibiotic prophylaxis is the development of antibiotic-resistant bacteria and increased infections in chronic disease situations<sup>[75]</sup>.

In this review, probiotics and synbiotics in liver cirrhosis are discussed. Probiotics were defined by the World Health Organization in 2001 as "live microorganisms, when administered in adequate amounts, confer a health benefit on the host". Prebiotics belong to a group of nondigestive food constituents that selectively alter the growth and/or activity of bacteria in the colon. The combined use of probiotics and prebiotics is called synbiotics. *Bifidobacteria* and *Lactobacilli*, the main species of probiotics, are considered as nonpathogenic to humans. The pathophysiologic basis for using probiotics in liver disease is as follows: (1) prevention of infection; (2) improvement of the hyperdynamic circulatory state of cirrhosis; (3) prevention of hepatic encephalopathy; (4) improvement of liver function; and (5) therapeutic potential of NAFLD<sup>[76]</sup>.

Infection, such as spontaneous bacterial peritonitis and endotoxemia, can be induced in compensated and decompensated cirrhotic patients with or without surgery. Rayes *et al.*<sup>[77,78]</sup> also reported the beneficial effects of probiotics against infectious complications in cirrhosis patients that underwent liver transplantation or liver resection. We reported that synbiotics (*Bifidobacterium*, *Lactobacillus*, and galactooligosaccharides) treatment attenuated the decrease in intestinal integrity as assessed by serum diamine-oxidase activity and reduced infectious complications after hepatic surgery<sup>[79]</sup>. Meta-analysis indicated an apparent reduction of infectious complications (odds ratio 0.24) in abdominal surgery<sup>[80]</sup>. However, a small size randomized controlled clinical trial showed that VSL#3<sup>®</sup> treatment to decompensated cirrhotic patients reduced plasma aldosterone, but did not reduce the incidence of spontaneous bacterial peritonitis<sup>[81]</sup>. As for hyperdynamic circulation, a prospective study reported that VSL#3<sup>®</sup> improved hemodynamic states, hepatic

**Table 2** Effects of the probiotics intervention on gut microbiota composition and its clinical and/or biochemical consequences

Type of study	Category of patients/duration of treatment	Probiotics	Clinical outcome	Ref.
RCT	36 cirrhotics/6 mo	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus bulgaricus</i> , <i>Bifidobacterium lactis</i> and <i>S. thermophilus</i>	Blood ammonia levels	[88]
RCT	65 cirrhotics/6 mo	<i>Lactobacilli</i>	Incidence of HE, hospital admission, plasma-ammonia level, serum bilirubin level	[83]
R	50 cirrhotics/14 d	<i>Bifidobacterium</i> , <i>L. acidophilus</i> and <i>Enterococcus</i> vs <i>Bacillus subtilis</i> and <i>Enterococcus faecium</i>	<i>Bifidobacterium</i> count, fecal pH, fecal and blood ammonia in both groups, endotoxin level only with <i>B. subtilis</i> and <i>E. faecium</i>	[89]
RCT	17 cirrhotics with HVPG > 10 mmHg/2 mo	VSL # 3 <sup>®</sup>	Plasma aldosterone	[81]
RCT	41 chronic liver disease/14 d	<i>Bifidobacterium bifidus</i> , <i>L. acidophilus</i> , <i>Lactobacillus bulgaricus</i> , and <i>S. thermophilus</i>	<i>E. coli</i> count, intestinal flora imbalance, improvement in debilitation, food intake, abdominal distension, and ascitic fluid	[90]
RCT	66 cirrhotics underwent liver transplantation/2 wk after the operation	<i>Pediococcus pentosaceus</i> , <i>Leuconostoc mesenteroides</i> , <i>Lactobacillus paracasei</i> and <i>Lactobacillus plantarum</i>	Infectious complication	[78]
RCT	39 cirrhotics/42 d	<i>E. coli</i> Nissle	Endotoxemia, Child-Pugh score, Restoration of normal colonic colonization	[91]
RCT	63 cirrhotics patients with large oesophageal varices without history of variceal bleeding/2 mo	Propranolol plus VSL # 3 <sup>®</sup>	HVPG, plasma TNF- $\alpha$ levels.	[92]
RCT	25 nonalcoholic minimal HE cirrhotics (defined by a standard psychometric battery)/60 d	Yogurt contained <i>L. bulgaricus</i> and <i>S. thermophilus</i>	Minimal HE	[93]
RCT	61 cirrhotics underwent hepatic surgery/2 wk before and after surgery	<i>Lactobacillus casei</i> strain Shirota, <i>Bifidobacterium breve</i> strain Yakult, and galactooligosaccharides	Intestinal integrity, infectious complication	[79]
RCT	63 cirrhotics underwent liver transplantation/12 d after the operation	<i>L. plantarum</i> 299 and oat fiber	Infectious complication	[77]
RCT	50 cirrhotics underwent living donor liver transplantation/2 d and 2 wk before and after the operation, respectively	<i>L. casei</i> strain Shirota, <i>B. breve</i> strain Yakult, and galactooligosaccharides	Infectious complication	[94]
RCT	30 cirrhotics with minimal HE/4 wk	<i>Lactobacillus</i> GG	Endotoxemia, gut dysbiosis, gut microbiome-metabolome linkages	[69]
RCT	138 cirrhotics/3 mo	VSL # 3 <sup>®</sup>	HE, small intestinal bacterial overgrowth	[84]

HE: Hepatic encephalopathy; HVPG: Hepatic venous pressure gradient; RCT: Randomized controlled trial; R: Randomized.

venous pressure gradients, cardiac index, heart rate, systemic vascular resistance, and mean arterial pressure, without any adverse reactions in cirrhosis patients with ascites<sup>[82]</sup>. Several reports showed that probiotics treatment to cirrhosis patients prevented hepatic encephalopathy with decreased blood ammonia or bilirubin levels<sup>[83,84]</sup>. The mechanism of hepatic encephalopathy prevention is the improvement of small intestinal bacterial overgrowth and gut dysbiosis<sup>[84]</sup>. VSL#3<sup>®</sup> treatment improved hepatic function, serum aspartate transaminase and alanine transaminase levels, both in NAFLD and cirrhosis patients with ALD and hepatitis C virus infection<sup>[85]</sup>. As for NAFLD, the immune-regulatory effects of probiotics may be beneficial in NAFLD treatment, and they should be considered a complementary therapeutic approach in NAFLD patients as indicated in a review by Ferolla *et al.*<sup>[86]</sup>. The mechanisms of action are increased fatty acid formation, change in colonic pH, growth factor induction, change in intestinal flora, bacterial adherence inhibition by colonization resistance, immune modulation, increased phagocyte

activity, increased IgA secretion and modulation of lymphocyte functions<sup>[87]</sup>.

Table 2<sup>[69,77-79,81,83,85,88-94]</sup> shows the main randomized controlled studies in cirrhosis patients. These reports suggest that probiotics treatment improved gut dysbiosis and bacterial translocation, leading to the improvement of cirrhosis prognosis. Trials with probiotics in general have been limited by a lack of stability of the products as a drug and differences among bacterial species and subspecies<sup>[93,95]</sup>. Therefore, the results have been heterogeneous with regard to the duration, type of organism or combination of organisms and outcomes, and mixed results been achieved. The properties of different probiotic species vary and can be strain-specific. This is also complicated by a lack of uniformity in batch-to-batch formulations and studies not being performed under an investigational new drug regulatory procedure. The variety of available probiotics also makes the accumulation of evidence difficult. Furthermore, a risk of bacterial sepsis and fungal sepsis should be considered in infants and immune-deficient patients<sup>[96]</sup>.

## GUT MICROBIOTA AND HOST METABOLISM IN LIVER CIRRHOSIS

The effect of gut microbiota on host metabolism has been reported in the context of host-gut microbiota metabolic interactions in dysbiosis related metabolic diseases (diabetes, obesity and chronic liver disease) as various obesity-associated mechanisms including insulin resistance, fibrosis, and abnormalities in lipid metabolism<sup>[8,86,97]</sup>. However, few studies on the association between gut microbiota and metabolism in cirrhosis have been reported.

We previously reported the measurement of fecal microbiota, organic acids, and plasma lipids in hepatic cancer patients in three different groups characterized by histopathology as normal liver, chronic hepatitis/liver fibrosis, and liver cirrhosis<sup>[46]</sup>. These data were obtained by fecal culture without using probiotics and by comparison among different liver diseases. The serum lipid levels of phospholipids, free fatty acids, eicosapentaenoic acid (EPA), EPA/arachidonic acid (AA) ratio, AA and docosahexaenoic acid (DHA) had significant correlations with specific fecal flora, such as *Bifidobacterium*, *Bacteroides*, *Lactobacillus*, *Enterococcus*, *Enterobacteriaceae*, and *Candida* (Figure 1). These correlations differed among the three groups suggesting that chronic liver disease itself modifies fatty acid metabolism induced by intestinal flora. These data indicate that the relationship between gut microbiota and host metabolism differs by metabolic activity of the liver, indicating that individual “the gut-microbiota-liver network” exists in each clinical disease entities and the importance to evaluate in future studies<sup>[11]</sup>.

With regards to polyunsaturated fatty acids, Wall *et al.*<sup>[98]</sup> performed a mouse study investigating the effects of *Bifidobacterium breve* NCIMB 702258 administration with coadministration of  $\alpha$ -linolenic acid on fatty acid composition of the liver, adipose tissues, large intestine and brain, and showed increased c9, t11 conjugated linoleic acid and EPA levels in the liver, while *Bifidobacterium* administration alone did not change the EPA levels in normal mice. Wall *et al.*<sup>[99]</sup> also demonstrated increased EPA levels in adipose tissues from severe combined immunodeficient mice after *Bifidobacterium breve* NCIMB 702258 administration. Conjugated linoleic acid is a microbial metabolite associated with the alleviation of NAFLD<sup>[100]</sup>. Kankaanpää *et al.*<sup>[101]</sup> reported the effects of 8 wk of *Bifidobacterium* Bb-12- or *Lactobacillus* CG-supplemented infant formula administration on the plasma fatty acid composition in infants. They found that *Bifidobacterium* decreased serum phospholipid EPA to 61% and AA levels to 77% compared with baseline values. In addition, *Lactobacillus* decreased EPA to 22% and AA to 62%. These reports described the effects of probiotics on host fatty acid compositions, but the results differed among the probiotics used and the host

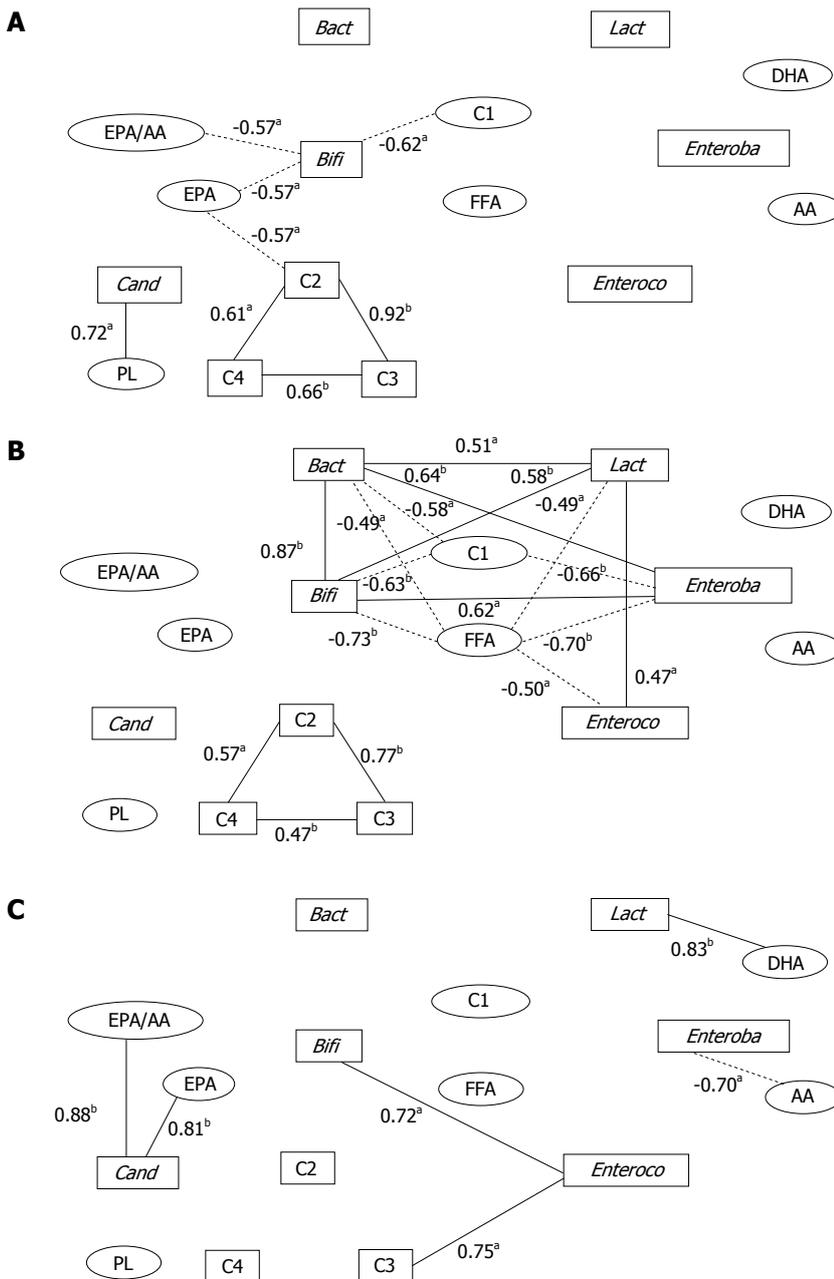
conditions. It was recently demonstrated that exposure of the human intestinal mucosa to *Lactobacillus plantarum* WCFSI induced the upregulation of genes in the intestinal mucosa involved in lipid/fatty acid transport, uptake and metabolism, such as CD36 and microsomal triglyceride transfer protein<sup>[102]</sup>. Several genes participating in mitochondrial and peroxisomal fatty acid metabolism were also upregulated<sup>[102]</sup>.

With regards to liver damage and metabolism in hepatitis C virus patients, hepatitis C virus genotype 3 infection perturbed glucose homeostasis through several direct and indirect mechanisms, leading to both hepatic and extrahepatic insulin resistance and accelerated disease progression including the development of hepatocellular carcinoma and type 2 diabetes<sup>[103]</sup>. Furthermore, changes in polyunsaturated fatty acids and lipid metabolism induced by hepatitis C core protein is thought to be involved in the pathogenesis of lipid metabolism disorders<sup>[102,104]</sup>. The administration of AA or EPA modulated the hepatitis C viral mechanism in hepatocytes<sup>[105]</sup>. Every step of the hepatitis C virus life cycle is intimately connected to lipid metabolism<sup>[106]</sup>.

Bajaj *et al.*<sup>[69]</sup> reported gut microbiota and serum/urine metabolome in a phase I randomized clinical trial using probiotic *Lactobacillus* GG (LGG) in patients with cirrhosis. They showed the safety and tolerance of 4 wk LGG administration in cirrhosis patients, which improved endotoxemia and gut dysbiosis. Furthermore, significant gut microbe-metabolome linkage was obtained by LGG as the results of system biology analysis. Figure 2 shows the correlation network among changed gut microbiota by LGG and metabolomic analysis. For example, a reduction in *Enterobacteriaceae* was associated with a linked change with anti-inflammatory cytokine IL-13 and ammoniagenic amino acids that was not seen in the placebo group. Changes in the levels of several vitamins in the blood were also observed following the co-administration of multivitamins with sufficient nutrition in both the LGG and placebo groups in their study.

Obesity-associated hepatocellular carcinoma was recently attributed to molecular mechanisms such as chronic inflammation caused by adipose tissue remodeling and pro-inflammatory adipokine secretion, ectopic lipid accumulation and lipotoxicity, altered gut microbiota, and disrupted senescence in stellate cells, as well as insulin resistance leading to increased levels of insulin and insulin-like growth factors. LPS, a pathogen-associated molecular pattern recognized by TLR4, initiated various inflammatory and oncogenic pathways to develop hepatocarcinogenesis and was enriched in the intestine of obese humans and rodents<sup>[97,107]</sup>.

The complexity of the gut microbiota could be revealed using a recent systems biology culturomics-based method, genomic- and metagenomic-based methods, and proteomic- and metabolomic-based

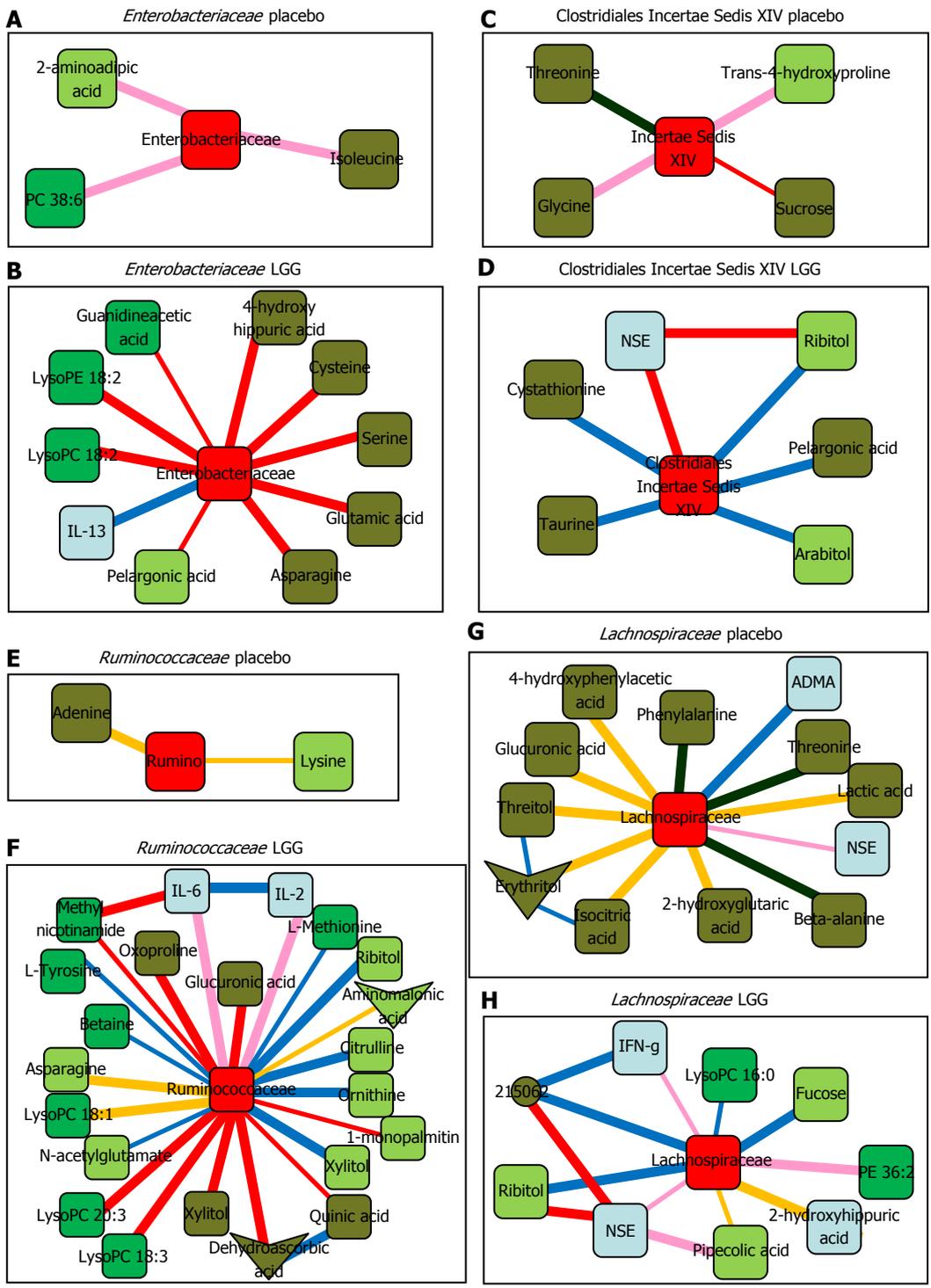


**Figure 1 Correlation networks among fecal microflora and organic acid and serum organic and fatty acid concentrations in hepatic cancer patients.** Square boxes indicate fecal components and ellipsoids indicate serum components. Solid lines indicate positive correlations and dotted lines indicate negative correlations. A: Normal liver group; B: Chronic hepatitis or liver fibrosis group; C: Liver cirrhosis group. <sup>a</sup>*P* < 0.05 and <sup>b</sup>*P* < 0.01 by Pearson's correlation coefficient test. *Bact*: Bacteroidaceae; *Bifi*: Bifidobacterium; *Lact*: Lactobacillus; *Enteroba*: Enterobacteriaceae; *Enteroco*: Enterococcus; *Cand*: Candida; C1: Formic acid; C2: Acetic acid; C3: Propionic acid; C4: Butyric acid; AA: Arachidonic acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; FFA: Free fatty acid; PL: Phospholipid. Data adapted from Usami *et al.*<sup>[46]</sup>.

methods<sup>[11]</sup>. Samples from the gut or other microbiota (e.g., feces and saliva) are assayed on solid media selective for axenic cultivation. Isolated microbial colonies are subjected to peptide extraction before matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF)-based mass-spectrometry processing and species identification by peptide fingerprinting in the culturomics-based method. After standardized DNA extraction and quality control protocols, metagenomic sequences from the microbiota are generated by prosequencing selected 16S rRNA

regions from microbial genomes by metagenomic-based methods. The detection of metabolites from samples such as feces, urine, blood, plasma and saliva, can be performed using metabolomic approaches including gas-chromatography mass spectrometry, proton nuclear magnetic spectroscopy (<sup>1</sup>H-NMR) and a liquid chromatography mass spectrometry in metabolomic-based method. These are recommended as platforms to understand further the gut-microbiota-liver metabolic network<sup>[11,108]</sup>.

This review highlighted recent studies that re-



**Figure 2** Sub-networks showing correlation network differences from baseline to week 8 in placebo and in *Lactobacillus* GG groups separately centered on selected bacterial taxa. Color of nodes: Blue, inflammatory cytokine; light green, serum metabolites; dark green, urine metabolites. Color of edges: pink, negative remained negative but there is a net loss of negative correlation; dark blue, negative changed to positive; yellow, positive remained positive but there is a net loss of positive correlation; red, positive to negative; dark green, complete shift of negative to positive; military green, complete shift of positive to negative. A, B: Sub-networks of correlation changes centered around *Enterobacteriaceae*; C, D: Sub-networks of correlation changes centered around Clostridiales Incertae Sedes XIV; E, F: Sub-networks of correlation changes centered around *Ruminococcaceae*; G, H: Sub-networks of correlation changes centered around Lachnospiraceae. NSE: Neuron-specific enolase; IL: Interleukin; IFN: Interferon; LysoPC: Lysophosphatidylcholine; LysoPE: Lysophosphatidylethanolamine; ADMA: Asymmetric dimethylarginine; Rumino: *Ruminococcaceae*. Data adapted from Bajaj *et al.*<sup>[69]</sup>.

ported an association between gut microbiota and host metabolism in cirrhosis. However, those reports mark the beginning of a new research area of the gut-liver axis. The liver is the central organ in host-

metabolism and future studies are important and will form a new research area in the setting of the gut-microbiota-liver metabolic network. Hopefully this will contribute to interventions for the development of

liver cirrhosis and related infectious and non-infectious complications including metabolic disturbances evoked by the gut-liver axis, especially in ALD, NAFLD and hepatocarcinogenesis.

## CONCLUSION

Gut microbiota can produce a diverse range of compounds that play a major role in regulating the activity of distal organs and the liver is strategically positioned downstream of the gut. We are gaining increased insight into the close relationship between the gut and the liver evoked by systemic metabolic changes. The evaluation of the gut-microbiota-liver metabolic network and the intervention of these relationships using probiotics, synbiotics, prebiotics with sufficient nutrition might aid the development of treatment and prevention for liver cirrhosis patients.

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