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REVIEW

Gut microbiota in alcoholic liver disease: Pathogenetic role and therapeutic perspectives

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Abstract

Alcoholic liver disease (ALD) is the commonest cause of cirrhosis in many Western countries and it has a high rate of morbidity and mortality. The pathogenesis is characterized by complex interactions between metabolic intermediates of alcohol. Bacterial intestinal flora is itself responsible for production of endogenous ethanol through the fermentation of carbohydrates. The intestinal metabolism of alcohol produces a high concentration of toxic acetaldehyde that modifies gut permeability and microbiota equilibrium. Furthermore it causes direct hepatocyte damage. In patients who consume alcohol over a long period, there is a modification of gut microbiota and, in particular, an increment of Gram negative bacteria. This causes endotoxemia and hyperactivation of the immune system. Endotoxin is a constituent of Gram negative bacteria cell walls. Two types of receptors, cluster of differentiation 14 and Toll-like receptors-4, present on Kupffer cells, recognize endotoxins. Several studies have demonstrated the importance of gut-liver axis and new treatments have been studied in recent years to reduce progression of ALD modifying gut microbiota. It has focused attention on antibiotics, prebiotics, probiotics and synbiotics.

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Key words: Alcoholic liver disease; Bacterial translocation; Dysbiosis; Prebiotics; Probiotics; Synbiotic; Gut microbiota; Endotoxin

Core tip: A close anatomical and functional relationship between gut and liver exists. Blood circulated in the portal vein transfers various toxic compounds for filtration by liver. Endotoxin is a lipopolysaccharide derived from the cell wall of Gram negative bacteria presents in the intestine, which is absorbed from intestinal epithelium and transported to the liver and Kupffer cells through the portal vein. A qualitative (dysbiosis) and quantitative (bacterial overgrowth) alteration of intestinal microbiome are the causes of an increase of endotoxins and subsequently, liver damage. The new treatments try to contrast dysbiosis and bacterial overgrowth decreasing evolution of alcohol liver disease.

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INTRODUCTION

Alcoholic liver disease (ALD) is the cause of a high rate of morbidity and mortality worldwide. It is the common-

est cause of cirrhosis in many Western countries[1]. It accounted for 3.8% of all deaths in 2004[2]. ALD consists of several types of disease such as fatty liver (steatosis), steatohepatitis, fibrosis, cirrhosis and ultimately hepatocarcinoma (HCC). Steatosis is reversible with alcohol abstention, but it is considered a risk factor for progression to fibrosis and cirrhosis[3,4].

The metabolism of alcohol is also regulated by intestinal bacteria ("bacteriocolonic" metabolism of ethanol). In 1984 Bode *et al*[5] demonstrated a qualitative and quantitative significant difference between flora in people with alcoholism and gut microflora of a control group. Intestinal homeostasis is influenced by several factors such as gut motility, gastric acidity, immunological defence factors, bile salts, and colonic pH[6].

The liver strategic position confers it with the important role of translating physiological and pathological processes within the gastrointestinal tract into metabolic and immunologic outcomes[7].

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE

Alcoholic steatohepatitis (ASH) and severe ALD occur in approximately 30% of heavy drinkers[8]. The pathogenesis of ALD is a dynamic and unknown process characterized by several interactions that involve the immune system and metabolic intermediates of alcohol. The poor understanding of these interactions contrasted with the progress in developing specific treatments for ALD[9-11]. Ethanol metabolism-associated oxidative stress, abnormal methionine metabolism, ethanol-mediated induction of leakage of gut endotoxins, and activation of Kupffer cells are all involved in the pathogenesis of ALD[12-14].

The fermentation of carbohydrates made by bacterial intestinal flora is itself responsible for production of endogenous ethanol. This is strongly enhanced in the presence of gut dysmotility (*e.g.*, from obesity, diabetes, or chronic alcohol use) or an excess of carbohydrates in the diet[15]. The intestinal oxidation of alcohol results in increasing concentrations of acetaldehyde[16,17], the first and most toxic product of ethanol metabolism responsible for alteration of intestinal permeability (gut leakiness) and microbiota homeostasis.

Apart from the liver, several organs contribute to ethanol metabolism resulting in acetaldehyde production, such as the pancreas, gastrointestinal tract, heart and brain[18-20]. Acetaldehyde is produced by bacterial alcohol dehydrogenase[21] and metabolised by aldehyde dehydrogenase in the colon[22]. In a recent study Kwon *et al*[23] evaluated the role of aldehyde dehydrogenase 2 deficiency in mouse in the progression of alcohol liver disease. They showed the role of acetaldehyde in hepatic inflammation and fibrosis.

Acetaldehyde is itself responsible for mitochondrial dysfunction and altered acetaldehyde metabolism that leads to its accumulation. It determines direct hepatocyte damage forming adducts with proteins and DNA by the interactions with amino, hydroxyl, and sulfhydryl groups[24]. Acetaldehyde is also responsible for increased paracellular intestinal permeability because of a redistribution of tight junction proteins (occluding and ZO-1) and adherent junction (E-cadherin and β-catenin) proteins inhibiting their phosphorylation by protein tyrosine phosphatase[25-27] (Figure 1).

The leakiness of gut activates the transcription of nuclear factor kappaB (*NF-κB*) gene and over-expression of nitric oxide (NO) synthesis.

NO is synthesized from *L*-arginine by nitric oxide synthases (NOS). Three isoforms of nitric oxide synthases exist: neuronal NOS (nNOS), endothelial NOS (eNOS), defined as constitutive NOS (cNOS), and inducible NOS (iNOS)[28]. NO production by cNOS is responsible for epithelial cell barrier integrity[29,30]. Otherwise NO produced by iNOS occurs in inflammation and it may contribute to aggravate integrity of the intestinal barrier[31].

iNOS is expressed in endothelial cells, hepatocytes, macrophages, neutrophils, and many other cell types[32]. An increased expression of iNOS and consequent production of NO is responsible for an augmented nitration and oxidation of tubulin. This leads to a decreased stability of tubulin and damage of the microtubule cytoskeleton with disruption of barrier function. Besides, the increased synthesis of NO results in oxidative stress in hepatocytes[33,34].

Epidermal growth factor (EGF) contrasts this process, promoting growth and differentiation of gastrointestinal mucosa. EGF stabilizes the cytoskeleton through down regulation of activity of iNOS[35,36].

INTESTINAL MICROFLORA

The intestinal microflora changes after fetal development and the major changes occur after weaning[37]. The microbiota is composed by more than 500 species of bacteria; some of them are fixed in the intestine, while the others only pass through the intestine[38]. According to the study by Neish, 109 CFU/mL and 1012 CFU/mL of bacteria may be found, respectively, in the terminal ileum and colon. Gram negative bacteria and anaerobes are dominant species in the intestinal lumen which are estimated to be 100 to 1000 times more than aerobic ones. *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus*, *Clostridium* and *Escherichia coli* (*E. coli*) are the most frequent ones[39]. The intestine also provides residence to more than 15 species-level bacteria phylotypes and in a healthy state they have a symbiotic relationship with its host. However, in each person, the pattern of the microorganism population is unique and different[40] (Table 1).

There is a close anatomical and functional relationship between the gut and the liver known as the gut-liver axis and in patients with liver cirrhosis, the intestinal balance is compromised.

Blood circulating in the portal vein transfers various toxic compounds such as bacteria and their derivatives

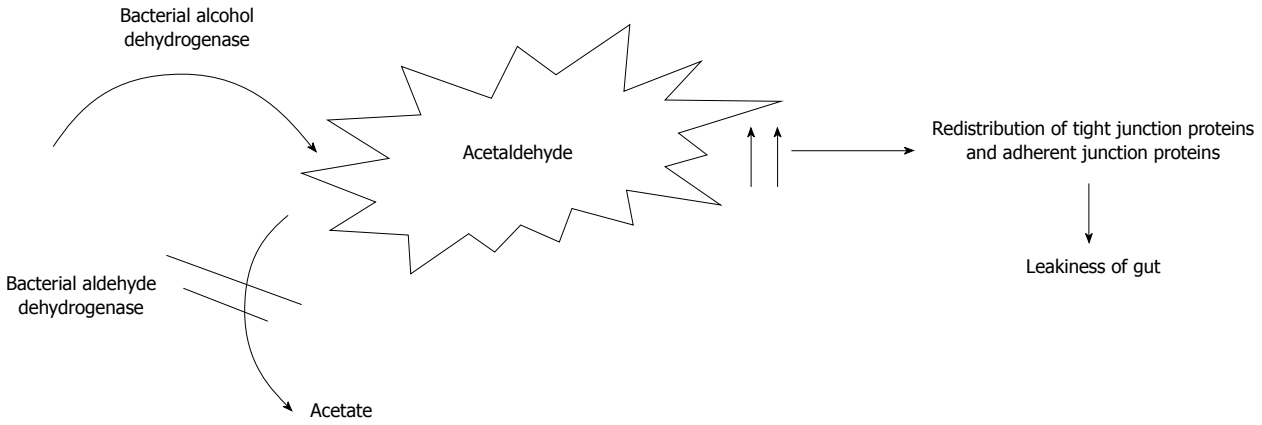

Figure 1 Metabolism of alcohol.

Table 1 Intestinal microbiota in the gastrointestinal compartments

Gastrointestinal tract	Microbiota
Oesophagus	*Streptococcus, Prevotella, Veilonella*
Stomach	*Streptococcus, Staphylococcus, Lactobacillus, Helicobacter pylori*
Duodenum	*Streptococcus, Staphylococcus, Lactobacillus, Helicobacter pylori, Veilonella, Yeasts*
Jeiunum	*Streptococcus, Staphylococcus, Lactobacillus, Helicobacter pylori, Veilonella, Yeasts*
Ileum	*Bifidobacterium, Bacteroides, Veilonella, Clostridium, Enterobacteriacea*
Colon	*Bacteroides, Bifidobacterium, Clostridium, Streptococcus, Ruminococcus, Peptostreptococcus, Eubacterium, Faecalibacterium*

(ethanol, ammonia, and acetaldehyde) for filtration by liver and modulates Kupffer cells activity and cytokine production. The increase of pathogen-associated molecular patterns and accumulation of metabolites in the liver can cause the liver harm. In return, the liver secretes bile acids to the intestine and modulates its activities[41].

Alterations in the type and amount of microorganisms are important elements in the dysfunctions of the liver; in fact liver disease causes quantitative (bacterial overgrowth) and qualitative (dysbiosis) changes in the intestinal microflora[42].

Dysbiosis is the alteration of intestinal homeostasis. Several studies have shown the role of continuous ethanol assumption in the breakdown of this balance. Bull-Otterson *et al*[43] studied the temporal effects of chronic ethanol consumption on commensally intestinal bacteria in a mouse model. They demonstrated that alcohol consumption over a long period elevates the growth of Gram negative bacteria and causes a decrease of both *Bacteriodetes* and *Firmicutes*, and an increase of *Actinobacteria* and *Proteobacteria*. *Proteobacteria* are Gram negative bacteria and include several pathogenic species such as *Salmonella*, *Helicobacter*, *Vibrio* and *Escherichia*, one of the main bacteria in the gut. Similar results were obtained by Mutlu *et al*[44]. They noted higher levels of *Proteobacteria* and lower abundance of *Bacteroidetes* in subjects with chronic alcohol consumption.

The breakdown of microbiota balance is responsible for different negative consequences (endotoxemia, translocation of lipopolysaccharides) that leads to hyperactivation of the immune system.

LPS is a constituent of the wall of Gram-negative bacteria[45] which induces macrophages to release proinflammatory cytokines, such as IL-1β and tumour necrosis factor (TNF)[46].

Endotoxin is a LPS, a component of the outer membrane Gram negative bacteria present in the gut. Generally only a little part of endotoxin is absorbed from the intestinal epithelial lining reaching the liver and the Kupffer cells inside the portal vein. In chronic alcohol consumption, bowel flora releases a bigger amount of endotoxins, responsible for the altered intestinal barrier and activation of the inflammatory process that leads to the progression of ALD[47], cirrhosis and HCC[48].

Hyper-permeability of the intestine following alcohol consumption leads to endotoxemia, which is filtrated by the liver and triggers the proinflammatory pathways for causing ASH.

Endotoxemia is responsible for elevated plasma levels of LPS-binding protein (LBP). The augmentation of endotoxins can prime and activate both hepatic and extra hepatic macrophages to overproduce inflammatory cytokines such as TNF-α, IL-6, IL-1 and IL-8[12].

Systemic endotoxemia and the cytokines produced in the inflammatory process increase intestinal permeability altering tight junctions. This leads to endotoxins passing into the circulation, creating a vicious cycle[49,50].

ALD also results in quantitative alterations of the intestinal microbioma. The small intestinal bacterial overgrowth (SIBO) is another cause of bacterial translocation.

To make a diagnosis of SIBO, it is necessary to find $\geqslant 1 \times 10^3$ bacteria (*i.e.*, CFU) per mL of proximal jejunal aspiration[51]. Bacterial overgrowth is advantaged by intestinal stasis that permits the proliferation of coliform bacteria[52]. Therefore, the bacteria generally recognized as SIBO are gram negative aerobes and anaerobes such as *E. coli*, *Enterococcus* spp. and *Proteus mirabilis*[53,54]. The main

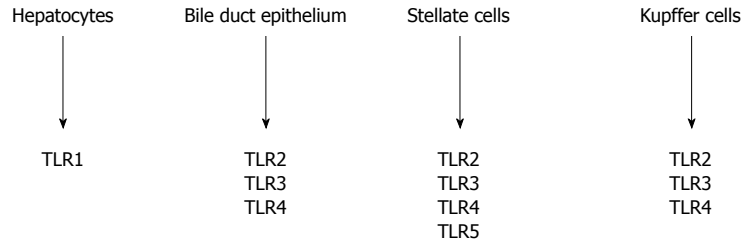

Figure 2 Liver cell types and their receptors. TLR: Toll-like receptor.

causes of SIBO are gastric achlorhydria, gastrocolic or coloenteric fistula and small intestine motility disorder[52]. Ethanol decreases intestinal motility which favours proliferation of luminal bacteria[16].

ROLE OF THE IMMUNE SYSTEM

Chronic ethanol consumption has been associated with immune suppression and increased morbidity and mortality[55]. Alcohol ingestion alters both the innate and adaptive immune system.

Ethanol increases the susceptibility of the gastrointestinal tract to bacteria through the suppression of natural killer cell activity and antibody-dependent cell-mediated cytotoxicity by lymphocytes[56,57].

The host immune system has an important role in the defence of the intestine. Several molecules are responsible for the limited expansion of pathogenic microorganisms, such as reactive oxygen species, IgA, β-defensins and cryptidins[39,58]. The innate immune system is also composed by Toll-like receptors (TLRs) that recognize specific pathogen-associated molecular patterns (PAMPs) such as LPS, lipoteichoic acid, peptidoglycan, unmethylated DNA and double-stranded RNA[59].

In humans 10 TLRs have been recognized. Multiple cells in the liver express significant levels of multiple TLRs and have long been recognized to be critical determinants in the pathogenesis of cirrhosis[60,61]. Every type of liver cell expresses specific TLR: TLR1 was found in hepatocytes, TLR2, 3, and 4 in stellate cells, bile duct epithelium and particularly in Kupffer cells. Bile duct epithelium expresses TLR5 too (Figure 2).

Endotoxins produced in the body cause an inflammatory reaction, activating Kupffer cells through their link with two types of receptors, cluster of differentiation 14 (CD-14) and TLR-4. These receptors are both essential to determine liver injury, but they present different structures. CD-14 is a surface receptor without a cytoplasmic domain, while TLR4 is a transmembrane protein with a cytoplasmic domain that can be associated with a soluble protein, MD-2, through a not covalently link.

CD14 binds LPS and this complex is recognized by TLR4. CD14 also has a soluble form that facilitates the transfer of LPS to the TLR4/MD-2 receptor complex[62]. The association between LPS and CD14 is facilitated by a soluble shuttle protein, LPS-binding protein (LBP)[63].

LPS recognition by TLR4 on macrophages and other cell types in the liver determines activation of downstream signaling pathways responsible for activation of transcription factors such as NF-κB and activator protein-1 (AP-1). This process causes an increased inflammatory cytokine production such as interferon gamma (IFNγ), TNF-α, interleukin-6 (IL-6), IL-1, chemokines and reactive oxygen species[64,65].

Furthermore LPS/TLR4 promotes fibrogenesis by sensitizing hepatic stellate cells (HSCs). The sensitised HSCs induce NF-κB activation, up-regulate gene expression of some chemokines (IL-8 and monocyte chemoattractant protein-1) and promote transforming growth factor beta (TGFβ) release by Kupffer cells[66]. The activated TLRs can enroll adapter molecules like myeloid differentiation factor-88 (MyD88)[67].

The CD14/TLR4 receptor complexes activate MyD88 dependent and MyD88 independent pathways that modulate survival and replication of apoptosis cells[68]. Furthermore, the MyD88-signaling pathway leads to production of oxidative stress and pro-inflammatory cytokines that causes hepatocellular damage[69-71].

The effects of alcohol are exerted on organs different from liver too. Blanco *et al*[69,70] demonstrated the role of ethanol in neuroinflammation. They showed that ethanol can directly induce downstream iNOS expression and activation of NF-κB through the translocation of TLR4 into lipid rafts. The activation of NF-signalling is also determined by acetaldehyde[71].

TREATMENT

Abstinence from alcohol is the foundation for treatment of alcoholic liver diseases. In every stage of liver damage, the cessation or marked reduction in alcohol consumption has been demonstrated to improve the histology and/or survival of patients[72].

In patients with elevated alcohol ingestion, high levels of plasma endotoxin may be determined by: (1) excessive production of endotoxin in the intestine through overgrowth of intestinal bacteria; (2) gut permeability; and (3) delayed clearance of endotoxin by Kupffer cells. Actually, the main treatments, such as antibiotics, prebiotics, probiotics and synbiotics, try to prevent endotoxemia by inhibiting the intestinal Gram negative overgrowth and preserving intestinal permeability.

Antibiotic

Acute and chronic ingestion of alcohol causes an increased endotoxin plasma level in humans and mice

Table 2 Properties of ideal probiotic strains

Properties of ideal probiotic strains
Resistance to bile
Resistance to hydrochloric acid
Resistance to pancreatic juice
Ability to tolerate stomach and duodenum conditions and gastric transport
Stimulation of the immune system
Improvement of intestinal function *via* adhering and colonizing the intestinal epithelium
Competition with pathogens
Modulation of permeability
Anticarcinogenic and antipathogenic activity

models[73,74]. Alcohol consumption causes changes in gut microbiota and it is associated with upper gastrointestinal bacterial overgrowth[75,76].

The antibiotic treatment controls large bowel bacterial overgrowth improving the prognosis of ALD[77]. However, despite improvement of liver function, prolonged use of antibiotics alters gut flora and this may favour pathogenic bacterial colonization.

Antibiotic treatment should be based on bacterial sensitivity testing to particular antibiotics, but this will require an excessive use of culture therefore it should be targeted at those intestinal bacteria generally responsible for SIBO[78,79].

Several antibiotics are considered suitable against overgrowth of Gram negative aerobes and anaerobes such as rifaximin, amoxicillin/clavulanate, metronidazole, ciprofloxacin, norfloxacin, and cephalexin. The fundamental role of rifaximin in the treatment of hepatic encephalopathy has been recently demonstrated, but it seems to have a role in treatment of ALD too[80].

The main advantage of rifaximin is that it is not absorbed and therefore presents few side effects. Furthermore there is little evidence for resistance[57,81-83].

Prebiotics

Antibiotics produce quantitative alterations of intestinal microflora whereas prebiotics act against dysbiosis. The prebiotics promote selectively the growth of protective gut bacteria (*Bifidobacteria* and *Lactobacilli*) increasing the body's natural resistance to invading pathogens[84].

Prebiotics are identified as "non digestible food ingredients that, when consumed in sufficient amounts, selective stimulate the growth and/or activity of one or a limited number of microbes in the colon, resulting in documented health benefits"[85].

They are complex carbohydrates that reach the small bowel because they cannot be metabolized by pancreatic and intestinal enzymes in gastrointestinal tract[86]. All prebiotics are resistant to gastric acidity but are susceptible to the metabolism by gut microbiota. While probiotics show strain specific beneficial effects, prebiotics of the same family present similar properties, though their degree of polymerisation distribution linkage type may differ[87].

The most commonly commercialized prebiotics are lactulose, fructo-oligosaccharides (FOS) and galacto-oligo-saccharides (GOS). GOS are nondigestible oligosaccharides derived from lactose, chains of galactose monomers that are naturally found in human milk. GOS, like other prebiotics, simulate pathogen binding sites present on the surface of gastrointestinal epithelial cells inhibiting enteric pathogen adhesion and successive infection[86,88-91].

FOS is naturally present in vegetables such as onions, asparagus, wheat, artichokes *etc*. They modulate gut microbiota, prevent pathogens adhesion and colonization, induce anti-inflammatory effects and regulate lipid and glucose metabolism. These prebiotics can exercise these effects thanks to their structural resistance to mammalian digestive enzymes.

Probiotics

Actually probiotics are defined as "monocultures or mixed culture of live microorganisms that, if administered to a person, positively influence the host by improving the properties of his/her own microflora". Probiotics modulate intestinal microbiota, favouring an anti-inflammatory milieu that contrast bacterial translocation, endotoxin production and improve intestinal barrier integrity.

The mechanisms by which probiotics exert their effects are largely unknown. Different actions have been reported in literature. They control inflammation reducing gut pH and compete with pathogens for binding and receptor sites[92-94]. To do this, they have to show specific characteristics, in particular they should be resistant to bile, hydrochloric and pancreatic juice in order to reach the small bowel (Table 2). Tolerating stomach and duodenum conditions, probiotics can stimulate the immune system and improve intestinal function *via* adherence and colonization of the intestinal epithelium.

The most common probiotics are lactose-fermenting *Lactobacilli* and *Bifidobacteria*. *Lactobacillus* strains, LAP5 and LF33 exert their effects by inhibiting the growth of *E. coli* and *Salmonella typhimurium in vitro*[95]. Furthermore, other studies have demonstrated that *Lactobacillus acidophilus* strain NP51 reduces the number of *E. coli* O157:H7 in the fecal samples of beef cattle[96,97]. *Bifidobacterium animalis* MB5 and *Lactobacillus rhamnosus* GG protect intestinal cells from the inflammation caused by *E. coli*[98]. Finally it has been demonstrated that *Lactobacillus* GG, administered to rats, reduced plasma levels of endotoxin and severity of liver injury[99].

They have been reported to stabilize mucosal barrier function and modulate the gut microflora, limiting the growth of pathogenic bacteria, by acidifying the gut lumen, competing for nutrients, and producing antimicrobial substances[100-103].

Developing nutritional practices, mucosal barrier repairing, apoptosis prevention due to providing of short chain acids, and improving intestinal epithelial viability are other probiotic effects which stabilize physiological luminal permeability together with lowering ammonia adsorption[104]. These functions alleviate tight junction

disturbance by pathogens[105], and are essential agents for lowering bacterial translocation. BT is also affected by probiotics because of their induction of anaerobes and gram positive bacteria growth, limiting gram negative bacteria, and preventing pathogen adherence[101].

Controlling flora bacteria quantity can lead to decreased endotoxins and other toxic compounds derived from bacteria such as ethanol, phenol, indoles which cause injury to the liver. Decreased levels of these substances in the liver result in lowering of proinflammatory production such as TNF-α, IL-6, and IFNγ *via* down-regulation of NF-κB[106]. On the other hand, they can depress urease activity of microflora bacteria followed by ammonia production and release into the portal system. Furthermore, probiotics decrease fecal pH value and reduce ammonia adsorption[107]. Therefore, probiotics determine an improvement in hepatic encephalopathy through a reduction of bacterial ammonia reaching the portal vein.

In 2010 Foster *et al*[108] demonstrated that probiotics effects on mental status were maintained during the wash out period.

Synbiotic

The synbiotic is a compound of probiotics and prebiotics that exercises its beneficial effects stimulating the growth of protective intestinal bacteria[102,103,109].

Prebiotics stimulate the growth of beneficial bacteria (*i.e.*, *Bifidobacteria* and *Lactobacilli*) in the gut and their effectiveness increases when they are used in association with probiotics[110,111]. On the other hand, the mixture of prebiotics and probiotics might enhance the survival and activity of probotics.

CONCLUSION

Several studies have demonstrated the central role of microbiota in the pathogenesis and development of liver disease[65,112]. For this reason therapeutic strategies to control ALD are focussed on the gut microbiome. Obviously the beneficial effects of probiotics depend upon a number of factors such as the duration, frequency and quantity of probiotics consumption and the health of the patients at the beginning of the treatment.

Probiotics have been shown to have several beneficial effects on intestinal function. They prolong remission in ulcerative colitis, maintaining and improving intestinal barrier integrity and stimulate mucosal immunity[113-116].

The treatment could prevent alcohol-induced gut leakiness and development of AHS and the possible mechanisms are the reduction of alcohol-induced intestinal and systemic oxidative stress. Actually the beneficial effects of probiotics in ALD are supported by numerous laboratory results and several studies have shown their potential, however, despite their demonstrated effects on intestinal barrier integrity, there is no high-quality clinical evidence. This is an important limit that does not always permit recommendation of the use of probiotics in clinical practice[117,118].

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