



Microbiota-based treatments in alcoholic liver disease

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Abstract

Gut microbiota plays a key role in the pathogenesis of alcoholic liver disease (ALD). Consumption of alcohol leads to increased gut permeability, small intestinal bacterial overgrowth, and enteric dysbiosis. These factors contribute to the increased translocation of microbial products to the liver *via* the portal tract. Subsequently, bacterial endotoxins such as lipopolysaccharide, in association with the Toll-like receptor 4 signaling pathway, induce a gamut of damaging immune responses in the hepatic milieu. Because of the close association between deleterious inflammation and ALD-induced microbiota imbalance, therapeutic approaches that seek to reestablish gut homeostasis should be considered in the treatment of alcoholic patients. To this end, a number of preliminary studies on probiotics have confirmed their effectiveness in suppressing proinflammatory cytokines and improving liver function in the context of ALD. In addition, there have been few studies linking the administration of prebiotics and antibiotics with reduction of alcohol-induced liver damage. Because these preliminary results are promising, large-scale randomized studies are warranted to elucidate the impact of these microbiota-based treatments on the gut flora and associated immune responses, in addition to exploring questions about optimal delivery. Finally, fecal microbiota transplant has been shown to be an effective method of modulating gut microbiota and deserve further investigation as a potential therapeutic option for ALD.

Key words: Alcoholic liver disease; Gut; Microbiota; Probiotics; Treatment

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Core tip: Alcoholic liver disease (ALD) brings about imbalance in the gut microbiota which results in deleterious immune responses that affect the liver. However, there is little research on therapy that targets this aspect of ALD pathophysiology. This review summarizes ALD-induced changes in gut microbiota and its associated inflammatory effects, and explores the gamut of latest research on microbiota-based treatments for ALD, which include probiotics, prebiotics, antibiotics, and fecal microbiota transplant.

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INTRODUCTION

The human gut microbiota is composed with trillions of bacteria which total 1-2 kg in mass. These microorganisms in the human gut, in maintaining a close relationship with the host, play an important role in promoting metabolism and digestion^[1,2]. Recent research has suggested that each person hosts a distinctive, personalized gut microbiota which may consist of *Bacteroides*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. However, a comprehensive understanding of the human gut microbiota and its variations across different geographical regions has yet to be established^[3]. Because the gut is connected to the liver by the portal tract, the disturbance of intestinal microbiota can lead to disease, especially in the liver. Indeed, a number of liver conditions, including alcoholic liver disease (ALD), have been associated with qualitative and quantitative changes in the gut microbiota^[4,5].

This review focuses on the ALD-induced changes in the intestinal microbiota and the concomitant immune responses that damage the liver. Further, novel therapeutic approaches such as probiotics are proposed for the management of ALD in promoting the reestablishment of gut homeostasis.

ALCOHOLIC LIVER DISEASE AND THE GUT-LIVER AXIS

ALD is one of the causes for chronic liver disease, which encompasses a wide spectrum of liver pathologies including steatosis, fibrosis, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma^[6,7]. Consumption of alcohol may induce small intestinal bacterial overgrowth (SIBO), particularly of Gram negative bacteria^[8]. Further, the damage caused by alcohol on the intestinal lumen results in the increased translocation of microbial

products, which include endotoxin, bacterial DNA, and pathogen-associated molecular patterns (PAMPs), from the gut to the liver. Toxic metabolites such as PAMPs, in turn, result in the triggering of the inflammatory cascade, and the induction of reactive oxygen species and other factors in various cells of the liver^[9,10]. Figure 1 depicts this process of alcohol consumption bringing about changes in the intestinal milieu and inducing consequent downstream immune responses in the liver. Expectedly, liver dysfunction has been observed to be closely associated with SIBO and the increased translocation of bacterial products^[11-14].

A potential clinical implication of advanced ALD in the gut-liver axis is the promotion of bacterial infections, often manifesting as subacute bacterial peritonitis, hepatic encephalopathy, or severe systemic infections^[15]. However, selective gut decontamination with rifaximin has been found to improve the conditions of patients with hepatic encephalopathy, highlighting the possible benefits of judicious antibiotic usage in treating conditions associated with advanced ALD^[16,17].

LIPOLYSACCHARIDE AND TOLL-LIKE RECEPTOR 4

Lipopolysaccharide (LPS), a bacterial endotoxin, plays a particularly integral role in the pathophysiology of ALD. Previous studies have revealed that levels of LPS are elevated in the plasma of both ALD patients and experimental animal models of ALD^[18,19]. Further, it has been seen that mice deficient in LPS receptor Toll-like receptor 4 (TLR4) or LPS co-receptor CD14 are resistant to alcohol-induced liver injury, underscoring the significance of LPS in context of ALD^[20,21]. It is worth noting that plasma endotoxin levels were not dissimilar between TLR4 deficient and wild type mice, which suggests that TLR4 signaling pathway is not involved in the modulation of gut leakiness.

As suggested above, TLR4 is also an important component in hepatic inflammation associated with ALD and, therefore, a brief discussion on TLR4 is merited. Toll receptors have gained attention in the immunology field when TLR4 was demonstrated to induce the expression of genes that mediate inflammatory responses^[22]. Additionally, a Tlr4 gene mutation in the mouse model was found to be hyporesponsive to LPS^[23]. Eventually, 10 proteins that are structurally similar to TLR4 were identified and classified under the TLR family^[24]. The physiological function of TLRs has been identified largely through genetic approaches; TLRs were soon identified as crucial components in the mammalian detection of microbial invasion, of which TLR-mediated recognition of specific pathogenic components is integral^[25].

In the context of ALD, it has been found that both chronic and acute alcohol consumption cause the expression of TLR4 and its co-receptors to in-

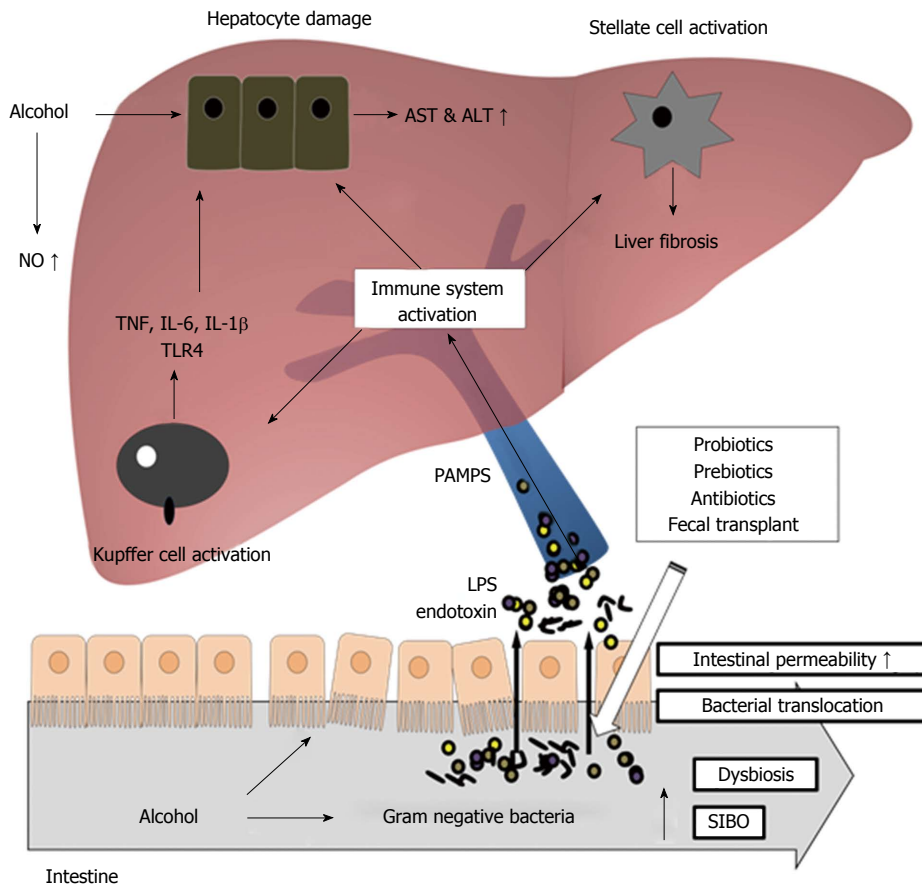


Figure 1 Mechanism of alcoholic liver disease. Consumption of alcohol leads to increased gut permeability, small intestinal bacterial overgrowth, and enteric dysbiosis. Increased translocation of microbial products to the liver via the portal tract induces a gamut of damaging immune responses in the hepatic milieu. The utilization of probiotics, prebiotics, antibiotics, or fecal microbiota transplant may promote the reestablishment of gut homeostasis, mitigating deleterious inflammation associated with ALD.

crease^[20,26-29]. As previously mentioned, TLR4 deficient mice were found to be protected from ALD, suggesting the key role of TLR4 in the pathogenesis of ALD^[30,31].

The TLR4 pathway is activated when LPS in portal and systemic circulation is initially bound by CD14 and LPS-binding protein (LBP), and the resultant complex binds to TLR4. The resulting signaling cascade causes the activation of Kupffer cells and multiple pro-inflammatory cytokines and, ultimately, the onset of alcohol-induced liver injury^[9,32-34]. The increased recruitment and activation of inflammatory cells and pro-inflammatory cytokines result in the modulation of hepatocyte function. Namely, liver cells respond to inflammation by the production of acute phase reactants, which include serum amyloid A, LBP, fibrinogen, C-reactive protein, and ceruloplasmin^[35-37]. One potential outcome of such LPS-induced alteration of hepatocyte function is cholestasis, in which the bile flow is decreased by impairment of hepatocytes^[38]. Other possible consequences include the exacerbation of alcohol-induced liver injury by the enhancement of LPS-induced signal transduction by LBP, an acute phase reactant, as confirmed in a study utilizing mouse model^[39]. Figure 1 summarizes the overall role of PAMPs, LPS, TLR4, and other immune components

in alcohol-induced damage to the liver.

Additionally to LPS, other bacterial products including bacterial DNA can also translocate from the intestine to other organs and extraintestinal space. Indeed, bacterial DNA was observed to be elevated in the plasma of ALD patients^[40]. Bacterial DNA, in turn, may be recognized by TLR9 which results in the sensitization of liver to injury induced by LPS^[41]. Summarily, translocation of bacterial products from the intestinal lumen to other organs such as the liver contribute significantly to the pathogenesis of ALD^[6].

In normal homeostasis, PAMPs such as LPS are scavenged by Kupffer cells and hepatocytes in the liver and are consequently metabolized^[42-44]. Nullification of LPS, in particular, is carried out by several possible mechanisms: first, molecules can bind to LPS, preventing it from activating TLR4. Alternately, enzymes can degrade the lipid A moiety of LPS, thereby decreasing the activity of the endotoxin^[45]. Still other mechanisms exist, including those involving serum lipoproteins and chylomicrons, resulting in the detoxification of LPS^[46-48].

In summary, a number of processes contribute to the clearance of LPS and prevent significant inflammatory cell activation. In the context of ALD,

however, LPS clearance by hepatocytes is found to be significantly impaired; it is unlikely that hepatocytes constantly exposed to alcohol retain the capability of detoxifying LPS^[49].

ALCOHOLIC LIVER DISEASE AND ENTERIC DYSBIOSIS

Chronic alcohol ingestion, in addition to causing intestinal overgrowth of bacteria, may also lead to enteric dysbiosis, in which the physiological composition of microbes becomes imbalanced^[50,51]. Several studies have demonstrated the role of heavy alcohol consumption in the breakdown of this balance. In mice, for instance, intragastric feeding of alcohol for three weeks led to the dominance of *Bacteroidetes* in the cecum, while in control mice, *Firmicutes* are the dominant species^[52]. In addition, *Akkermansia* and *Bacteroides* became more numerous, while *Lactobacillus* decreased in number^[52]. Further, in rats that underwent daily alcohol gavage for 10 wk, an alteration in the mucosa-associated microbiota composition was observed in the colon^[53].

In context of humans, consumption of excessive alcohol was also found to be associated with significant changes in microbial composition in the intestinal system. Namely, an increase of *Prevotellaceae* in the feces was observed for patients with alcoholic liver cirrhosis compared to healthy controls^[54]. On the other hand, a significant decrease of *Bacteroidaceae* was found for ALD patients when compared with the control group^[55]. Another study revealed that excessive alcohol consumption over long period leads to the reduction of *Bacteroidetes* and *Firmicutes*, and the elevation of Gram negative bacteria such as *Actinobacteria* and *Proteobacteria*^[56]. *Proteobacteria*, in particular, includes a number of pathogenic species such as *Salmonella*, *Vibrio*, *Helicobacter*, and *Escherichia*. A separate study also implicated increase of *Proteobacteria* and decrease of *Bacteroidetes*, specifically in the context of ALD patients^[4]. In a genetic study, it was demonstrated that the amount of *Enterobacteriaceae* bacterial DNA was increased in the feces of patients with ALD compared to those of the control group^[57]. Finally, in studying ascites from ALD patients, 50% of samples were found to contain *Enterobacteriaceae*, *Clostridium leptum*, or *Lactobacillus*^[57,58].

MICROBIOTA-BASED TREATMENTS IN ALCOHOLIC LIVER DISEASE

Immediate abstinence from alcohol is the most critical and effective treatment for patients with ALD^[59,60]. Abstinence was found to improve both the survival and prognosis of ALD patients; it can also stop the progression of disease to liver cirrhosis by bringing about histologic improvement and reduction

in portal pressure^[61,62]. As emphasized above, the pathophysiology of ALD has been found to be clearly linked with the overgrowth of intestinal bacteria. In addition, enteric dysbiosis has been demonstrated to be associated with ALD. Consequentially, reestablishing the balance of microbes through the administration of probiotics, prebiotics, antibiotics, or fecal microbiota transplantation (FMT) may be effective in preventing bacterial translocation and deleterious inflammatory responses that may result from ALD-associated changes in gut microbiota, and may forestall the progression of disease to serious conditions such as cirrhosis, fibrosis, or hepatocellular carcinoma^[63]. Therefore, further discussion on these microbiota-based treatments as potential therapy for ALD patients is merited.

Probiotics

Probiotics are defined as monocultures or mixed cultures of microorganisms that can be administered to potentially improve the properties of the gut microbiota. Specifically, probiotics promote an anti-inflammatory milieu in which the intestinal barrier integrity is upheld while bacterial translocation and endotoxin production are inhibited^[8]. Four potential mechanisms have been proposed through which probiotics bring about their beneficial effects^[64]: first, probiotic bacteria such as *Lactobacillus reuteri* may produce antimicrobial agents that suppress the growth, epithelial binding, and invasion of pathogenic bacteria^[65]. Second, probiotic bacteria may enhance intestinal barrier function by promoting intestinal epithelial cell survival and growth^[66]. Third, the immune system may be modulated to suppress the release of proinflammatory cytokines such as TNF- α ^[67] and to induce the release of protective cytokines such as IL-10^[68] and TGF- β . Finally, probiotic microorganisms may induce the expression of microopioid and cannabinoid receptors, conferring analgesic properties in the context of intestinal pain^[69].

In the clinical setting, the administration of probiotics has been demonstrated to be effective in reducing endotoxemia and improving liver function, a result observed in a study enrolling cirrhotic patients^[70]. These beneficial effects of probiotics have been further confirmed in larger study involving patients with alcohol-induced liver injury, in which a probiotic preparation containing *Bifidobacterium bifidum* and *Lactobacillus plantarum* was utilized^[71]. The reestablishment of microbiota balance through probiotics also has been shown to restore neutrophil dysfunction in patients with compensated alcoholic cirrhosis, in which *Lactobacillus casei* Shirota was administered^[72,73]. In another study enrolling alcoholic hepatitis patients, intake of *Lactobacillus subtilis* and *Streptococcus faecium* led to the reduction of gut-derived microbial LPS^[74], which, as discussed earlier, plays an integral role in the pathophysiology of ALD

Table 1 Microbiota-based treatment with probiotics in alcoholic liver disease - clinical trial

Patients	Enroll criteria or alcohol amount	Treatment	Results	Ref.
Compensated LC [alcohol: 22 (56.4%)] Age = 53 M/F = 1.8:1	Liver biopsy Biochemical study Endotoxin level Stool microbiota	<i>Escherichia coli</i> Nissle ($2.5\text{-}25 \times 10^9$ for 42 d)	<i>Lactobacillus</i> and <i>Bifidobacterium</i> sp. ↑ <i>Proteus hausei</i> and <i>Citrobacter</i> sp. ↓ <i>Morganella</i> sp. and endotoxemia ↓ improvement of liver functions	[70]
Alcohol-related psychosis [66 (73.3%)] Age = 42.3 ± 1.1	Consumed 750 mL of Russian vodka (40% ethanol, daily)	<i>Bifidobacterium bifidum</i> (0.9×10^8 CFU for 5 d) <i>Lactobacillus plantarum</i> 8PA3 (0.9×10^9 CFU for 5 d)	Bifidobacteria and Lactobacilli ↑ AST and ALT ↓	[71]
All males LC [alcohol: 12 (48%)] Age = 51.2 ± 1.8 M/F = 2:1	LC	<i>Lactobacillus casei</i> Shirota (19.5×10^9 CFU for 28 d)	Neutrophil phagocytic capacity ↑ sTNFR1 ↓ sTNFR2 ↓ IL10 ↓ TLR4 ↓	[72]
AH [60 (51.3%)] Age = 52.7 ± 11.3 M/F = 5.3:1	AST/ALT > 1 AST and ALT level ↑ Alcohol intake > 40 g/d for female > 60 g/d for male	<i>Lactobacillus subtilis</i> , <i>Streptococcus faecium</i> (1500 mg/d for 7 d)	Serum LPS level ↓ TNF-α ↓	[74]

LC: Liver cirrhosis; AH: Alcoholic hepatitis; ALT: Alanine transaminase; AST: Aspartate transaminase; IL: Interleukin; sTNFR: Soluble tumor necrosis factor; TNF: Tumor necrosis factor; M: Male; F: Female; LPS: Lipopolysaccharide; CFU: Colony forming unit.

(Table 1).

In two separate studies utilizing mouse, the efficacy of probiotics has been implicated directly in the context of ALD. When a probiotics diet consisting of *Lactobacillus rhamnosus* and *Lactobacillus acidophilus* was administered to mouse model of ALD for four weeks, TLR4 levels were found to be significantly lower in the probiotics group compared to the control group^[75,76]. The TLR4 pathway has been previously described as the central component through which ALD-induced changes in microbiota bring about eventual inflammatory responses that damage the liver. The study also demonstrated that the administration of probiotics led to the decrease in deleterious cytokines such as IL-1β and TNF-α^[75]; this result aligns with the finding that probiotics inhibit the TLR-4 pathway, which is known to induce release of pro-inflammatory cytokines (Table 2).

Other treatments

In addition to probiotics, other treatments such as prebiotics, antibiotics, and FMT might help promote the reestablishment of gut homeostasis, and also deserve attention as potential treatment options for ALD. Prebiotics are identified as ingredients that support the growth and activity of a selection of microbes in the gastrointestinal-tract, resulting in health benefits for the host^[77]. As complex carbohydrates that are not metabolized by pancreatic and intestinal enzymes^[52], prebiotics reach the large bowel and act as substrates for advantageous gut bacteria such as *Bifidobacteria* and *Lactobacilli*, which promotes the body's resistance to invading pathogens^[78]. In a study utilizing rats, the administration of prebiotics has been demonstrated to decrease the liver damage caused by alcohol^[79].

Further, in cirrhotic patients, prebiotics intake was found to be very effective in treating subclinical hepatic encephalopathy^[80]. Beyond this, however, studies that explore the potential effectiveness of prebiotics in the context of ALD are few and limited. Synbiotics, in which probiotics and prebiotics are synergistically co-administered^[81], also warrant study as potential treatment for ALD.

Antibiotics, on the other hand, are antimicrobials which may reduce the population of deleterious bacteria, decreasing the amount of LPS released and diminishing the associated inflammatory response. In a preliminary study involving a small number of ALD patients, treatment with antibiotics (*neomycin* and *norfloxacin*) led to an improvement in the Child-Pugh score, a measure of severity of chronic liver disease^[82]. As previously noted, *rifaximin*, a broad-spectrum antibiotic, has been administered to treat hepatic encephalopathy and was found to improve not only the prognosis of patients^[16] but also cirrhosis-related thrombocytopenia^[83]. The latter finding might be related to the reduction of endotoxemia resulting from intestinal decontamination, and highlight the therapeutic potential of antibiotics in treating ALD (Table 3).

Finally, FMT refers to the transfer of fecal material, which contains the microflora of a healthy individual, to a diseased recipient^[84]. The main mechanism of FMT likely involves the establishment of non-pathogenic bacterial strains in the gut and production of the antimicrobial components (*e.g.*, bacteriocins) produced by these microbes^[84]. When FMT was first introduced to the medical community, it understandably attracted both interest and significant controversy. However, FMT is becoming increasingly accepted as a legitimate and

Table 2 Microbiota-based treatment in alcoholic liver disease - animal studies

Animal model	Alcohol amount	Treatment	Results	Ref.
6-wk-old male 10 C57BL/6 mice	Lieber-DeCarli liquid diet with 10% alcohol for 6 wk	<i>Lactobacillus rhamnosus</i> R0011, <i>Lactobacillus acidophilus</i> R0052 (1 mg/mL per day for 4 wk)	TLR-4 ↓ IL-1β ↓	[75]
4-wk-old male 20 C57BL/6 mice (10 Normal diet, 10 High-fat diet)	Oral administration 5 g/kg per day, twice/wk, for 9 wk	<i>Lactobacillus rhamnosus</i> R0011, <i>Lactobacillus acidophilus</i> R0052 (1 mg/mL per day for 2 wk)	In normal diet groups TNF-α ↓ IL-1 ↓ TLR4 ↓ TLR4/GADPH ↓	[76]
Male Sprague-Dawley rats	Dose gradually increased every 2 to 3 d up to a maximum of 8 g/kg per day by 2 wk 6 g/kg per day for final 10 wk	Oats (10 g/kg per day)	In high-fat diet groups: IL-10 ↑ Tight junctions in colon ↓ Disorganization of actin cytoskeleton ↓ Oxidative stress ↓ NO overproduction ↓ Oxidative tissue damage ↓ Nitrotyrosine ↓ Carbonyl ↓	[79]

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; IL: Interleukin; NO: Nitrooxidative; TLR: Toll-like receptor; TNF: Tumor necrosis factor.

Table 3 Microbiota-based treatment with prebiotics and antibiotics in alcoholic liver disease-clinical trial

Patients	Enroll criteria or alcohol amount	Treatment	Results	Ref.
HE [alcohol 140 (46.8%)] Age = 56 ± 10 M/F = 1.2:1	≥ two episodes of overt HE (Conn score ≥ 2) LC (MELD ≤ 25)	Rifaximin (1100 mg/d, for 6 mo)	Episode of encephalopathy ↓ (HR = 0.42)	[16]
LC with subclinical HE [alcohol 36 (48%)] Age = 62.0 ± 7.3 M/F = 1.2:1	Psychometric tests -Trail making test A -Wechsler adult intelligence scale -Symbol digit -Block design tests	Lactulose (45 mL/d for 8 wk)	Number of the abnormal psychometric test ↓ Prevalence of subclinical HE ↓	[80]
LC [alcohol 12 (35.3%)] Age = 57.6 M/F = 0.8:1	Laboratory investigations -Liver biopsy -Endoscopy	Norfloxacin (800 mg/d) Neomycin (1500 mg/d) alternating periods of 15 d for 6 mo	Small-intestinal motor activity ↑ Transit time ↓ Small intestinal bacterial overgrowth ↓ Child-Pugh Score ↓	[82]
TC [alcohol 13 (56.5%)] Age = 58 ± 3 M/F = 11.5:1	For LC -Liver biopsy -Laboratory findings For hematological indices -Platelet count ≤ 150000/μL	Rifaximin (1200 mg/d, for 4 wk)	Platelet count ↑ Endotoxin ↓ IL-1 ↓ IL-6 ↓ TNF-α ↓	[83]

HE: Hepatic encephalopathy; IL: Interleukin; LC: Liver cirrhosis; PT: Patient; TC: Thrombocytopenic cirrhosis; TNF: Tumor necrosis factor.

effective therapeutic approach in addressing various conditions characterized by microbiota imbalance; for instance, FMT has been found to be highly valuable in treating ulcerative colitis, in which FMT successfully modulated the gut microbiota and minimized colonic inflammatory responses^[85]. Other studies also highlight the potential of FMT in addressing both gastrointestinal and non-gastrointestinal diseases in which therapeutic modulation of gut microbiota might be beneficial^[86,87]. However, despite showing promise as a cost-effective method of promoting gut homeostasis, FMT has not yet been studied as a potential therapeutic option for ALD.

CONCLUSION

Changes in gut microbiota are an important factor in the pathogenesis of ALD and can be considered a novel therapeutic target for ALD. Thus far, a number of preliminary studies have been carried out to evaluate the effectiveness of probiotics, prebiotics, and antibiotics in modulating the gut flora and treating ALD patients. In both clinical and non-clinical settings, the administration of probiotics has been found to be effective in reducing harmful immune responses and improving liver function in the context of ALD. However, to confirm these results, randomized clinical

trials of large sample size are necessary to further elucidate the role of probiotics in the treatment of ALD. In addition, questions on which patient population should be treated and which bacterial strains should be utilized need to be answered before probiotics gain widespread acceptance as clinical therapy for ALD.

While research on the efficacy of prebiotics and antibiotics in treating ALD is limited, prebiotics have been associated with reduction of alcohol-induced liver damage in rats and antibiotics have been implicated in improving the conditions of ALD patients. In consideration of these promising results, these approaches warrant further clinical studies to clarify their impact on the gut flora and associated immune responses. Synbiotics, which combine prebiotics and probiotics synergistically, also remain as an interesting area of exploration for the treatment of ALD.

Recently, FMT has gained attention as an effective method of addressing the imbalance of gut microbiota, which is associated with various medical conditions. FMT should be explored as a potential therapeutic approach for ALD. In addition to evaluating the efficacy of FMT in improving symptoms associated with ALD, investigation is required for unsolved questions on protocol, which include the route of administration, the optimal time of delivery, and the most effective amount of microflora. Finally, long-term clinical benefits and the safety of FMT should be evaluated in a clinical setting involving a large number of randomized ALD patients.

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