# Role of Probiotics and Synbiotics in Mitigating Alcohol-Induced Liver Damage

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## 16.1 Introduction

Globally, in many societies and households alcohol drinking has become a part of daily life as a result of modernization and changing eating habits. Long-term alcohol consumption was the leading cause of liver failure and death related to liver dysfunction (Fuenzalida et al. 2021). Physiologically, long-term alcohol consumption can cause hepatic injury, which can lead to carcinogenesis and liver damage.

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N. Mishra et al. (eds.), *Synbiotics for the Management of Cancer*,
https://doi.org/10.1007/978-981-19-7550-9_16

"According to the Who statistics, the annual mortality toll from hepatic cirrhosis was 14 lakhs in 2010, making it the ninth largest cause of death in Western countries attributable to drug-induced damage" (Saleem et al. 2010). Alcoholic liver disease (ALD) is one of the leading causes of morbidity among alcohol use disorder (AUD) (Fuenzalida et al. 2021). On a global scale, ALD is the reason for 4.6% of all disability-adjusted life-years and 3.8% of all mortality-adjusted life-years, respectively (Lam et al. 2016). It is also the second most common reason for liver transplantation, affecting around 3.3 million patients every year (Mandayam et al. 2004; Lam et al. 2016; Dinis-Oliveira et al. 2015; Rehm et al. 2009).

## 16.2 Sequelae of Alcohol-Induced Pathogenesis

Globally, ALD is a common cause of cirrhosis, with substantial morbidity and death. The complicated interplay between the many metabolic intermediates of alcohol is thought to be responsible for its pathophysiology. Genetic and environmental variables, the immunological response, and the gut-liver axis connection are involved in triggering ALD (Fuenzalida et al. 2021). Chronic drinking alters the gut microbiota and consequentially causes liver dysfunction by affecting the barrier function in intestine and triggers free radical generation and inflammation. Alcohol metabolites such as acetaldehyde, malondialdehyde (MDA), which is produced as a by-product of lipid peroxidation and protein adducts are hepatotoxins that can cause severe damage by exacerbating systemic inflammation (Fuenzalida et al. 2021). Ethanol crosses the blood–brain barrier (BBB), triggers oxidative stress and inflammation, and culminates in damage irreversible changes in central nervous system (CNS) structures and brain functions (Fuenzalida et al. 2021).

## 16.3 Biochemical Metabolism of Alcohol

Biochemically, alcohol dehydrogenase (ADH) converts alcohol enzymatically through the oxidation process, resulting in ALD. As a result (Lieber 2004; Thurman et al. 1999; Zakhari 2006), acetaldehyde and acetate are produced. Acetaldehyde forms DNA and protein adducts and alters the structure and cell function (Lieber 1994; Mandayam et al. 2004; Zakhari 2006; Lam et al. 2016). The released acetaldehyde is harmful to mitochondria and their organelles, aggravating the oxidative stress (Lieber 2004). Microvesicular steatosis, nonalcoholic steatohepatitis (NASH), and cytolytic hepatitis are all linked events that damage mitochondrial DNA and its functioning (Jaeschke et al. 2002). The redox cellular state is altered and the generated reactive oxygen species (ROS) activate transcription factors of the genes involved in lipid production (Jaeschke et al. 2002). The most important are sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs) (Ansari et al. 2016). In both alcoholic and non-alcoholic steatohepatitis, an increase in lipogenic transcription factors SREBPs and PPARs activates fatty liver formation (Ansari et al. 2016). Furthermore, the

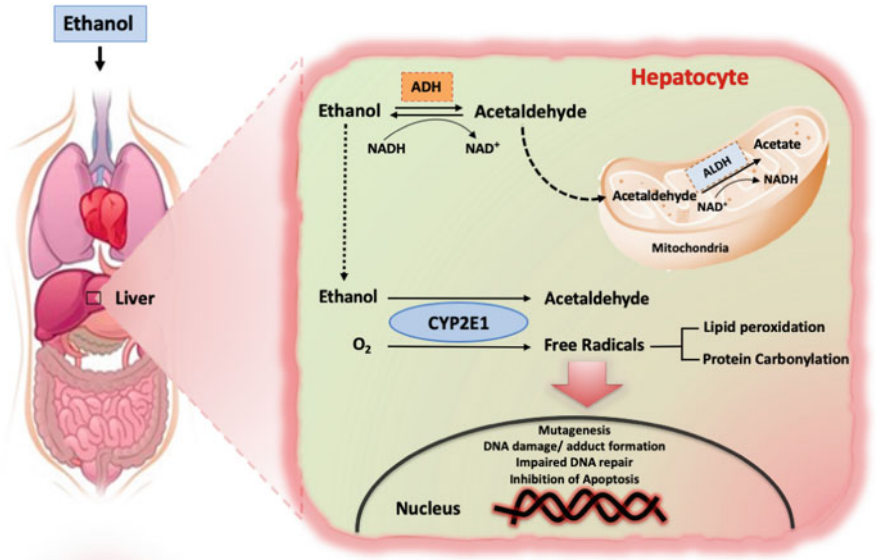


**Fig. 16.1** Ethanol is converted to acetaldehyde by alcohol dehydrogenase (ADH) and, subsequently to acetate by aldehyde dehydrogenase (ALDH). Acetate is conjugated to coenzyme A and the resulting acetyl-CoA can be metabolized in the Krebs cycle, or utilized for the synthesis of fatty acids. In addition, a small fraction of ethanol is metabolized by cytochrome P450 2E1 (CYP2E1). The breakdown of alcohol triggers generation of free radicals which along with acetaldehyde leads to Mutagenesis, DNA damage/ adduct formation, Impaired DNA repair, Inhibition of Apoptosis all of which contribute to carcinogenesis.

acetaldehyde produced reacts with the carboxyl-terminal pro-peptide of procollagen and triggers collagen synthesis in hepatic stellate cells, (Lieber 2004). The mechanism is represented in Fig. 16.1.

## 16.4 Alcohol and Free Radical Generation

Chronic ethanol use causes free radicals to form, as well as increased hepatic oxygen demand and pathogenic alterations (Rehm et al. 2009; Dinis-Oliveira et al. 2015; Lam et al. 2016). Evidence also suggests that, alcohol metabolism also affects immune system functioning and lipid metabolism and the resulting hyper-lipid production complicates the underlying pathogenesis (Thurman et al. 1999; Lieber 2004; Lam et al. 2016). The simultaneous rise in ROS production activates the nuclear factors erythroid-2-related factor-2 (Nrf2) and hypoxia-inducible factor (HIF), making hepatocytes resistant to ethanol's harmful effects (Ansari et al. 2016). Inflammation is triggered and exacerbated by oxidative stress. Subsequently, these changes aggravate pathophysiology by increasing the synthesis of tumor necrosis factor-alpha, a proinflammatory cytokine in the liver's Kupffer cells (Lieber 2004).

Studies have also shown that cytochrome P450 system (CYP2E1) of liver microsomes is another metabolic pathway involved in alcohol poisoning and results in toxic end products (Lieber 1994; Lieber 2004; Zakhari 2006). The end products are cytotoxic than alcohol in damaging the liver damage. 4-hydroxynonenal, for example, is a peroxidative molecule that promotes collagen production and liver fibrosis (Lieber 2004). The acetaldehyde production, induction of CYP2E1, ROS generation, increased inflammatory responses, altered mitochondrial function, compromised antioxidant mechanisms; oxidative stress cumulatively causes death of hepatocytes by necrosis or apoptosis (Lieber 2004; Zakhari 2006).

## 16.5 Pathological Classification

The ALD spectrum is divided into three categories from a pathological standpoint. Fatty liver/hepatic steatosis is the first group. It refers to the fat buildup in the hepatic system of alcoholics. The second category includes alcoholic hepatitis, which causes inflammation to destroy liver cells, as well as alcoholic cirrhosis. Hepatic cirrhosis with extensive fibrosis and nodular regeneration causes sinusoidal intensification, increased vascular resistance, and deformed liver architecture. The destruction and consequent structural degradation results in severe functional damage, which can lead to other organs such as the brain, kidneys, and lungs malfunctioning (Fuenzalida et al. 2021). Although alcoholic cirrhosis and severe alcoholic hepatitis are associated with poor outcomes, a small number of people can recover with continued abstinence and supportive care (Fuenzalida et al. 2021). Finally, the severity of the disease may lead to liver cancer as a result of increased alcohol consumption (Lam et al. 2016). However, reports suggest only a small percentage of alcoholics progresses to hepatocellular carcinoma (HCC) and that cirrhosis, which is caused by excessive alcohol consumption, accounts for 40–90% of the 26,000 yearly deaths (DuFour et al. 1993).

## 16.6 Role of Gut Microbiota

The portal vein connects the gut with the liver in a bidirectional manner, both anatomically and physiologically. Bacteria, viruses, yeasts, and fungi are among the microorganisms that live in the gastrointestinal system, and their ratio always plays an important role in human physiology. This healthy habitat develops a long-term relationship with the host, resulting in a range of beneficial roles (Leclercq et al. 2019). Several studies have shown that both of these organs, as well as the microbiome and food, have a variety of consequences on liver disease and termed as “Gut-Liver Axis” (Albillos et al. 2020). Human intestine is home to nearly 500–1000 gut microbes, and a healthy balance between commensals and pathogenic microorganisms is maintained. The intestinal epithelium serves as a barrier between the microbiome and the liver and is a contact between the gut microbiota present in lumen and host immune cells (Albillos et al. 2020).

The usefulness of probiotics and synbiotics in preventing alcohol-induced hepatic damage and liver cancer has been extensively researched and affirmed to be beneficial to humans. Probiotics are live, non-pathogenic bacteria that can colonize the mucosa of the colon (Elzouki 2016). "In 2001, the Food and Agriculture Organization (FAO) in collaboration with World Health Organization (WHO) classified probiotics as live bacteria that, when given in sufficient proportions, promote the host's health" (Soccol et al. 2010). Probiotics are mentioned in ancient Hindu and Biblical literature as being beneficial to human health. The most typical probiotics are lactic acid bacillus (LAB) or Bifidobacterium (Bifidobacterium) strains, which are normal components of the gut flora (Ehrstrom et al. 2010). They are facultative or anaerobic bacilli that are Gram-positive and non-spore-forming (Shalev 2002). Their natural sources are milk and other dairy products such as curd and yogurt and Nobel laureate Illya Ilyich Metchnikoff linked the benefits of human health with yogurt intake to the microorganisms (Mackowiak 2013). Additionally, Tissier found that infants who were nursed had higher levels of Bifidobacterium-producing microorganisms in their stomachs, and that this helped to maintain healthy intestinal flora and prevent infections (Mackowiak 2013).

With concerted efforts scientists were eventually able to discover the impacts of probiotics on the metabolic, trophic, and protective effects on the human body after significant investigation for decades. The metabolic effects are ascribed to the digestion of non-digestible dietary lipids, endogenous mucus, nutrient absorption, and energy conservation. Trophic effects include epithelial cell proliferation control, homeostasis, and immune system regulation. The actions against pathogens and the improvement of barrier functions are the protective effects.

Gibson defined "a probiotic in 1995 as a non-digestible food item that benefits the host by selectively boosting the development and/or activity of one or a small number of bacteria in the colon, and thus improves host health" (Gibson et al. 2004). Additionally in 2016, an expert panel of the International Scientific Association for Probiotics and Prebiotics (ISAPP) updated the previous definition to the current form, which is a "substrate that is selectively used by host bacteria giving health benefit" (Gibson et al. 2017). It refers to a variety of dietary carbohydrate compounds, such as indigestible polysaccharides, oligosaccharides, galacto-oligosaccharides (GOS), or fructo-oligosaccharides (FOS), fructan (e.g., inulin) that selectively boost the colon's natural commensal microbiota and provide health advantages (Gibson et al. 2017).

Terminologically, the association of probiotics and prebiotics is termed "Symbiotic" and is useful to humans. This word was recently modified in 2019 by the ISAPP as "a mixture comprising living microorganisms and substrate (s) selectively utilized by host microorganisms that confers a health benefit on the host" (Swanson et al. 2020). Synbiotics are employed as nutritional and medicinal supplements as they have synergism that includes prebiotic selectivity for probiotic metabolism, ensuring bacterial survival and development in GI tract (Swanson et al. 2020; Gibson et al. 2004). In the recent past, targeted therapy for the gut microbiota is becoming more popular as a way to protect the body from the effects of alcohol-induced damage (Lu and Wang 2021). The colonic microbiome of patients with

hepatic diseases differs from that of normally healthy people. Previously, practitioners employed non-absorbable disaccharides to change the gut microbial environment to treat liver illnesses, such as hepatic encephalopathy, where lactulose was used to reduce the colonic pH and enhance ammonia excretion. Selective gut decontamination was a name used to describe this process. Prebiotics, probiotics, and synbiotics are three current approaches being investigated. With regard to the microbes, it is important that it can withstand the stomach's acidity and the bile's alkaline pH. Recently, a slew of commercially available versions of the aforementioned have flooded the market. They should, however, only be utilized in circumstances where unequivocal benefits can be demonstrated. Prebiotics and synbiotics have been found to have a favorable effect and can be utilized as an alternative therapy for ethanol-induced liver damage and cancer, according to recent research.

## 16.7 Probiotic Organisms

Lactobacilli are facultative anaerobes that can be found in the mouth, stomach, intestine, and even adult vaginal flora. During reproductive age, the glycogen in the epithelia of adult vagina ferments to lactic acid, lowering the pH to an acidic level, which protects against infections. In addition to biotin, vitamin B12, and vitamin K, lactobacilli in the colon synthesize a few minerals (Baati et al. 2000). Lactobacilli produce lactic acid from lactose and other sugars and vital for making cheese and other dairy products (Shalev 2002). They make antimicrobial chemicals like hydrogen peroxide, which inhibit disease growth, and they live in symbiosis with pathogens (Gänzle 2015). They also make biosurfactants, which prevent adhesion and stimulate macrophages, leukocytes, cytokines, and the immune system (Gudiña et al. 2011). Lactate is produced by the homofermentative process of glycolysis of hexoses, and hexoses are metabolized by the heterofermentative process of phosphoketolase to lactate, carbon dioxide, and ethanol or acetic acid. *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus gasseri, Lactobacillus casei, Levilactobacillus brevis, Limosilactobacillus reuteri*, and *Limosilactobacillus fermentum* are among the lactobacilli strains known as lactic acid bacteria (LAB).

### 16.7.1 *Lactobacillus acidophilus*

*Lactobacillus acidophilus* is a Gram-positive bacillus found in gut of both humans and animals. They use a homofermentative technique to ferment sugar (Baati et al. 2000). It contains probiotics and is used to make yogurt, together with Streptococcus thermophiles. These bacteria reduce blood cholesterol while raising feces cholesterol when fed to pigs, which have a gut similar to humans. *Clostridium perfringens,* S*taphylococcus aureus, Escherichia coli*, and *Salmonella typhimurium* are also prevented from growing (Gilliland and Speck 1977). They also lessen the effects

of *Streptococcus mutans*-caused dental plague. They protect against infection by yeast such as *Candida albicans* because they are part of a healthy vaginal flora. It may cause bacteremia when given to those who are immuno-compromised/suppressed, have central venous catheters, or are preterm newborns (Durchschein et al. 2016).

### 16.7.2 *Lactobacillus plantarum* or *Lactiplantibacillus plantarum*

*Lactobacillus plantarum*, commonly known as *Lactiplantibacillus plantarum*, is a homofermentative, aerotolerant bacteria that produces both lactic acid isomers. In the presence of heme and menaquinone, they produce cytochrome and use oxygen for respiration (Pedersen et al. 2012). Insects and vertebrates have these in their intestines. They thrive in a pH range of 3.4–8.8. Dairy products and fermented vegetables such as brined olives (Randazzo et al. 2010), sausages, and stock fish contain them. It contains antioxidant properties and aids in preserving intestinal permeability. It helps with inflammatory bowel syndrome (IBS) because it inhibits the usual gas-forming bacteria in the intestine (Bixquert Jimenez 2009) and produces antibacterial compound against other bacteria.

### 16.7.3 *Lactobacillus gasseri*

*Lactobacillus gasseri* is also found in the natural flora of the vaginal cavity. Lactocillin and bacteriocin gassericin A are produced. When *Lactobacillus gasseri* was given to rats that had been provided with acute dose of alcohol, the serum alcohol and acetaldehyde levels were less when compared to controls (Lim et al. 2021). When the strains of *L. gasseri* isolated from the feces of healthy newborn child were investigated for the basic adhesion and aggregation properties, both the viable a non-viable forms autoaggregated and co-aggregated with the pathogenic *Cronobacter sakazakii* (ATCC 29544) and *Clostridium difficile* (1296). A clinical trial performed to evaluate the effects of *L. gasseri* in healthy individuals vaccinated with trivalent Influenza (A/H1N1 and B) vaccine showed that the protective antibody titer was increased in probiotic administered group (Nishihira et al. 2016). Thus, this strain increases the immunity in healthy individuals.

### 16.7.4 *Lactobacillus casei*

*Lactobacillus casei* is an anaerobic LAB that can be found in the human reproductive and gastrointestinal tracts. It is utilized in the fermentation of dairy products and has probiotic effects. It produces amylase, a carbohydrate digesting enzyme. They have an inhibitory effect on *Helicobacter pylori* in vivo. When compared to a control group in a clinical trial, they reduced infection by *Clostridium difficile* and diarrhea due to antibiotic administration (McFarland 2009). They've been utilized to reduce

the amount of chemicals that cause flatulence caused by natural bean fermentation (Takeda and Okumura 2007).

### 16.7.5 *Levilactobacillus brevis*

*Levilactobacillus brevis* is a heterofermentative LAB that can be discovered in the human intestine and vagina (Zheng et al. 2020). They may live in anaerobic conditions. It can be present in fermented foods such as pickles, and it can also cause beer to deteriorate. It makes dextran and kefiran polysaccharides, as well as biogenic amines including tyramine and phenylethylamine (Pidoux 1989). Due to the high quantity of hydrogen peroxide produced, its presence in the vaginal area inhibits infection with yeast and Trichomonas species (Eschenbach et al. 1989). They can't turn milk into yogurt, but when combined with milk in geriatric patients, they help to improve cellular immunity.

### 16.7.6 *Limosilactobacillus reuteri*

*Limosilactobacillus reuteri* is found in the intestine and feces of people, as well as livestock such as chickens, sheep, and pigs. Reuterin, reutericin, and reutericyclin are bacteriocins produced by them. Reuterin is a new broad-spectrum antibacterial material made from glycerol fermentation (Talarico et al. 1988) and inhibits a range of bacteria, fungi, and protozoa (Talarico and Dobrogosz 1989), as well as other unicellular parasites. In children, it has been utilized as an adjuvant therapy for *H. pylori*. They have a cidal effect on *Streptococcus mutans* in the oral cavity. They have conferred high levels of resistance to *Salmonella typhimurium, Escherichia coli* in chicken, and *Cryptosporidium parvum* in mice and pigs in animal models such as mice (Casas and Dobrogosz 2000).

### 16.7.7 *Limosilactobacillus fermentum*

*Limosilactobacillus fermentum* is a heterofermentative LAB found in vertebrate intestines. This bacterium has inherent antibiotic resistance and is a possible carrier of resistance genes to humans from animals or the environment (Klein 2011). It has excellent bile tolerance, survive at pH 3 and is ideal for use as a probiotic (Pan et al. 2011). They can also lower cholesterol by speeding up cholesterol metabolism and increasing the demand for bile salt, which is generated from cholesterol (Pan et al. 2011). They reduce pathogenic *Salmonella* spp., *Shigella* spp. in the intestine, and UTI caused by *E.coli* and *Staphylococcus* spp. as a probiotic in dairy products (Mikelsaar and Zilmer 2009).

### 16.7.8 *Bifidobacterium* Species

*Bifidobacterium* species are anaerobic bacteria that are Gram positive, nonmotile, and Y-shaped. They're found in mammals' lower female genital tracts and gastrointestinal tracts. In adults and children, they are classed as plant-derived fructooligosaccharides or dairy-derived galactooligosaccharides, respectively, based on metabolism (Mayo 2010). Because it maintains intestinal microbe homeostasis, inhibits pathogens and harmful bacteria, modulates local and systemic immune responses, produces vitamins, and produces bioactive molecules from dietary substances, *Bifidobacterium* are ideal probiotics in managing ulcerative colitis (Ghouri et al. 2014). They are known as scavengers of the intestines. They are engaged in the carbon and energy metabolism of complex oligosaccharides. They use glucosaminidases and mannosidases to ferment galactomannan-rich natural gum, which ferments glucosamine and mannose, respectively. *Bifidobacterium longum* and *Bifidobacterium breve* are two common probiotic bacteria. *Bifidobacterium longum* helps to regulate the immune system, reducing the duration and intensity of the common cold. *Bifidobacterium breve*, a bacteria obtained from human newborn feces, has been found to help with ulcerative colitis, *Helicobacter pylori* treatment, and irritable bowel syndrome pain, bloating, and constipation. With *B. breve*, pre-obese people were able to avoid or reverse obesity (Mayo 2010; Ghouri et al. 2014).

### 16.7.9 Probiotics in Mitigating Alcohol-Induced Liver Damage

LAB strains such as *Limosilactobacillus fermentum*, *Limosilactobacillus reuteri*, and *Levilactobacillus brevis* have been demonstrated to protect ethanol-induced HepG2 cells in several experiments. By modulating CYP2E1, antioxidant enzymes (SOD, GPX, and CAT), lipid synthesis factors (SREBP1C and FAS), and lipid oxidation factors (PPAR, ACO, and CPT-1), these strains protected the liver from alcohol-induced hepatic damage (Liu et al. 2021). Ethanol-induced damage and detrimental post-translational changes of heat shock protein (Hsp60) chaperones were significantly reduced in *L. fermentum*. Following probiotic therapy, steatosis, iNOS levels, and Hsp60 levels all decreased (Barone et al. 2016). *L. plantarum* HFY09 (LP-HFY09) showed a decrease in various hepatic parameters like serum triglyceride (TG), total cholesterol (TC), SGOT, SGPT, hyaluronidase (HAase), and precollagen III (PC III) and a rise in liver alcohol dehydrogenase (ADH) and acetaldehyde dehydrogenase in mice with ALDH. *Lactobacillus plantarum* HFY09 helped to reduce inflammation by increasing interleukin 10 (IL-10) levels and lowering proinflammatory factors [IL-6, IL-1, and tumor necrosis factor (TNF)].

*Lactobacillus plantarum* HFY09 increased hepatic superoxide dismutase (SOD) and glutathione (GSH) levels while lowering liver malondialdehyde levels (MDA).

When compared to commercial *Lactobacillus delbrueckii* preparations, it showed improved modulation of hepatoprotective activities. The upregulation of peroxisome proliferator activated receptors, SOD1, SOD2, glutathione peroxidase (GSH-Px), nicotinamide adenine dinucleotide phosphate (NADPH), and catalase (CAT), as well as the downregulation of cyclooxygenase-1 (COX1), c-Jun N-terminal kinase (JNK), and additional ERK. For persons who consume alcohol often, the administration of LP-HFY09 could be a potential intervention (Gan et al. 2021).

Toll-like receptors (TLR) are found in immune cells and hepatocytes, and they recognize bacterial components that go from the stomach to the portal vein. In the absence of microbial components, ethanol activates TLR, resulting in an increase in proinflammatory cytokine production. According to research, *L. casei* MYL01 reduced ethanol-induced proinflammatory responses and increased TLR tolerance to ethanol activation. This was attributable to increased IL-10 synthesis, toll interacting protein (TOLLIP), and suppressor of cytokine signaling (SOCS)1 and SOCS3 expression via TLR1, TLR2, TLR6, and TLR9 activation, which cross-regulated ethanol-TLR4-nuclear factor B signaling events. All of these substances suppressed the pro-inflammatory response and boosted hepatocyte defenses against ethanol-induced injury (Chiu et al. 2014). Additionally, extract derived from green tea (*Camellia sinensis*) and fermented with *Lactobacilli fermentum* strain OCS19 mitigated acute alcohol-induced liver damage in both HepG2 hepatic cell line and in mouse model of study (Park et al. 2012). Administering the *L. fermentum*-fermented green tea extract (FGTE) increased the activity of hepatic alcohol dehydrogenase (ADH) and its mRNA expression indicating that combining green tea extract with *L. fermentum* fermentation reduces the risk of ethanol-induced liver damage (Park et al. 2012).

## 16.8 Conclusions

The current review highlights the use of probiotics by inhibiting and mitigating the ethanol-induced hepatic damage (Fig. 16.2). Multiple pathways are triggered to mitigate these effects and the principal are the antioxidant, anti-inflammatory and the protective events in the gut-liver axis. Future endeavors should be focused towards understanding the usefulness of probiotics in well-planned randomized clinical trials as the outcome of these will be useful for both fraternity and the society.

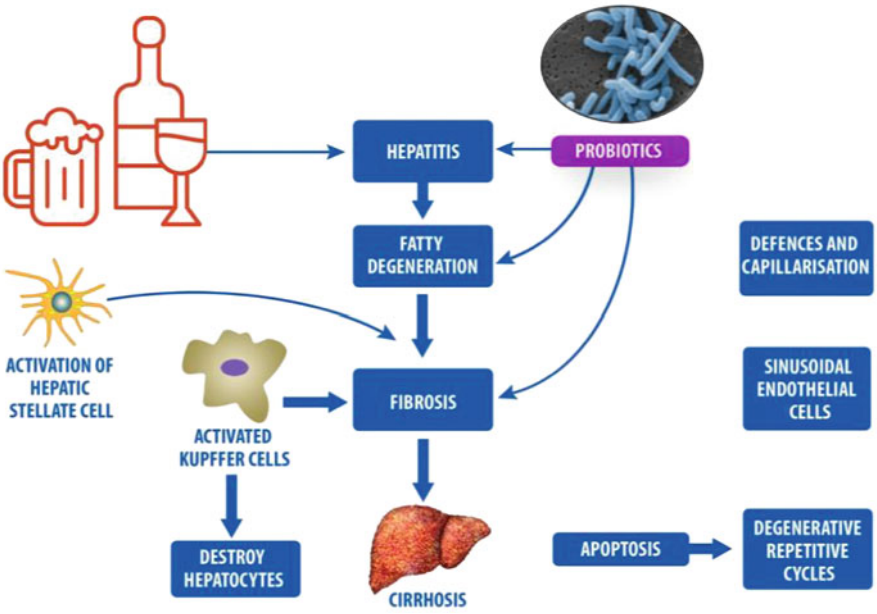


**Fig. 16.2** Mechanism/s by which probiotics mediate the hepatoprotective effects against the alcohol induced liver damage

## References

Albillos A, De Gottardi A, Rescigno M (2020) The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol 72:558–577

Ansari RA, Husain K, Rizvi SA (2016) Role of transcription factors in steatohepatitis and hypertension after ethanol: the epicenter of metabolism. Biomol Ther 6:29

Baati L, Fabre-Gea C, Auriol D, Blanc PJ (2000) Study of the cryotolerance of lactobacillus acidophilus: effect of culture and freezing conditions on the viability and cellular protein levels. Int J Food Microbiol 59:241–247

Barone R, Rappa F, Macaluso F, Caruso Bavisotto C, Sangiorgi C, Di Paola G, Tomasello G, Di Felice V, Marciano V, Farina F, Zummo G, Conway De Macario E, Macario AJ, Cocchi M, Cappello F, Marino Gammazza A (2016) Alcoholic liver disease: a mouse model reveals protection by Lactobacillus fermentum. Clin Transl Gastroenterol 7:e138

Bixquert Jimenez M (2009) Treatment of irritable bowel syndrome with probiotics. An etiopathogenic approach at last? Rev Esp Enferm Dig 101:553–564

Casas IA, Dobrogosz WJ (2000) Validation of the probiotic concept: Lactobacillus reuteri confers broad-spectrum protection against disease in humans and animals. Microb Ecol Health Dis 12: 247–285

Chiu YH, Tsai JJ, Lin SL, Lin MY (2014) Lactobacillus casei MYL01 modulates the proinflammatory state induced by ethanol in an in vitro model. J Dairy Sci 97:2009–2016

Dinis-Oliveira RJ, Magalhaes T, Queiros O, Proenca JB, Moreira R, De Lourdes Bastos M, Carvalho F (2015) Signs and related mechanisms of ethanol hepatotoxicity. Curr Drug Abuse Rev 8:86–103

DuFour MC, Stinson FS, Caces MF (1993) Trends in cirrhosis morbidity and mortality: United States, 1979–1988. Semin Liver Dis 13:109–125
Durchschein F, Petritsch W, Hammer HF (2016) Diet therapy for inflammatory bowel diseases: the established and the new. World J Gastroenterol 22:2179–2194
Ehrstrom S, Daroczy K, Rylander E, Samuelsson C, Johannesson U, Anzen B, Pahlson C (2010) Lactic acid bacteria colonization and clinical outcome after probiotic supplementation in conventionally treated bacterial vaginosis and vulvovaginal candidiasis. Microbes Infect 12: 691–699
Elzouki AN (2016) Probiotics and liver disease: where are we now and where are we going? J Clin Gastroenterol 50(Suppl 2) proceedings from the 8th probiotics, Prebiotics & new Foods for microbiota and human health meeting held in Rome, Italy on September 13-15, 2015:S188–S190
Eschenbach DA, Davick PR, Williams BL, Klebanoff SJ, Young-Smith K, Critchlow CM, Holmes KK (1989) Prevalence of hydrogen peroxide-producing lactobacillus species in normal women and women with bacterial vaginosis. J Clin Microbiol 27:251–256
Fuenzalida C, Dufeu MS, Poniachik J, Roblero JP, Valenzuela-Perez L, Beltran CJ (2021) Probiotics-based treatment as an integral approach for alcohol use disorder in alcoholic liver disease. Front Pharmacol 12:729950
Gan Y, Tong J, Zhou X, Long X, Pan Y, Liu W, Zhao X (2021) Hepatoprotective effect of lactobacillus plantarum HFY09 on ethanol-induced liver injury in mice. Front Nutr 8:684588
Gänzle MG (2015) Lactic metabolism revisited: metabolism of lactic acid bacteria in food fermentations and food spoilage. Curr Opin Food Sci 2:106–117
Ghouri YA, Richards DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW (2014) Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. Clin Exp Gastroenterol 7:473–487
Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB (2004) Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev 17:259–275
Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K, Reid G (2017) Expert consensus document: The international Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14:491–502
Gilliland SE, Speck ML (1977) Antagonistic action of lactobacillus acidophilus toward intestinal and foodborne pathogens in associative cultures (1). J Food Prot 40:820–823
Gudiña EJ, Teixeira JA, Rodrigues LR (2011) Biosurfactant-producing lactobacilli: screening, production profiles, and effect of medium composition. Appl Environ Soil Sci 2011:201254
Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ (2002) Mechanisms of hepatotoxicity. Toxicol Sci 65:166–176
Klein G (2011) Antibiotic resistance and molecular characterization of probiotic and clinical lactobacillus strains in relation to safety aspects of probiotics. Foodborne Pathog Dis 8:267–281
Lam P, Cheung F, Tan HY, Wang N, Yuen MF, Feng Y (2016) Hepatoprotective effects of Chinese medicinal herbs: a focus on anti-inflammatory and anti-oxidative activities. Int J Mol Sci 17:465
Leclercq S, Starkel P, Delzenne NM, De Timary P (2019) The gut microbiota: a new target in the management of alcohol dependence? Alcohol 74:105–111
Lieber CS (1994) Alcohol and the liver: 1994 update. Gastroenterology 106:1085–1105
Lieber CS (2004) Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. Alcohol 34:9–19
Lim TJ, Lim S, Yoon JH, Chung MJ (2021) Effects of multi-species probiotic supplementation on alcohol metabolism in rats. J Microbiol 59:417–425
Liu SY, Tsai IT, Hsu YC (2021) Alcohol-related liver disease: basic mechanisms and clinical perspectives. Int J Mol Sci 22:5170
Lu X, Wang F (2021) Lactobacillus acidophilus and vitamin C attenuate ethanol-induced intestinal and liver injury in mice. Exp Ther Med 22:1005

Mackowiak PA (2013) Recycling metchnikoff: probiotics, the intestinal microbiome and the quest for long life. Front Public Health 1:52

Mandayam S, Jamal MM, Morgan TR (2004) Epidemiology of alcoholic liver disease. Semin Liver Dis 24:217–232

Mayo BSDV (2010) Bifidobacteria : genomics and molecular aspects. Caister Academic, Norfolk, UK

McFarland LV (2009) Evidence-based review of probiotics for antibiotic-associated diarrhea and Clostridium difficile infections. Anaerobe 15:274–280

Mikelsaar M, Zilmer M (2009) Lactobacillus fermentum Me-3–an antimicrobial and antioxidative probiotic. Microb Ecol Health Dis 21:1–27

Nishihira J, Moriya T, Sakai F, Kabuki T, Kawasaki Y, Nishimura M (2016) Lactobacillus gasseri SBT2055 stimulates immunoglobulin production and innate immunity after influenza vaccination in healthy adult volunteers: a randomized, double-blind, placebo-controlled, parallel-group study. Funct Foods Health Dis 6:544

Pan DD, Zeng XQ, Yan YT (2011) Characterisation of lactobacillus fermentum Sm-7 isolated from koumiss, a potential probiotic bacterium with cholesterol-lowering effects. J Sci Food Agric 91: 512–518

Park J, Kim Y, Kim S (2012) Green tea extract (Camellia sinensis) fermented by lactobacillus fermentum attenuates alcohol-induced liver damage. Biosci Biotechnol Biochem 76(12): 2294–2300

Pedersen MB, Gaudu P, Lechardeur D, Petit MA, Gruss A (2012) Aerobic respiration metabolism in lactic acid bacteria and uses in biotechnology. Annu Rev Food Sci Technol 3:37–58

Pidoux M (1989) The microbial flora of sugary kefir grain (the gingerbeer plant): biosynthesis of the grain fromLactobacillus hilgardii producing a polysaccharide gel. World J Microbiol Biotechnol 5:223–238

Randazzo, C., Rajendram, R. & Caggia, C. 2010. Lactic acid bacteria in table olive fermentation.

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J (2009) Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 373:2223–2233

Saleem SM, Madhusudhana C, Ramkanth DS, Rajan VST, Kumar K, Karunakaran G (2010) Hepatoprotective herbs–A review. Int J Res Pharm Sci 1:1–15

Shalev E (2002) Ingestion of probiotics: optional treatment of bacterial vaginosis in pregnancy. Isr Med Assoc J 4:357–360

Soccol CR, Vandenberghe LPS, Spier MR, Medeiros ABP, Yamaguishi CT, Lindner JDD, Pandey A, Thomaz-Soccol V (2010) The potential of probiotics: a review. Food Technol Biotechnol 48:413–434

Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, Scott KP, Holscher HD, Azad MB, Delzenne NM, Sanders ME (2020) The international scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nat Rev Gastroenterol Hepatol 17:687–701

Takeda K, Okumura K (2007) Effects of a fermented milk drink containing lactobacillus casei strain Shirota on the human NK-cell activity. J Nutr 137:791S–793S

Talarico TL, Dobrogosz WJ (1989) Chemical characterization of an antimicrobial substance produced by Lactobacillus reuteri. Antimicrob Agents Chemother 33:674–679

Talarico TL, Casas IA, Chung TC, Dobrogosz WJ (1988) Production and isolation of reuterin, a growth inhibitor produced by lactobacillus reuteri. Antimicrob Agents Chemother 32:1854–1858

Thurman RG, Bradford BU, Iimuro Y, Frankenberg MV, Knecht KT, Connor HD, Adachi Y, Wall C, Arteel GE, Raleigh JA, Forman DT, Mason RP (1999) Mechanisms of alcohol-induced hepatotoxicity: studies in rats. Front Biosci 4:e42–e46

Zakhari S (2006) Overview: how is alcohol metabolized by the body? Alcohol Res Health 29:245–254

Zheng J, Wittouck S, Salvetti E, Franz C, Harris HMB, Mattarelli P, O'toole PW, Pot B, Vandamme P, Walter J, Watanabe K, Wuyts S, Felis GE, Ganzle MG, Lebeer S (2020) A taxonomic note on the genus lactobacillus: description of 23 novel genera, emended description of the genus lactobacillus Beijerinck 1901, and union of Lactobacillaceae and Leuconostocaceae. Int J Syst Evol Microbiol 70:2782–2858