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The potential of short-chain fatty acids-producing probiotics as a treatment for liver disease: a systematic review

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ABSTRACT

Recent insights reveal that liver diseases influence not only hepatic function but also disrupt gut microbial balance through the gut–liver axis. The gut–liver axis establishes a bidirectional relationship between the intestines and the liver, allowing microbial by-products such as short-chain fatty acids (SCFAs) to influence liver function and health. Short-chain fatty acids are known to maintain intestinal epithelial integrity, reduce inflammation, and support liver function. Probiotic bacteria including *Lactobacillus, Bifidobacterium,* and *Clostridium*, are natural SCFA producers and may offer therapeutic potential for liver disease by targeting the gut-liver axis. This systematic review was conducted using the PRISMA 2020 methodology to identify and evaluate preclinical studies examining the impact of SCFA-producing probiotics on liver disease. We searched PubMed, Scopus, and Google Scholar from August to October 2023, using predefined inclusion criteria based on the PICO framework. The SYRCLE risk of bias tool was employed to evaluate potential biases. A total of 14 animal studies fulfilled the inclusion criteria and were incorporated into the final analysis. The included studies demonstrated that SCFA-producing probiotics improved liver function by reducing serum liver enzymes (ALT, AST), increasing tight junction proteins (occluding, ZO-1), modulating pro-inflammatory cytokines (IL-1β, IL-6, TNF-α,), and improving lipid metabolism. These outcomes were mediated by increases in SCFA levels and improved gut barrier integrity in models of NAFLD, ALD, NASH, and autoimmune hepatitis. These findings support the promising potential of SCFA-producing probiotics as adjunctive therapies for liver disease through modulation of the microbiota-gut-liver axis. Yet, continued research is needed to determine strain-specific efficacy, optimal dosage, long-term safety, and clinical applicability. Future research should also explore personalized probiotic strategies and the integration of probiotic therapy into standard liver disease management.

Keywords:
liver disease;
probiotics;
short-chain fatty acids;
gut-liver axis;
liver enzymes

ABSTRAK

Mikrobiota usus diketahui memiliki hubungan erat dengan berbagai penyakit hati, seperti sirosis, *non-alcoholic fatty liver disease* (NAFLD), dan *alcoholic fatty liver disease* (ALD). Sumbu usus-hati menghubungkan usus dan hati, memungkinkan metabolit mikroba seperti asam lemak rantai pendek (*short-chain fatty acids*/SCFA) untuk memodulasi kesehatan hati. Asam leman rantai pendek diketahui dapat menjaga integritas epitel usus, mengurangi peradangan, dan mendukung fungsi hati. Bakteri probiotik seperti *Lactobacillus, Bifidobacterium*, dan *Clostridium* merupakan penghasil SCFA alami dan dapat menawarkan potensi terapeutik untuk penyakit hati dengan menargetkan sumbu usus-hati. Tinjauan sistematis ini dilakukan menggunakan metodologi PRISMA 2020 untuk mengidentifikasi dan mengevaluasi studi praklinis yang menyelidiki efek probiotik penghasil SCFA pada penyakit hati. Kami mencari di PubMed, Scopus, dan Google Scholar dari Agustus hingga Oktober 2023, menggunakan kriteria inklusi yang telah ditentukan berdasarkan kerangka kerja PICO. Risiko bias dinilai berdasarkan SYRCLE. Empat belas penelitian pada hewan memenuhi kriteria inklusi dan dimasukkan dalam sintesis akhir. Penelitian yang disertakan menunjukkan bahwa probiotik penghasil SCFA meningkatkan fungsi hati dengan mengurangi enzim hati serum (ALT, AST), meningkatkan protein *tight junction* (ZO-1, occludin), memodulasi sitokin pro-inflamasi (IL-1β, IL-6, TNF-α), dan meningkatkan metabolisme lipid. Efek-efek ini dimediasi oleh peningkatan kadar SCFA dan peningkatan integritas penghalang usus pada model NAFLD, ALD, NASH, dan hepatitis autoimun. Temuan ini mendukung potensi yang menjanjikan dari probiotik penghasil SCFA sebagai terapi tambahan untuk penyakit hati melalui modulasi sumbu mikrobiota-usus-hati. Namun, penelitian lanjutan diperlukan untuk menganalisis kemanjuran spesifik strain, dosis optimal, keamanan jangka panjang, dan penerapan klinis. Penelitian di masa depan juga harus mengeksplorasi strategi probiotik yang dipersonalisasi dan integrasi terapi probiotik ke dalam manajemen penyakit hati standar.

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INTRODUCTION

Gut microbiota is an association of microorganisms—comprise by bacteria, fungi, viruses, and archaea—that inhabit and colonize the gastrointestinal tract.[1] The human digestive tract represents a large ecosystem of microbiota. Research shows that there are at least 9.9 million microbial genes based on analysis of human fecal samples from 1,200 individuals across the United States, China, and Europe.[2] Approximately 2 kg of microbes inhabit adults' digestive tract, with around 100 trillion microbes. This number is nearly tenfold higher than the total number of human host cells.[3]

Gut microbial community contributes significantly to development of host immunity and disease resistance. Several studies report the influence of gut microbial composition on the development of atherosclerosis, metabolic disorders, asthma, autism spectrum disorder (ASD), and various liver disorder.[1,4] Those incidences may be attributed to the interconnected roles of the gut-brain and the gut-liver axes. The gut-brain axis generally reflects bidirectional communication between the digestive system and the central nervous system. The gut-brain axis regulates many physiological functions, such as appetite control, energy intake, glucose and lipid metabolism, insulin production and responsiveness, and bone homeostasis.[5] The gut-liver axis refers to bidirectional interaction linking the intestines (including microbiota and the compounds therein) and the liver. The gut-liver axis mediates bacterial translocation from the gastrointestinal system to hepatic tissue. Bacterial toxins, especially lipopolysaccharides (LPS), reach the liver and generate the LPS-cluster of differentiation (CD)-14 complex, spurring the production of pro-inflammatory mediators, including interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ.[6,7] Through this mechanism, the intestinal microbiota can stimulate inflammation in the liver.

Liver disease is almost always followed by dysbiosis, namely an altered gut microbial profile, modified metabolic activity, or uneven bacterial distribution within the intestine.[7–9] Short-chain fatty acids (SCFA) are formed by anaerobic microorganisms from the catabolism of food ingredients that are indigestible in the intestines. Bifidobacteriaceae, such as *Bifidobacterium longum*, can generate the SCFA acetate and lactate, whereas the Lachnospiraceae family, *Clostridium* XIVa, and *Blautia* were able to produce butyrate.[10] Short-chain fatty acids serve as key regulators of the "intestinal flora-immune axis". Short-chain fatty acids can increase the growth of intestinal mucosal epithelial cells, and help preserve mucosal integrity, preventing epithelial atrophy. Additionally, they inhibit the expression of various pro-inflammatory factors, thereby minimizing inflammation-related damage in both intestine and liver.[7] A decrease in SCFA production, commonly observed in dysbiosis, has been linked to increased gut barrier permeability and liver inflammation. Restoration of SCFA levels is therefore considered as a novel therapeutic approach for liver disorders.

Probiotics are defined as live microorganisms that provide health benefits to the host when consumed in sufficient quantities. These probiotics strains are widely incorporated into fermented foods or formulated as nutritional supplements. Among the most widely studied probiotic genera are *Lactobacillus*, *Bifidobacterium*, and certain species of *Clostridium*, which are known for their capacity to synthesize SCFAs like acetate, propionate, and butyrate. These SCFA-producing probiotics are essential for maintaining intestinal balance, supporting immune regulation, and preserving intestinal

barrier integrity—all of which are central in preventing or mitigating liver disease through the gut-liver axis. Their dual role as both probiotics and SCFA producers makes them a compelling candidate for liver disease intervention along the gut-liver signaling pathway.

Given the growing evidence linking gut microbial dysbiosis, SCFA deficiency, and liver disease progression, this systematic review designed to evaluate and summarize preclinical studies exploring how SCFA-producing probiotics affect liver disease in animal models. In this review, we systematically identify, assess, and synthesize studies examining probiotic interventions aimed to increase SCFA level and their impact on liver damage and intestinal barrier function in the context of liver disease.

MATERIAL AND METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020.[11] During August-October 2023, the author conducted a systematic review by searching multiple databases that contained research findings on the relatable topic, including PubMed, Scopus, and Google Scholar. The eligibility of the study topic will be determined using the Population Intervention Comparison Outcomes (PICO) methodology. The PICO is a method used to dissect clinical issues into keywords that may be easily searched.[12] For the research to qualify, studies had to meet the following criteria:

The article's results from animal liver disease models, evidence of alterations in liver injury markers, and reports of the addition of SCFA-producing bacteria or increased SCFA in the gut were among the inclusion criteria for this study. We excluded the article review and the article that did not report changes in the liver injury marker and did not use animal liver disease models. A combination of short-chain fatty acids, bacteria, probiotics, liver cirrhosis, and their synonyms was used in this instance. After searching all databases using these keywords, 304 articles were found. Additionally, we removed eighteen duplicate articles. Potentially eligible titles' abstracts were filtered. Out of the total of 286 items that may have been considered, 272 were determined to be ineligible. Since they still need to meet the inclusion and exclusion standards. Fourteen papers met the inclusion standards and were qualified for evaluation. We used the SYRCLE risk of bias tool, developed by Systematic Review Centre for Laboratory Animal Experimentation, to assess study quality.[13] FIGURE 1 present the procedure followed for article selection.

RESULTS

Risk of bias and quality of included studies

TABLE 2 present the risk of bias assessment outcomes for the 14 studies included in this systematic review. The risk of bias in all included studies was unclear. Several common limitations were identified across the included studies, including insufficient randomization, poor allocation concealment, limited description of baseline characteristics, and a lack of detail information regarding whether the animal assessor was blinded or not.

TABLE 1. PICO table to determine the eligibility of the research question

Criteria	Determinants
Population	Animal model studies of liver disease of any etiology.
Intervention	Any form of administration of probiotics or short-chain fatty acid-producing bacteria that may increase SCFA concentrations.
Comparison	Non-intervention or administration of other drugs.
Outcomes	Studies should assess changes in liver injury markers.

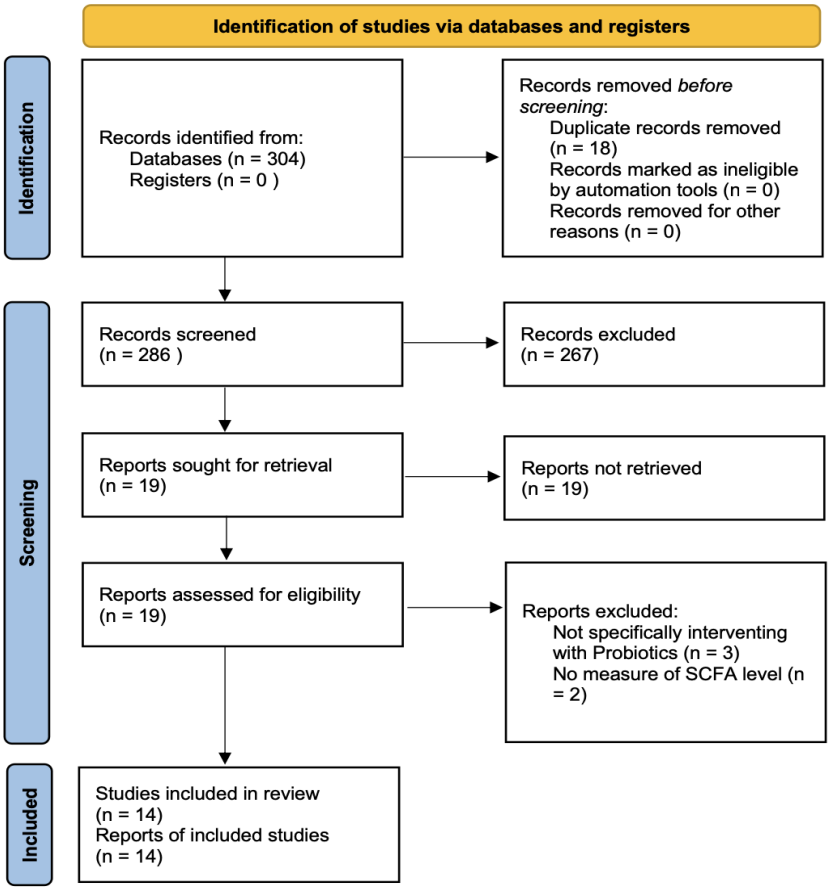

FIGURE 1. Study selection diagram flow

TABLE 2. Risk of bias assessment

First author, year	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Yoon *et al.*[14]	U	U	U	+	-	+	U	+	+	+
Jiang *et al.*[15]	U	+	U	+	+	+	U	+	+	+
Hong *et al.*[16]	U	U	U	U	U	+	U	+	+	+
Yan *et al.*[17]	U	U	U	+	-	+	U	+	+	+
Liang *et al.*[18]	U	U	U	+	U	+	U	+	+	+
Zhang *et al.*[19]	U	U	U	+	+	+	U	+	+	+
Zheng *et al.*[20]	U	+	U	+	-	+	U	+	+	+
Endo *et al.*[21]	U	+	U	U	U	+	+	+	+	+
Yang *et al.*[22]	U	-	U	+	U	+	U	+	+	+
Li *et al.*[23]	U	U	U	+	-	+	U	+	+	+
Wang *et al.*[24]	U	+	U	-	-	+	U	+	+	+
el-Din *et al.*[25]	U	U	U	+	U	+	U	+	+	+
Cao *et al.*[26]	U	U	U	+	U	+	U	+	+	+
Zhou *et al.*[27]	U	U	U	+	U	+	U	+	+	+

(1) Sequence generation; (2) Baseline characteristics; (3) Allocation concealment; (4) Random housing; (5) Blinding; (7) Random outcome assessment; (7) Blinding; (8) Incomplete outcome data; (9) Free of selective outcome reporting; (10) Other sources of bias; U indicates unclear; + indicates that the criterion was met; - indicates that the criterion was not met.

Description of included studies

Among the 14 included studies, various models of liver disease were used, including alcoholic liver disease (ALD), autoimmune hepatitis, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The majority of studies administered SCFA-producing probiotics such as *Bifidobacterium*, *Clostridium,* and *Lactobacillus* strains, either individually or in combination, over treatment durations ranging from 4 to 12 wk. The summary of the selected paper is shown in TABLE 3.

Several studies reveal the effectiveness of SCFA-producing bacterial supplementation in reducing liver disease. Hong *et al.*,[16] found that *Desulfovibrio vulgaris* effectively reduces hepatic steatosis in mice, probably via generating acetic acid and modulating hepatic lipid metabolism. Additional investigation revealed that the supplementation of *L. acidophilus* KLDS1.0901 elevated the SCFA level, enhanced the epithelial barrier function, diminished the synthesis of inflammatory cytokines, and provided protection against injury to the hepatic and colon tissues. Additionally, it controls the expression of genes involved in glucose and fat metabolism by downregulating the expression of GSK-3β, FAS, and SREBP-1c while upregulating Akt expression.[17] Liang *et al.*,[18] also show the improvement effect of SCFA-producing probiotic compound supplementation in NAFLD rats. The administration of compound probiotics consisting of *Lactobacillus* and *Bifidobacterium* results in a significant decrease in body weight, fat accumulation, as well as hepatic TC, TG, and circulating levels of ALT, FFA, IL-1β, IL-18, LPS, and TG.[18]

Two studies reported improvements in microbial diversity following supplementation with specific probiotic strains. Zhang *et al.*,[19] observed dysbiosis in an autoimmune hepatitis (AIH) mouse model, characterized by a reduction in *Lactobacillus* and increases in *Bacteroides* and *Ruminococcus*. After five weeks of supplementation with *B. animalis*, microbial composition shifted,

with *Lactobacillus* levels increasing and *Bacteroides* and *Ruminococcus* decreasing. Similarly, Zheng *et al*.,[20] reported that feeding mice a high-fat diet resulted in higher abundance of *Ruminiclostridium, Romboutsia*, and Lachnospiraceae_UCG_006, while beneficial genera such as *Bifidobacterium*, *Desulfovibrio, Faecalibaculum, Lactobacillus,* and *Ruminococcaceae_* UCG_014 were significantly lower than in the normal control group. Among the probiotic strains tested, *L. reuteri* FGSZY33L6 was associated with modulation of Desulfovibrioceae and *Romboutsia*, whereas *L. rhamnosus* FJSYC4-1 impacted, *Lachnospiraceae_* UCG_006, *Lactobacillus,* and *Ruminiclostridium*. Zhang *et al*.,[19] also showed that supplementing *L. gasseri* RW2014 in hepatic steatosis model rats resulting in reduction in a relative abundance of harmful bacteria, such as *Bacteroides* and *Ruminococcus*. In contrast, the abundance of *Lactobacillus* was restored.[19]

TABLE 3. SCFA-producing probiotics as a treatment in liver disease

Liver disease	Age, species	Probiotics, dosage	Treatment duration	Effects	Ref
NAFLD	6 wk old, male C57BL/6 J mice	*B. breve* CKDB002 and *B. longum* CKDB004, 10^9 CFU/g	9 wk	AST, ALT, TBIL, Cholesterol↓ NAFLD activity score (NAS)↓ SCFA and Tryptophan ↑ Sterol regulator element-binding protein-1 (SREBP-1c) ↓ Peroxisome proliferator–activated receptor α (PPARα) ↑ TNF-α, IL-6 and IL-1β↓	Yoon *et al*.[14]
ALD	8 to 10wk old, C57BL/6 mice	*P. pentosaceus* CGMCC 7049, 2 × 10^9 CFU	10 d	ALT and AST ↓ Lipopolysaccharide-binding protein (LBP) ↓ TLR4↓ IL-5, TNF-α, Macrophage inflammatory protein-1 alpha (MIP-1α) and Monocyte chemoattractant protein-1 (MCP-1)↓ Acetic acid, propionic acid, butyric acid, isobutyric acid, 2-methylbutyric acid, and valeric acid↑ ZO-1 and Mucin 2↑	Jiang *et al*.[15]
NAFLD	4 wk old, male C57BL/6 J mice	*D. vulgaris*, 1 × 10^9 CFU	12 wk	Acetic acid↑ Fatty acid synthase (FAS), CD36, and Glucokinase↓ PPAR-α ↑ IL-1β and TNF-α ↓	Hong *et al*.[16]
Liver injury by hepatic lipid	3 wk old, male C57BL/6J mice	*L. acidophilus* 34 KLDS1.1003 and KLDS1.0901, 1 × 10^9 CFU/day	6 wk	IL-8, TNF-α and IL-1β↓ FAS, SREBP-1c↓ Kinase Akt↑ SCFA↑	Yan *et al*.[17]
NAFLD	6 wk old, male Sprague Dawley rats	*L. casei* Zhang ≥10×10^{10} CFU, *L. plantarum* HM-P8 ≥10×10^{10} CFU, *L. paracasei* HM-P9 ≥5×10^{10} CFU, *L. rhamnosus* HM-R1 ≥5×10^{10} CFU, *L. acidophilus* HM-A2 ≥5×10^{10} CFU, *L. bulgaricus* HM-B1 ≥5×10^{10} CFU, *B. lactis* HM-V9 ≥10×10^{10} CFU, *B. adolescentis* HM-A1 ≥5×10^{10} CFU, *B. longum* HM-L4 ≥5×10^{10} CFU	16 wk	Weigh, fat vacuoles, and fat accumulation↓ Total cholesterol, TG, LDL, and FFA↓ Hepatic sinusoid and cord structure↑, LPS, TNF-α, IL-1β, IL-18↓ AST and ALT↓ SCFA levels↑	Liang *et al*.[18]

TABLE 3. Cont.

Liver disease	Age, species	Probiotics, dosage	Treatment duration	Effects	Ref
Autoimmune hepatitis	6 wk old, female C57BL/6 mice	*B. animalis ssp. Lactis* 420, 10^9 CFU/200ul	4 wk	SCFA levels↑, AST and ALT↓, Microbial alpha diversity↑ ZO-1 and Occludin↑ TNF- α, IL-6 and IL-1β↓	Zhang *et al.*[19]
MS is linked to NAFLD	5 wk old, male C57BL/6J mice	*L. rhamnosus* FZJJH6L2, *L. rhamnosus* FJSYC4-1, *L. reuteri* FGSYC2L3, *L. reuteri* FGSZY33L6, (5×10^9 CFU)	12 wk	Weight gain, food intake, and energy efficiency↓ TC, LDL-C and LDL-C/HDL-C↓, IL-6 ↓ Butyric acid↑ Microbial alpha diversity↑	Zheng *et al.*[20]
NAFLD	N/A, male Fischer 344 rats	*C. butyricum* (8.5 x 10^9 CFU/g	8 wk	Adenosine monophosphate protein kinase (AMPK) phosphorylation↑, PPAR-α↑, SREBP-1c, uncoupling protein 2 (UCP2), and PPAR-γ↓, Serum endotoxin↓ ZO-1 and occludin↑ NF-kB, ALT, and TNF-α↓, 4-Hydroxynonenal (4-HNE) and malondialdehyde (MDA)↓, Hepatic protein levels of fibrosis-related factors (α-SMA and collagen I)↓ Placental glutathione S-transferase (GST-P) ↓, heme oxygenase 1 (HO1), and NAD(P)H quinone oxidoreductase 1 (NQO1)↑	Endo *et al.*[21]
NAFLD	8 wk old, male C57BLKS/J background Lepdb/Lepdb (db/db) rats	*C. butyricum*, 5×10^7 CFU kg^{-1}	6 wk	ZO-1 and occludin↑ IL-1β, IL-6 and TNF-α↓ TGR5 protein and GLP-1↑ ALT, AST, and ALP levels↓ Size of fat vacuoles, body, and liver weight ↓ TLR4, MyD88, NF-κB↓ LDLC, TC, and TG levels↓ Lipid droplet accumulation in the liver↓	Yang *et al.*[22]
Hepatic steatosis	N/A, Sprague Dawley rats	*L. gasseri* RW2014, 2×10^9 CFU/mouse	5 wk	IL-6, IL-1β, TNF-α, MCP-1↓ SCFA (isovaleric acid, isobutyric acid, valeric acid, butyric acid, and hexanoic acid) ↑ Fecal Bile Acids↑	Li *et al.*,[23]
NAFLD	4 wk old, male C57BL/6J mice	*L. rhamnosus*: LGG, L7-1, L10-1; *B. adolescentis*: BA3, BA5, Z25; 1.0×10^9 CFU/mL	23 wk	Weight gain↓ Water and energy intake↑ TC, LDL-C, LDL-C/HDL-C, liver TC and TG, and epididymal fat index↓ TNF-α, IL1β, and IL-6↓ ZO-1 and occludin↑ SCFA↑ (*B. adolescentis* strain)	Wang *et al.*[24]
NAFLD	N/A, male Sprague Dawley rats	*L. reuteri* DSM 17938 ($2x10^9$ CFU/day) + metronidazole	4 wk	Glutathione (GSH) and MDA, ALT, and AST serum levels↓ LPS, NF-kB, and TNF-α↓ Faecal acetate, propionate, and butyrate↑ TLR4↓	el-Din *et al.*[25]

TABLE 3. Cont.

Liver disease	Age, species	Probiotics, dosage	Treatment duration	Effects	Ref
NAFLD	8 wk old, male C57BL/6 mice	*L. plantarum* ZJUIDS14, 10^9 CFU/every other day\	12 wk	Lipid droplet sizes↓ NAS↓ ALT and AST↓ TG, FFA, and LDL-C levels↓ PPAR-α, SREBP-1c, FATP2 and FATP5 ↑ MDA↓ Total Superoxide Dismutase (T-SOD) ↑ TNF-α, IL-1β↓ Claudin-1 and ZO-1↑ SCFA↑	Cao *et al.*[26]
NASH	N/A, male C57BL/6 mice	*C. butyricum* B1 (CB), 10^9 CFU	8 wk	ALT, AST↓ NAS score↓ TG and cholesterol↓ PPAR-α and PPAR-γ↑ TNF-α, MCP-1, IL-1β, IL-2, IL-6 and IL-10↓ Fibrosis associated genes (TGF-β1, α-SMA, SMAD7, and SMAD2)↓ TLR4 and Myd88↓ Forkhead box P3 (Foxp3), IL-4 and IL-22↑ IFN-γ and IL-17↓ Caecal butyrate↑	Zhou *et al.*[27]

Most studies reported significant improvements in liver enzyme levels, especially ALT and AST, after probiotic administration. Improvements in gut barrier integrity were observed in the form of elevated tight junction protein expression. Recent findings have shown that in many animal models of liver disease, the expression of ZO-1 and occludin downregulated but was restored after supplementation with probiotics.[15,19,21,22]

Inflammatory cytokines such as IL-1β, IL-6, and TNF-α were significantly downregulated in several models. Several studies have reported that supplementing SCFA-producing probiotics, including *B. animalis ssp. Lactis* 420, *B. breve* CKDB002, and *B. longum* CKDB004 downregulate the expression of IL-1β, IL-6, and TNF-α.[14,19] An additional hepatoprotective effect of SCFA-producing probiotic supplementation is the significant reduction in serum levels of ALT, AST, and ALP.[22,27] Inflammation in the liver is also reduced by suppressing the TLR4, MyD88, and NF-κB in NAFLD-induced mice.[19,25,27,28]

Additionally, SCFA concentrations, especially butyrate, were elevated, and these changes were often associated with downregulation of lipogenic genes and reduction in hepatic triglyceride and cholesterol levels. Several included studies demonstrated that supplementation with SCFA-producing probiotics significantly reduced serum cholesterol and lipid levels, along with suppression lipid-regulating genes and cholesterol metabolism, including SREBP-1c and HMG-CoA reductase.[14,22,29] While the magnitude and scope of effects varied across studies, the overall trend supports the beneficial impact of SCFA-producing probiotics on gut-liver axis function, inflammation, and lipid metabolism in liver disease models.

DISCUSSION

Mechanism of liver disease progression

Liver disease is defined as many conditions that impair or prevent the liver from functioning properly. Common clinical manifestation of include abdominal pain, jaundice, and elevated liver enzymes test results.[30] Liver disease encompasses a wide range of conditions, such as fatty liver and cirrhosis. Fatty liver is classified into three main types i.e. NAFLD, ALD, and steatosis resulting from secondary or rare causes. Meanwhile, liver cirrhosis and hepatocellular carcinoma represent advanced stages in the progression of liver disease.[28]

The pathogenic mechanism of fatty liver disease develops from steatosis to steatohepatitis and fibrosis. As the condition progresses, it may develop into cirrhosis and, in certain cases, advance to hepatocellular carcinoma.[24] Fatty liver occurs due to abnormal accumulations of fat in the hepatic tissue caused by metabolic syndrome (T2DM, obesity, hypertension, and dyslipidemia), which is related to unhealthy dietary patterns and sedentary lifestyles.[28,31] High fructose and fat diets cause energy uptake, and fat adipocytes also increase. Insulin resistance also contributes to NAFLD via increasing de novo lipogenesis and resulting in the extensive mobilization of free fatty acids (FFAs) from lipid-laden adipocytes into the liver.[26] Free fatty acids are esterified into triglycerides in lipid droplets.[32] The increased hepatic triglyceride content result in the development of liver steatosis.[33]

Short-chain fatty acids producing-probiotics

Probiotics refer to viable microorganisms, including certain bacteria and yeasts, that are intended for human consumption to promote the positive effect of maintaining the balance of gut microorganisms. Probiotics are widely used in food products such as yoghurt, cheese, and fermented milk. Probiotics have significant benefits in maintaining gut homeostasis. The idea that preserving a balanced gut microbiota may offer defense against gastrointestinal illnesses such as gastrointestinal infections, inflammatory bowel diseases, liver disease, psychiatric disorders, and even cancer is increasingly supported by scientific research.[34-37]

Short-chain fatty acid-producing probiotics are microorganisms with the ability to produce SCFAs. Indigestible carbohydrate diets and fibers are essential substrates to produce SCFAs. Consumption of SCFA-producing probiotics can enhances the concentration of SCFAs within the digestive system. The human intestine primarily contains three SCFAs: acetate (C2), propionate (C3), and butyrate (C4).[38,39]

There are two distinct pathways for producing acetate. First, pyruvate can be decarboxylated to produce acetyl-CoA and then hydrolyzed by acetyl-CoA hydrolase to form acetate. Second, acetogenic bacteria can also use the Wood-Ljungdahl pathway to convert acetyl-CoA into acetate. Here, carbon dioxide undergoes reduction to carbon monoxide, which subsequently reacts with a methyl group and coenzyme-A molecule to produce acetyl-CoA. Acetyl-CoA is used as a substrate for the simultaneous production of acetate.[40] Many members of the gut microbiota can produce acetate, but it is mainly produced by *Akkermansia, Bacteroides, Bifidobacterium, Prevotella, Ruminococcus, Escherichia, Blautia, Clostridium, and Streptococcus*.[38]

Propionate is produced via three primary biosynthetic pathways, namely the acrylate, propanediol, and

succinate pathways. Electron transfer in the succinate pathway involves the use of phosphoenolpyruvate (PEP), which is carboxylated to oxalate, and then converted to fumarate and malate alternately. Furthermore, fumarate reductase will produce succinate. Propionate and carbon dioxide are produced when succinate is converted to methylmalonate at a low partial pressure of carbon dioxide. The acrylate pathway involves the reduction of lactate to form propionate by a lactoyl-CoA dehydratase. In the propanediol pathway, deoxy sugars can be converted to 1.2-propanediol. Following this step, 1.2-propanediol is metabolized to propionaldehyde and propionyl-CoA, forming propionate.[40] Propionate level increased associated with improved Firmicutes and Bacteroides.[15]

Butyrate is formed through two pathways, both share a common initial step involving the condensation of two acetyl-CoA molecules to generate acetoacetyl-CoA. Subsequently, acetoacetyl-CoA undergoes a series of reductions to form β-hydroxybutyryl-CoA, crotonyl-CoA, and ultimately, butyryl-CoA to form butyrate. In the first pathway, the transformation of butyryl-CoA into butyrate is modulated by the enzymes phosphotransbutyrylase and butyrate kinase. In the alternative pathway, the enzyme butyryl-CoA:acetate CoA-transferase catalyzes the conversion of butyryl-CoA into butyrate and acetyl-CoA.[39] *Clostridium butyricum* is one of the species that produce butyrate in the gut.[21,27] Another study has shown the recovered butyrate level in mice after *Lactobacillu*s supplementation.[20]

Liver disease is often accompanied by dysbiosis, characterized by an imbalance in microbial populations. According to Wang *et al.*,[41] biliary atresia in infants is associated with higher levels of *Streptococcus*, *Klebsiella*, and *Enterococcus*, and reduced levels of beneficial taxa such as *Bifidobacterium*, *Faecalibacterium*, and *Blautia*. Wessel *et al.*,[42] also reported the higher abundance of the *Acinetobacter* genera and the Clostridiaceae family. In contrast, an abundance of the Enterobacteriaceae family, including *Klebsiella, Salmonella, Trabulsiella, and Bifidobacterium*, was lower in patients with biliary atresia. In NAFLD, there was a decrease in Prevotellaceae and Ruminococcaceae.[43] Bajaj *et al.*,[44] showed a lower abundance of Lachnospiraceae, Ruminococcaceae, and Clostridiales XIV in liver cirrhosis patients.

A diminished presence of SCFA-producing bacteria could be detrimental, given the critical role of SCFAs in preserving intestinal epithelial barrier integrity. Thus, SCFA-producing probiotics have been shown to elevate SCFAs concentration in the gut, supporting gut barrier integrity and mitigating liver inflammation associated with liver disease.

Effect of SCFA on liver disease

Short-chain fatty acids play a key regulatory role in the communication along the microbiota–gut–liver axis. Latest findings have shown that SCFAs are essential in preventing and ameliorating inflammation in the gut and liver.[19] Short-chain fatty acids influencing liver disease progression through mechanisms along the gut–liver axis including modulation gut microbial composition, enhancement of gut barrier integrity, suppression of gut and hepatic inflammation, and regulation of lipid metabolism.[19,23]

Short-chain fatty acid plays an essential role in shaping the gut microbial composition, stability, and resilience. This mechanism happens with cross-feeding activity, which makes any member of the microbial community and their metabolites can influence the growth and activity of various microbial species and strains through interspecies

interactions. Those interactions can vary, including mutualism, commensalism, parasitism/predation, amensalism, or competition.[45] Recent studies show that SCFA supplementation can increase the alpha diversity of gut microbiomes. Lee *et al*.,[46] reported that butyrate supplementation can elevate the relative abundances of both protective and aggressive microbes, including Verrucomicrobia and Proteobacteria. At the same time, the number of butyrate-producing bacteria was not affected.

Short-chain fatty acids may directly affect the gut barrier integrity. Zonula occludens-1 (ZO-1) and occludin are proteins that have an important role in organizing tight junctions in epithelial mucosa. Tight junctions in the intestinal mucosa are crucial to prevent unwanted leakage, such as endogenous endotoxin, which is known as an essential substrate in the development of NAFLD, NASH, and insulin resistance.[15,19] Short-chain fatty acids, particularly butyrate, is the main energy substrate utilized by colonocytes and they strengthen tight junctions through the upregulation of ZO-1 and occludin, thus reducing gut permeability.[47] This barrier function is essential to prevent translocation of pathogen-associated molecular patterns (PAMPs), like LPS, that would otherwise trigger hepatic inflammation via TLR4 and MyD88 signaling pathways.

Within the liver, SCFAs mediate anti-inflammatory activity by suppressing histone deacetylases (HDACs), leading to reduced transcription of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α. SCFAs also interact with G-protein-coupled receptors (GPR41, GPR43, and GPR109A), modulating immune cell activity and minimizing oxidative stress.[48] This anti-inflammatory cascade contributes to decreased necroinflammation and fibrogenesis in chronic liver disease models. Prior research has emphasized the involvement of SCFAs in affecting inflammation-related cytokines. Both supplementation of sodium butyrate and *C. butyricum* in NAFLD and NASH mice/rats models has been reported to attenuate inflammatory responses by suppressing IL-1β, IL-6, and TNF-α in the colon, caecum, and liver.[21,22,27]

Lipid and fat metabolism are also affected by SCFA. Propionate serves as a precursor for gluconeogenesis, while butyrate promotes fatty acid oxidation and thermogenesis by upregulating mitochondrial uncoupling protein-1 (UCP-1) and PGC-1α expression in brown adipose tissue, as well as promoting AMPK phosphorylation and PGC-1α activation in both muscle and liver tissues.[49] These metabolic effects have been observed across several animal studies and suggest that SCFAs can ameliorate steatosis and metabolic dysregulation, both hallmarks of NAFLD and ALD. Those conditions were found in animal models of NAFLD, NASH, and ALD since lipid and glucose metabolism play an essential role in those disease progressions. Yoon *et al*.[14] showed the significant up-regulation of SREBP-1c/PPARα in NAFLD mouse models. Sterol receptor element-binding protein-1c (SREBP-1c) drive fat production in the liver, whereas peroxisome proliferator-activated receptor-alpha (PPAR-α) regulates fatty acid breakdown via β-oxidation. In other words, the greater the SREBP-1c/PPARα ratio, the greater the lipid concentration. After the treatment of probiotics that increase SCFA levels in the gut, there was a decrease in the SREBP-1c/PPARα ratio.[14,17,21] This fact is in line with the decrease in lipid droplet size and concentration in the liver after probiotic administration.[22,26] In addition, several studies also found a reduction in weight gain after probiotic treatment, which is very good for fatty liver disease.[22,29]

Studies have demonstrated that SCFAs can influence both total cholesterol and LDL levels in the blood. Propionate,

which is generated in the intestine, inhibits hydroxymethylglutaryl CoA reductase, he main enzyme controlling cholesterol synthesis, thereby enhancing lipid metabolism in the liver.[50] Probiotics can elevate SCFA influx in the liver, causing suppression of angiopoietin-like protein 4 (ANGPTL4), which inhibits circulating lipoprotein lipase (LPL) and lipid clearance. Angiopoietin-like protein 4 is a downstream target gene regulated by peroxisome proliferator-activated receptors (PPARs).[51] Bernini *et al.*[50] reveals the significant reduction of LDL and Total cholesterol in the probiotic group using SCFA-producing bacteria. A randomized controlled trial further validated propionate's lipid-lowering effect in humans, demonstrating significant reductions in multiple blood lipid parameters following 8 wk of oral supplementation. These findings suggest that SCFAs possess significant cholesterol-lowering properties.[52]

Bile acids have a critical function in altering the parameters mentioned above. Imbalance in intestinal bile acids might cause higher absorption of LPS, which in turn may initiate systemic inflammatory responses and stimulate hepatic stellate cell proliferation.[53] Bile acids buildup in the liver may result in hepatic fibrosis and cirrhosis.[54] The gut microbiota influences liver fibrosis by altering bile acid metabolism, including the transformation of primary bile acids into their secondary and unconjugated forms. Cheng *et al.*,[55] demonstrate that LGG protects against liver injury and fibrosis in mice by blocking the intestinal farnesoid X receptor (FXR) signaling pathway, decreasing fibroblast growth factor (FGF)-15 expression, preventing bile acid production from the beginning, and improving bile acid removal. Probiotic supplementation elevates SCFA levels, providing therapeutic and preventive benefits for chronic liver illnesses via the regulation of intestinal flora, improvement of mucosal barrier integrity, prevention of liver inflammation, and regulation of lipid metabolism.

Several studies support the therapeutic benefit of probiotics in managing liver disease. Bernini *et al.*,[50] performed a randomized controlled trial with *B. lactis* supplementation in patients with metabolic syndrome, resulting in significant reductions in LDL and total cholesterol levels. Similarly, Ayob *et al.*,[56] conducted a randomized, six-month clinical trial in NAFLD patients using a multistrain probiotic (MCP® BCMC®) containing six *Lactobacillus* and *Bifidobacterium* species. They found significant shift in the small intestinal microbiota composition, notably with decreased levels of unclassified Proteobacteria, *Streptococcus*, and *Stenotrophomonas*. In contrast, the placebo group showed reductions in potentially pathogenic species such as *P. melaninogenica* and *Rothia mucilaginosa.* Importantly, mucosal IFN-γ and TNF-α levels were significantly decreased in the probiotic group (IFN-γ: -7.9 ± 0.44; TNF-α: -0.96 ± 0.25), although IL-6 unexpectedly increased.[56]

Lynch and Pedersen[1] emphasized the microbiome's critical role in modulating systemic inflammation and liver health, further establishing the foundation for probiotic-based interventions in Western populations.[1] Moreover, Haghikia *et al.*,[52] explored the SCFA propionate's ability to reduce systemic cholesterol and inflammation in human subjects, providing translational insight into the probiotic–SCFA–host axis and its relevance to cardiovascular and hepatic health.[52] These findings collectively support the idea that probiotic strategies targeting SCFA production are not only promising in animal models but also hold translational value across different populations and healthcare systems.

CONCLUSION

This systematic review included numerous studies investigating the effect of SCFA-producing probiotics in various animal models of liver disease,

including NAFLD, ALD, autoimmune hepatitis, and NASH. These studies consistently demonstrated the broad potential of SCFA-producing probiotics such as *Bifidobacterium*, *Clostridium*, and *Lactobacillus* strains led to improvements in liver injury markers (ALT, AST), reductions in pro-inflammatory mediators (IL-1β, IL-6, TNF-α), enhanced gut barrier integrity (increased ZO-1 and occludin expression), and favorable modulation of lipid metabolism (e.g., lower hepatic TG, TC, and LDL levels). While it may be too early to definitively conclude that SCFA-producing probiotics are impactful in preventing and ameliorating liver injury, it is apparent that SCFA-producing probiotics may serve as a multi-targeted approach in preventing or attenuating liver injury, particularly by addressing dysbiosis and its systemic consequences. Although almost all studies showed a positive effect on both gut permeability and liver inflammation. Several uncertainties remain concerning the exact mechanistic pathways, sustainability of effects, consequences of treatment discontinuation, influencing variables, and potential adverse effects associated with SCFA-producing probiotic therapy.

Future research should explore the sustained impact of probiotic administration, the comparative effectiveness of different bacterial strains, and their use in combination with other dietary or pharmacological interventions. Moreover, translating these preclinical findings into human clinical trials will be essential to evaluate safety, optimal dosages, and efficacy across various liver disease etiologies. Personalized probiotic strategies based on individual microbiome profiles may also enhance therapeutic precision and outcome predictability in liver disease management.

ABBREVIATIONS

α-SMA: α-smooth muscle actin; 4-HNE: 4-Hydroxynonenal; ALD: alcoholic liver disease; ALT: alanine transaminase; ALP: alkaline phosphatase; AMPK: adenosine monophosphate protein kinase; ANGPTL-4: angiopoietin-like protein 4; ASD: autism spectrum disorder; AST: aspartate aminotransferase; CD: cluster of differentiation; DAMPs: damage-associated molecular patterns (DAMPs); FA: fatty acid; FAS: fatty acid synthase; FATP: fatty acid transport protein; FFA: free fatty acids; FGF: fibroblast growth factor; Foxp3: fork head box P3; FXR: farnesoid X receptor; GSH: glutathione; GST-P: placental glutathione S-transferase; HDL: high-density lipoprotein; HO1: heme oxygenase 1; (IFN)-γ: interferon gamma; IL: interleukin; LDL: low-density lipoprotein; LPS: lipopolysaccharide; MDA: malondialdehyde; MIP-1α: macrophage inflammatory protein-1 alpha; MPC-1: monocyte chemoattractant protein-1; MyD88: myeloid differentiation factor 88; NAFLD: non-alcoholic fatty liver disease; NF-κB: nuclear factor kappa B; NAS: NAFLD activity score; NASH: non-alcoholic steatohepatitis; NQO1: NAD(P)H quinone oxidoreductase 1; PAMPs: pathogen-associated molecular pattern molecules; NOD: nucleotide oligomerization domain; PEP: phosphoenolpyruvate; PPAR: peroxisome proliferator-activated receptor; LBP: lipopolysaccharide-binding protein; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SMAD: suppressor of mothers against decapentaplegic; SCFA: short-chain fatty acid; SREBP-1c: sterol regulator element-binding protein-1; T-SOD: total superoxide dismutase; TNF-α: tumor necrosis factor alpha; TC: total cholesterol; TG: triglyceride; TGF-β1: transforming growth factor beta; TGR5: G protein-coupled bile acid receptor; TLR: toll-like receptors; ZO-1, Zonula occludens-1.

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REFERENCES

1. Lynch S V, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016; 375(24):2369-79. https://doi.org/10.1056/nejmra1600266
2. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, *et al*. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol 2014; 32(8):834-41. https://doi.org/10.1038/nbt.2942
3. Akimbekov NS, Digel I, Sherelkhan DK, Lutfor AB, Razzaque MS. Vitamin d and the host-gut microbiome: a brief overview. Acta Histochem Cytochem 2020; 53(3):33-42. https://doi.org/10.1267/ahc.20011
4. Yang T, Yang S, Zhao J, Wang P, Li S, Jin Y, *et al*. Comprehensive analysis of gut microbiota and fecal bile acid profiles in children with biliary atresia. Front Cell Infect Microbiol 2022; 12:914247. https://doi.org/10.3389/fcimb.2022.914247
5. Romijn JA, Corssmit EP, Havekes LM, Pijl H. Gut-brain axis. Curr Opin Clin Nutr Metab Care 2008; 11(4):518-21. https://doi.org/10.1097/MCO.0b013e328302c9b0
6. Song W, Sun LY, Zhu ZJ, Wei L, Qu W, Zeng ZG, *et al*. Association of gut microbiota and metabolites with disease progression in children with biliary atresia. Front Immunol 2021; 12:698900. https://doi.org/10.3389/fimmu.2021.698900
7. Jain V, Alexander EC, Burford C, Verma A, Dhawan A. Gut microbiome: a potential modifiable risk factor in biliary atresia. J Pediatr Gastroenterol Nutr 2021; 72(2):184-93. https://doi.org/10.1097/MPG.0000000000002973
8. Degruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current understanding of dysbiosis in disease in human and animal models. Inflamm Bowel Dis 2016; 22(5):1137-50. https://doi.org/10.1097/MIB.0000000000000750
9. Zhou S, Wang Z, He F, Qiu H, Wang Y, Wang H, *et al*. Association of serum bilirubin in newborns affected by jaundice with gut microbiota dysbiosis. J Nutr Biochem 2019; 63:54-61. https://doi.org/10.1016/j.jnutbio.2018.09.016
10. Rivière A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Front Microbiol 2016; 7:979. https://doi.org/10.3389/fmicb.2016.00979
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71
12. Schiavenato M, Chu F. PICO: What it is and what it is not. Nurse Educ Pract 2021; 56:103194. https://doi.org/10.1016/j.nepr.2021.103194
13. Hooijmans CR, Rovers MM, De Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014; 14:43. https://doi.org/10.1186/1471-2288-14-43
14. Yoon SJ, Yu JS, Min BH, Gupta H, Won SM, Park HJ, *et al*. Bifidobacterium-derived short-chain fatty acids and indole compounds attenuate nonalcoholic fatty liver disease by modulating gut-liver axis. Front Microbiol 2023; 14:1129904. https://doi.org/10.3389/fmicb.2023.1129904
15. Jiang XW, Li YT, Ye JZ, Lv LX, Yang LY, Bian XY, *et al*. New strain of *Pediococcus pentosaceus* alleviates ethanol-induced liver injury by modulating the gut microbiota and short-chain fatty acid metabolism.

World J Gastroenterol 2020; 26(40):6224-40. https://doi.org/10.3748/wjg.v26.i40.6224
16. Hong Y, Sheng L, Zhong J, Tao X, Zhu W, Ma J, *et al*. *Desulfovibrio vulgaris*, a potent acetic acid-producing bacterium, attenuates nonalcoholic fatty liver disease in mice. Gut Microbes 2021; 13(1):1-20. https://doi.org/10.1080/19490976.2021.1930874
17. Yan F, Li N, Shi J, Li H, Yue Y, Jiao W, *et al*. *Lactobacillus acidophilus* alleviates type 2 diabetes by regulating hepatic glucose, lipid metabolism and gut microbiota in mice. Food Funct 2019; 10(9):5804-15. https://doi.org/10.1039/c9fo01062a
18. Liang Y, Liang S, Zhang Y, Deng Y, He Y, Chen Y, *et al*. Oral administration of compound probiotics ameliorates HFD-induced gut microbe dysbiosis and chronic metabolic inflammation via the G protein-coupled receptor 43 in non-alcoholic fatty liver disease Rats. Probiot Antimicrob Proteins 2019; 11(1):175–85. https://doi.org/10.1007/s12602-017-9378-3
19. Zhang H, Liu M, Liu X, Zhong W, Li Y, Ran Y, *et al*. *Bifidobacterium animalis* ssp. lactis 420 mitigates autoimmune hepatitis through regulating intestinal barrier and liver immune cells. Front Immunol 2020; 11:569104. https://doi.org/10.3389/fimmu.2020.569104
20. Zheng F, Wang Z, Stanton C, Ross RP, Zhao J, Zhang H, *et al*. *Lactobacillus rhamnosus* FJSYC4-1 and *Lactobacillus reuteri* FGSZY33L6 alleviate metabolic syndrome via gut microbiota regulation. Food Funct 2021; 12(9):3919-30. https://doi.org/10.1039/d0fo02879g
21. Endo H, Niioka M, Kobayashi N, Tanaka M, Watanabe T. Butyrate-producing probiotics reduce nonalcoholic fatty liver disease progression in rats: new insight into the probiotics for the gut-liver axis. PLoS ONE 2013; 8(5):63388. https://doi.org/10.1371/journal.pone.0063388
22. Yang T, Yang H, Heng C, Wang H, Chen S, Hu Y, *et al*. Amelioration of non-alcoholic fatty liver disease by sodium butyrate is linked to the modulation of intestinal tight junctions in db/db mice. Food Funct 2020; 11(12):10675-89. https://doi.org/10.1039/d0fo01954b
23. Li X, Xiao Y, Huang Y, Song L, Li M, Ren Z. *Lactobacillus gasseri* RW2014 ameliorates hyperlipidemia by modulating bile acid metabolism and gut microbiota composition in rats. Nutrients 2022; 14(23):4945. https://doi.org/10.3390/nu14234945
24. Wang G, Jiao T, Xu Y, Li D, Si Q, Hao J, *et al*. *Bifidobacterium adolescentis* and *Lactobacillus rhamnosus* alleviate non-alcoholic fatty liver disease induced by a high-fat, high-cholesterol diet through modulation of different gut microbiota-dependent pathways. Food Funct 2020; 11(7):6115-27. https://doi.org/10.1039/c9fo02905b
25. Seif el-Din SH, Salem MB, El-Lakkany NM, Hammam OA, Nasr SM, Okasha H, *et al*. Early intervention with probiotics and metformin alleviates liver injury in NAFLD rats via targeting gut microbiota dysbiosis and p-AKT/mTOR/LC-3II pathways. Humd Expl Toxicol 2021; 40(9):1496-509. https://doi.org/10.1177/0960327121999445
26. Cao F, Ding Q, Zhuge H, Lai S, Chang K, Le C, *et al*. *Lactobacillus plantarum* ZJUIDS14 alleviates non-alcoholic fatty liver disease in mice in association with modulation in the gut microbiota. Front Nutr 2023; 9:1071284. https://doi.org/10.3389/fnut.2022.1071284
27. Zhou D, Pan Q, Liu XL, Yang RX, Chen YW, Liu C, *et al*. *Clostridium butyricum* B1 alleviates high-fat diet-induced steatohepatitis in mice via enterohepatic immunoregulation. J Gastroenterol Hepatol 2017; 32(9):1640-8. https://doi.org/10.1111/jgh.13742

28. Rowell RJ, Anstee QM. Alcohol and health. Clin Med 2015; 15(6): s77-82. https://doi.org/10.7861/clinmedicine.15-6-s77
29. Wang L, Jiao T, Yu Q, Wang J, Wang L, Wang G, *et al*. *Bifidobacterium bifidum* shows more diversified ways of relieving non-alcoholic fatty liver compared with *Bifidobacterium adolescentis*. Biomedicines 2022; 10(1):84. https://doi.org/10.3390/biomedicines10010084
30. Khan RS, Houlihan DD, Newsome PN. Investigation of jaundice. Medicine 2019; 47(11):713-7. https://doi.org/10.1016/j.mpmed.2019.08.011
31. Khan A, Ding Z, Ishaq M, Bacha AS, Khan I, Hanif A, *et al*. Understanding the effects of gut microbiota dysbiosis on nonalcoholic fatty liver disease and the possible probiotics role: recent updates. Int J Biol Sci 2021; 17(3): 818-33. https://doi.org/10.7150/ijbs.56214
32. Bessone F, Razori MV, Roma MG. Molecular pathways of nonalcoholic fatty liver disease development and progression. Cell Mol Life Sci 2019; 76(1):99-128. https://doi.org/10.1007/s00018-018-2947-0
33. Aron-Wisnewsky J, Gaborit B, Dutour A, Clement K. Gut microbiota and non-alcoholic fatty liver disease: new insights. Clin Microbiol Infect 2013; 19(4):338-48. https://doi.org/10.1111/1469-0691.12140
34. Cheng Y, Liu J, Ling Z. Short-chain fatty acids-producing probiotics: a novel source of psychobiotics. Crit Rev Food Sci Nutr 2022; 7929-59. https://doi.org/10.1080/10408398.2021.1920884
35. Górska A, Przystupski D, Niemczura MJ, Kulbacka J. Probiotic bacteria: a promising tool in cancer prevention and therapy. Curr Microbiol 2019; 76(8):939-49. https://doi.org/10.1007/s00284-019-01679-8
36. Dargenio VN, Castellaneta S, Panico S, Papagni ME, Dargenio C, Schettini F, *et al*. Probiotics and gastrointestinal diseases. Minerva Pediatr (Torino) 2022; 74(6):703-23. https://doi.org/10.23736/S2724-5276.22.07031-8
37. Pohl K, Moodley P, Dhanda A. The effect of increasing intestinal short-chain fatty acid concentration on gut permeability and liver injury in the context of liver disease: a systematic review. J Gastroenterol Hepatol 2022; 37(8):1498-506. https://doi.org/10.1111/jgh.15899
38. Zhang D, Jian YP, Zhang YN, Li Y, Gu LT, Sun HH, *et al*. Short-chain fatty acids in diseases. Cell Commun Signal 2023; 21(1):212. https://doi.org/10.1186/s12964-023-01219-9
39. Portincasa P, Bonfrate L, Vacca M, De Angelis M, Farella I, Lanza E, *et al*. Gut microbiota and short chain fatty acids: implications in glucose homeostasis. Int J Mol Sci 2022; 23(3):1105. https://doi.org/10.3390/ijms23031105
40. Nogal A, Valdes AM, Menni C. The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. Gut Microbes 2021; 13(1):1-24. https://doi.org/10.1080/19490976.2021.1897212
41. Wang J, Qian T, Jiang J, Yang Y, Shen Z, Huang Y, *et al*. Gut microbial profile in biliary atresia: a case-control study. J Gastroenterol Hepatol 2020; 35(2):334-42. https://doi.org/10.1111/jgh.14777
42. Van Wessel D, Nomden M, Bruggink J, De Kleine R, Kurilshikov A, Verkade H, *et al*. Gut microbiota composition of biliary atresia patients before kasai portoenterostomy associates with long-term outcome. J Pediatr Gastroenterol Nutr 2021; 73(4):485-90. https://doi.org/10.1097/MPG.0000000000003234
43. Shen F, Zheng RD, Sun XQ, Ding WJ, Wang XY, Fan JG. Gut microbiota dysbiosis in patients with non-

alcoholic fatty liver disease. Hepatobiliary Pancreat Dis Int 2017; 16(4):375-81. https://doi.org/10.1016/S1499-3872(17)60019-5
44. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, *et al*. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014; 60(5):940-47. https://doi.org/10.1016/j.jhep.2013.12.019
45. Culp EJ, Goodman AL. Cross-feeding in the gut microbiome: Ecology and mechanisms. Cell Host Microbe 2023; 31(4):485-99. https://doi.org/10.1016/j.chom.2023.03.016
46. Lee JG, Lee J, Lee AR, Jo SV, Park CH, Han DS, *et al*. Impact of short-chain fatty acid supplementation on gut inflammation and microbiota composition in a murine colitis model. J Nutr Biochem 2022; 101:108926. https://doi.org/10.1016/j.jnutbio.2021.108926
47. Hodgkinson K, El Abbar F, Dobranowski P, Manoogian J, Butcher J, Figeys D, *et al*. Butyrate's role in human health and the current progress towards its clinical application to treat gastrointestinal disease. Clin Nutr 2023; 42(2):61-75. https://doi.org/10.1016/j.clnu.2022.10.024
48. Du Y, He C, An Y, Huang Y, Zhang H, Fu W, *et al*. The role of short chain fatty acids in inflammation and body health. Int J Mol Sci 2024; 25(13):7379. https://doi.org/10.3390/ijms25137379
49. Du B, Mu K, Sun M, Yu Z, Li L, Hou L, *et al*. Biliary atresia and cholestasis plasma non-targeted metabolomics unravels perturbed metabolic pathways and unveils a diagnostic model for biliary atresia. Sci Rep 2024; 14(1):15796. https://doi.org/10.1038/s41598-024-66893-2
50. Bernini LJ, Simão ANC, Alfieri DF, Lozovoy MAB, Mari NL, de Souza CHB, *et al*. Beneficial effects of *Bifidobacterium lactis* on lipid profile and cytokines in patients with metabolic syndrome: a randomized trial. Effects of probiotics on metabolic syndrome. Nutrition 2016; 32(6):716-9. https://doi.org/10.1016/j.nut.2015.11.001
51. He M, Shi B. Gut microbiota as a potential target of metabolic syndrome: the role of probiotics and prebiotics. Cell Biosci 2017; 7:54. https://doi.org/10.1186/s13578-017-0183-1
52. Haghikia A, Zimmermann F, Schumann P, Jasina A, Roessler J, Schmidt D, *et al*. Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism. Eur Heart J 2022; 43(6):518-33. https://doi.org/10.1093/eurheartj/ehab644
53. Jia X, Lu S, Zeng Z, Liu Q, Dong Z, Chen Y, *et al*. Characterization of gut microbiota, bile acid metabolism, and cytokines in intrahepatic cholangiocarcinoma. Hepatology 2020; 71(3):893-906. https://doi.org/10.1002/hep.30852/suppinfo
54. Liu Y, Chen K, Li F, Gu Z, Liu Q, He L, *et al*. Probiotic *Lactobacillus rhamnosus* GG prevents liver fibrosis through inhibiting hepatic bile acid synthesis and enhancing bile acid excretion in mice. Hepatology 2020; 71(6):2050-66. https://doi.org/10.1002/hep.30975
55. Cheng L, Shi J, Peng H, Tong R, Hu Y, Yu D. Probiotics and liver fibrosis: an evidence-based review of the latest research. J Funct Foods 2023; 109(3):105773. https://doi.org/10.1016/j.jff.2023.105773
56. Ayob N, Nawawi KNM, Mohamad Nor MH, Raja Ali RA, Ahmad HF, Oon SF, *et al*. The effects of probiotics on small intestinal microbiota composition, inflammatory cytokines and intestinal permeability in patients with non-alcoholic fatty liver disease. Biomedicines 2023; 11(2):640. https://doi.org/10.3390/biomedicines11020640