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Review Article

Gut Microbiota and Drug-Related Liver Injury: Challenges and Perspectives

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Drug-related liver injury (DILI) is increasing in the incidence of liver injury due to nonviral liver disease and has become a health problem that should not be underestimated. As a hot research topic in recent years, gut microbiota have been studied in various tumors, cardiovascular metabolic diseases, and human immunity. However, there is still a lack of research related to gut microbiota and DILI. It is known that they can influence each other through the regulation of the "gut-liver axis," and the relationship between them and the possible mechanisms of action are still at the research stage. Human leukocyte antigen (HLA) gene polymorphisms are closely related to the development of DILI, and the gene can also affect changes in the composition of gut microbes. In this paper, we review the possible relationships and mechanisms between DILI and gut microbiota in order to provide new research directions for the prevention and treatment of DILI in the future. In the future, untargeted therapies using antibiotics, probiotics, or FMT will be replaced by personalised and precision medicine approaches, such as bioengineered bacterial strains or drugs that modulate specific bacterial enzymes and metabolic pathways.

1. Background

Drug-related liver injury (DILI) occurs in 23.8 per 100,000 people in China [1] and 2.7-14 per 100,000 people in Europe and the United States [2, 3]. This shows that the incidence of DILI in China is much higher than that in Western countries, and the incidence of DILI has been increasing year by year. DILI has become a major cause of drug development interruptions during clinical studies and drug withdrawals from the pharmaceutical market [4]. In the United States, DILI accounts for more than 50% of patients with acute liver failure (ALF), and acute DILI can evolve into chronic liver injury and liver failure, which requires liver transplantation and even leads to death [5]. Thus, DILI has become a health problem that should not be ignored.

DILI is divided into two types, which includes DILI and specific DILI [6]. DILI is usually attributed to the toxicity of the drug itself and the drug dose, but the mechanism and the pathogenesis of specific DILI are not known. An article published in Cell in 2016 stated that each adult had 3 billion of its own cells and 4 billion of bacteria [7]. The gut microbiota affects the metabolism of the drug and can also be affected by the drug [8, 9]. There is growing evidence that shows that gut microbes play an important role in DILI, and the two are linked in the "gut-liver axis" [10, 11], a theory first proposed by Marshall in 1998 [12]. Under normal circumstances, the intestinal barrier is the first line to protect the body from exogenous substances. The liver provides a second line against antigens and inflammatory factors that escape gastrointestinal mucosal immune surveillance [13, 14]. When the intestine is in a pathological state, the barrier is damaged. It increases the intestinal permeability, and then bacteria and its metabolites in the intestine will enter the liver from the portal vein. Then, it will activate Kupffer cells in the liver and release a series of inflammatory factors, which aggravate liver injury and disease progression [15, 16]. In turn, decreased phagocytosis of Kupffer cells, reduced synthesis of immune proteins, and the presence of altered hemodynamics during cirrhosis contribute to impaired intestinal function. These have been demonstrated in nonalcoholic fatty liver disease, cirrhosis, and liver fibrosis, but little is known in DILI [17, 18]. In this review, we will discuss gut microbiota changes after DILI, and gut microbiota affects individual susceptibility to DILI.

2. Gut Microbiota Changes after DILI

2.1. Gut Microbiota Changes in DILI due to Acetaminophen (APAP). In APAP-induced liver injury in rats, APAP is absorbed from the intestine and broken down by the liver. After hepatic monophasic metabolism, most of APAP was eliminated by binding with glucuronic acid or sulfuric acid. While a small part was oxidized to N-acetyl-p-benzoquinone imine (NAPQI) by cytochrome P450 proteins1A2 (CYP1A2) and cytochrome P450 proteins2E1 (CYP2E1), then NAPQI was eliminated by binding to reduced glutathione (GSH) [19, 20]. However, when there is excessive intake of APAP, GSH cannot completely eliminate the metabolic production of NAPQI. Excessive NAPQI will cause mitochondrial dysfunction, lead to oxidative damage, and promote inflammatory promotion, apoptosis, and necrosis of hepatocytes [21]. Another study on APAP-induced liver injury in rats found that the gut microbiota metabolite 1-phenyl-1,2-propanediol (PPD) was involved. It resulting in a decrease in liver GSH levels, suggesting that gut microbiota may be a potential target for alleviating acute liver injury induced by APAP [22]. This may be due to the change of gut microbiota in mice after DILI, resulting in an increase in the production of PPD and a decrease in the level of GSH in the liver, which leads to liver damage. Further, given oral enzyme, bacteria to mice with liver injury result a decrease in PPD and a reduction in liver injury [23].

2.2. Gut Microbiota Changes in DILI due to Antituberculosis Drugs. In the study of DILI caused by antituberculosis drugs, it showed that the gut microbiota of pulmonary tuberculosis mice changed only slightly before antituberculosis drug treatment [24]. However, gut microbiota has changed after antituberculosis drug treatment (isoniazid, rifampin, pyrazinamide, and ethambutol). Anti-TB therapy caused a rapid, significant alteration in the community structure. The relative abundance of members of genus Clostridiales of the phylum Firmicutes significantly decreased during anti-TB treatment, while many members of genus Bacteroides, including Bacteroides OTU230 and Bacteroides fragilis, were among the taxa that increased. OTU8 and OTU2972 assigned to family Erysipelotrichaceae of the phylum Firmicutes showed a dramatic increase 1 week after the start of therapy, while the other members of this family decreased [25]. Some studies have shown that the changes of liver function and morphology are closely related to the abundance of clostridium [25]. Antituberculosis drugs will lead to decrease the abundance of clostridium and long-term imbalance of gut microbiota. It leads to the development of DILI, but the exact mechanism of DILI is now unclear [26].

2.3. Gut Microbiota Changes in DILI due to Iron. It is estimated that approximately 2 billion people worldwide suffer from iron-deficiency anemia (IDA) [27]. Oral iron is an effective treatment, but excessive iron can cause damage to human and animal health. Some studies have shown that free iron can catalyze the formation of reactive oxygen species (ROS) in the gut, which can damage the intestinal mucosal barrier [28]. Recent studies have shown that oral excessive iron can elevate ALT and AST in mice, which are higher than those of the control group. And excessive iron can damage the intestinal mucosa of mice and destroy the intestinal barrier. The toxins were produced by the liver through the intestinal-liver axis, and then, the gut microbiota changed. The gut microbiota of mice overdosed with iron was analyzed in some studies. Results also showed that the abundance of two kinds of probiotics in Lachnospiraceae (Clostridium) and mycoplasma (Allobaculum) decreased significantly [29].

2.4. Gut Microbiota Changes in DILI due to Other Drugs. The drugs that can cause DILI are far more than paracetamol, anti-tuberculosis drugs and iron drugs. Many studies have shown that there are changes in gut microbiota in liver injury caused by triclosan [30], carbon tetrachloride [31], copper [32], and D-galactosamine [33]. The characteristics of gut microbiota changes are summarized in Table 1. More and more evidences find that the gut microbiota of DILI patients will change. It is not only that the drug can cause changes in gut microbiota but also that the gut microbiota can cause different responses to the drug in individuals. But these changes can only be specific to a genus, not to a specific bacterium, so we need to meet a bigger challenge.

3. Gut Microbiota Affects Individual Susceptibility to DILI

3.1. Human Leukocyte Antigen (HLA) Contributes to Individual Susceptibility to DILI by Gut Microbiota Affecting Drug Metabolism. When using the same drug, only a small number of susceptible individuals will develop obvious DILI, which may be related to the mechanism of liver immune tolerance and the single nucleotide polymorphism of HLA gene [34]. The HLA gene may have made the choice for us; in the genome-wide association study of a large number of cases of DILI, it was found that most of the DILI caused by flucloxacillin [35], amoxicillin-clavulanic acid [36], fenofibrate [37], terbinafine [38], lampatinib [39], and trimethoprim-sulfamethoxazole [40] were located in the major histocompatibility complex (MHC) region. And DILI is mainly associated with HLA gene. These associations may not be reliable enough to screen HLA alleles before using drugs, but it suggests immunological pathogenesis. Some studies have shown that specific $CD4^+$T cells can be detected in patients with DILI by amoxicillin-clavulanic acid. Further studies have shown that amoxicillin can combine with lysine residues to form protein adducts and then activate T cells [41].

HLA may indirectly select people with DILI by gut microbiota to regulate the host's immune system, affecting the content of sex hormones and changing the expression of drug metabolic genes. The association of MHC class II genes with the risk of developing autoimmune diseases has been well-described. MHC class II molecules play a central role in the maturation of T-cells and thus can affect the autoreactivity of an individual's T-cell population [42]. In the genome-wide association study of a large number of cases of DILI, Indeed, multiple HLA genes in humans such as

Table 1: Changes of gut microbiota after DILI.

Drugs	Research method	Characteristics of gut microbiota change	References
APAP	Animal experiment	The ratio of thick-walled bacteria to Bacillus pseudomallei decreased	[22]
Antituberculosis drugs	Case-control study	Reduced abundance of Clostridium perfringens spp. in thick-walled phylum Increased abundance of Bacillus spp. and Bacteroides fragilis spp.	[25]
Liquid iron	Animal experiment	The abundance of Lachnospiraceae and mycoplasma decreased	[29]
Triclosan	Animal experiment	Increased abundance of Proteobacteria and Enterobacteriaceae Reduced abundance of Firmicutes and Bacteroidetes	[30]
Carbon tetrachloride	Animal experiments	Reduced abundance of *Adlercreutzia*, *Flavonifractor*, *Lactobacillus*, and *Turicibacter* Increased abundance of *Enterococcus*, *Enterorhabdus*, *Oscillibacter*, and *Oscillospira*	[31]
Copper	Animal experiments	Reduced the abundance of probiotics and the ratio of Firmicutes to Bacteroidetes	[32]
D-Galactosamine	Animal experiments	Reduced the abundance of gut Actinobacteria and Firmicutes	[33]

HLA-B*57:01, HLA-A*02:01, and HLA-DRB1*07:01 have been associated with DILI susceptibility. It has been shown that the HLA can alter the gut microbiota of the population, and a significant reduction in the abundance of Coprococcus and Enterorhabdus was found in AH8.1 haplotype carriers [43]. A study shows that HLA class II molecules influence the composition of the gut microbiome [44]. Gut microbiota can directly or indirectly influence drug metabolism, which involved in drug reductive metabolism and hydrolysis, which includes demethylation, deamination, dehydroxylation deacylation, decarboxylation, and oxidation reactions, and may have an impact on drug metabolism [45]. Some studies have confirmed that gut microbiota may also affect drug metabolism by changing the expression of drug metabolism genes [46]. Later, some people have compared the mRNA transcription level in the liver of aseptic mice and conventional mice. It has been proved that gut microbiota affect the development of various drug metabolism genes in the liver in a sex-specific way [47]. The HLA gene alters the gut microbiota and thus affects drug metabolism. So, the HLA gene largely determines who will develop DILI.

3.2. Gut Microbiota Affects Liver Immunity Leading to Individual Susceptibility to DILI. More and more studies have shown that gut microbiota plays an important role in the maturation of the human immune system, and dynamic changes in gut microbiota have a fine-tuning effect on the human immune system [48]. In the genome-wide association study of a large number of cases of DILI, the liver is a specific immune organ, and antigens entering the liver cause an immune response in the liver. To avoid this, the immune tolerance mechanism of the liver is particularly important, and immune tolerance is a necessary adaptation to protect hepatocytes from damage caused by a persistent inflammatory state in the liver [49]. A good example here is liver transplantation, where 20% of liver transplant patients are completely free from immunosuppression, which may be related to hepatic immune tolerance [50]. It is known that the liver and gut microbiota are linked to the enterohepatic axis, and the excretion of bile acids from the liver to the intestine can affect the gut microbiota. Conversely, the metabolites of the gut microbiota can be reintroduced to the liver through the enterohepatic cycle, and the flora products can be used as antigens to activate immune cells and produce cytokines, which can then initiate the host immune response [51–53]. It has been shown in several papers that gut microbiota can promote the host immune system, and the immune system can also influence the composition of the gut microbiota. And it has been shown that germ-free mice have impaired development and maturation of gut-associated lymph node tissue compared to normal mice [54, 55]. This suggests that gut microbiota can indeed influence the immune system of the host, when the venous blood carries intestinal bacteria and their products back to the liver. They will be neutralized by the immune cells of the liver, if the number of intestinal bacteria and their products is relatively small, so that the immune cells of the liver will produce immune tolerance to specific gut microbiota. However, when the number and composition of intestinal microorganisms change, intestinal permeability can be increased, and the number of bacteria and their products returning to the liver will increase. And more foreign antigens will be exposed to the immune cells of the liver, and it will break the established immune tolerance. Then, it will lead to liver injury, and people with changes in gut microbiota may break the established immune tolerance [56]. Previous studies have shown that people who take long-term acid-suppressing drugs disrupted their gut microbiota and more susceptible to liver failure [57]. It has been hypothesized that gut microbiota may be a potential mechanism for individual susceptibility to DILI, the above evidence provides evidence for our hypothesis, and we expect more results to confirm [58].

3.3. Gut Microbiota Contributes to Individual Susceptibility to DILI by Affecting the Level of Sex Hormones. Recent animal experiments have shown that gut microbiota may be related to gender differences in diseases, and gut microbiota may affect the content of sex hormones, which leads to

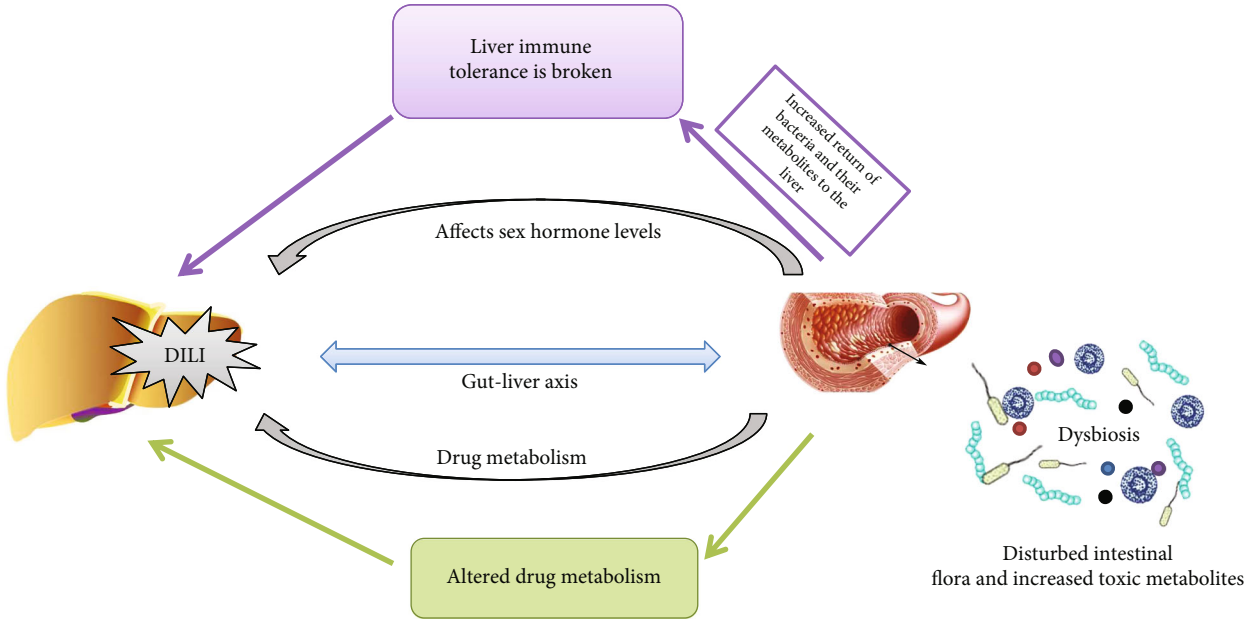

Figure 1: The role of gut microbiota in susceptibility of the DILI population. Drug metabolism, sex hormone expression, and hepatic immune tolerance will lead to individual differences in DILI, such as that women are more likely to develop DILI in the population.

gender differences in diseases. For example, the gender difference in the incidence of rheumatoid arthritis and multiple sclerosis decreases with the increase of age, which is consistent with the decrease of testosterone [59, 60]. Women are more likely to suffer from autoimmune hepatitis [61]. In the study of liver injury caused by inhaled anesthetic halothane, it was found that all the patients with severe liver injury were women, and the same pattern was found in subsequent animal experiments. When the mice were treated with estradiol and progesterone, it was found that the sex difference disappeared [62]. Therefore, we hypothesize that gut microbiota may be involved in the development of DILI by affecting sex hormones.

HLA can indirectly select people with DILI by gut microbiota to regulate the host's immune system, affecting the content of sex hormones and changing the expression of drug metabolic genes, as shown in Figure 1. But this is only at a theoretical stage, and we need more clinical trials to confirm.

4. Regulating Gut Microbiota Can Be a New Target for Liver Protection

4.1. Reduce Liver Injury by Regulating Gut Microbiota through Dietary Modifications. Recent studies have shown that Western diet (high in saturated fat and sucrose and low in fiber) aggravates CCl4-induced chronic liver injury by disrupting intestinal microflora and affecting bile acid metabolism, including reducing the richness of Salmonella and increasing the richness of Streptococcus [63]. A retrospective analysis of DILI in the United States shows that African-Americans are more likely to develop DILI than Caucasians [64]. It is also indicated in another literature that the probability of DILI is also different among people of different races [65]. It is possible that different diets lead to different gut microbiota, resulting in different metabolic abilities of drugs. Some studies have shown that in cirrhosis and nonalcoholic fatty liver disease, liver preservation can be achieved through dietary regulation of intestinal flora, which may be related to bile acid metabolism [66–69]. In the mouse model of liver injury induced by carbon tetrachloride, it was found that mice fed with goat milk could reduce the damage DILI caused by carbon tetrachloride. And it was found that the damage caused by carbon tetrachloride could even be prevented by taking goat milk for 7 days in advance. Sequencing of the gut microbiota of mice showed that the flora of mice after taking goat milk was closer to that of normal mice [31], although some studies have confirmed that whether changing the diet or supplementing certain dietary ingredients can reduce liver injury. And the foothold of these studies will eventually come back to the gut microbiota. But the gut microbiota is a huge whole, and we only know that through diet can change the gut microbiota and then achieve the goal of reducing liver damage. However, we do not know what happened, what bacteria are affected by these dietary regulation, and what role the gut microbiota play in this, all of which are still a huge challenge.

4.2. Regulating Gut Microbiota through Probiotic Supplementation to Reduce Liver Injury. Compared with dietary regulation, the supplement of live bacteria is more controllable. In recent years, more and more attention has been paid to probiotics as auxiliaries in the prevention or treatment of gastrointestinal diseases. Saccharomyces boulardii is a probiotics yeast that is often used to treat gastrointestinal disorders [70]. An animal study showed that oral

Table 2: Improvement of liver injury after supplementation of probiotics.

Drugs	Probiotics	Research method	Supplementary methods	Improvements	References
D-Galactosamine	Saccharomyces boulardii	Animal experiments	Oral	Decreased ALT and AST levels, reduced inflammatory response, and reduction of Mycobacterium-like bacteria and Aspergillus	[75]
D-Galactosamine	Lactobacillus helveticus R0052	Animal experiments	Oral	The levels of ALT and AST are decreased, and the inflammatory reaction is alleviated	[76]
D-Galactosamine	Bifidobacterium longum R0175	Animal experiments	Oral	The levels of ALT and AST decreased, alleviated the inflammatory reaction, and improved the bile acid metabolism of intestinal microorganisms	[77]
D-Galactosamine	Bifidobacterium pseudocarinii LI09 Bifidobacterium chain LI10	Animal experiments	Oral	Reduction of plasma M-CSF, MIP-1, and MCP-1 and reduction of bacterial translocation	[78]
D-Galactosamine	Porphyromonas OTU170_ and Bacteroides OTU12_	Animal experiments	Oral	Improve the composition of intestinal flora	[79]
CCl4	Probiotic Clostridium typhimurium	Animal experiments	Gavage	Decreasing ALT and AST, reducing the inflammatory response of the liver, and increased the abundance of thick-walled Porphyromonas and the mimicry proportion decreases	[80]
Antituberculosis drugs	Lactobacillus	Randomized controlled trial	Oral	Its modification on blood lipopolysaccharide, intestinal barrier function and gut microbiota.	[81]

administration of Saccharomyces boulardii decelerates the progress of liver fibrosis in rats with carbon tetrachloride-induced cirrhosis, as evidenced by reductions in liver fibrosis markers such as alpha smooth muscle actin (SMA), transforming growth factor beta (TGF), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and malondialdehyde (MDA) [71]. Decreased numbers of Bacteroidetes and Aspergillus have been reported to be associated with a variety of liver diseases, including cirrhosis [72] and nonalcoholic fatty liver disease [73], and Saccharomyces boulardii can reverse the aforementioned changes in the flora [74]. Many studies in recent years have shown that supplementation with live bacteria can indeed improve DILI as shown in Table 2[75–81]. Supplementation of probiotics can not only improve gut microbiota and strengthen intestinal barrier to improve liver injury but also affect host immune status to improve liver injury. Study also found that Lactobacillus can activate intestinal intrinsic lymphocytes to produce IL-22 and increase the level of systemic IL-22. Intestinal-derived IL-22 can enhance mucosal barrier function and promote regulatory dendritic cells (CDC) to recruit to the liver. These CDC are activated by TLR9 to produce IL-10 and TGF, thereby preventing further liver inflammation and reducing the level of liver injury [82]. A recent meta-analysis indicated that supplementation with probiotics or prebiotics has a significant ameliorative effect on acute liver injury through the enterohepatic axis. It can upregulate tight junction proteins, correct ileal flora abundance, reduce endotoxin invasion, and inhibit oxidative stress and proinflammatory mediators, thereby in turn improving liver biochemical parameters [83]. In the model of liver injury caused by carbon tetrachloride in mice, the degree of liver injury was reduced by supplementation with Lactobacillus fermentum and Lactobacillus plantarum [84]. Probiotic supplementation can alleviate liver injury by regulating gut microbiota, strengthening intestinal barrier, and affecting host immunity. But it only stays at the level of animal experiments. After all, there are inherent differences in gut microbiota between humans and animals. This still requires a large number of clinical trials to verify its efficacy.

4.3. Fecal Microbiota Transplantation (FMT) Reduces Liver Injury by Regulating Gut Microbiota. If supplementation with live bacteria is using one type of bacteria to affect the entire gut microbiota, FMT replicates the entire intestinal microenvironment, which may be more convincing. It has now been shown that in ulcerative colitis, the nonalcoholic fatty liver disease mouse model, regulating gut microbiota has been achieved to reduce colonic inflammation and liver injury [85–87]. And now, studies have confirmed that FMT could change the diversity of gut microbiota in patients with liver cirrhosis and change the cognition of patients with hepatic encephalopathy [88]. In the D-galactose amine-induced liver injury mice model, it has been shown that FMT can increase butyrate-producing bacteria, improve liver inflammation, and reduce the extent of liver injury [89]. Another study showed that FMT improved acute liver failure caused by D-galactosamine by regulating the expression of Treg/Th17 cytokines [90].

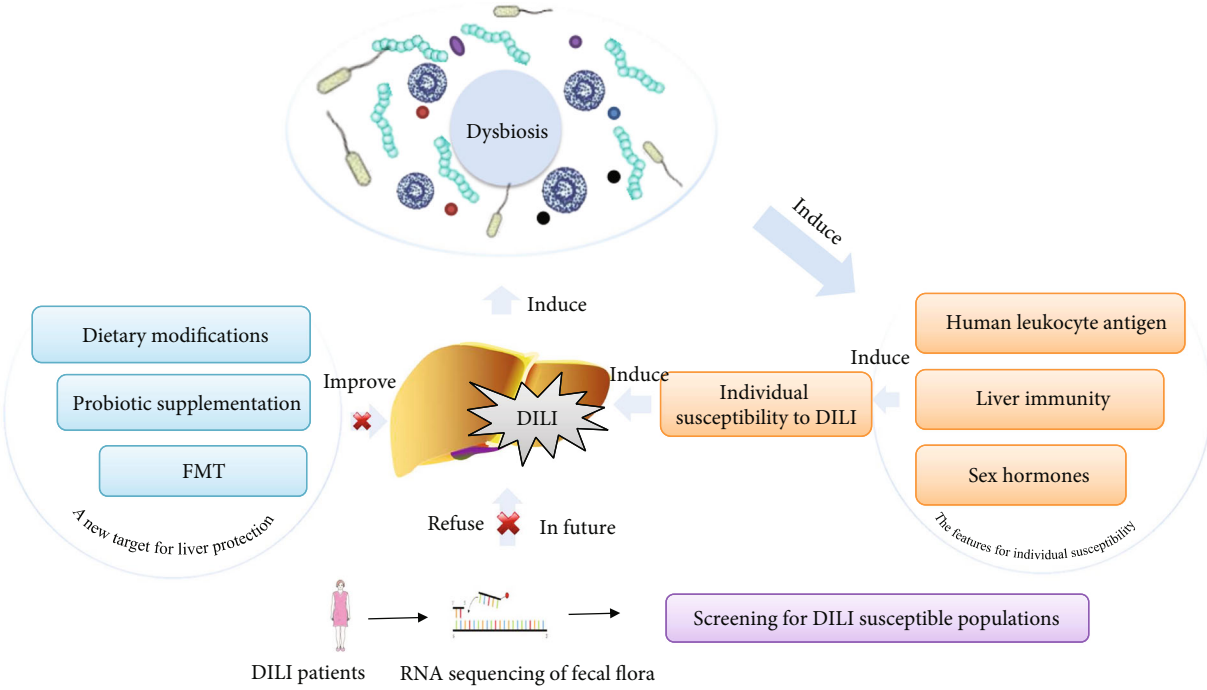

Figure 2: The table of contents. Gut microbiota will change after DILI, human leukocyte antigen (HLA), liver immunity, and sex hormones contribute to individual susceptibility to DILI, regulating gut microbiota by dietary modifications, and probiotic supplementation and FMT can be a new target for liver protection. In the future, by analyzing the gut microbiota of people prone to DILI, RNA sequencing of their gut microbiota was performed to summarize the sequencing characteristics. Screening for DILI-prone individuals and to achieve precision medicine.

At present, there are not many studies on FMT in the treatment of DILI and the published result of microbiota of the host after FMT. These changes may improve the permeability of intestinal mucosal barrier, which remain at the level of "phenomenon." What we know is that significant changes have taken place in the gut microeffect bile acid metabolism and affect host immune function, thus alleviating liver injury. If we focus our efforts on the gut microbiota and change the gut microbiota by changing the diet, oral supplementation of live bacteria or FMT to treat DILI or to reduce the degree of liver injury, this may be a new mechanism to protect the liver, but it is undoubtedly also a great challenge.

5. Prospect

DILI is associated with changes in the gut microbiota, reducing the degree of liver injury of DILI via probiotic supplementation, dietary modifications, and FMT, in which dysbiotic changes seem to contribute to hepatic disease. Although we have gained some insight into the interactions between gut microbial communities and host, a comprehensive understanding of the gut microbiota's function during DILI is lacking. In fact, we need more clinical trials to confirm that restoring disturbed gut microbiota can reduce DILI. A better characterisation of the intestinal microbiome, metabolome, and host response using different preclinical models, stages of liver disease, and larger cohorts of patients is required. This will allow us to determine subtypes or groups of patients that would benefit most from therapies targeting the gut microbiota. Microbiome and metabolome analyses in patients with DILI might become a routine diagnostic test to stratify patients for tailored microbiome treatment approaches. A study shows that recent advances in sequencing technologies and computational tools have allowed an increasing number of metagenomic studies to be performed [91]. These technological advances enable a more thorough study of the genomics of the gut. In the future, untargeted therapies using antibiotics, probiotics, or FMT will be replaced by personalised and precision medicine approaches, such as bioengineered bacterial strains or drugs that modulate specific bacterial enzymes and metabolic pathways as shown in Figure 2.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

[1] T. Shen, Y. Liu, J. Shang et al., "Incidence and etiology of drug-induced liver injury in mainland China," *Gastroenterology*, vol. 156, no. 8, pp. 2230–41.e11, 2019.

[2] X. Lei, J. Chen, J. Ren et al., "Liver Damage Associated with *Polygonum multiflorum* Thunb.: A Systematic Review of Case Reports and Case Series," *Evidence-based Complementary and Alternative Medicine*, vol. 2015, Article ID 459749, 9 pages, 2015.

[3] V. J. Navarro, I. Khan, E. Björnsson, L. B. Seeff, J. Serrano, and J. H. Hoofnagle, "Liver injury from herbal and dietary supplements," *Hepatology*, vol. 65, no. 1, pp. 363–373, 2017.

[4] D. K. Wysowski and L. Swartz, "Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions," *Archives of Internal Medicine*, vol. 165, no. 12, pp. 1363–1369, 2005.

[5] W. Liu, X. Zeng, Y. Liu et al., "The immunological mechanisms and immune-based biomarkers of drug-induced liver injury," *Frontiers in Pharmacology*, vol. 12, article 723940, 2021.

[6] J. H. Hoofnagle and E. S. Björnsson, "Drug-induced liver injury-types and phenotypes," *The New England Journal of Medicine*, vol. 381, no. 3, pp. 264–273, 2019.

[7] R. Sender, S. Fuchs, and R. Milo, "Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans," *Cell*, vol. 164, no. 3, pp. 337–340, 2016.

[8] D. Laukens, B. M. Brinkman, J. Raes, M. de Vos, and P. Vandenabeele, "Heterogeneity of the gut microbiome in mice: guidelines for optimizing experimental design," *FEMS Microbiology Reviews*, vol. 40, no. 1, pp. 117–132, 2016.

[9] A. N. Ananthakrishnan, "Epidemiology and risk factors for IBD," *Nature Reviews Gastroenterology & Hepatology*, vol. 12, no. 4, pp. 205–217, 2015.

[10] A. Tripathi, J. Debelius, D. A. Brenner et al., "The gut-liver axis and the intersection with the microbiome," *Nature Reviews Gastroenterology & Hepatology*, vol. 15, no. 7, pp. 397–411, 2018.

[11] P. C. Konturek, I. A. Harsch, K. Konturek et al., "Gut-liver axis: how do gut bacteria influence the liver?," *Medical Science*, vol. 6, no. 3, p. 79, 2018.

[12] N. Gupta, J. A. Buffa, A. B. Roberts et al., "Targeted inhibition of gut microbial trimethylamine N-oxide production reduces renal tubulointerstitial fibrosis and functional impairment in a murine model of chronic kidney disease," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 40, no. 5, pp. 1239–1255, 2020.

[13] S. C. Ganal-Vonarburg and C. U. Duerr, "The interaction of intestinal microbiota and innate lymphoid cells in health and disease throughout life," *Immunology*, vol. 159, no. 1, pp. 39–51, 2020.

[14] S. V. Lynch and O. Pedersen, "The human intestinal microbiome in health and disease," *The New England Journal of Medicine*, vol. 375, no. 24, pp. 2369–2379, 2016.

[15] P. I. Costea, F. Hildebrand, M. Arumugam et al., "Enterotypes in the landscape of gut microbial community composition," *Nature Microbiology*, vol. 3, no. 1, pp. 8–16, 2018.

[16] N. Taniki, N. Nakamoto, P. S. Chu et al., "Intestinal barrier regulates immune responses in the liver via IL-10–producing macrophages," *JCI Insight*, vol. 3, no. 12, 2018.

[17] S. K. Sarin, A. Pande, and B. Schnabl, "Microbiome as a therapeutic target in alcohol-related liver disease," *Journal of Hepatology*, vol. 70, no. 2, pp. 260–272, 2019.

[18] B. Saberi, A. S. Dadabhai, Y. Y. Jang, A. Gurakar, and E. Mezey, "Current management of alcoholic hepatitis and future therapies," *Journal of Clinical and Translational Hepatology*, vol. 4, no. 2, pp. 113–122, 2016.

[19] E. G. Zoetendal, J. Raes, B. van den Bogert et al., "The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates," *The ISME Journal*, vol. 6, no. 7, pp. 1415–1426, 2012.

[20] O. Kučera, R. Endlicher, D. Rychtrmoc, H. Lotková, O. Sobotka, and Z. Červinková, "Acetaminophen toxicity in rat and mouse hepatocytesin vitro," *Drug and Chemical Toxicology*, vol. 40, no. 4, pp. 448–456, 2017.

[21] A. van Rongen, P. A. J. Välitalo, M. Y. M. Peeters et al., "Morbidly obese patients exhibit increased CYP2E1-mediated oxidation of acetaminophen," *Clinical Pharmacokinetics*, vol. 55, no. 7, pp. 833–847, 2016.

[22] S. Gong, T. Lan, L. Zeng et al., "Gut microbiota mediates diurnal variation of acetaminophen induced acute liver injury in mice," *Journal of Hepatology*, vol. 69, no. 1, pp. 51–59, 2018.

[23] C. A. Thaiss, D. Zeevi, M. Levy et al., "Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis," *Cell*, vol. 159, no. 3, pp. 514–529, 2014.

[24] S. Namasivayam, M. Maiga, W. Yuan et al., "Longitudinal profiling reveals a persistent intestinal dysbiosis triggered by conventional anti-tuberculosis therapy," *Microbiome*, vol. 5, no. 1, p. 71, 2017.

[25] Y. Hu, Q. Yang, B. Liu et al., "Gut microbiota associated with pulmonary tuberculosis and dysbiosis caused by anti-tuberculosis drugs," *The Journal of Infection*, vol. 78, no. 4, pp. 317–322, 2019.

[26] C. C. Chiu, Y. H. Ching, Y. P. Li et al., "Nonalcoholic fatty liver disease is exacerbated in high-fat diet-fed Gnotobiotic mice by colonization with the gut microbiota from patients with nonalcoholic steatohepatitis," *Nutrients*, vol. 9, no. 11, p. 1220, 2017.

[27] G. A. Stevens, M. M. Finucane, L. M. De-Regil et al., "Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non- pregnant women for 1995-2011: a systematic analysis of population- representative data," *The Lancet Global Health*, vol. 1, no. 1, pp. e16–e25, 2013.

[28] J. Jeung, S. Ashour, and L. Fuller, "Iron pill-induced duodenitis: a distinct pattern of duodenal mucosal injury in a patient with a duodenal mass," *Pathology, Research and Practice*, vol. 216, no. 5, article 152916, 2020.

[29] S. Fang, Z. Zhuo, X. Yu, H. Wang, and J. Feng, "Oral administration of liquid iron preparation containing excess iron induces intestine and liver injury, impairs intestinal barrier function and alters the gut microbiota in rats," *Journal of Trace Elements in Medicine and Biology*, vol. 47, pp. 12–20, 2018.

[30] P. Zhang, L. Zheng, Y. Duan et al., "Gut microbiota exaggerates triclosan-induced liver injury via gut-liver axis," *Journal of Hazardous Materials*, vol. 421, article 126707, 2022.

[31] J. Zhang, Z. Wang, D. Huo, and Y. Shao, "Consumption of goats' milk protects mice from carbon tetrachloride-induced acute hepatic injury and improves the associated gut microbiota imbalance," *Frontiers in Immunology*, vol. 9, 2018.

[32] J. Dai, X. Yang, Y. Yuan et al., "Toxicity, gut microbiota and metabolome effects after copper exposure during early life in SD rats," *Toxicology*, vol. 433-434, article 152395, 2020.

[33] H. Jiang, R. Yan, K. Wang et al., "*Lactobacillus reuteri* DSM 17938 alleviates d-galactosamine-induced liver failure in rats," *Biomedicine & Pharmacotherapy*, vol. 133, article 111000, 2021.

[34] L. Dara, Z. X. Liu, and N. Kaplowitz, "Mechanisms of adaptation and progression in idiosyncratic drug induced liver injury, clinical implications," *Liver International*, vol. 36, no. 2, pp. 158–165, 2016.

[35] A. K. Daly, P. T. Donaldson, P. Bhatnagar et al., "*HLA-B* 5701* genotype is a major determinant of drug-induced liver injury due to flucloxacillin," *Nature Genetics*, vol. 41, no. 7, pp. 816–819, 2009.

[36] M. I. Lucena, M. Molokhia, Y. Shen et al., "Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles," *Gastroenterology*, vol. 141, no. 1, pp. 338–347, 2011.

[37] J. Ahmad, J. A. Odin, P. H. Hayashi et al., "Identification and characterization of fenofibrate-induced liver injury," *Digestive Diseases and Sciences*, vol. 62, no. 12, pp. 3596–3604, 2017.

[38] R. J. Fontana, E. T. Cirulli, J. Gu et al., "The role of HLA-A* 33:01 in patients with cholestatic hepatitis attributed to terbinafine," *Journal of Hepatology*, vol. 69, no. 6, pp. 1317–1325, 2018.

[39] W. Tangamornsuksan, C. Kongkaew, C. N. Scholfield, S. Subongkot, and M. Lohitnavy, "*HLA-DRB1* 07:01* and lapatinib-induced hepatotoxicity: a systematic review and meta-analysis," *The Pharmacogenomics Journal*, vol. 20, no. 1, pp. 47–56, 2020.

[40] Y. J. Li, E. J. Phillips, A. Dellinger et al., "Human leukocyte antigen B*14:01 and B*35:01 are associated with trimethoprim- sulfamethoxazole induced liver injury," *Hepatology*, vol. 73, no. 1, pp. 268–281, 2021.

[41] A. Tailor, X. Meng, K. Adair et al., "HLA DRB1*15:01-DQB1* 06:02-restricted human CD4+ T cells are selectively activated with amoxicillin-peptide adducts," *Toxicological Sciences*, vol. 178, no. 1, pp. 115–126, 2020.

[42] E. R. Unanue, V. Turk, and J. Neefjes, "Variations in MHC class II antigen processing and presentation in health and disease," *Annual Review of Immunology*, vol. 34, no. 1, pp. 265–297, 2016.

[43] J. R. Hov, H. Zhong, B. Qin et al., "The influence of the autoimmunity-associated ancestral HLA haplotype AH8.1 on the human gut microbiota: a cross-sectional study," *PLoS One*, vol. 10, no. 7, article e0133804, 2015.

[44] S. K. Shahi, S. Ali, C. M. Jaime, N. V. Guseva, and A. K. Mangalam, "HLA class II polymorphisms modulate gut microbiota and experimental autoimmune encephalomyelitis phenotype," *Immuno Horizons*, vol. 5, no. 8, pp. 627–646, 2021.

[45] I. D. Wilson and J. K. Nicholson, "Gut microbiome interactions with drug metabolism, efficacy, and toxicity," *Translational Research*, vol. 179, p. 204, 2017.

[46] T. Toda, K. Ohi, T. Kudo et al., "Ciprofloxacin suppresses Cyp3a in mouse liver by reducing lithocholic acid- producing intestinal flora," *Drug Metabolism and Pharmacokinetics*, vol. 24, no. 3, pp. 201–208, 2009.

[47] F. P. Selwyn, S. L. Cheng, T. K. Bammler et al., "Developmental regulation of drug-processing genes in livers of germ-free mice," *Toxicological Sciences*, vol. 147, no. 1, pp. 84–103, 2015.

[48] T. E. Adolph, C. Grander, A. R. Moschen, and H. Tilg, "Liver-microbiome axis in health and disease," *Trends in Immunology*, vol. 39, no. 9, pp. 712–723, 2018.

[49] G. M. Williams and M. J. Iatropoulos, "Alteration of liver cell function and proliferation: differentiation between adaptation and toxicity," *Toxicologic Pathology*, vol. 30, no. 1, pp. 41–53, 2002.

[50] D. H. Adams, A. Sanchez-Fueyo, and D. Samuel, "From immunosuppression to tolerance," *Journal of Hepatology*, vol. 62, no. 1, pp. S170–S185, 2015.

[51] C. Bunchorntavakul and K. R. Reddy, "Acetaminophen-related hepatotoxicity," *Clinics in Liver Disease*, vol. 17, no. 4, pp. 587–607, 2013, viii.

[52] J. Boursier, O. Mueller, M. Barret et al., "The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota," *Hepatology*, vol. 63, no. 3, pp. 764–775, 2016.

[53] M. C. C. Canesso, N. L. Lacerda, C. M. Ferreira et al., "Comparing the effects of acute alcohol consumption in germ-free and conventional mice: the role of the gut microbiota," *BMC Microbiology*, vol. 14, no. 1, p. 240, 2014.

[54] J. Zaneveld, P. J. Turnbaugh, C. Lozupone et al., "Host-bacterial coevolution and the search for new drug targets," *Current Opinion in Chemical Biology*, vol. 12, no. 1, pp. 109–114, 2008.

[55] D. Bouskra, C. Brézillon, M. Bérard et al., "Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis," *Nature*, vol. 456, no. 7221, pp. 507–510, 2008.

[56] A. J. Czaja, "Factoring the intestinal microbiome into the pathogenesis of autoimmune hepatitis," *World Journal of Gastroenterology*, vol. 22, no. 42, pp. 9257–9278, 2016.

[57] K. M. Schneider, C. Elfers, A. Ghallab et al., "Intestinal dysbiosis amplifies acetaminophen-induced acute liver injury," *Cellular and Molecular Gastroenterology and Hepatology*, vol. 11, no. 4, pp. 909–933, 2021.

[58] R. J. Fontana, P. H. Hayashi, H. Barnhart et al., "Persistent liver biochemistry abnormalities are more common in older patients and those with cholestatic drug induced liver injury," *The American Journal of Gastroenterology*, vol. 110, no. 10, pp. 1450–1459, 2015.

[59] M. F. Doran, G. R. Pond, C. S. Crowson, W. M. O'Fallon, and S. E. Gabriel, "Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period," *Arthritis and Rheumatism*, vol. 46, no. 3, pp. 625–631, 2002.

[60] B. G. Weinshenker, "Natural history of multiple sclerosis," *Annals of Neurology*, vol. 36, no. S1, pp. S6–S11, 1994.

[61] J. G. Markle, D. N. Frank, S. Mortin-Toth et al., "Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity," *Science*, vol. 339, no. 6123, pp. 1084–1088, 2013.

[62] Y. Toyoda, T. Miyashita, S. Endo et al., "Estradiol and progesterone modulate halothane-induced liver injury in mice," *Toxicology Letters*, vol. 204, no. 1, pp. 17–24, 2011.

[63] L. Yang, Y. Li, S. Wang et al., "Western diet aggravated carbon tetrachloride-induced chronic liver injury by disturbing gut microbiota and bile acid metabolism," *Molecular Nutrition & Food Research*, vol. 65, no. 7, article e2000811, 2021.

[64] N. Chalasani, K. R. K. Reddy, R. J. Fontana et al., "Idiosyncratic drug induced liver injury in African-Americans is associated with greater morbidity and mortality compared to Caucasians," *The American Journal of Gastroenterology*, vol. 112, no. 9, pp. 1382–1388, 2017.

[65] A. Baehr, J. C. Peña, and D. J. Hu, "Racial and ethnic disparities in adverse drug events: a systematic review of the literature," *Journal of Racial and Ethnic Health Disparities*, vol. 2, no. 4, pp. 527–536, 2015.

[66] J. S. Bajaj, R. Idilman, L. Mabudian et al., "Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort," *Hepatology*, vol. 68, no. 1, pp. 234–247, 2018.

[67] I. A. Kirpich, J. Petrosino, N. Ajami et al., "Saturated and unsaturated dietary fats differentially modulate ethanol-induced changes in gut microbiome and metabolome in a mouse model of alcoholic liver disease," *The American Journal of Pathology*, vol. 186, no. 4, pp. 765–776, 2016.

[68] C. Yang, M. Wan, D. Xu et al., "Flaxseed powder attenuates non-alcoholic steatohepatitis via modulation of gut microbiota and bile acid metabolism through gut-liver axis," *International Journal of Molecular Sciences*, vol. 22, no. 19, p. 10858, 2021.

[69] X. Yan, X. Ren, X. Liu et al., "Dietary ursolic acid prevents alcohol-induced liver injury via gut-liver axis homeostasis modulation: the key role of microbiome manipulation," *Journal of Agricultural and Food Chemistry*, vol. 69, no. 25, pp. 7074–7083, 2021.

[70] P. Pais, V. Almeida, M. Yılmaz, and M. C. Teixeira, "*Saccharomyces boulardii*: what makes it tick as successful probiotic?," *Journal of Fungi*, vol. 6, no. 2, p. 78, 2020.

[71] M. Li, L. Zhu, A. Xie, and J. Yuan, "Oral administration of saccharomyces boulardii ameliorates carbon tetrachloride-induced liver fibrosis in rats via reducing intestinal permeability and modulating gut microbial composition," *Inflammation*, vol. 38, no. 1, pp. 170–179, 2015.

[72] T. Oikonomou, G. V. Papatheodoridis, M. Samarkos, I. Goulis, and E. Cholongitas, "Clinical impact of microbiome in patients with decompensated cirrhosis," *World Journal of Gastroenterology*, vol. 24, no. 34, pp. 3813–3820, 2018.

[73] F. de Faria Ghetti, D. G. Oliveira, J. M. de Oliveira, L. E. de Castro Ferreira, D. E. Cesar, and A. P. Moreira, "Influence of gut microbiota on the development and progression of nonalcoholic steatohepatitis," *European Journal of Nutrition*, vol. 57, no. 3, pp. 861–876, 2018.

[74] L. Yu, X. K. Zhao, M. L. Cheng et al., "*Saccharomyces boulardii* Administration Changes Gut Microbiota and Attenuates D-Galactosamine-Induced Liver Injury," *Scientific Reports*, vol. 7, no. 1, p. 1359, 2017.

[75] Q. Wang, L. Lv, H. Jiang et al., "Lactobacillus helveticus R0052 alleviates liver injury by modulating gut microbiome and metabolome in D-galactosamine-treated rats," *Applied Microbiology and Biotechnology*, vol. 103, no. 23-24, pp. 9673–9686, 2019.

[76] K. Wang, L. Lv, R. Yan et al., "Bifidobacterium longum R0175 protects rats againstd-galactosamine-Induced acute liver failure," *Msphere*, vol. 5, no. 1, 2020.

[77] R. V. Bubnov, L. P. Babenko, L. M. Lazarenko et al., "Comparative study of probiotic effects of lactobacillus and Bifidobacteria strains on cholesterol levels, liver morphology and the gut microbiota in obese mice," *The EPMA Journal*, vol. 8, no. 4, pp. 357–376, 2017.

[78] D. Fang, D. Shi, L. Lv et al., "*Bifidobacterium pseudocatenulatum* LI09 and *Bifidobacterium catenulatum* LI10 attenuate D-galactosamine-induced liver injury by modifying the gut microbiota," *Scientific Reports*, vol. 7, no. 1, p. 8770, 2017.

[79] H. Zha, D. Q. Fang, A. van Der Reis et al., "Vital members in the gut microbiotas altered by two probiotic Bifidobacterium strains against liver damage in rats," *BMC Microbiology*, vol. 20, no. 1, p. 144, 2020.

[80] J. Liu, Y. Fu, H. Zhang et al., "The hepatoprotective effect of the probiotic clostridium butyricum against carbon tetrachloride-induced acute liver damage in mice," *Food & Function*, vol. 8, no. 11, pp. 4042–4052, 2017.

[81] K. Xiong, J. Cai, P. Liu et al., "Lactobacillus casei alleviated the abnormal increase of cholestasis-related liver indices during tuberculosis treatment: a post hoc analysis of randomized controlled trial," *Molecular Nutrition & Food Research*, vol. 65, no. 16, article e2100108, 2021.

[82] N. Nakamoto, T. Amiya, R. Aoki et al., "Commensal *lactobacillus* controls immune tolerance during acute liver injury in mice," *Cell Reports*, vol. 21, no. 5, pp. 1215–1226, 2017.

[83] S. Xu, M. Zhao, Q. Wang et al., "Effectiveness of probiotics and prebiotics against acute liver injury: a meta-analysis," *Frontiers in Medicine*, vol. 8, article 739337, 2021.

[84] X. Chen, J. Zhang, R. Yi, J. Mu, X. Zhao, and Z. Yang, "Hepatoprotective effects of lactobacillus on carbon tetrachloride-induced acute liver injury in mice," *International Journal of Molecular Sciences*, vol. 19, no. 8, p. 2212, 2018.

[85] X. Wen, H. G. Wang, M. N. Zhang, M. H. Zhang, H. Wang, and X. Z. Yang, "Fecal microbiota transplantation ameliorates experimental colitisviagut microbiota and T-cell modulation," *World Journal of Gastroenterology*, vol. 27, no. 21, pp. 2834–2849, 2021.

[86] W. Zhang, G. Zou, B. Li et al., "Fecal microbiota transplantation (FMT) alleviates experimental colitis in mice by gut microbiota regulation," *Journal of Microbiology and Biotechnology*, vol. 30, no. 8, pp. 1132–1141, 2020.

[87] L. Craven, A. Rahman, S. Nair Parvathy et al., "Allogenic fecal microbiota transplantation in patients with nonalcoholic fatty liver disease improves abnormal small intestinal permeability: a randomized control trial," *The American Journal of Gastroenterology*, vol. 115, no. 7, pp. 1055–1065, 2020.

[88] J. S. Bajaj, Z. Kassam, A. Fagan et al., "Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial," *Hepatology*, vol. 66, no. 6, pp. 1727–1738, 2017.

[89] L. D. Fan, Y. M. Liu, and M. L. Cheng, "Probiotics enhance the efficacy of fecal microbiota transplantation in severe acute liver injury," *Chinese Journal of Hepatology*, vol. 28, no. 4, pp. 345–350, 2020.

[90] Y. Liu, L. Fan, Z. Cheng et al., "Fecal transplantation alleviates acute liver injury in mice through regulating Treg/Th17 cytokines balance," *Scientific Reports*, vol. 11, no. 1, p. 1611, 2021.

[91] M. A. Malla, A. Dubey, A. Kumar, S. Yadav, A. Hashem, and E. F. Abd_Allah, "Exploring the human microbiome: the potential future role of next-generation sequencing in disease diagnosis and treatment," *Frontiers in Immunology*, vol. 9, 2019.