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Inflammation-targeted strategies for alcohol-associated liver injury: Insights into probiotics, prebiotics, synbiotics, and postbiotics

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ABSTRACT: Alcohol-related liver injury is a widespread global health concern caused by chronic excessive alcohol consumption, with inflammation serving as the central mechanism driving disease progression. Although contemporary medical interventions offer diverse therapeutic options for alcohol-related liver disease (ALD), their efficacy is limited and may induce undesirable adverse effects. Probiotics, prebiotics, synbiotics, and postbiotics have emerged as promising therapeutic strategies due to their food-grade safety and anti-inflammatory properties. To date, there remains a lack of a comprehensive review on the impact of these biotic interventions on alcohol-related liver injury. This review examines how the metabolic byproducts generated during alcohol metabolism trigger inflammatory responses and explores the potential mechanisms linking inflammation to the progression of ALD. It also highlights that probiotics, prebiotics, synbiotics, and postbiotics represent promising therapeutic strategies due to their food-grade safety and anti-inflammatory properties.

Keywords: Alcohol-related liver injury, probiotics, prebiotics, synbiotics, postbiotics, inflammation

1. Introduction

Alcohol-related liver injury, caused by excessive alcohol consumption, involves a continuous progression from mild fatty liver to severe hepatitis, liver fibrosis, and even cirrhosis. The global alcohol per capita consumption (APC) reached 5.5 liters in 2019, according to the statistical report published by the World Health Organization[1]. Compared to the global targets of a minimum 10% reduction by 2025 and at least 20% by 2030, a faster pace of decline is necessary. In 2025, a report by the US Surgeon General on alcohol consumption and cancer risk highlights alcohol use as a leading, preventable cause of cancer worldwide, with links to various cancers, including hepatocellular carcinoma and intrahepatic cholangiocarcinoma, and calls for mandatory cancer warnings on all alcohol beverage labels[2]. As alcohol consumption continues to rise, the incidence of alcohol-related liver disease (ALD) has steadily increased, making cirrhosis one of the top ten causes of death in some regions. This imposes a growing burden on

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global public health[1]. Recently, studies have confirmed that the occurrence of ALD is usually accompanied by neurological disorders, including depression and alcohol use disorder[3]. Despite significant advancements in understanding the pathophysiology of ALD, no "magic bullet" therapy is available. Clinically, synthetic pharmacological agents such as corticosteroids and N-acetylcysteine are widely used to manage ALD. However, the desired outcomes are often not achieved due to high treatment costs and severe side effects, including hepatotoxicity. Thus, a concerted effort to broaden the limited treatment options would significantly enhance the clinical management of ALD.

Current evidence indicates that the progression of ALD is modulated by multiple pathogenic mechanisms, including alcohol-induced hepatotoxicity, oxidative stress, dysregulated lipid metabolism, and inflammatory cascades[4-5]. Among the multifactorial risk factors, inflammation is the primary driver of alcohol-related liver injury[6]. According to reports, the global markets for probiotics, prebiotics, synbiotics, and postbiotics are expected to reach USD 220,138.1 million, USD 21,772.6 million, USD 1,677.0 million, and USD 624.7 million, respectively, by 2030. Given the enormous market potential and essential role of these biotic interventions in regulating inflammation, probiotics, prebiotics, synbiotics, and postbiotics are emerging as promising treatments for ethanol-induced liver damage. They function by modulating immune factors, reducing oxidative stress, and regulating gut microbiota, thereby mitigating the inflammatory response. These biotic treatments have also been extensively employed in diverse preclinical models and clinical investigations of human diseases, including psychiatric disorders, dental caries, inflammatory bowel disease, and nonalcoholic fatty liver disease (NAFLD) because of their modulatory effects on neuroinflammation, immune function, and interactions with intestinal microbiota[7-10].

Despite extensive research on the immunomodulatory mechanisms in ALD, a comprehensive understanding of inflammatory regulation and recent advancements remains limited. In this review, we focus on several newly identified inflammation-related mechanisms that play key roles in the development of ethanol-induced liver damage. These mechanisms may pave the way for emerging therapeutic strategies, particularly those involving probiotics, prebiotics, synbiotics, and postbiotics. Finally, we outline future directions for translating inflammation research into practical applications.

2. The metabolic pathways of alcohol in the body

Alcohol is a prevalent psychoactive substance that undergoes intricate metabolic processes in the body, which is rapidly distributed across multiple organs and systems, thereby influencing inflammation and organ function. The specific metabolic pathway is illustrated in Figure 1.

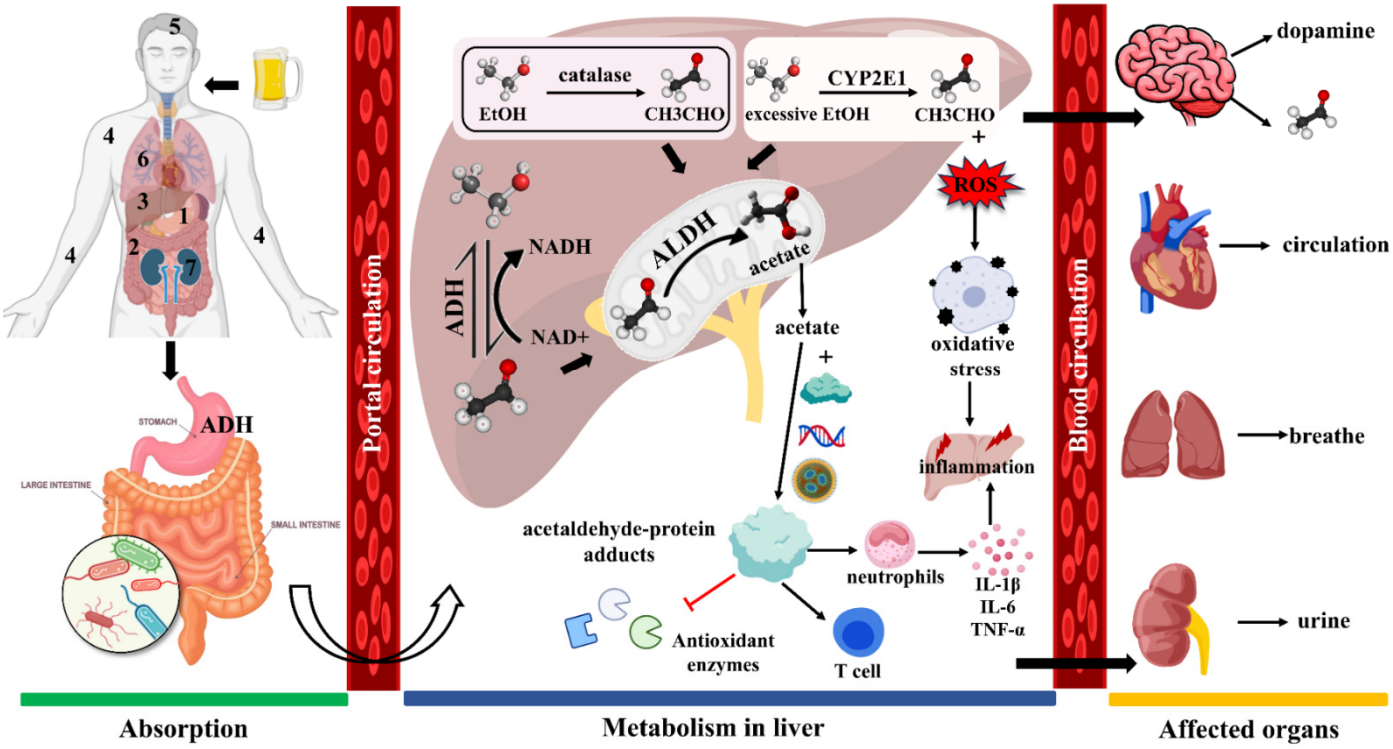

Figure 1. Schematic illustration of systemic alcohol metabolism with an emphasis on inflammatory pathways. Some visual elements were adapted from BioRender.com.

After entering the body, alcohol is partially oxidized to acetaldehyde by gastric alcohol dehydrogenase in the stomach. The unmetabolized alcohol then passes into the small intestine, where most absorption occurs via passive diffusion into the portal vein. A small amount of alcohol may be metabolized by intestinal microorganisms, some of which (e.g., *Clostridium*) can convert alcohol into acetic acid or other metabolites. Once absorbed from the small intestine, alcohol is transported to the liver via the portal vein, where enzymes metabolize over 90% of ethanol, with the remainder being excreted through the lungs and kidneys. In the liver, ethanol is primarily metabolized via oxidative and non-oxidative pathways. The oxidative pathway is the predominant mechanism, consisting of two stages: first, ethanol is oxidized to acetaldehyde by alcohol dehydrogenase (ADH); subsequently, acetaldehyde is converted to acetate by aldehyde dehydrogenase (ALDH). The resulting acetate enters the tricarboxylic acid (TCA) cycle, where it is further oxidized to carbon dioxide and water, releasing energy. Although acetate is non-hepatotoxic, it can modulate the inflammatory response by stimulating the production of pro-inflammatory cytokines in macrophages[11]. Under conditions of high alcohol intake, the activity of CYP2E1 is significantly upregulated, increasing the production of acetaldehyde and reactive oxygen species (ROS)[12]. Acetaldehyde covalently binds to proteins, DNA, and lipids, forming adducts that activate T cells, recruit inflammatory cells, and induce pro-inflammatory cytokine release[13]. Additionally, aldehyde-protein adducts can bind to antioxidant enzymes, such as glutathione peroxidase, inhibiting their activity and causing ROS accumulation[14]. Excessive ROS production triggers oxidative stress, which subsequently amplifies and sustains inflammatory signaling pathways, ultimately contributing to chronic liver damage.

Then, alcohol and its metabolites compromise blood-brain barrier (BBB) integrity, facilitating the infiltration of peripheral immune cells and inflammatory mediators, thereby exacerbating neuroinflammation[15]. A fraction of alcohol crosses the BBB and is metabolized locally in the brain via three pathways: (1) ADH in astrocytes, (2) catalase in microglia and neurons convert ethanol to acetaldehyde, and (3) CYP2E1 generates ROS[16]. These metabolites collectively induce neuroinflammation, oxidative stress, and dopaminergic dysregulation, forming the molecular basis of alcohol dependence. Moreover, chronic alcohol consumption triggers excessive activation of microglia and astrocytes, resulting in the release of inflammatory mediators in the brain. These mediators exacerbate neuroinflammation, disrupt neuronal homeostasis, and contribute to cognitive deficits[17]. Furthermore, alcohol induces gut microbiota remodeling and promotes cardiovascular disease[18].

3. Mechanisms underlying the inflammatory response in alcohol-related liver injury progression

3.1 Inflammatory immune mediators in alcohol-related liver injury

3.1.1 Innate immune factors

Increasing evidence underscores the critical roles of innate and adaptive immunity in the pathogenesis of alcohol-induced liver damage. Inflammatory cells, particularly macrophages, play an essential role in orchestrating hepatic inflammation[19]. A Phase I clinical trial demonstrated that injected autologous macrophages expressing markers of inflammation resolution improved liver function[20]. Although the therapy failed to achieve the primary endpoint in Phase II trials targeting improvements in cirrhosis-related outcomes, it transiently reduced pro-inflammatory cytokine levels while enhancing anti-inflammatory cytokines in patients with cirrhosis[21]. Kupffer cells, the resident macrophages of the liver, respond to ethanol-induced injury by upregulating miR-155, subsequently downregulating key suppressors of inflammation such as Src Homology 2 domain-containing Inositol 5'-Phosphatase 1 (SHIP1) and CCAAT/Enhancer-Binding Protein Beta (C/EBPβ), potentially contributing to alcohol-related hepatitis[22]. MicroRNAs (miRNAs), including miR-147 and miR-21, regulate macrophage activity by modulating the NF-κB and IFN pathways, thereby suppressing inflammation induced by pathogen-associated molecular patterns (PAMPs)[23-24]. Kupffer cells and recruited monocyte-derived macrophages secrete TGF-β1, pro-inflammatory factors, and chemokines (e.g., CCL2 and CCL5), activating hepatic stellate cells (HSCs) and recruiting additional inflammatory cells, further exacerbating inflammation[25]. Moreover, HSCs are activated by ROS and pro-inflammatory signals from Kupffer cells, with cytokines such as TGF-β and IL-13 further enhancing their activation, ultimately promoting fibrosis progression[26]. Natural killer (NK) cells, typically involved in eliminating infected or transformed cells, also play crucial roles in the progression of ALD. In ALD, impaired recruitment of NK cells to injury sites and reduced cytotoxic activity against HSCs contribute to disease progression by allowing HSCs to evade immune surveillance. Circulating neutrophils are typically in a “resting” state and can be activated through receptors such as Toll-like receptor (TLR)2 and TLR9, which can recognize both PAMPs and damage-associated molecular patterns (DAMPs)[27]. These interactions prime neutrophils for a stronger

activation response. Additionally, binge ethanol intake enhances the number of circulating neutrophils and elevates their infiltration into the liver, as observed in patients with severe alcohol-associated hepatitis[28].

CD44, a cell surface glycoprotein primarily expressed by immune cells and involved in cell adhesion and migration, has been identified in both murine models and clinical studies as a critical regulator of liver inflammation in ALD[29]. CD44 also regulates neutrophil mobilization and function, and targeting can partially alleviate alcohol-induced liver inflammation and injury[30].

3.1.2 Adaptive immune factors

Adaptive immune cells, including T cells and B cells, also significantly influence ALD pathogenesis. T helper (Th) cells regulate immune responses primarily by secreting cytokines and activating other immune cells such as cytotoxic T cells and B cells[31]. Alcohol-induced increases in Th17 cells intensify gut inflammation, disturbing intestinal immune homeostasis. Elevated levels of IL-17 produced by Th17 cells exacerbate inflammatory responses, potentially contributing to gut immune dysregulation[32].

3.2 Inflammatory signaling pathways in alcohol-related liver injury

Alcohol-related liver injury progresses through inflammatory signaling cascades, from early detection to immune activation and eventual resolution via anti-inflammatory pathways.

3.2.1 Initiation phase of inflammation

Toll-like receptors (TLRs), particularly TLR4, serve as key pattern recognition receptors (PRRs) that detect PAMPs and initiate early inflammatory responses. TLR4 recognizes lipopolysaccharides (LPS) in concert with co-receptors such as CD14, MD-2, and LPS-binding protein (LBP)[33]. Upon activation, TLR4 induces a robust release of inflammatory mediators, partly through the activation of the NLRP3 inflammasome[34]. Through the activation of Caspase-1, the NLRP3 inflammasome cleaves pro-IL-1β and pro-IL-18 into their mature forms, thereby amplifying the inflammatory response[35]. In parallel, TLR2 has attracted considerable attention for its pivotal role in detecting bacterial lipoproteins and peptidoglycans. Notably, Pimentel-Nunes et al.[36] discovered that patients with stable alcohol-related chronic liver disease exhibit an attenuated TLR2-mediated innate immune response. This attenuation is independent of TLR2 or co-receptor expression and TLR4 activation, potentially reflecting a key mechanism of acquired immunodeficiency present from early disease stages. TLR4 activation stimulates downstream signaling via the MyD88-dependent pathway, ultimately promoting IκB phosphorylation, NF-κB nuclear translocation, and subsequent MAPK pathway activation[37].

In addition to MyD88-dependent signaling, TLR4 can signal through a MyD88-independent (TRIF-dependent) pathway. This pathway leads to the activation of interferon regulatory factor 3 (IRF3), which promotes the expression of type I interferons and contributes to liver inflammation, particularly in the context of chronic alcohol exposure[38]. Moreover, oxidative stress induced by alcohol metabolism facilitates the release of DAMPs, such as High Mobility Group Box 1 (HMGB1), which further engage pattern recognition receptors (PRRs) such as TLR9 and amplify the innate immune response[39-40].

3.2.2 Amplification phase of inflammation

In the amplification phase of inflammation, multiple interconnected pathways act synergistically to perpetuate and expand the inflammatory response initiated by alcohol exposure[41]. The NF-κB pathway amplifies inflammatory signals by inducing the expression of cytokines (IL-6, TNF-α, and IL-1β). Cytokine signaling also involves Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) proteins, which regulate inflammation-related genes[42]. The JAK/STAT pathway is activated downstream of cytokine receptors such as IL-6, leading to the phosphorylation and nuclear translocation of STAT3[43]. Notably, STAT3 is generally considered a key driver of M2 macrophage polarization, primarily activated by cytokines such as IL-10, IL-4, and IL-13, contributing to anti-inflammatory effects in chronic liver injury[44]. Additionally, TLR4-induced TAK1 activation initiates mitogen-activated protein kinases (MAPK) pathways (ERK, JNK, and p38), modulating inflammatory mediator expression[45]. These MAPKs regulate inflammatory gene expression through transcription factors such as Activator Protein-1 (AP-1), cellular Jun proto-oncogene (c-Jun), and Activating Transcription Factor 2 (ATF2), contributing to cytokine production, ROS generation, and hepatocyte damage[46]. Additionally, alcohol intake induces mitochondrial DNA (mtDNA) release, which acts as a DAMP that activates the cGAS-STING pathway, driving ER stress, hepatocyte apoptosis, and fibrosis[47]. Sustained cGAS-STING activation promotes hepatic fibrosis via stellate cell activation and drives chronic inflammation through the induction of the senescence-associated secretory phenotype (SASP), which comprises multiple pro-inflammatory cytokines that perpetuate liver injury[47]. This mechanistic framework is supported by in vivo evidence showing that the expression levels of hepatic cGAS-STING pathway components are enhanced in alcohol-exposed mice[48].

Emerging studies suggest crosstalk between the NF-κB, JAK/STAT, MAPK, and cGAS-STING pathways, establishing a feedforward loop that intensifies hepatic inflammation[49]. The interplay of these signaling pathways may drive the progression from acute liver injury to chronic disease, highlighting the need for therapeutic strategies that simultaneously target multiple inflammatory pathways.

3.2.3 Resolution phase of inflammation

During the later phase of alcohol-induced hepatic inflammation, the Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2 (Keap1-Nrf2) pathway plays a pivotal role in reestablishing redox balance and restoring tissue homeostasis through its antioxidative and anti-inflammatory effects[50]. Under physiological conditions, Keap1 acts as a cytoplasmic repressor, facilitating the ubiquitination and subsequent proteasomal degradation of Nrf2[51]. Oxidative stress caused by chronic alcohol exposure induces conformational changes in Keap1, primarily via cysteine residue oxidation, thereby weakening its ability to promote Nrf2 degradation[52]. As a result, Nrf2 accumulates and translocates into the nucleus, where it activates genes encoding antioxidative enzymes (e.g., HO-1 and SOD), detoxifying enzymes (e.g., glutathione S-transferase, NAD(P)H quinone dehydrogenase 1), and anti-inflammatory mediators (e.g., IL-10 and NQO1)[53]. This transcriptional activation confers protection against ROS-induced cellular damage and dampens the inflammatory cascade triggered by prolonged ethanol exposure. Other studies have

found that Nrf2 also negatively regulates pro-inflammatory signaling, including the NF-κB and ROS pathways, thereby attenuating oxidative stress and neuronal inflammation[54-55]. Importantly, dysregulation of the Keap1-Nrf2 axis has been implicated in exacerbated liver injury and delayed resolution of inflammation in ALD models[56], indicating that therapeutic targeting of this pathway may offer promising strategies to suppress inflammation.

Current research on ALD has predominantly focused on the end-stage outcomes of liver damage, whereas the dynamic progression of inflammatory responses over time remains insufficiently characterized. Future studies should integrate temporal biomarkers to map inflammatory timelines for targeted interventions. The specific mechanisms underlying the inflammatory response in alcohol-related liver injury, including the involvement of innate and adaptive immune mediators as well as key inflammatory signaling pathways, are summarized in Figure 2.

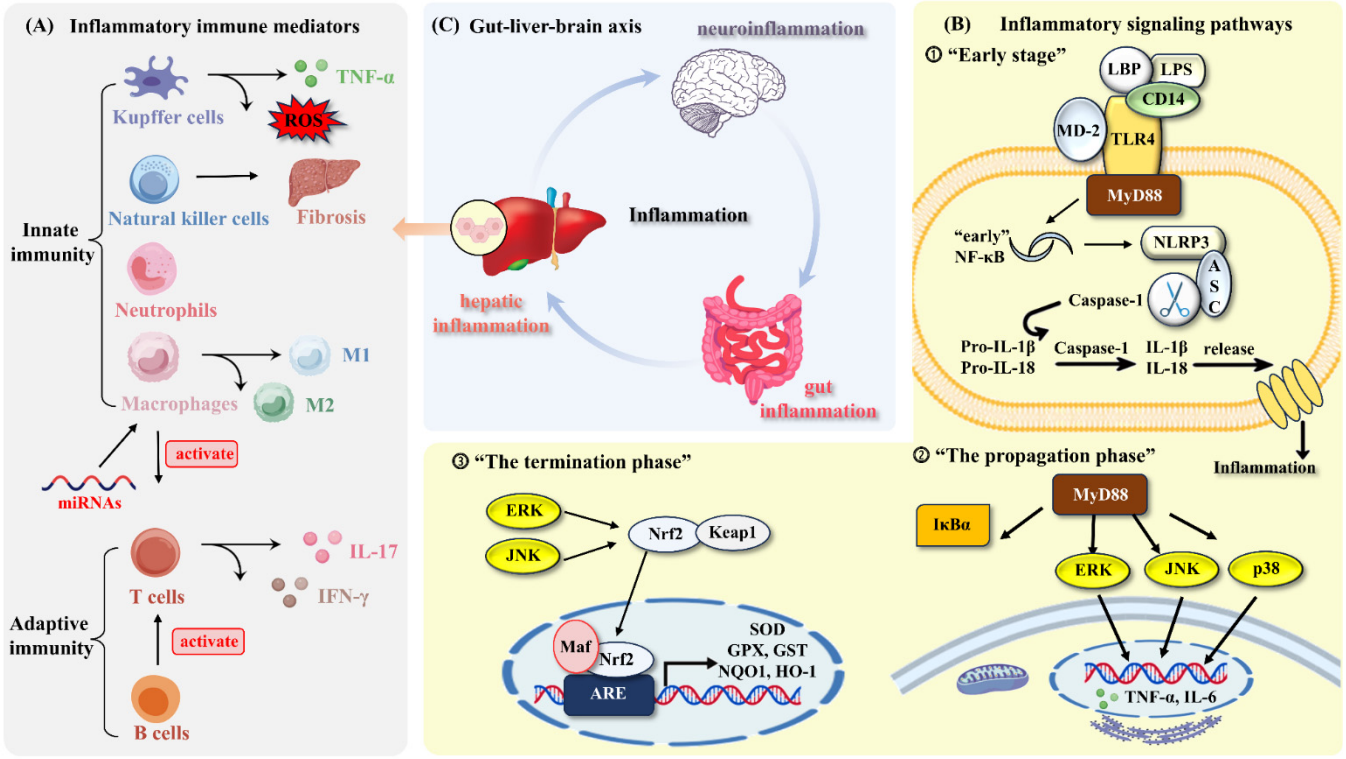

Figure 2. Mechanisms underlying the inflammatory response in the progression of alcohol-related liver injury. (A) inflammatory immune mediator in alcohol liver injury, (B) inflammatory signaling pathways in alcohol liver injury, (C) the gut-liver-brain axis and inflammation connections. Some visual elements were adapted from BioRender.com.

3.3 Connections between the gut microbiome and inflammation

Alcohol alters the composition of the gut microbiome by increasing viral diversity, reducing fungal diversity, and promoting *Candida* overgrowth[57]. On the bacterial side, alcohol decreases the abundance of beneficial microbiota (e.g., butyrate-producing bacteria) and increases inflammation-associated taxa such as *Proteobacteria*, *Enterobacteriaceae*, and *Enterococcus*[58]. Concurrently, microbial metabolites such as butyrate are significantly reduced, whereas LPS levels are markedly elevated. Since the gut microbiota in alcohol-exposed mice or patients with ALD is influenced by various factors, the patterns of microbial

alterations reported across studies often vary considerably. These findings highlight the close interplay between gut microbiota alterations and inflammatory responses in alcohol-related liver disease (Figure 3).

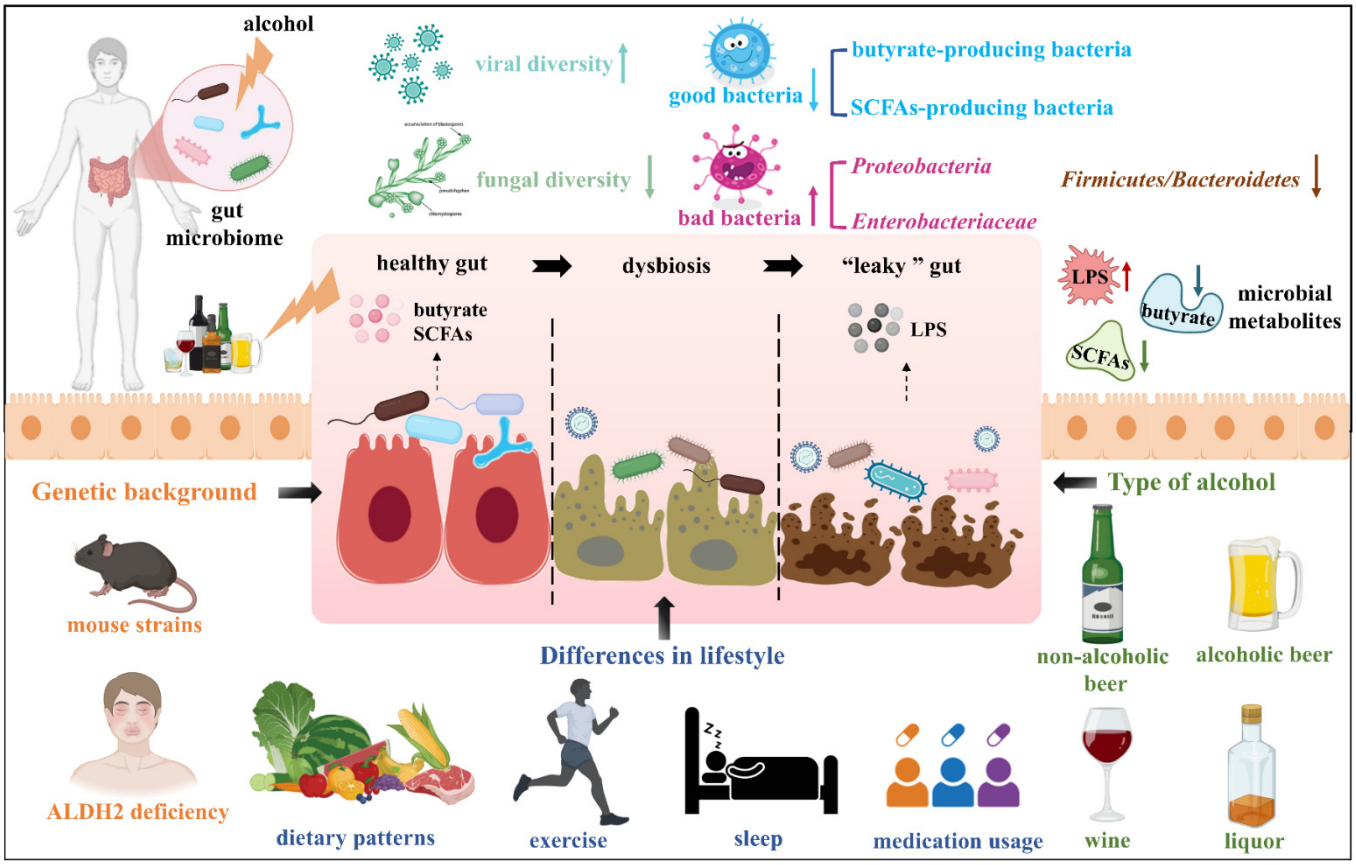

Figure 3. Connections between the gut microbiome and inflammation. Some visual elements were adapted from BioRender.com.

3.3.1 Genetic background

In animal models, distinct mouse strains exhibit varied alterations in gut microbiota and inflammatory responses following alcohol exposure. C57BL/6J mice, known for their high alcohol preference, develop pronounced inflammation, whereas other strains show milder changes[59-60]. These findings suggest that genetic heterogeneity in humans may also contribute to inter-individual variability in gut microbiota response to alcohol. For instance, more than 560 million individuals worldwide, particularly East Asians, carry an inactive mitochondrial ALDH2 variant due to a dominant-negative mutation (*ALDH2**2), which increases their susceptibility to alcohol-associated liver injury. *Aldh2* knockout mice exhibit intestinal microbiota dysbiosis, characterized by a notably elevated relative abundance of the proinflammatory bacteria *Proteobacteria*[61].

3.3.2 Type of alcohol

The type of alcohol consumed, including beer, wine, and spirits, can also affect the composition of the gut microbiota[62]. Recent evidence indicates that beer's effects on the gut microbiota may be largely independent of its ethanol content, with its rich polyphenolic profile playing a pivotal role. The antioxidant properties of phenolic acids in non-alcoholic beer have been associated with improvements in host health,

including enhanced microbial diversity and elevated alkaline phosphatase activity[63]. In contrast, the consumption of alcoholic beers such as stouts correlates with a distinct microbial signature, characterized by an enhanced relative abundance of potentially deleterious taxa (e.g., *Streptococcus*) and a reduction in beneficial genera such as *Blautia* and *Akkermansia*[64]. Previous studies demonstrate that moderate wine consumption enhances gut microbiota α-diversity, enriches key health-associated taxa (e.g., *Akkermansia* and *Eubacterium_fissicatena*) along with their derived metabolites (short-chain fatty acids, SCFAs) and regulates inflammatory responses, likely due to wine's rich polyphenol content[65-67]. Chinese liquor, a common distilled spirit in China, modulates the gut microbiota by enhancing the abundance of beneficial bacteria (e.g., *Lactobacillus* and *Akkermansia*) and elevating serum metabolites associated with anti-inflammatory activity[68-69].

3.3.3 Differences in lifestyle

Various lifestyle factors, such as dietary patterns, exercise, sleep, and medication usage, can modulate the impact of alcohol on the gut microbiota. In particular, irregular diets and nutrient deficiencies may influence these effects through multiple mechanisms. Patients with AUD often consume monotonous diets with imbalanced energy intake. As a result, they exhibit deficiencies in key nutrients, such as dietary fibers, amino acids, and fatty acids, that are essential for the growth of beneficial bacteria[70]. In contrast, bacteria that tolerate alcohol or utilize its metabolic byproducts may thrive under such conditions. Meanwhile, high alcohol intake not only displaces other nutritional components but also directly impairs the intestinal barrier and triggers low-grade inflammation. This inflammatory state disrupts the intestinal microenvironment by promoting the growth of pro-inflammatory bacteria and reducing the abundance of beneficial microbes. The interplay between barrier dysfunction and microbial dysbiosis creates a vicious cycle that further exacerbates gut microbiota imbalance. Ensuring moderate exercise and adequate sleep are conducive to restoring immune function and maintaining gut microbial balance[71-72], suggesting that these measures may partially mitigate the negative impact of alcohol on the microbiome. Although these studies do not directly address alcohol exposure, they support the pivotal role of lifestyle factors in regulating the gut microbial ecosystem and provide a theoretical foundation for further exploration of their interplay with alcohol's effects. Moreover, prolonged or excessive use of antibiotics and other medications can diminish gut microbial diversity and stability, thereby exacerbating the adverse effects of alcohol on the gut[73].

3.4 Inflammation and the gut-liver-brain axis interactions

Alcohol disrupts gut microbiota, leading to an increase in Gram-negative bacteria (such as *Proteobacteria*), which subsequently elevates LPS production. This microbial dysbiosis is also associated with marked alterations in microbial metabolite profiles, notably a reduction in SCFAs production and an increase in secondary bile acid levels. These changes further impair intestinal barrier function. Intestinal barrier disruption is characterized by decreased expression and abnormal localization of tight junction proteins (e.g., occluding and ZO-1), which facilitates the translocation of bacterial endotoxins such as LPS into the portal circulation[60]. Upon reaching the liver, LPS activates hepatic inflammation via the TLR4

signaling pathway, resulting in increased hepatic production of pro-inflammatory cytokines, such as IL-6 and TNF-α[34].

Persistent hepatic inflammation leads to sustained hepatocyte injury and progressive liver fibrosis, which promotes the systemic release of various inflammatory mediators, including cytokines, chemokines, and damage-associated molecular patterns. These inflammatory molecules disseminate through systemic circulation, inducing chronic low-grade inflammation throughout the body[74]. Under these persistent inflammatory conditions, the integrity of the blood-brain barrier (BBB) is compromised, primarily due to increased expression of matrix metalloproteinases (e.g., MMP-9) and disruption of endothelial tight junction proteins (e.g., claudin-5, occludin, and ZO-1)[75]. The compromised BBB facilitates the entry of circulating pro-inflammatory mediators and immune cells into the central nervous system (CNS). Once within the brain, these cytokines activate microglial cells, initiating a neuroinflammatory response that is a hallmark of neurological disorders such as Alzheimer's disease and hepatic encephalopathy[76].

Studies have demonstrated that sustained neuroinflammation significantly affects the structure and function of the mesolimbic system, particularly dopamine-related neuronal circuits associated with reward, such as those in the nucleus accumbens (NAc) and ventral tegmental area (VTA)[77]. Neuroinflammation triggers microglial activation and the subsequent release of numerous pro-inflammatory mediators, which directly act on midbrain dopaminergic neurons. This results in adaptive changes in dopamine neurotransmission and reduced sensitivity of reward circuits[78]. Furthermore, glial activation induced by chronic inflammation disrupts the homeostasis of excitatory neurotransmitters, especially glutamate, within the CNS. Glutamate is the primary neurotransmitter in the central nervous system, essential for neural signal transmission and synaptic plasticity. However, excessive glutamate can induce neurotoxicity under pathological conditions[79]. Prolonged neuroinflammatory states reduce the expression of glutamate transporters, leading to elevated extracellular glutamate concentrations, excitotoxicity, and impaired synaptic plasticity. Consequently, this imbalance in glutamate signaling weakens inhibitory control mechanisms and enhances vulnerability to alcohol addiction and relapse. Chronic alcohol consumption exacerbates these processes by enhancing peripheral inflammation, altering the gut microbiota, and disrupting BBB integrity, thereby amplifying neuroinflammatory responses, as witnessed in AUD patients[80].

Taken together, alcohol-induced neuroinflammation disrupts critical neurotransmitter systems, including dopamine and glutamate pathways, thereby impairing inhibitory control and altering reward sensitivity processing[81]. Therefore, neuroinflammation is not only a key pathological mechanism of alcohol-induced neuronal damage but also an important neurobiological foundation of alcohol addiction and relapse. Targeting neuroinflammation may thus offer promising therapeutic avenues for preventing and treating alcohol dependence.

Given the central role of inflammation in alcohol-related liver injury, increasing attention has been directed toward therapeutic strategies that target inflammatory pathways. Notably, interventions such as

probiotics, prebiotics, synbiotics, and postbiotics have garnered interest due to their capacity to modulate the gut microbiota and reduce inflammatory signaling. These biotic strategies are generally considered as food-grade interventions and offer a favorable safety profile compared to conventional pharmacologic treatments.

4. Inflammation-targeted strategies for improving alcohol-related liver injury: Probiotics, prebiotics, synbiotics, and postbiotics

Probiotics, prebiotics, synbiotics, and postbiotics ameliorate alcohol-induced liver damage by targeting inflammation through multiple mechanistic pathways. Evidence from rodent models is summarized in Table 1, while findings from human studies are presented in Table 2.

Table 1. Comprehensive summary of probiotic, prebiotic, symbiotic, and postbiotic treatment research of alcohol-related liver injury using rodent models.

Intervention （Type and dosage）	Models	Duration	Key results	Ref.
Probiotic: *Levilactobacillus brevis* MG5311 (1×10^9 CFU)	Male C57BL/6J mice	33 days	The hepatic MDA ↓, GPx ↑, and regulate the protein expression levels associated with lipid metabolism.	[85]
Probiotic: *L. rhamnosus* NKU FL1-8 (5×10^9 CFU)	Male C57BL/6J mice	3 weeks	The hepatic gene and protein expressions of TNF-α, IL-6, and IL-1β ↓, and serum LPS ↓.	[86]
Probiotic: *Bifidobacterium lactis* TY-S01 (1×10^9 CFU)	Male ICR mice	28 days	The levels of the hepatic inflammatory cytokines ↓, serum endotoxin ↓, and prevent intestinal microbiota dysbiosis.	[87]
Probiotic: *L. plantarum* J26 (1×10^7, 1×10^8, 1×10^9CFU)	Male C57BL/6J mice	8 weeks	Maintain the mitochondrial homeostasis, and the expressions of Nrf2, NQO1, and HO-1 in the liver ↓.	[88]
Probiotic: *L. plantarum* HFY09 (1×10^9 CFU)	Male Kunming mice	7 days	The level of IL-10 ↑, the levels of pro-inflammatory factors ↓, and the hepatic COX1, JNK, and ERK ↓.	[89]
Probiotic: *Weizmannia coagulans* BC99 (1×10^6, 1×10^7, and 1×10^8 CFU/g·bw)	Male Sprague-Dawley rats	19 days	The CYP2E1 expression ↓, and the activities of antioxidant enzymes ↑ through the Nrf2/SKN-1 pathway.	[92]
Probiotic: 15 strains from *Bifidobacterium* & *Lactobacillus* (7.5×10^9 CFU)	Male C57BL/6 mice	5 days	The hepatic LPS ↓, the relative abundance of *Proteobacteria* ↓, inhibits the TLR4/NF-κB signaling pathway.	[94]
Probiotic: *Escherichia coli* strain Nissle 1917 (10^{10} cells)	Female mice	28 days	The serum IL-1β and TNF-α ↓, hepatic SOD and GSH levels ↑, and the gene expression of TLR4 and NF-κB ↓, inhibit extensive inflammatory cell infiltration in the crypts and lamina propria.	[98]
Probiotic: Human ADH1B-expressing probiotic, a recombinant *Lactococcus lactis* (1×10^9 CFU)	Male C57BL/6J mice	20 minutes	The alcohol absorption ↓, the alcohol tolerance time ↑, alleviates the gut damage and reduces fat content in the liver and blood.	[99]
Probiotic: Selenium-Enriched *L. fermentum* FZU3103 (10^9 CFU/mouse)	Kunming mice	42 days	The transcription of the Cd36 gene ↓, and the transcription of Cyp7a1, Cpt-1, Acox1, and Acsl1 genes ↑, the activities of antioxidant enzymes and alcohol metabolizing enzymes in the liver ↑.	[100]
Probiotic: Selenium-Enriched *L. rhamnosus* GG (10^9 CFU/day)	Kunming mice	42 days	The protein expression of ZO-1, Occludin, and Claudin-1 in the jejunal ↑, and the activities of CAT and GSH-Px ↑.	[102]
Prebiotic: Fructooligosaccharides	C57/B6 mice	1 day, 1/3 week(s)	The intestinal levels of the antimicrobial protein Reg3g ↓, the gut bacterial overgrowth ↓.	[113]
Prebiotic: Psyllium fiber (100 mg/kg)	Male C57BL/6J mice	12 hours	The expression of pro-inflammatory genes such as *Adh1*, *Tnf*, and *Il1b* ↓, and neutrophil frequency↓.	[114]

Intervention （Type and dosage）	Models	Duration	Key results	Ref.
Prebiotic: Lentinan (100, 200, 400 mg/kg)	Male C57BL/6J mice	3 weeks	The hepatic TNF-α, IL-6, and IL-1β ↓, the relative abundance of pathogenic bacteria that induce inflammation (*Osillospiraceae*) ↓, and beneficial bacteria that help anti-inflammatory properties (*Dubosiella* and *Erysipelotrichaceae*) ↑.	[115]
Prebiotic: Pectin (3.9%, 4.5%)	Female C57BL/6J mice	21 days	The mRNA expression in the liver for the CCL2, TGFβ ↓, and IL-10 ↑, the proportion of *Enterobacteriaceae* ↑.	[116]
Prebiotic: Inulin & oligofructose (20%)	Female C57BL/6J mice	10 days	The percentage and the total number of neutrophils in the liver ↓.	[117]
Prebiotic: Butyrylated high-amylose maize starch (5%, 15%)	Female C57BL/6J mice	4 weeks	The ROS and MDA levels ↓, the hepatic CAT, SOD, and GSH ↑, the Nrf2-mediated antioxidant signaling pathway ↑, and the abundance of *Proteobacteria* ↓.	[119]
Prebiotic: Polysaccharides from *Cistanche deserticola* (200, 500, 800 mg/kg)	Male C57BL/6 mice	4 weeks	Reduce the presence of inflammatory cytokines both in serum and liver, and the abundance of *Proteobacteria* and *Enterococcus* ↓.	[120]
Prebiotic: *Enteromorpha prolifera* polysaccharide (5, 10 mg/mL)	Male C57BL/6 mice	27 days	The alcohol metabolism ↑, modulates the Nrf2/HO-1 signaling pathway and restores the levels of lipid metabolites to normalcy.	[121]
Synbiotic: *L. rhamnosus* 1.0320 (10^9 CFU/mouse/d), and Dihydromyricetin (50 mg/kg/d)	Male C57BL/6 J mice	10 days	The levels of IL-1β, MPO, TNF-α and IL-6 ↓, and IL-10 ↑ in the liver.	[129]
Synbiotic: *Faecalibacterium prausnitzii* 27766 (FP) (6log10 CFU/10 μL/) &potato starch (20% *w/v*, 20 μL)	Female C57BL/6 mice	6 h	The expression of E-cadherin in the liver ↑, the number of $F4/80^+$ hepatic macrophages ↑, and intestinal microbial abundance and diversity ↑.	[130]
Synbiotic: Aged garlic extract (AGE) (200 mg/kg) and *L. rhamnosus* MTCC1423 (10^9 CFU)	Male Wistar rats and Caco-2 cells	5 weeks	The colonic inflammatory markers TNF-α and IL-6 ↓, the mRNA expression of ZO-1, occluding, and IL-10 in the colon ↑, and MDA levels in the serum and liver ↓.	[131]
Synbiotic: 11 probiotics (10^9 CFU) and inulin	Male and female C57BL/6J mice	48 days	The escalation and relapse to alcohol intake ↓, and *Akkermansia* and *Ruminococcaceae* UCG-014 ↑.	[132]
Postbiotic: *L. rhamnosus* GG culture supernatant (10^9 CFU)	Male C57BL/6N mice	5 days	The plasma LPS ↓, hepatic TNF-α expression and MPO activity ↓, and intestinal permeability ↓.	[137]
Postbiotic: Heat-killed *L. brevis* SBC8803 (100/500 mg/kg)	Male C57BL/6N mice	35 days	The expression of TNF-α, SREBP-1, and SREBP-2 mRNA in the liver ↓, and the expression of Hsp25 mRNA in the small intestine ↑.	[138]
Postbiotic: A mixture of inactivated yeast and LAB powder) (1.25 g/L)	Male BALB/c mice	14 days	The TNF-α positive areas in the liver ↓, the hepatic inflammatory markers (Ccl2, Ccl3, andTGF-β) ↓, and the relative abundance of *Proteobacteria* ↓.	[139]
Postbiotic: Tributyrin (2.5, 5 mmol/L)	Female C57BL/6 mice	4 days	The plasma LPS ↓and mucosal vascular addressin cell-adhesion molecule-1 (MAdCAM-1) ↓.	[140]
2×10^7 and 2×10^9 CFU/ mL	Male C57BL/6J mice	8 weeks	The serum LPS ↓, the hepatic SOD, CAT, and GPx ↑, and MPO, TNF-α, and IL-6 in the liver ↓.	[142]
Postbiotic: Inactive *L. paracasei* CCFM1120 (5×10^9 CFU/ mL)	Male C57BL/6 mice	20 days	The serum TNF-α, IL-6, and IL-1β↓, the TLR4/MyD88/NF-κB pathway ↓, and butyrate-producing bacteria (*Lachnospiraceae*) ↑.	[143]
Postbiotic: Postbiotic from *L. johnsonii*	Male C57BL/6J Gpt mice	8 weeks	The immunoregulatory substances from gut bacteria ↑, the NOD2-IL-23-IL-22 innate immune axis ↑.	[144]

Table 2 Comprehensive summary of probiotic, prebiotic, symbiotic, and postbiotic treatment research of alcohol-related liver injury using human models.

Intervention （Type and dosage）	Models	Duration	Key results	Ref.

Intervention （Type and dosage）	Models	Duration	Key results	Ref.
Probiotic: Yakult (containing 1.95×10^{10} CFU *L. casei Shirota*)	Alcohol-related cirrhosis patients	28 days	Baseline neutrophil phagocytic capacity ↑, plasma TNFR1, IL-10 ↓, and TNFR2 ↑, and the protein expression of TLR4 ↓.	[103]
Probiotic: *Lacticaseibacillus rhamnosus* R0011& *L. helveticus* R0052 (120 mg)	Males and females AH patients	7 days	The serum LPS ↓, the proportion of *Proteobacteria*, and *Fusobacteria* ↓.	[104]
Probiotic: *L. rhamnosus* GG (10.49×10^{10} CFU)	Males and females with AUD and mAH	1/2/3 month(s)	The ALT: AST ratio ↓, and the heavy alcohol intake ↓.	[105]
Probiotic: *L. casei* (2×10^{10} cells)	ALD patients	60 days	The serum MCP-1, IL-6, IL-1β, TNF-α ↓, and IL-10 ↑, and *Lactobacillus* and *Bifidobacterium* ↑.	[106]
L. casei Shirota	Cirrhotic Patients	6 months	The levels of IL-1β and MCP-1 ↓ in the serum.	[107]
Prebiotic: Inulin (From 4 to 16 g)	AUD patients	17 days	The sociability score ↑, the depression, anxiety, and alcohol craving scores ↓, and serum BDNF ↑.	[126]
Synbiotic: 7 probiotic species (2.5×10^{10} CFU) and 3 prebiotic types (2, 4 grams)	Male AUD patients	8 weeks	The levels of lipopolysaccharide ↓ and immunoglobulin A in the serum ↑.	[133]
Synbiotic: *L. acidophilus* (12.5×10^{9} CFU), *Bifidobacterium lactis* (12.5×10^{9} CFU), and prebiotics Larch Gum	38 healthy participants (21 females and 17 males)	8 weeks	The relative abundances of *L. acidophilus*, and *Bifidobacterium lactis* ↑.	[134]

Abbreviations: MDA: Malondialdehyde, GPX: Glutathione Peroxidase, TNF-α: Tumor Necrosis Factor-α, IL-6: Interleukin-6, IL-1β: Interleukin-1β, LPS: Lipopolysaccharide, IL-10: Interleukin-10, COX-1: Cyclooxygenase-1, COX-2: Cyclooxygenase-2, JNK: c-Jun N-terminal kinase, ERK: Extracellular signal-regulated kinase, Nrf2: Nuclear factor erythroid 2 – related factor 2, NQO1: NAD(P)H: Quinone Oxidoreductase 1, HO-1: Heme oxygenase-1, TLR4: Toll-like receptor 4, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, MCP-1: Monocyte Chemoattractant Protein-1, IL-22: Interleukin-22, MPO: Myeloperoxidase, iNOS: inducible Nitric Oxide Synthase, AMPK: AMP-activated protein kinase, SOD: Superoxide Dismutase, GSH: Glutathione, TNFR1: Tumor Necrosis Factor Receptor 1, TNFR2: Tumor Necrosis Factor Receptor 2, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, CCL-2: Chemokine (C-C motif) ligand 2, CCL-3: Chemokine (C-C motif) ligand 3, TGF-β: Transforming Growth Factor-β, ROS: Reactive Oxygen Species, MDA: Malondialdehyde, CAT: Catalase, BDNF: Brain-Derived Neurotrophic Factor, SREBP-1: Sterol Regulatory Element-Binding Protein-1, SREBP-2: Sterol Regulatory Element-Binding Protein-2, Hsp25: Heat Shock Protein 25, FGF15: Fibroblast Growth Factor 15, CD36: Cluster of Differentiation 36, ChREBP: Carbohydrate-Responsive Element-Binding Protein.

4.1 Probiotics

Probiotics, first introduced in 1974, are defined as "live microorganisms that confer a health benefit when consumed in adequate amounts," a definition established by the Food and Agriculture Organization (FAO) of the World Health Organization (WHO) in 2002. Probiotics are of interest for their capacity to optimize gut microbiota balance, strengthen immune function, and mitigate inflammation, presenting a promising therapeutic approach for alcohol-induced liver injury[82]. Whole genome analyses of *Lactobacillus* and *Bifidobacterium* strains have identified inflammation-related genes, including *DnaK*, *SlpA*, *ltaS*, and *groEL*[83-84].

4.1.1 Preclinical evidence

Common ALD models include acute alcohol exposure, chronic alcohol feeding, and chronic-plus-binge ethanol feeding, with chronic models being the most widely used. Numerous studies have investigated the anti-inflammatory effects of probiotics in alcohol-related hepatic damage, primarily focusing on

Lactobacillus and *Bifidobacterium* genera, including *Levilactobacillus brevis*[85], *L. rhamnosus*[86], *B. lactis*[87], *L. plantarum*[88-89]. Next-generation probiotic candidates such as *Bacillus subtilis*[90], *Roseburia spp.*[91], and *Weizmannia coagulans*[92] also show anti-inflammatory properties. Notably, *Bacteroides thetaiotaomicron* has been proposed as a novel potential probiotic that restores microbial balance and reduces systemic inflammation by enhancing IL-23 expression in intestinal epithelial cells[93].

Probiotics alleviate alcohol-induced inflammation by modulating gut microbiota, strengthening gut barrier integrity, reducing LPS translocation, and limiting TLR4-mediated inflammation[94]. They also reduce mitochondrial dysfunction, suppress oxidative stress, and regulate genes related to mitochondrial dynamics (e.g., *Mfn2* and *Opa1*)[60, 88]. Additionally, psychotropic probiotics such as *L. johnsonii* BS15[95] and *L. casei* ATCC393T[96] impact the microbiota-gut-brain axis, thereby mitigating alcohol-induced neuroinflammation and enhancing brain antioxidant defenses. As a chronic disorder marked by relapse, AUD exacerbates neurofunctional deficits by perturbing the gut microbiota-gut-brain axis and triggering inflammation. Post-antibiotic administration of *LGG* markedly suppresses relapse ethanol intake and hippocampal oxidative stress[97], underscoring the promise of probiotics as an adjunct therapy to combat recurrent neuroinflammation and oxidative stress.

Strain specificity plays a critical role in therapeutic efficacy. Novel strategies involving genetically encoded probiotics expressing enzymes like ADH, ALDH, and oral human ADH1B effectively detoxify ethanol metabolites, mitigating liver and intestinal damage[98-99] Probiotics enriched with trace elements, such as selenium (*L. fermentum* FZU3103 and *L. rhamnosus* GG) and zinc (*L. plantarum* DNZ-4), enhance antioxidant capacity, demonstrating advanced hepatoprotective properties[100-102]. These advanced approaches may represent groundbreaking therapeutic strategies compared to conventional natural probiotics. However, the efficacy of probiotics is not only strain - and disease-specific but also influenced by individual factors such as diet, sex, and microbiota composition. These variables contribute to heterogeneous results, highlighting the need for personalized and high-quality probiotic strains.

4.1.2 Clinical evidence

Stadlbauer et al. conducted an open-label trial demonstrating that *L. casei Shirota* supplementation reduced TLR4 expression while restoring neutrophil phagocytic capacity in patients with compensated alcohol-related cirrhosis[103]. This early study laid the foundation for subsequent probiotic-based interventions in ALD. Subsequent clinical studies explored the roles of *L. rhamnosus*[104-105], *L. casei*[106-107], and *Weizmannia coagulans*[108] in mitigating alcohol-related liver injury. Moreover, combined use of *L. rhamnosus* R0011 and *L. acidophilus* R0052 has been shown to improve liver function and inflammatory markers in patients with alcohol-related hepatitis by reducing gut-derived microbial LPS levels and decreasing the abundance of *Proteobacteria*[109]. Conversely, some clinical trials have found that probiotics did not significantly improve total bilirubin (TBIL), TNF-α, or IL-6 levels in ALD patients[110]. Although substantial progress has been made in understanding the effects of probiotics on early-stage ALD (e.g.,

steatosis and hepatitis), evidence regarding their efficacy in advanced liver disease or hepatocellular carcinoma remains scarce.

Probiotics are generally recognized as safe for human consumption. However, rare cases of infections and bacteremia have been reported, with an estimated incidence ranging from 0.05% to 0.4%. This should be approached with caution in individuals with severe illness or compromised immune function[111]. Moreover, probiotic viability is a critical factor, as adverse environmental conditions during delivery can diminish the number of live microorganisms and compromise their efficacy[112].

In summary, probiotics represent a promising intervention for alcohol-induced liver damage (Figure 4). Supplementing with probiotics or probiotic-fermented foods is beneficial for public health. Furthermore, well-designed clinical trials are required to comprehensively assess their efficacy and safety across different stages of alcohol-related hepatic damage.

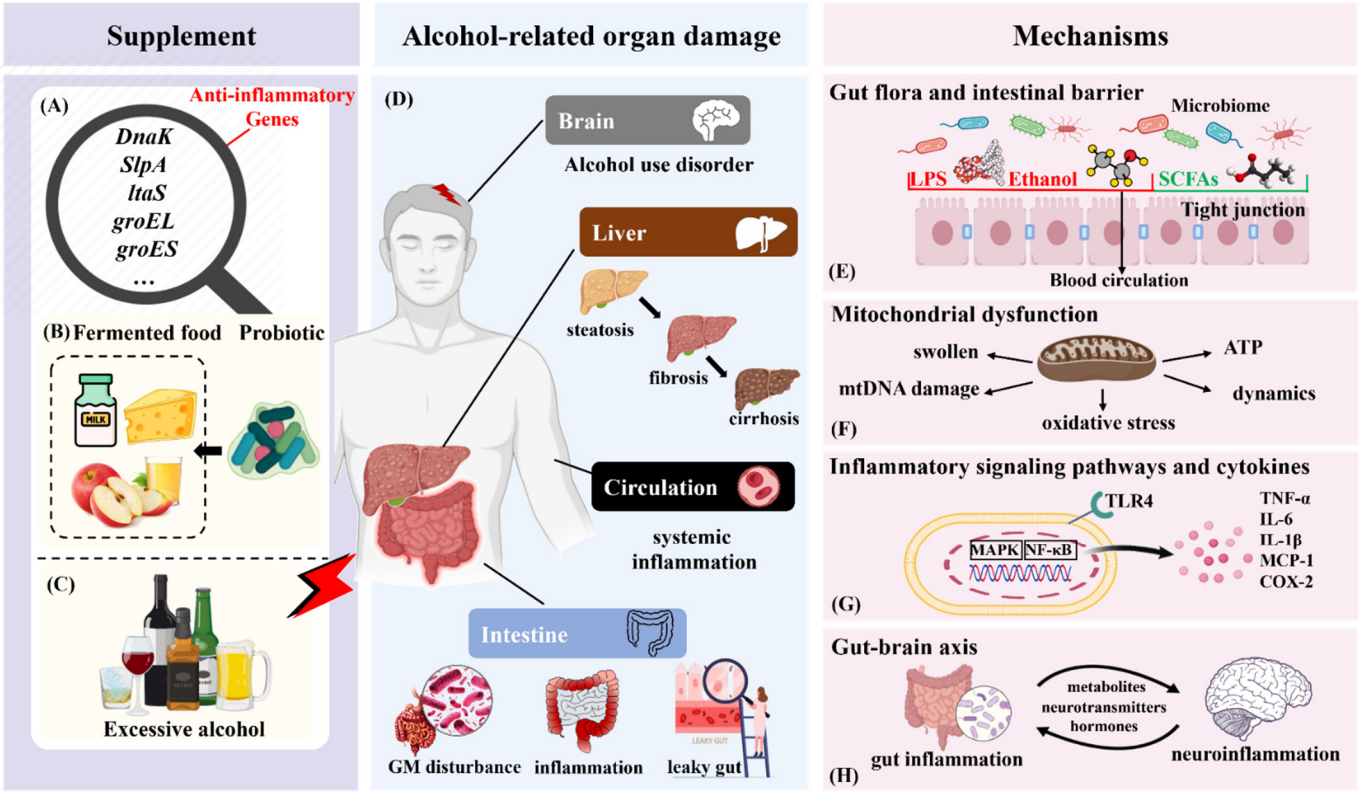

Figure 4. Mechanisms underlying the ameliorative effects of probiotics on alcohol-related liver injury. (A) inflammation-associated genes in probiotic genomes, (B) probiotics and their fermented products, including fermented milk, cheese, apple juice, et al., (C) alcohol, (D) Alcohol-related organ damage, including the brain, cardiovascular system, liver, gut, and systemic circulation, and mechanisms underlying the ameliorative roles of probiotics on alcohol-induced liver damage, including modulating gut flora and intestinal barrier (E), regulating mitochondrial dysfunction (F), inhibiting the activation of inflammatory signaling pathways and secretion of pro-inflammatory cytokines (G), and regulating the gut-brain axis (H). Some visual elements were adapted from BioRender.com.

4.2 Prebiotics

Prebiotics, defined as "substances selectively promoting the growth or activity of probiotics delivering health benefits", modulate hepatic inflammation by altering the gut microbiota[8]. Among prebiotic types, carbohydrate-based prebiotics, including pectin, inulin, fructooligosaccharides (FOS),

galactooligosaccharides (GOS), water-soluble dietary fiber, and certain plant polysaccharides, hold significant therapeutic potential in alcohol-related liver injury (Table 1).

4.2.1 Preclinical evidence

Several animal studies have confirmed that carbohydrate-based prebiotics effectively alleviate alcohol-induced hepatic inflammation. The initial investigation conducted in 2011 indicated that dietary FOS reduced bacterial overgrowth and alleviated alcohol-related steatohepatitis[113]. Subsequent studies demonstrated effects on inflammatory markers[114], gut microbiota[115-117], and inflammatory signaling pathways[118]. Novel prebiotics like resistant starch[119] and polysaccharides[120-121] have also been reported to regulate inflammation and oxidative stress. In addition, a bio-orthogonal layer-by-layer strategy was adopted to coat *L. plantarum* with the prebiotic (β-glucan) as a protective coating, which not only significantly improved probiotics survival in the gut but also enabled colon-targeted release, thereby more effectively regulating the levels of inflammatory factors, improving intestinal flora imbalance, and promoting the production of SCFAs, further enhancing its anti-inflammatory properties and health effects[122]. Notably, Xu et al.[119] developed a butylated high-amylose maize starch (HAMSB), a potent dietary supplement optimized for butyrate production, and demonstrated its efficacy in mitigating acute alcohol-related liver injury by improving hepatic steatosis and gut microbiota composition. Unexpectedly, HAMSB counteracted the alcohol-induced elevation in *Lactobacillus* abundance, which is inconsistent with previous findings. This discrepancy may be attributed to differences in prebiotic type or mechanism. For example, lentinan selectively promotes *Lactobacillus* growth without affecting competition among other metabolically active bacteria. In contrast, HAMSB's butyrate production may drive the expansion of butyrate-producing microbes (e.g., *Faecalibacterium* and *Roseburia*), potentially suppressing *Lactobacillus* proliferation.

However, some studies have reported that an inulin-based high-fiber diet markedly increases eosinophil levels in mice and the relative abundance of *Bacteroides*. This bacterial community produces a large amount of bile acid under the action of bile salt hydrolase (BSH), and bile acid induces epithelial cells and stromal cells to express IL-33, thereby activating innate lymphoid cells type 2 (ILC2) and promoting their secretion of IL-5, ultimately triggering the occurrence of Type 2 Inflammation[123]. This suggests that future research should explore precision dietary interventions, taking into account microbiome composition, immune status, and bile acid dynamics to optimize health benefits while minimizing potential risks. Additionally, the immune effects of various types of dietary fiber across different health and disease states remain to be explored.

4.2.2 Clinical evidence

Prebiotics have potentially shown promise in clinical trials by mitigating alcohol-induced gut dysbiosis and brain impairments. Notably, Amadieu et al. reported a marked reduction in fructan intake (e.g., FOS and GOS) among AUD patients[70], suggesting that supplementation with prebiotic fibers might restore microbial balance and serve as an effective intervention for ALD. Carbohydrate-based prebiotics, including inulin and pectin, promote the growth of beneficial gut microbes, which produce SCFAs, particularly butyrate.

Butyrate, in turn, functions as the principal energy substrate for colonic epithelial cells, fortifying the intestinal barrier and exhibiting potent anti-inflammatory roles. The combined intervention of rifaximin and lactulose significantly reduced the recurrence risk of overt hepatic encephalopathy compared with lactulose monotherapy in patients with alcohol-related cirrhosis[124]. A study by Herting (2025) demonstrated that patients with alcohol-related cirrhosis treated with lactulose had significantly higher mortality compared with non-users. Although lactulose is inherently safe, its role as the first-line therapy for hepatic encephalopathy means that its prescription record serves as a surrogate marker for both advanced disease and the presence of hepatic encephalopathy, thereby accounting for the observed increase in mortality[125]. However, a randomized, double-blind, placebo-controlled trial showed that inulin supplementation failed to alleviate liver damage in AUD patients[126], underscoring the need for further research with larger sample sizes, extended supplementation durations, and comprehensive liver parameter monitoring.

In summary, prebiotics hold significant potential in mitigating alcohol-induced liver damage. Therefore, individuals may reduce the risk of alcohol-induced liver damage by regularly consuming prebiotic-rich foods, including citrus fruits, onions, legumes, chicory root, oats, and whole grains. It is also important to recognize the limitations of prebiotic interventions. High doses of prebiotics may cause gastrointestinal discomfort (e.g., gas and bloating) in ALD patients, and their broad activity may promote the growth of opportunistic pathogens (e.g., *Enterobacteriaceae*)[127]. Furthermore, the effectiveness of prebiotics may be limited in ALD patients with severely imbalanced microbial diversity.

4.3 Synbiotics

By definition, synbiotics are categorized into two types: complementary synbiotics, consisting of probiotics and prebiotics, and synergistic synbiotics, in which substrates are designed to be selectively utilized by microorganisms[128].

4.3.1 Preclinical evidence

Synbiotic supplementation has been shown to protect against alcohol-induced liver damage by reducing hepatic and colonic proinflammatory cytokines, increasing the number of $F4/80^+$ hepatic macrophages, preserving hepatocyte and sinusoidal barrier integrity, and restoring the gut barrier via enhanced SCFAs production[129-131]. Synbiotics have also been shown to mitigate inflammation in adipose tissue by reducing inflammatory markers and oxidative stress.

Interestingly, Pizarro et al.[132] demonstrated that synbiotics exerted sex-specific effects during chronic alcohol intake, alleviating behavioral disturbances and improving gut-brain axis function. Moreover, combinations of probiotics and inulin have been linked with improvements in alcohol-induced anxiety-like behavior and cognitive deficits, specifically in female mice but not males[132]. This intriguing finding clarifies inconsistent synbiotic efficacy and guides the design of sex-specific research.

4.3.2 Clinical evidence

Currently, most research on synbiotics focuses on improving NAFLD, with relatively little attention given to their potential in ALD. A clinical trial involving patients with an Alcohol Use Disorders Identification Test (AUDIT) score of 8 or above reported that a synbiotic formulation not only improved brain function but also reduced alcohol consumption and alcohol dependence in long-term drinkers, as evidenced by significant improvements in AUDIT scores. This highlights the need for further research on the role of synbiotic supplementation in modulating the gut-brain axis to alleviate alcohol-induced neuroinflammation in high-risk heavy drinkers[133]. Notably, Irwin et al.'s clinical trial indicated that an 8-week supplementation of a synbiotics formulation comprising *L. acidophilus*, *Bifidobacterium lactis*, and Larch Gum increased *L. acidophilus* and *Bifidobacterium lactis* abundance. However, this enhancement in bacterial colonization did not lead to measurable improvements in acute alcohol metabolism[134].

Notably, the effects of synbiotic supplementation differ between healthy individuals and critically ill patients. In healthy individuals, synbiotics have been shown to reduce systemic inflammation and lower levels of pro-inflammatory bacteria such as *Parabacteroides*. However, these beneficial effects require a prolonged intervention period, typically lasting at least eight weeks to achieve significant immune modulation[135]. In contrast, synbiotic intervention effectively reduces serum LPS levels and systemic inflammatory markers in critically ill patients. Despite these biochemical improvements, clinical outcomes such as hospital stay duration and mortality rates remain largely unchanged, likely due to the short duration of intervention[135]. This observation suggests that synbiotics may have limited therapeutic efficacy in advanced disease states, such as alcohol-related cirrhosis.

4.4 Postbiotics

Due to limitations associated with probiotics, such as viability challenges, strain-specific effects, and storage instability, postbiotics have gained increasing attention for their exceptional stability and convenience in storage. According to the International Scientific Association for Probiotics and Prebiotics (ISAPP), postbiotics are defined as formulations composed of non-viable microorganisms and their constituents that confer health benefits to the host[136]. Common methods for producing postbiotics include generating cell-free supernatant (CFS), heat inactivation, freeze drying, enzymatic hydrolysis, ultrasonic treatment, and microwave treatment, with CFS and thermally inactivated probiotic strains being the primary forms used in managing ALD.

4.4.1 Preclinical evidence

Various postbiotic formulations have been demonstrated to preserve gut barrier integrity and counteract systemic inflammation. For instance, *L. rhamnosus* GG supernatants[137], heat-killed *L. brevis* SBC8803[138], inactivated lactic acid bacteria (LAB) powder[139], and the postbiotic tributyrin[140] mitigate the alcohol-induced downregulation of tight junction proteins (ZO-1, claudin-1, and occludin). These interventions maintain gut epithelial and microvascular barrier function and restore intestinal microbiota homeostasis by upregulating IL-22[91]. Additionally, dysregulated miRNAs contribute to intestinal inflammation and barrier dysfunction. Alcohol exposure enhances miR-122a expression and decreases

miR-146a levels in intestinal epithelial cells, thereby promoting inflammation and compromising the gut barrier. However, supernatants from LGG cultures protect the gut barrier by suppressing miR-122a levels[141]. Additional strains, including heat-inactivated *L. brevis* PDD-2, *L. paracasei* CCFM1120, and *L. johnsonii*, contribute to ameliorating ALD by reducing oxidative stress, suppressing pro-inflammatory cytokine secretion, interfering with the TLR4 pathway, and activating the Nucleotide-binding oligomerization domain 2 (NOD2) - IL-23 - IL-22 immune axis alongside liver STAT3 signaling[142-144]. Moreover, postbiotic treatment effectively enhanced intestinal immunity and mitigated inflammation in colitis rats, as evidenced by less severe colon tissue impairment and decreases in serum pro-inflammatory cytokines[145-147]. However, some postbiotics fail to exhibit protective effects against alcohol-induced damage. For example, pasteurized *B. acidifaciens* shows no significant improvement in alcohol-induced hepatic inflammation, hepatocyte apoptosis, or lipid metabolism disorders[117]. Similarly, heat- or ultrasound-treated SN13T not only failed to alleviate symptoms of alcohol intoxication but resulted in high mortality, whereas *L. plantarum* SN13T significantly improved these symptoms, highlighting the critical role of microbial viability in determining therapeutic efficacy[148]. Furthermore, postbiotics have been shown to modulate the gut-brain axis by suppressing neuroinflammatory cascades and reducing the production of brain pro-inflammatory cytokines, thereby contributing to neuroprotection[149-150]. These findings highlight the neuroprotective potential of postbiotics and suggest their future therapeutic application in alleviating alcohol-induced neuroinflammation.

Notably, postbiotics cannot proliferate or dynamically regulate the gut microbiota, resulting in transient effects that diminish after the supplementation ends. This passive mode of action may limit their long-term therapeutic potential. Therefore, novel sustained-release or delivery systems for postbiotics, such as microcapsules or liposomes, could be developed to prolong their retention time and activity within the gut.

4.4.2 Clinical evidence

Most current research on postbiotics for ameliorating ALD has been conducted in animal models and in *vitro* experiments. In response to the Global Clinical Trials Forum's call[151], further well-designed randomized controlled trials investigating postbiotics are urgently needed to translate preclinical findings into clinical applications and improve public health outcomes. Future clinical trials should address several critical considerations to ensure the safe and effective implementation of postbiotics. First, although the lack of live microorganisms in postbiotics theoretically reduces the risk of infection, careful surveillance is essential to identify potential adverse effects, including microbial dysbiosis associated with long-term use. Second, the route of administration and dosing regimen are critical determinants of therapeutic efficacy and should be carefully optimized. As the bioactivity of postbiotics components may vary by delivery method, systematic comparisons of administration routes, such as oral and injectable options, are necessary to determine the most effective and safe therapeutic strategy.

In summary, an integrated schematic of the protective mechanisms of prebiotics, synbiotics, and postbiotics against alcohol-related liver injury is presented in Figure 5.

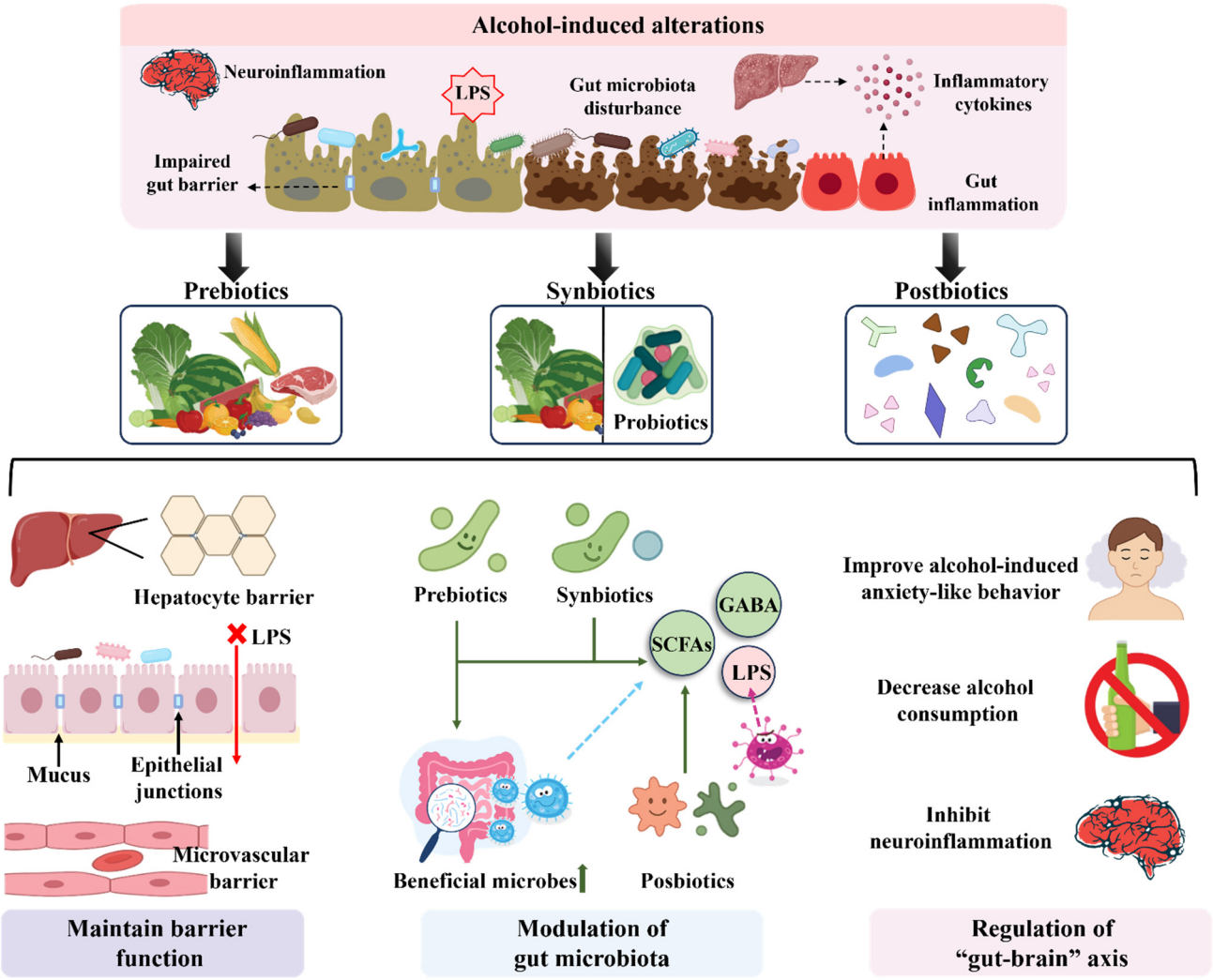

Figure 5. Integrated schematic of the protective mechanisms of prebiotics, synbiotics, and postbiotics against alcohol-induced liver injury. Some visual elements were adapted from BioRender.com.

4.5 Dietary Considerations in Probiotic, Prebiotic, Synbiotic, and Postbiotic Interventions for ALD

Diet is a key determinant of gut microbiota composition and profoundly influences the efficacy of probiotics, prebiotics, synbiotics, and postbiotics in the management of ALD[152-153].

Long-term dietary patterns profoundly impact both the gut microbiome and host inflammation, being associated with either pro-inflammatory or anti-inflammatory microbial profiles[154]. Low-fiber, high-fat, and high-sugar "Western" diets promote the overgrowth of LPS-producing bacteria and reduce beneficial SCFA-producers. This pro-inflammatory microbiome, along with increased intestinal permeability, exacerbates endotoxemia, hepatic inflammation, and neuroinflammation in the context of chronic alcohol consumption[155]. In experimental models, obesity or a high-saturated-fat diet synergistically aggravates alcohol-induced liver damage compared to balanced diets. By contrast, plant-based diets rich in vegetables, legumes, and whole grains support a diverse microbiota that produces anti-inflammatory metabolites, improves gut barrier integrity, and reduces LPS translocation, thereby alleviating liver stress. In particular,

plant-based foods rich in dietary fiber and pectin serve as prebiotic substrates that can synergize with probiotics to form dietary synbiotics, thereby enhancing the protective effects of probiotics against ALD.

Recently, fermented foods have gained increasing attention due to their safety and hepatoprotective properties. Probiotic fermented foods, including LAB-fermented dairy products[156-158] and plant-based fermented foods[159-160], are rich in both viable probiotics and fermentation-derived metabolites, such as SCFAs, bioactive peptides, polysaccharides, and antioxidant compounds[161-162]. They primarily ameliorate ALD by reducing serum alcohol levels and hepatic pro-inflammatory factors, inhibiting the NF-κB signaling pathway, and modulating gut microbiota composition. In addition, polyphenol-rich foods such as berries and citrus fruits exhibit synergistic effects with probiotics in suppressing inflammation and mitigating liver injury. These polyphenols are partially metabolized by the gut microbiota into bioactive compounds with anti-inflammatory and antioxidant properties[163]. Probiotic strains, particularly *Lactobacillus* species, can enhance polyphenol bioavailability and further amplify their protective effects[164]. Recent studies suggest that combining probiotics with polyphenol-rich compounds, such as goji berry puree and dihydromyricetin, can suppress the levels of hepatic and colonic inflammatory cytokines following acute alcohol exposure and modulate gut microbiota composition[129, 165]. These interactions offer promising opportunities for integrated dietary strategies in the management of ALD.

In addition to dietary factors, safety considerations are critical when implementing probiotics, prebiotics, synbiotics, and postbiotics for managing ALD. Although generally recognized as safe, particularly those with GRAS (Generally Recognized As Safe) status and Drug Administration or QPS (Qualified Presumption of Safety) status, such interventions may still pose risks in vulnerable populations, including immunocompromised individuals, critically ill patients, and neonates[136, 166]. Therefore, a thorough evaluation of strain specificity, dosage, host condition, and possible microbial interactions is necessary in both preclinical and clinical applications.

4.6 Similarities and Differences Among Probiotic, Prebiotic, Synbiotic, and Postbiotic Strategies for ALD

Although probiotics, prebiotics, synbiotics, and postbiotics differ in composition and biological characteristics, they share overlapping therapeutic roles in ALD. This section summarizes the similarities and differences among these strategies in terms of mechanisms of action, clinical applications, and safety profiles, providing a comparative perspective for their potential use in ALD management.

4.6.1 Similarities

Probiotics, prebiotics, synbiotics, and postbiotics all demonstrate therapeutic potential in ALD, primarily through modulation of the gut-liver axis and regulation of inflammatory responses. These strategies share several common mechanisms, including modulation of intestinal microbiota composition, enhancement of gut barrier integrity, and suppression of key inflammatory pathways such as TLR4, NF-κB, and MAPK signaling pathways. They also exhibit antioxidant properties by upregulating endogenous defense systems (Nrf2/HO-1 signaling pathway) or increasing microbial metabolites like SCFAs[8, 10].

In addition to their mechanistic convergence, these biotic interventions share practical and biological features that further underscore their therapeutic relevance. All four strategies are fundamentally dependent on the host's gut microbial ecosystem, either by modulating existing microbial communities (probiotics, prebiotics, synbiotics) or by exerting functional effects through microbial-derived metabolites and structural components (postbiotics)[167]. This microbiota-centered mode of action underscores the importance of a receptive microbial environment for efficacy. Moreover, their delivery through oral administration facilitates their integration into functional food applications. This approach enhances patient adherence and supports current dietary strategies aimed at regulating the gut microbiota for the management of ALD[168].

4.6.2 Differences

Mechanistically, probiotics exert protective effects by colonizing the gastrointestinal tract, mitigating alcohol-induced microbiota disturbances, reducing endotoxin translocation, and suppressing inflammatory signaling pathways[169]. In contrast, prebiotics function indirectly by selectively promoting the growth and activity of beneficial microbes, leading to increased production of SCFAs (butyrate), which exert potent anti-inflammatory effects in alcohol-induced mouse and human models[170]. Synbiotics combine probiotics and prebiotics, aiming to exert synergistic effects. They not only enhance microbial colonization but also improve intestinal SCFAs levels, resulting in amplified modulation of immune signaling[10]. Nevertheless, their effectiveness depends on the compatibility between probiotic strains and prebiotic substrates. Postbiotics, consisting of inactivated microorganisms and their metabolites, provide a stable alternative to live probiotics[171]. They improve gut barrier function, regulate cytokine production, suppress oxidative stress, and exhibit neuroprotective properties[137, 142-143, 149].

The clinical applications of these four strategies also differ, reflecting variations in safety, stability, and suitability for specific patient populations. Probiotics and synbiotics show promise in both early and moderate stages of ALD but may pose infection risks in immunocompromised individuals[10]. Prebiotics are generally considered safe; however, high doses may cause gastrointestinal discomfort[127]. Although postbiotics are often considered to be safer than probiotics due to the absence of live microorganisms, the safety of the source strain does not necessarily guarantee the overall harmlessness of the postbiotics product[172]. Therefore, dedicated regulatory guidelines are needed to address their potential risks and ensure safe application.

5. Conclusions and Future Research Directions

ALD has emerged as a major global health concern, contributing to significant economic, social, and public health burdens due to its chronic progression and severe complications. This review highlights the therapeutic potential of modulating the inflammatory response in preventing and treating ALD, partly attributable to the immunomodulatory properties of probiotics, prebiotics, synbiotics, and postbiotics. These agents exert anti-inflammatory effects through multiple mechanisms, including improving microbiome dysbiosis, suppressing inflammatory signaling activation, ameliorating mitochondrial dysfunction, and inhibiting neuroinflammation by regulating the gut-brain axis. Despite their promising anti-inflammatory

potential in ALD, the underlying mechanisms of probiotics, prebiotics, synbiotics, and postbiotics remain incompletely understood, necessitating further investigation:

(I) During the research, these biotic therapies still face some challenges, such as stability, efficacy, and host variability. Therefore, future studies should focus on personalized biotic interventions and advanced delivery technologies (e.g., microencapsulation)[173-176] to overcome these limitations and improve the translational application in ALD management.

(II) A clear mechanistic link between alcohol metabolism, inflammation, and gut-immune interactions remains elusive. Over the past two decades, the application of omics technologies, including microbiome profiling, proteomics, transcriptomics, and genomics, to both preclinical and clinical models of ethanol-induced liver damage has provided valuable insights into the signaling pathways that drive disease progression[177]. Future research should systematically elucidate the complex interactions between the microbiota and host immune responses to better delineate the regulatory mechanisms by which various bioagents modulate key inflammatory signaling pathways.

(III) Despite advancements, the current approaches for predicting, classifying, and prognosticating ethanol-induced liver damage remain limited by the lack of robust diagnostic biomarkers and the constraints of traditional methodologies. AI and machine learning models have shown promise in utilizing multi-omics approaches to identify diagnostic biomarkers and improve the prediction, classification, and prognosis of ALD[178-179]. By integrating deep learning techniques with clinical data through multi-center collaborations that generate large-scale omics datasets, future studies can fully harness the potential of AI to advance research in this field. This approach would not only facilitate the development of AI-based predictive models but also enable the identification of biomarkers directly associated with the roles of probiotics, prebiotics, synbiotics, and postbiotics.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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