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Targeting Microbiota and Liver Diseases: from Basic Prospective to Recent Advance Treatments

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Abstract: The diverse community of microorganisms residing in the human digestive tract, known as the intestinal microbiome, plays a crucial role in the development and progression of various liver diseases. Disruptions in the gut-liver axis have been associated with various liver conditions, including non-alcoholic fatty liver disease, alcoholic liver disease, viral hepatitis, cirrhosis of liver, and hepatocellular carcinoma. Intestinal dysbiosis can worsen liver disease by promoting systemic inflammation, influencing immune responses, and altering metabolic pathways. This review explores the intricate connection between gut microbiome and liver diseases, highlighting fecal microbiome transplantation as a potential therapeutic approach. Considering search through databases using keywords including "liver disease" AND "microbiome" we found 62 clinical trials out of total 3,303 articles on microbiome changes to find promising treatment of liver disease. Totally 55 articles were assessed, of which most of the studies were about using probiotics, the diet and exercise, and finally FMT. NAFLD was the most predominant liver disease targeted for intervention and treatment. Most of studies (47/55: 85.45%) reported targeting microbiome as an effective and promising treatment. Probiotics and prebiotics also show promise in mitigating liver dysfunction by modulating gut microbiome and influencing adipokines, key regulators in metabolic and inflammatory processes. Despite advancements, significant gaps persist, particularly regarding FMT applications in chronic viral hepatitis and HCC. Further clinical trials are essential to optimize gut microbiome-targeted therapies for liver disease management. This review emphasizes the need for a multidisciplinary approach to bridge the gap between microbial science and therapeutic innovations in hepatology.

Keywords: Gut Microbiome; Liver Diseases; NAFLD; Fecal Microbiota Transplantation; Modulation of Microbiome

1. Introduction

As obesity rates continue to rise worldwide [1], there has been a parallel increase in associated health complications and mortality [2]. Obese individuals face a higher risk of developing health complications such as non-alcoholic fatty liver disease, cardiovascular diseases, and diabetes [3,4]. Non-alcoholic fatty liver disease is now the most prevalent liver disorder and a major contributor to chronic liver disease [5]. It is considered the hep-

atic manifestation of metabolic syndrome [6], characterized mainly by the excessive buildup of free fatty acids and triglycerides in liver tissue. Visceral obesity is associated with non-alcoholic fatty liver disease, and when both conditions coexist, the likelihood of advancing to severe liver disease increases considerably. Currently, NAFLD poses health challenges globally and stands out as a significant contributor to mortality rates, being acknowledged as one of the primary causes of death [7]. Non-alcoholic fatty liver disease leads to elevated transaminase levels and takes a vital role in cryptogenic cirrhosis as well as hepatocellular carcinoma [8]. An examination of the link between NAFLD, metabolic syndrome, and genetic factors reveals that visceral obesity is notably influential in the development of non-alcoholic fatty liver disease [9]. Investigation made on a cohort of individuals suffering from non-alcoholic fatty liver disease indicated a notable correlation between NAFLD and the levels of serum adipokines [10]. Recent systematic reviews highlight the potential of microbiome-targeted therapies (MTTs) in liver cirrhosis and NAFLD. Jiang et al. (2022) proposed a comprehensive meta-analysis on probiotics, prebiotics, synbiotics, and FMT in cirrhosis, while Naghipour et al. (2023) found significant improvements in lipid profiles of NAFLD patients receiving microbial therapy [11,12].

The microbiome encompasses the diverse community of microorganisms, including bacteria, viruses, and fungi, that reside within the human body. The gut serves as both the primary digestive organ and a significant component of the immune system, housing about 80 percent of the human microbiome [13]. More than 99% of the microorganisms located in the human GI tract consist of bacteria, along with other types such as fungi and viruses [13]. The digestive tract is home to around 1,000 species of bacteria, each consisting of two thousands of genes. On average, the human gut contains approximately 2 million genes, a figure that exceeds the estimated number of human genes by a factor of 100. Within these bacterial populations, some serve as probiotics while others act as pathogens. The intricate equilibrium among various bacterial species within the gut is crucial for preserving its overall health and functionality, which in turn influences essential processes such as digestion, metabolism (energy production and metabolic functions), and immune responses in the body. Various elements, including nutrition, pharmaceuticals, illnesses, metabolic conditions, and autoimmune disorders, have a significant influence on the development of this gut-related balance [14]. Disruptions in the normal gut microbiome play a role in the development and progression of several intestinal and systemic disorders, including disorders of the liver, DM, WBC disorders, and septic conditions. Consequently, changing or modifying the gut microbiome may aid in addressing conditions related to intestinal dysbiosis. Several strategies have been employed to influence and manage both the composition and metabolic activity of gut microorganisms; these include dietary changes, prebiotics, probiotics, and antibiotics [15,16]. Even though the previously mentioned methods have achieved a series of therapeutic effects, the results have not been as satisfactory as they should have been. Fecal microbiome transfer (FMT) may date back about 1700 years; however, it has only recently attracted the attention of doctors and researchers. FMT can be considered a reliable therapeutic method or regimen for directly regulating the intestinal microbiome [17]. This approach involves transferring processed fecal material from well-matched donors to recipients to restore and enhance the composition and diversity of their gut microbiome. There is widespread agreement that fecal microbiome transfer is an effective treatment for resistant and persistent *Clostridium difficile* infection. Recently, increasing evidence suggests that FMT can successfully alleviate and manage conditions such as severe constipation, inflammatory bowel disorders (IBD), excess weight, and DM type two. Moreover, the link between intestinal dysbiosis and various liver diseases has underscored the potential of FMT as a therapeutic approach for hepatic disorders. The imbalance of intestinal microbiome is closely associated with the development, progression, and outcomes of several liver diseases, including acute hepatic injury, viral hepatitis, cirrhosis of liver, autoimmune liver conditions, alcohol-related liver disorders, and metabolic-associated fatty liver disease (MAFLD) [18,19]. Fecal microbiome transfer plays a crucial role in promoting recovery from diseases by re-establishing the normal balance of the intestines in individuals suffering from liver conditions [20].

Aims: This review explores the relationship of gut microbiome and various liver diseases.

2. Methods

This review was conducted using PubMed and Scopus databases. A systematic search was performed using the keywords “gut microbiome,” “fecal microbiome transplantation,” “liver diseases,” and “probiotics.” The inclusion criteria for article selection were: studies published between 1998 and 2024, peer-reviewed clinical trials, systematic reviews, and meta-analyses focusing on microbiome and liver diseases, and studies evaluating interventions such

as probiotics, prebiotics, and FMT in liver disease management. Exclusion criteria included: non-peer-reviewed articles, editorials, and opinion pieces, animal studies without direct clinical application, studies lacking primary data or clear methodological descriptions, duplicates, or retracted publications.

3. The Relationship Between Liver Diseases and Intestinal Microbiome

The liver, the body's primary digestive organ, plays a vital role in the defending of body and maintains a strong connection with the gut. Studies suggest that intestinal dysbiosis is linked to the development of various hepatic disorders [20,21]. Moreover, this dysbiosis influences the extent and severity of liver fat accumulation (steatosis), inflammation, fibrosis, and even the progression to liver cancer. It exerts these effects through complex interactions with the host immune system and various cell types. The connection between hepatic disorders and intestinal microbiome involves different types of mechanisms that remain inadequately defined and comprehended [22]. Liver disorders can cause a disruption in the intestinal microbiome, and this disturbance may further aggravate liver disease progression, thereby intensifying the effects of these conditions as they advance.

3.1. The Gut-Liver Axis: A Two-Way Communication System

First identified in 1987, the intestinal-liver connection represents a two-way signaling network between the liver and intestine, functioning in a continuous cycle. In normal physiological circumstances, the liver releases bile acids (BAs) along with various bioactive substances into the intestine to facilitate nutrient absorption and metabolic processes. Throughout this mechanism, both liver metabolites and intestinal byproducts enter the bloodstream from the gastrointestinal tract; additionally, exotoxins also reach the liver through this route, impacting overall systemic homeostasis of the organism. In healthy individuals, the intestinal structure primarily consists of mucosal epithelial cells, intestinal mucosa layers, and a balanced microbiome which collectively function as a protective mucosal barrier. This physiological gut protective layer takes a crucial place in restricting the entry of bacterial substances. However, conditions such as liver disease can compromise this mucosal barrier (see Figure 1). The movement of bacteria from the intestine into the circulatory system or through the intestine-hepatic connection may worsen pathological conditions.

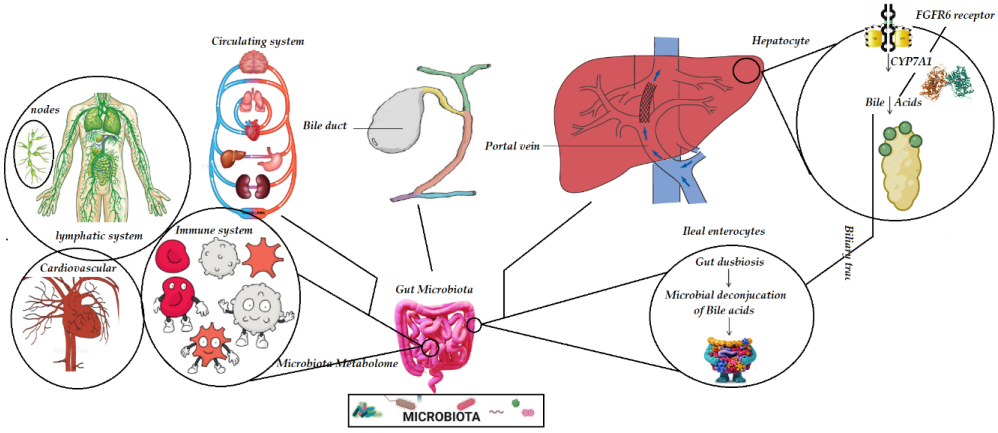

Figure 1. The Underlying Cause of Interaction Between the Microbiome and the Liver.

3.2. Impact of Gut Microbiome Alterations on Liver Disorders

Metabolic-associated fatty liver disease (MAFLD) is a prevalent clinical disorder that arises from factors unrelated to alcohol intake or any established hepatic injury. Studies suggest that changes in gut microbiome may play a key role in both the development and progression of NAFLD. Approximately two decades ago, studies reported that probiotics have the potential to inhibit not only fat accumulation but also lipid transformation around the liver [23]. Le Roy et al. demonstrated that microbiome of intestine contributes to the onset of non-alcoholic fatty lover diseases in germ-free mice, independent of obesity [24]. Along with that, Gómez-Hurtado et al. showed that microbial antigenic rearrangements cause widespread inflammatory response with NAFLD [25]. Other hep-

atic disorders are associated with changes in the composition of the gut microbiome communities as well [26]. Multiple studies revealed that individuals with NAFLD exhibit gut microbiome dysbiosis, marked by a decreased presence of *Bacteroidetes* and *Akkermansia muciniphila* [27], along with an increased abundance of *Proteobacteria* [28]. Individuals diagnosed with PBC experience microbial imbalance, characterized by reduced microbial variety in comparison to well-balanced individuals. Conversely, those suffering from PSC demonstrate an increased presence of specific bacterial groups, including *Enterococcus* and *Veillonella* while showing a diminished quantity of the commensal *Clostridium* [29]. Patients suffering from acute and chronic liver damage linked to hepatitis B exhibit elevated concentrations of DNA of bacteria in the bloodstream and a reduction in bacterial variety when compared to healthy individuals [30–32]. Additionally, research conducted by Wang et al. revealed that those with cirrhosis of liver possess a distinct microbiome of intestine profile, characterized by increased amounts of *Prevotella*, *Streptococcus*, *Staphylococcus*, and *Enterococcus* alongside decreased levels of *Ruminococcus* and *Clostridium* [33]. Aside of that, multiple studies have demonstrated that *A. muciniphila* supplementation can alleviate ethanol-induced liver disorders, emphasizing its potential as a probiotic [34]. Thus, imbalances of the microbiome of intestine have been identified in a different type of hepatic disorders and may take a critical place in disease development.

4. The Role of Gut Microbiome in Liver Damage and Chronic Liver Diseases

The imbalance of microbiome of intestine can worsen damage to liver and is probably linked to the advancement of several chronic liver conditions, like alcoholic liver disease and non-alcoholic fatty liver disease [35,36], primary biliary cholangitis [37,38], viral hepatitis [33], cirrhosis [39], particularly in relation to hepatic encephalopathy [40,41].

4.1. Gut Microbiome Alterations in Hepatic Encephalopathy

Hepatic encephalopathy is a severe disorder of the CNS that occurs because of liver failure and can arise from different forms of both chronic and acute hepatitis, as well as decompensated cirrhosis. This condition exhibits significant mortality rates and prevalence. The precise mechanism underlying HE remains unclear currently. Among various proposed models or theories, ammonia toxicity stands out as the most recognized factor associated with this disease. Elevated levels of ammonia in blood may heighten the risk of developing hepatic encephalopathy by worsening edema of cerebellum. The situation is intricately linked to an imbalance in intestinal microbiome along with changes in gut-brain communication pathways [42]. The makeup of the gut microbiome in individuals with cirrhosis, hepatic encephalopathy (HE) shows notable differences compared to that found in healthy people; specifically, there is an observed rise in *Escherichia coli* and *Enterococcus* [43]. The proliferation and appearance of bacteria can result in heightened ammonia levels. An imbalance within the gut microbiome may also compromise the mucosal barrier, leading to greater integrity of the gut barrier and facilitating the movement of bacterial endotoxins. These factors significantly contribute to the onset of hepatic encephalopathy (HE). Conversely, poisoning from endotoxins (endotoxemia) has been linked with liver failure and brings about complications like HE. Furthermore, endotoxemia is a key factor in the hyperdynamic circulation noted among individuals suffering from cirrhosis [44]. Several researchers did emphasize that the intestinal-hepatic-cerebral connection can have significant and essential impacts on hepatic encephalopathy through the intestinal microbiome [45,46], and the pathogenesis of hepatic encephalopathy is also related to the intestinal microbiome. In other words, the liver obtains 75–80 percent of the liver or hepatic volume of blood through the vena portae, which later enters the circulatory system. In order to prevent microbes from entering the circulatory system, the stability of the gut barrier is capable of isolating the contents within the lumen (materials inside the intestine) from the internal environment. Proof suggests that hydrogen nitride and bacterial toxins are linked to the progression and occurrence of HE in the event of impaired gut barrier function [47]. When intestinal function is impaired, bacteria and their products migrate from the gastrointestinal pathway to the hepatic organ. Ammonia, as the important byproduct of bacterial metabolism, may cause significant hepatotoxicity. Also, neuroglial cellular structures are also stimulated by ammonia, resulting in the generation of pro-inflammatory molecules. These factors cause damage to brain tissue, which leads to cognitive impairment in the brain. In addition, a series of clinical and preclinical studies indicates a two-way or reciprocal relation of the brain and the intestinal microbiom. It has been shown that intestinal microorganisms communicate with the brain through neural, hormonal and immune signaling pathways. The nature and quantity of information and intestinal

microbes signaling that reach the cerebrum largely depend on the microbes residing in that area of the intestine. Alterations in intestinal microbiome can be linked to compromised cognitive function through the intestinal-brain connection. According to Kang et al., dysbiosis within the intestinal microbiome can play a role to both widespread inflammatory response and neuroinflammation associated with cirrhosis, influencing their development and progression [48]. Distinct changes in the gut microbiome influence various facets of brain function. This could provide insight into the mechanisms associated with hepatic encephalopathy (HE) from a different viewpoint. Bajaj et al. employed 16S rRNA sequencing to examine the fecal and oral microbiome of individuals with fibrosis, discovering that patients exhibiting minimal or mild hepatic encephalopathy (MHE) exhibited an increased proportion of *Lactobacillaceae*, which may enhance MHE diagnostic practices [49].

4.2. The Influence of Intestinal Microbiome in the Treatment of Liver Disorders

There is substantial proof showing that changes in gut microbiome, along with alterations in liver function, are pivotal in the onset of numerous short-term and long-term hepatic disorders and their related consequences [50, 51]. Imbalances within the intestinal microbiome significantly play a role in the development of underlying mechanisms of this condition. In individuals suffering from acute liver cirrhosis, these imbalances can result in systemic inflammation and endotoxemia, which may cause related complications such as spontaneous peritonitis and intestinal infections [52], which reduce the effectiveness of therapeutic interventions and may lead to exacerbation of the disease and potentially fatal outcomes. The medical study indicated that individuals suffering from fibrosis frequently receive antibiotic treatment, which diminishes the richness and abundance of gut microbial species. This alteration disrupts the general structure and variety of intestinal microbiome, ultimately influencing the effectiveness of treatments. Consequently, microbial elements are regarded as significant contributors to various liver diseases across all stages and levels of severity. These results carry significant therapeutic implications, highlighting the necessity of placing greater emphasis on and valuing intestinal microbiome in hepatic disorders therapy. Regulating and altering the microbiome through diverse approaches, such as probiotics, innovative probiotics, antibiotics, or fecal microbiome transplantation, can be considered as a crucial treatment strategy. Regarding the substantial impact of FMT, it is worth noting that this method could emerge as a leading solution and benchmark for rectifying imbalances in gut microbiome in the future.

5. Recent Advances in the Therapy of Hepatic Disorders

5.1. Latest Medical Research Studies on Microbiome Changes to Find Promising Treatment of Liver Disease

Considering search through databases using keywords including “liver disease” AND “microbiome” we found 62 clinical trials out of total 3,303 articles on microbiome changes to find promising treatment of liver disease (**Table 1**) [53–107]. After excluding studies that were not clinical trials, only protocols, and retracted articles, totally 55 articles were assessed. Most of the studies were about using probiotics, the diet and exercise, and finally fecal microbiome transplantation (FMT). NAFLD was the most predominant liver disease targeted for intervention and treatment. Most of studies (47/55: 85.45%) reported targeting microbiome as an effective and promising treatment. The function of intestinal microbiome enhancement is pivotal in improvement hepatic disorders outcome. Several interventions may lead to gut microbiome modification: Pro and Prebiotic supplementation orally; Lifestyle modifications with diet and exercises; Bioactive Supplementations (Curcumin, Fish Oil, Vitamin D, etc.); Fecal microbiome transplantation (FMT) and Bile Acid Controle. Further role each of them and their efficacy will be described in detail in chronic liver disorders.

Table 1. Latest Clinical Trials Available in the Literature on Microbiome Changes to Find Promising Treatment of Liver Disease.

Author, Reference, Country	Intervention, Duration	Disease, Sample	Microbiome Evaluation	RCT Code	Findings
Agrinier et al., 2024 [53], Canada	Berry camu-camu, 12-week	hepatic steatosis, 30 adults	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT04130321	Effective
Jin et al., 2024 [54], China	Silymarin, 24-week	MASLD, 83 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	ChiCTR2200059043	Effective

Table 1. *Cont.*

Author, Reference, Country	Intervention, Duration	Disease, Sample	Microbiome Evaluation	RCT Code	Findings
Lin et al., 2024 [55], Taiwan	Probiotic, 8-week	MASLD, 120 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT06183801	Effective
Tian et al., 2024 [56], USA	Sulforaphane, 12-week	NAFLD, 36 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	—–	Effective
Reshef et al., 2024 [57], Israel	Prebiotic, 12-week	NAFLD, 19 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT02642172	Not Effective
He et al., 2024 [58], China	Curcumin supplementation, 24-week	NAFLD, 9 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	ChiCTR2200058052	Effective
Liu et al., 2024 [59], China	Qushi Huayu, an empirical herbal formula, 24-week	NAFLD, 246 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	ChiCTR-IOR-17013491	Effective
Li et al., 2024 [60], China	Fish oil plus vitamin D3, 12-week	NAFLD, 61 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	—–	Effective
Ni et al., 2024 [61], China	Probiotic, 24-week	NAFLD, 120 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	ChiCTR-IOR-15007519	Effective
Gómez-Pérez et al., 2023 [62], Spain	lifestyle intervention with the Mediterranean diet, 48-week	NAFLD, 297 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	ISRCTN89898870	Effective
Escouto et al., 2023 [63], Brazil	Probiotic, 24-week	NASH, 48 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT02764047	Effective
He et al., 2022 [64], China	A Freshwater Fish-Based Diet, 12-week	NAFLD, 34 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	ChiCTR1900025074	Effective
Chayanupatkul et al., 2022 [65], Thailand	Litchi extract or oligonol, 24-week	NAFLD, 38 patients	Changes 16S ribosomal RNA sequencing	TCTR20200814001	Effective
Xue et al., 2022 [66], China	FMT, 4-week	NAFLD, 80 patients	Changes 16S ribosomal RNA sequencing	PRJNA782181	Effective
Manzhalii et al., 2022 [67], Ukraine	Probiotic Escherichia coli Nissle, 4-week	HE, 45 patients	Stool flora evaluated by specialized nonculture techniques	NCT04787276	Effective
Calabrese et al., 2022 [68], Italy	Aerobic exercise and diet, 12-week	NAFLD, 109 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT02347696	Effective
Cheng et al., 2022 [69], China	Aerobic exercise and diet, 24-week	NAFLD, 115 participants	Alterations in intestinal microbiome by 16S rRNA sequencing	ISRCTN 42622771	Effective
Amadieu et al., 2022 [70], Belgium	Dietary fiber with Inulin supplementation, 17 days	AUD, 50 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT03803709	Not Effective
Mohamad Nor et al., 2021 [71], Malaysia	Multi-strain probiotics, 24-week	NAFLD, 39 patients	gut microbiome analyses	NCT04074889	Not Effective
Patel et al., 2022 [72], UK	Rifaximin-α 550 mg BID, 12-week	Cirrhosis and HE, 38 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT02019784	Effective
Amerikanou et al., 2021 [73], European	Mastiha supplementation, 24-week	NAFLD, 98 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT03135873	Effective
Traussnigg et al., 2021 [74], Austria	PX-104 orally, 4 weeks	NAFLD, 12 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT01999101	Effective
Bajaj et al., 2021 [75], USA	FMT, 24-week	AUD-related cirrhosis, 20 patients	Stool microbiome composition	NCT03416751	Effective
Jian et al., 2021 [76], Finland	Diet, 3-week	Overweight and obesity, 38 patients	Alterations in intestinal microbiome by 16S rRNA sequencing	NCT02133144	Not Effective
Zhuo et al., 2020 [77], China	Formulated food, 24-week	NAFLD, 120 patients	Changes of intestinal flora abundance	ChiCTR1800016178	Effective
van Trijp et al., 2020 [78], Netherlands	WGW, 12-week	NAFLD, 37 patients	Changes in gut microbiome by 16S rRNA sequencing	NCT02385149	Effective

Table 1. *Cont.*

Author, Reference, Country	Intervention, Duration	Disease, Sample	Microbiome Evaluation	RCT Code	Findings
Loomba et al., 2020 [79], USA	Aldafermin, 12-week	NASH, 176 patients	Changes in gut microbiome by 16S rRNA sequencing	NCT02443116	Effective
Quiroga et al., 2020 [80], Spain	Combined strength and endurance exercise, 12-week	Obesity, 39 patients	Changes in gut microbiome by 16S rRNA sequencing	—–	Effective
Craven et al., 2020 [81], Canada	FMT, 48-week	NAFLD, 21 patients	Changes in gut microbiome by 16S rRNA sequencing	NCT02496390	Not Effective
Chong et al., 2020 [82], New Zealand	Inulin, 12-week	NAFLD, 62 patients	Changes in gut microbiome by 16S rRNA sequencing	12613001002774	Effective
Scorletti et al., 2020 [83], UK	Synbiotic, 48-week	NAFLD, 104 patients	Changes in gut microbiome by 16S rRNA sequencing	NCT01680640	Not Effective
Huber et al., 2019 [84], Germany	Exercise, 8-week	NAFLD, 44 patients	Stool flora evaluated by specialized nonculture techniques	NCT02526732	Effective
Chen et al., 2019 [85], China	Conventional yogurt or milk, 24-week	NAFLD, 100 patients	Changes in gut microbiome by 16S rRNA sequencing	ChiCTR-IPR-15006801	Effective
Bajaj et al., 2019 [86], USA	FMT capsules, 24-week	Cirrhosis with recurrent HE, 20 patients	Changes in gut microbiome by 16S rRNA sequencing	NCT03152188	Effective
Chambers et al., 2019 [87], UK	Inulin, 6-week	NAFLD, 18 patients	Gut microbiome-derived metabolites change	ISRCTN71814178	Effective
Ahn et al., 2019 [88], Korea	Probiotic Mixture, 12-wee	k NAFLD, 68 patients	Changes in gut microbiome composition	KCT0001588	Effective
Allegretti et al., 2019 [89], USA	FMT, 24-week	PSC, 10 patients	Changes in gut microbiome composition	NCT02424175	Effective
Chashmniam1 et al., 2018 [90], Iran	Phospholipid curcumin, 8-week	NAFLD, 59 patients	Gut microbiome-derived metabolites change	IRCT2015052322381N1	Effective
Schutte et al., 2018 [91], Netherlands	WGW, 12-week	Overweight, 50 participants	Changes in gut microbiome composition	NCT02385149	Effective
Tenorio-Jiménez et al., 2018 [92], Spain	Probiotics, 12-week	IRS, 60 participants	Changes in a 16S metagenomics sequencing	NCT02972567	Effective
Kobyliak et al., 2018 [93], Italy	Probiotics with omega-3, 8-week	NAFLD, 48 patients	Gut microbiome-derived metabolites change	NCT03528707	Effective
Bajaj et al., 2018 [94], USA	Periodontal therapy, 4-week	Cirrhotic with chronic generalized gingivitis, 50 patients	Changes in gut microbiome by 16S rRNA sequencing	NCT03030820	Effective
Scorletti et al., 2018 [95], UK	Synbiotic treatment, 48-week	NAFLD, 55 patients	16S ribosomal RNA gene sequencing	NCT01680640	Effective
Kobyliak et al., 2018 [96], European	Probiotic, 8-week	NAFLD, 58 patients	Gut microbiome-derived metabolites change	NCT03434860	Effective
Manzhalii et al., 2017 [97], Ukraine	Probiotic Cocktail, 12-week	NASH, 75 patients	Change in composition of stool microbiome	Registration No. 942 of December 9, 2015	Effective
Sherf-Dagan et al., 2017 [98], Israel	Probiotics, 24-week	NAFLD, 100 patients	16S ribosomal RNA gene sequencing	NCT01922830	Not Effective
Bajaj et al., 2017 [99], UK	FMT, 24-week	Cirrhosis with recurrent HE, 20 patients	16S ribosomal RNA gene sequencing	NCT02636647	Effective
Ferolla et al., 2016 [100], Brazil	Synbiotic, 12-week	NAFLD, 27 patients	Gut microbiome-derived metabolites change	–	Effective
Lambert et al., 2015 [101], Canada	Prebiotic, 24-week	NAFLD, 30 patients	Changes in stool microbiome composition	NCT02568605	Effective
Engstler et al., 2015 [102], Germany	Probiotic, 12-week	NAFLD, 20 participants	Change in intestinal and fecal microbiome	NCT01306396	Effective
Kwak et al., 2014 [103], Korea	Probiotic, 4-week	Chronic Liver Disease, 25 patients	16S ribosomal RNA gene sequencing	KCT0000081	Not Effective
Alisi et al., 2014 [104], Italy	Probiotic, 16-week	NAFLD, 22 children	Gut microbiome-derived metabolites change	NCT01650025	Effective

Table 1. *Cont.*

Author, Reference, Country	Intervention, Duration	Disease, Sample	Microbiome Evaluation	RCT Code	Findings
Liu et al., 2014 [105], China	Aerobic exercise, 24-week	NAFLD, 200 patients	16S ribosomal RNA gene sequencing	ISRCTN42622771	Effective
Lunia et al., 2014 [106], India	Probiotics, 12-week	Cirrhosis without HE, 86 patients	Change in intestinal and fecal microbiome	CTRI-2012-07-002807	Effective
Jayakumar et al, 2013 [107], Canada	Probiotic, 8-week	Decompensated cirrhosis, 15 patients	Change in intestinal and fecal microbiome	NCT01032941	Effective

Food frequency questionnaires (FFQ); metabolic dysfunction-associated steatotic liver disease (MASLD); Chronic Liver disease (CLD), Non-Alcoholic Steatohepatitis (NASH); Fecal microbiome transplantation (FMT); Alcohol use disorder (AUD); Hepatic encephalopathy (HE); Whole grain wheat (WGW); Primary sclerosing cholangitis (PSC); Insulin Resistance Syndrome (IRS); Non-alcoholic fatty liver disease (NAFLD)

A recent systematic review by Jiang et al. (2022) examined the effects of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) in cirrhosis patients [11]. Their findings highlighted that probiotics and prebiotics significantly modulate gut microbiota and may contribute to reducing cirrhosis-related complications such as hepatic encephalopathy. Also FMT, despite its promising potential, has not been systematically evaluated in previous studies, indicating the need for further research. Meta-analyses on minimal hepatic encephalopathy (MHE) and overt hepatic encephalopathy (HE) showed inconsistent conclusions, possibly due to variations in study design and intervention types [11]. A 2023 umbrella meta-analysis by Naghipour et al. systematically reviewed the effects of microbial therapies on lipid metabolism in NAFLD patients [12]. Their study found that probiotics, prebiotics, and synbiotics significantly reduced total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) levels, reinforcing their potential as an adjunctive therapy for NAFLD. Aside from that, no significant effects on high-density lipoprotein (HDL) levels were observed, suggesting a limited influence of microbial therapies on HDL metabolism. Despite positive outcomes, inconsistencies in dosage and duration of treatment across studies highlight the need for standardized clinical trials [12].

5.2. The Role of FMT

Fecal microbiome transplantation is an innovative therapeutic procedure that includes transferring processed and screened donor fecal material into a recipient's upper or lower gastrointestinal tract. This procedure aims to replenish a deficient microbiome and rectify bacterial imbalances within the recipient's gut. FMT has garnered widespread recognition for its effectiveness against Clostridium difficile infection (CDI) and various intestinal and extra-intestinal disorders. Consequently, contemporary research efforts are increasingly focused on exploring its prospective therapeutic applications in both short-term and long-term hepatic disorders. FMT is not only one of the safest but also most effective methods in promoting gut microbiome quality. This method is effective for modifying the gut microbiome because it directly introduces a complex, fully formed community of microbes into the recipient's gut. It might reduce hospitalizations [32]. FMT may be delivered by enema or in a capsule. FMT delivered by enema was found effective in AUD-related cirrhosis and recurrent hepatic encephalopathy (HE) patients [33,35]. Harmless of FMT was estimated by Allegretti et al [89]. A one-time fecal microbiome transplantation (FMT) administered via colonoscopy in individuals with Primary Sclerosing Cholangitis was performed. Consequently, alkaline phosphatase (ALP) levels showed a significant reduction [35]. FMT found most effective way to support microbiome in lean NAFLD patients as compare obese ones [36]. Another study found that it may improve insulin resistance [37]. FMT without antibiotics using the capsular route also found as safe as antibiotics prior FMT [38].

FMT treatment protocols can vary greatly depending on the disease, and what is important is the selection of the donor. Healthy donors can be individuals without familial ties, close relatives, or members of the same family. Nonetheless, existing guidelines and policies indicate that the optimal source for donors is an unrelated person. This recommendation arises from the fact that close kin and household members typically have comparable environmental conditions and eating patterns to the recipient. In contrast, unrelated individuals have very different communities in their gut microbiome.

In order to ensure the success of the transplant, the donor needs to be screened and undergo a series of strict dos and don'ts according to an approved protocol [108]. Fresh fecal material is processed and blended into a suitable consistency [109]. Preserved fecal matter may occasionally be utilized [110]. Nevertheless, the microbial diversity in preserved samples may be reduced compared to fresh ones. Latest research involving individuals with

Clostridium difficile infection demonstrated that preserved fecal material was less effective than fresh material. The techniques and delivery pathways differ as well. Microbiome of feces can be introduced into the intestinal tract by endoscopy, capsule, and colonoscopy [111]. However, the optimal route of FMT has not yet been fully determined. In China, retention enema is the primary approach as it is both safe and cost-effective; however, its capacity to facilitate microbiome colonization and establishment is restricted. Oral capsules are also a noninvasive method and are preferred by patients, but their cost is so high that they are often discouraged. Additionally, it is essential to emphasize that significant data must be collected at the time of FMT testing, which can include micronutrient and macronutrient information, including use of PPIs, metformin, history of diabetes, excess weight, use of antibiotics, history of gastrointestinal surgeries, inflammatory bowel diseases, and other diseases of gut [112].

There are a significant number of clinical trials that aim to investigate the diseases in which FMT can be used to increase efficiency and effectiveness, as well as safety. To date, FMT is considered the last hope for managing severe of severe Clostridium difficile infection [113]. In other words, evidence has shown that fecal microbiome transplantation serves as a reliable and efficient therapy for Clostridium difficile infection [114, 115]. Moreover, FMT has demonstrated potential in managing various conditions, including gastrointestinal disorders, liver ailments, and neurological issues [116, 117]. Numerous studies indicate that fecal microbiome transplantation is largely well-tolerated, adaptable, and significantly more efficient than traditional approaches to modulating intestinal microbiota, such as pre-, pro-, and antibiotics [118]. A study revealed that among 536 individuals diagnosed with Clostridium difficile infection who underwent fecal microbiome transplantation, the clinical improvement rate reached up to 87%, with no reported adverse events [119]. The other investigation involved 20 CDI patients treated with frozen fecal capsules, and a response rate of 90% was observed following a few treatment courses, again without any side effects. Collectively, these studies imply that fecal microbiome transplantation is reliable and beneficial for individuals suffering from Clostridium difficile infection. In 2019, it was documented that two individuals with CDI experienced bacteremia following fecal microbiome transplantation, one of which led to a fatal outcome. Notably, both patients were administered capsules with feces from the identical donor, indicating that fecal microbiome transplantation carries potential risks. Therefore, it is imperative to strengthen and improve donor assessment to minimize and reduce the spread of microbes which can lead to incompatible and invasive pathogen-induced conditions [120]. In a randomized study of 70 individuals with UC, the incident of disease onset was 24% in the fecal microbiome transplantation-treated cohort and 5% in the placebo-controlled cohort [121]. Furthermore, unremarkable differences were observed in the incidence of results and adverse events between the 2 cohorts. Thus, FMT significantly increased the rate of onset of remission in UC patients compared with placebo, and there were no additional incompatible and problematic complications. Yu et al. assessed the effectiveness and safety of oral fecal microbiome transplantation capsules among 22 obese adults in a randomized, double-blind study [122]. The findings indicated that the capsules were generally well accepted and resulted in lasting changes in the intestine microbiome akin to those observed in lean donors. Nevertheless, fecal microbiome transplantation (FMT) did not achieve a reduction in BMI among adipose individuals when compared to a placebo group.

Ethical Challenges and Risks of FMT

While FMT has shown promising potential in the treatment of various liver-related conditions, several ethical and safety concerns must be considered before its widespread adoption. Donor selection is a critical step in ensuring the safety and efficacy of FMT. According to existing guidelines, the preferred donor is often an unrelated, healthy individual rather than a family member, as genetic and environmental similarities may limit microbial diversity transfer. Donor screening involves rigorous clinical and laboratory assessments to exclude transmissible infections, antibiotic-resistant bacteria, metabolic disorders, and underlying gastrointestinal diseases. Ethical dilemmas arise in donor compensation, informed consent, and long-term health monitoring of both the donor and recipient. Despite extensive screening, FMT carries the inherent risk of transmitting infections. In 2019, a case of drug-resistant *E. coli* bacteremia was reported in two immunocompromised patients who received FMT capsules from the same donor, resulting in one fatality. This highlights the need for continuous improvements in donor screening, standardized protocols, and regulatory oversight. Although most FMT procedures are well-tolerated, some studies have reported mild to moderate side effects, including diarrhea, bloating, and transient fever. Rare but severe complications such as systemic infections, inflammatory responses, and autoimmune disease exacerbation have also been observed. In patients with liver diseases, the long-term effects of FMT on liver function and gut microbiome stability remain unclear, necessitating further research. Unlike conventional pharmaceutical treatments,

FMT is not yet universally standardized, leading to variations in donor screening, preparation methods (fresh vs. frozen stool samples), and administration routes (capsule, enema, endoscopy). Different countries have varying regulatory frameworks, and there is an ongoing debate about whether FMT should be classified as a drug, biological therapy, or tissue-based transplant.

5.3. Probiotics and Adipokines in Liver Disease

The liver predominantly obtains its blood supply via the portal system, positioning it as the primary defense mechanism against intestinal toxins. Consequently, the intestine microbiome is essential in the pathophysiology of Non-Alcoholic Steatohepatitis (NASH). Moreover, due to their positive impact on metabolic processes, these beneficial bacteria exhibit anti-inflammatory properties. Nutrition with a lot of fiber decreases the *Firmicutes* to *Bacteroides* ratio in humans, elevates *Bifidobacterium* levels, and supports calorie restriction, ultimately contributing to improvements in NASH [123]. Probiotics comprise a diverse array of advantageous bacteria that can help restore the balance of intestinal flora, modulate lipid toxin metabolic processes by controlling intestine microbiome, and enhance liver function. Results indicate that after probiotic therapy, hepatic functionality (Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase) in patients improves remarkably [124]; triglyceride and cholesterol levels are reduced [125]. Liver conditions caused by alcohol consumption can be managed with beneficial bacteria through modulation of the gut-liver connection. The administration of probiotics leads to changes in intestine microbiome structure and mitigates metabolic disorders by lowering serum lipid levels and inflammatory markers [126]. Adipokines, which are bioactive substances released by adipose tissue, have diverse impacts on health outcomes. They are essential for the regulation of metabolism, inflammation, immunological reaction, cardiovascular health, and cancer progression [127]. Adipokines significantly influence insulin sensitivity by impacting different tissues, including the hepatic, muscles, pancreas, and adipose tissue. They are crucial in both the normal functioning of the liver and the onset of multiple acute and long-term hepatic disorders. Furthermore, adipokines are instrumental in mechanisms like hepatic inflammation, hepatocyte apoptosis, and fibrosis.

Their role encompasses the development of Non-Alcoholic Fatty Liver Disease (NAFLD) and its advancement to NASH, mediated through their metabolic functions as well as pro-inflammatory or anti-inflammatory activities [128]. The mechanisms by which prebiotics and probiotics affect adipokines concentrations are not yet fully understood; however, research indicates that their impact is influenced by alterations in the microbiome [129].

5.4. Pro and Prebiotic Supplementation

There is available controversial data regarding effectiveness of Pro and Prebiotic supplementation in liver disorders. However majority studies found that pre or probiotic administration may improve liver diseases outcome. Oral probiotic supplementation was revealed as beneficial in many studies [1,2]. Lactobacillus fermentum TSF331, Lactobacillus reuteri TSR332 and Lactobacillus plantarum TSP05 support orally improved LFT [3]. Serum ammonia and Stroop test scores in HE were normalized by probiotic Escherichia coli Nissle (EcN) 1917 strain addition [4]. L. acidophilus, L. rhamnosus, P. pentosaceus, B. lactis, and B. breve were increased in gut microbiome as a result of probiotic mixture administration in 68 NAFLD patients, leading to intrahepatic fat (IHF) and triglyceride reduction [5]. The intake of the multiprobiotic "Symbiter," which comprises a dense consortium of 14 probiotic bacterial genera, including, Lactococcus, Lactobacillus and Propionibacterium, Bifidobacterium, led to reductions in both the liver stiffness (LS) and fatty liver index (FLI) in individuals with DM type 2 suffering from NAFLD after an 8-week period [6]. Symbiotic intervention fructo-oligosaccharides (4 g/twice day) + Bifidobacterium animalis subsp. LactisBB-12 shows an effect in liver fat reduction compared to placebo [130]. Inulin is a dietary fiber and a type of prebiotic; alone, it did not show an effect in 19 NAFLD patients [131]. However, its supplementation in combination with propionate in 18 participants for 42 days [7] and inulin with metronidazole in 62 patients were found useful in NAFLD [8]. This result could be explained by the role of metronidazole, as it controls harmful bacterial overgrowth. A similar positive effect was found by rifaximin-α, which reduced species richness [4,9]. On another hand some studies reported that oral pre and probiotic supplementation is useless in liver disorders. Despite almost same number of participants and intervention duration with, Multi-strain probiotic administration was ineffective in 39 NAFLD patients [10]. As seen in the work of Sherf-Dagan et al., liver fat content did not significantly decrease in the probiotic group as compared to the control group [13]. Failure of supplementation therapy could be because of the short time of intervention period duration [13,16]. A combination of omega-3 polyunsaturated fatty acids and live

multi-strain probiotics targeting the liver stiffness (LS) and fatty liver index (FLI) [14].

5.5. Adjustments in Daily Habits, Including Dietary Alterations and Physical Activity

These interventions can alter gut microbiomes and have been found to be a highly effective way to manage individuals who have liver disease associated with fat deposition in the liver. All provided data found their positive impact on NAFLD. Liu et al. reported that low-carbohydrate diet (LCh) with individualized aerobic exercise (AEx) strengthens gut microbiome composition with improving liver diseases outcome [16]. Another website-based individualized exercise reduced levels of AST and ALT significantly in non-alcoholic fatty liver disease patients and stayed within normal levels for 12 weeks even after completing the program [15]. Efficacy of the synergistic effect of the Mediterranean diet with or without the combination with exercise was proven in many studies. Mediterranean diet and physical activity may change the liver steatosis (HSI). Intervention duration period in terms of diet modification with exercise played an important role in slowing liver fibrosis [132]. Other studies showed that including a probiotic-containing Cocktail ameliorates gut microbiome composition and betterment of CAP parameters in steatosis levels [17,18]. Some authors found that combined strategy like diet modification with exercise may result individually but not same in all NAFLD patients [19]. Formulated food with lifestyle modification can normalize MRI-PDFF [133]. Insulin resistance was improved with yogurt intake in NAFLD [21,133]. Two studies estimated that whole-grain wheat is powerful in NAFLD through a changed composition of microbiom [22,23]. Curcumin supplementation leads to gut microbiome-dependent BA betterment with reduced fat deposition [24]. Qushi Hua and Sulforaphane increase the presence of helpful microbes while minimizing pathogenic microbes [25]. The cohort of patients who administered Qushi Huayu had less fat liver content and liver enzyme levels [26]. Fish-based diet showed efficacy in NAFLD [27]. Fish oil and vitamin D are more effective in combination than when taken alone. Zhang et al. revealed their effectiveness in NAFLD by promoting beneficial bacterial growth [28]. The products that may encourage the proliferation of helpful microbe like Bifidobacterium and Lactobacillus while suppressing harmful bacteria, such as pathogenic bacteria (Clostridium difficile, Escherichia coli), by Qushi Huayu significantly impact on NAFLD patients positively [26,29]. The improvement of gut dysbiosis by oligonol, is a low-molecular-weight oligomer from the Litchi extracts and Amazonian berry camu-camu (CC), leading to betterment in steatosis [30,31].

6. Interdisciplinary Contributions to Liver Health

Hepatologists and gastroenterologists are at the forefront of liver disease diagnosis and treatment. Their role extends from recognizing microbiota-liver axis disruptions to implementing therapeutic strategies such as probiotic supplementation and fecal microbiota transplantation (FMT). Recent systematic reviews highlight that probiotics, prebiotics, and synbiotics effectively mitigate cirrhosis complications, with FMT being explored as a viable intervention for advanced hepatic disorders [11]. This collaboration provides a foundation for refining clinical guidelines and developing personalized therapeutic protocols. Microbiologists play a pivotal role in investigating gut microbiota alterations associated with liver disease progression. Akkermansia muciniphila, for instance, has been identified as a beneficial bacterium in ethanol-induced liver damage [12]. Furthermore, Naghipour et al. (2023) demonstrated that microbial therapies significantly improve lipid metabolism in NAFLD patients, reinforcing the microbiota's role in hepatic homeostasis [12]. These insights facilitate the development of targeted microbiome-based therapies, optimizing intervention strategies. And nutritionists contribute to liver health by designing dietary interventions that modulate gut microbiota composition. Probiotic and prebiotic-rich diets have been linked to reduced liver fat accumulation and lower inflammatory markers in NAFLD. Additionally, dietary modifications emphasizing fiber intake and fermented foods enhance gut-liver axis stability, reinforcing the role of nutrition in hepatic disease prevention and treatment [12].

7. Upcoming Opportunities

With a prevalence rate of 7–8%, hepatitis B virus (HBV) infection continues to exert a significant impact on healthcare systems [134]. If untreated, the disease may progress to fibrosis or cancer of liver. Thus, the effective therapy of hepatitis B virus is essential for lowering the occurrence of fibrosis or cancer of liver. Wang et al. compared the normal gut flora of individuals with chronic viral hepatitis B (CHB) with that of healthy controls and found that the abundance of Bacteroides was reduced in chronic viral hepatitis B patients based on sequencing of the V3-

V4 region of the 16S rRNA gene of the gut microbiome [33]. Furthermore, the structural changes of the gut microbiome caused by liver disease and disease severity are mutually random. These changes are likely to influence the transformation of CHB into cirrhosis, liver cancer, or liver failure. Research conducted on mice has indicated that intestine microbiome has the potential to impact the immune response of the host and its efficacy in eliminating HBV infection [135]. Therefore, fecal microbiome transplantation may be a possible treatment approach for modulating the immune system in individuals with CHB infection. In a non-randomized controlled study, 14 HBe-Ag (antigen) positive patients were treated with 6 cycles of gastroscopic fecal microbiome transplantation and concomitant antiviral therapy [136]. ALI, characterized by acute liver injury and necrosis, can arise from various factors such as excessive alcohol consumption, acetaminophen toxicity, restricted blood flow to the liver, viral and autoimmune hepatitis, as well as liver damage caused by medications. If individuals go unrecognized and untreated in a timely manner, ALI can advance to acute liver failure (ALF), a condition with a mortality rate of up to 40% within 90 days [137]. Over fifty percent of ALF cases progress to the point where they need the transplantation of liver. An excessive whole-body inflammatory response appears to play a crucial role in the transition from acute lung damage (ALI) to severe liver failure (ALF). Disruptions within the gut microbiome have been associated with both this systemic inflammation and ALI. Notably, Lactobacillus salivarius L101 has been documented to mitigate liver damage effectively [138]. Probiotics are commonly prescribed during the course of ALI or ALF, but they have little benefit for survival. FMT is a potential therapeutic strategy for ALI and ALF to regulate the gut microbiome. In a study of 18 HBeAg-positive patients, two out of five patients who received FMT achieved complete clearance of HBeAg, while none of the 13 controls did [139]. These results indicate that fecal microbiome transplantation (FMT) shows efficacy in treating HBV infections. Nevertheless, the long-term implications of FMT for chronic HBV infection remain largely unclear [140]. More comprehensive research is essential to establish definitive conclusions regarding the application of fecal microbiome transplantation (FMT) in treating hepatitis. Hepatocellular carcinoma (HCC) ranks as the third most common cause of cancer-related fatalities globally and has strong correlations with infections from hepatitis B virus (HBV) and hepatitis C virus. Studies conducted on mice, both experimental and laboratory-based, indicate that a disrupted gut microbiome heightens the likelihood of developing HCC, while probiotics have been found to impede tumor proliferation [141]. These investigations indicate that adjusting and altering the gut microbiome could enhance results for patients with hepatocellular carcinoma (HCC). As a therapeutic approach for managing HCC, fecal microbiome transplantation (FMT) demonstrates considerable potential. Nonetheless, our literature review to this point has not revealed any clinical trials specifically examining the application of FMT in HCC treatment, highlighting a need for additional research. Ongoing challenges and current trials evaluating FMT in individuals suffering from liver conditions like HBV and HCC are documented on Clinicaltrials.gov. And while Jiang et al. (2022) identified the potential of FMT, its therapeutic role in liver function improvement remains unclear [11]. Future clinical trials should address this gap by evaluating FMT in different cirrhosis stages. The inconsistencies in microbial therapy effects on HDL levels indicate the necessity for more detailed subgroup analyses and long-term randomized controlled trials (RCTs).

8. Conclusions

This study has provided a comprehensive analysis of the relationship between gut microbiota and liver diseases, highlighting the potential therapeutic benefits of microbiome-targeted interventions. The findings suggest that microbiota modulation, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT), plays a crucial role in liver disease management. Specifically, microbial therapy has demonstrated significant effects on lipid metabolism, inflammatory markers, and overall hepatic function, making it a promising adjunctive approach for conditions such as NAFLD and cirrhosis.

Despite these promising results, several challenges remain. Variability in microbial composition, differences in study methodologies, and the need for long-term safety data require further investigation. Current systematic reviews indicate that inconsistencies in dosage, treatment duration, and patient populations contribute to variations in treatment efficacy [12]. Addressing these gaps through well-designed, large-scale randomized controlled trials (RCTs) will be critical in determining the optimal use of microbial therapies. In conclusion, the growing body of evidence supports the integration of microbiome-based therapies in liver disease management. However, further clinical validation and regulatory standardization are necessary to fully realize the potential of these interventions in hepatology. Future research should focus on refining therapeutic protocols, optimizing patient selection, and

ensuring long-term treatment efficacy to maximize clinical benefits.

Author Contributions

Conceptualization, P.T., M.S.H., I.K.J., O.A.N., K.W., and R.J.K.; methodology, P.T. and M.S.H.; validation K.W., O.A.N., and R.J.K; formal analysis, P.T., M.S.H., and R.J.K.; investigation, P.T. and M.S.H.; writing—original draft preparation, P.T. and M.S.H.; writing—review and editing, I.K.J., O.A.N., K.W., and R.J.K.; supervision, P.T. and M.S.H. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (Ethics Committee) of Osh State University (protocol code №1, approved on 14 February 2025).

Informed Consent Statement

Not applicable.

Data Availability Statement

No data were used in the present research.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Zhou, X.-D.; Chen, Q.-F.; Yang, W.; et al. Burden of disease attributable to high body mass index: an analysis of data from the Global Burden of Disease Study 2021. *EClinicalMedicine* **2024**, *76*. [CrossRef]
2. Abdelaal, M.; le Roux, C.W.; Docherty, N.G. Morbidity and mortality associated with obesity. *Ann. Transl. Med.* **2017**, *5*, 161. [CrossRef]
3. Wang, X.; You, J.; Tang, J.; et al. Interaction between non-alcoholic fatty liver disease and obesity on the risk of developing cardiovascular diseases. *Sci. Rep.* **2024**, *14*, 24024. [CrossRef]
4. Bhatt, H.B.; Smith, R.J. Fatty liver disease in diabetes mellitus. *Hepatobiliary Surg. Nutr.* **2015**, *4*, 101–108. [CrossRef]
5. Pouwels, S.; Sakran, N.; Graham, Y.; et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. *BMC Endocr. Disord.* **2022**, *22*, 63. [CrossRef]
6. Kim, C.H.; Younossi, Z.M. Nonalcoholic fatty liver disease: a manifestation of the metabolic syndrome. *Cleve. Clin. J. Med.* **2008**, *75*, 721–728. [CrossRef]
7. Golabi, P.; Paik, J.M.; Eberly, K.; et al. Causes of death in patients with Non-alcoholic Fatty Liver Disease (NAFLD), alcoholic liver disease and chronic viral Hepatitis B and C. *Ann. Hepatol.* **2022**, *27*.
8. Chávez-Tapia, N.C.; Méndez-Sánchez, N.; Uribe, M. Role of nonalcoholic fatty liver disease in hepatocellular carcinoma. *Ann. Hepatol.* **2009**, *8*, S34–S39.
9. Lonardo, A.; Mantovani, A.; Lugari, S.; et al. Epidemiology and pathophysiology of the association between NAFLD and metabolically healthy or metabolically unhealthy obesity. *Ann. Hepatol.* **2020**, *19*, 359–366.
10. Jamali, R.; Hatami, N.; Kosari, F. The Correlation Between Serum Adipokines and Liver Cell Damage in Non-Alcoholic Fatty Liver Disease. *Hepat. Mon.* **2016**, *16*, e37412.
11. Jiang, H.; Peng, Y.; Zhang, W.; et al. Gut microbiome-targeted therapies in liver cirrhosis: a protocol for systematic review and meta-analysis. *Syst Rev* **2022**, *11*, 181.

12. Naghipour, A.; Amini-Salehi, E.; Gorabzarmakhi, O.M.; et al. Effects of gut microbial therapy on lipid profile in individuals with non-alcoholic fatty liver disease: an umbrella meta-analysis study. *Syst Rev* **2023**, *12*, 144.
13. Sherf-Dagan, S., et al. The effect of probiotics on hepatic steatosis: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition* **2018**, *37*, 80–86.
14. Olvera-Rosales, L.B.; Cruz-Guerrero, A.E.; Ramírez-Moreno, E.; et al. Impact of the Gut Microbiome Balance on the Health-Disease Relationship: The Importance of Consuming Probiotics and Prebiotics. *Foods* **2021**, *10*(6).
15. Vieira, A.T.; Fukumori, C.; Ferreira, C.M. New insights into therapeutic strategies for gut microbiome modulation in inflammatory diseases. *Clin. Transl. Immunol.* **2016**, *5*(6), e87.
16. Liu, W.Y.; Lu, D.J.; Du, X.M.; et al. Effect of aerobic exercise and low carbohydrate diet on prediabetic non-alcoholic fatty liver disease in postmenopausal women and middle aged men – the role of gut microbiota composition: study protocol for the AELC randomized controlled trial. *BMC Public Health* **2014**, *14*, 48.
17. Gu, X.; Lu, Q.; Zhang, C.; et al. Clinical Application and Progress of Fecal Microbiome Transplantation in Liver Diseases: A Review. *Semin. Liver Dis.* **2021**, *41*, 495–506.
18. Stojic, J.; Kukla, M.; Grgurevic, I. The Intestinal Microbiome in the Development of Chronic Liver Disease: Current Status. *Diagnostics* **2023**, *13*.
19. Won, S.M.; Park, E.; Jeong, J.J.; et al. The Gut Microbiome-Derived Immune Response in Chronic Liver Disease. *Int. J. Mol. Sci.* **2021**, *22*.
20. Yadegar, A.; Pakpour, S.; Ibrahim, F.F.; et al. Beneficial effects of fecal microbiome transplantation in recurrent *Clostridioides difficile* infection. *Cell Host Microbe* **2023**, *31*, 695–711.
21. Valentin-Cortez, F.J.; Córdova-Gallardo, J.; Méndez-Sánchez, N. Narrative review of gut microbiome and liver diseases: facts and fictions. *Dig. Med. Res.* **2022**, *5*.
22. Llorente, C.; Schnabl, B. The gut microbiome and liver disease. *Cell. Mol. Gastroenterol. Hepatol.* **2015**, *1*, 275–284.
23. Paolella, G.; Mandato, C.; Pierri, L.; et al. Gut-liver axis and probiotics: their role in non-alcoholic fatty liver disease. *World J. Gastroenterol.* **2014**, *20*, 15518–15531.
24. Le Roy, T.; Llopis, M.; Lepage, P.; et al. Intestinal microbiome determines development of non-alcoholic fatty liver disease in mice. *Gut* **2013**, *62*, 1787–1794.
25. Gómez-Hurtado, I.; Gallego-Durán, R.; Zapater, P.; et al. Bacterial antigen translocation and age as BMI-independent contributing factors on systemic inflammation in NAFLD patients. *Liver Int.* **2020**, *40*, 2182–2193.
26. Wahlström, A. Outside the liver box: The gut microbiome as pivotal modulator of liver diseases. *Biochim. Biophys. Acta Mol. Basis Dis.* **2019**, *1865*, 912–919.
27. Khan, A.; Ding, Z.; Ishaq, M.; et al. Understanding the Effects of Gut Microbiome Dysbiosis on Nonalcoholic Fatty Liver Disease and the Possible Probiotics Role: Recent Updates. *Int. J. Biol. Sci.* **2021**, *17*, 818–833.
28. Zhang, Y., Ma, C., Liu, C., et al. Combined effects of vitamin D and omega-3 fatty acids on gut microbiota and NAFLD improvement: Evidence from a randomized controlled trial. *Nutrients* **2021**, *13*, 2681.
29. Özdirik, B.; Müller, T.; Wree, A.; et al. The Role of Microbiome in Primary Sclerosing Cholangitis and Related Biliary Malignancies. *Int. J. Mol. Sci.* **2021**, *22*.
30. Boursier, J.; Mueller, O.; Barret, M.; et al. The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiome. *Hepatology* **2016**, *63*, 764–775.
31. Lin, M.J.; Su, T.H.; Chen, C.C.; et al. Diversity and composition of gut microbiome in healthy individuals and patients at different stages of hepatitis B virus-related liver disease. *Gut Pathog.* **2023**, *15*, 24.
32. Li, Y.G.; Yu, Z.J.; Li, A.; et al. Gut microbiome alteration and modulation in hepatitis B virus-related fibrosis and complications: Molecular mechanisms and therapeutic inventions. *World J. Gastroenterol.* **2022**, *28*, 3555–3572.
33. Wang, Y.; Pan, C.Q.; Xing, H. Advances in Gut Microbiome of Viral Hepatitis Cirrhosis. *Biomed. Res. Int.* **2019**, *2019*, 9726786.
34. Sparfel, L.; Ratodiarivony, S.; Boutet-Robinet, E.; et al. *Akkermansia muciniphila* and Alcohol-Related Liver Diseases. A Systematic Review. *Mol Nutr Food Res* **2024**, *68*, 1–12.
35. Ebrahimzadeh Leylabadlo, H.; Sanaie, S.; Sadeghpour Heravi, F.; et al. From role of gut microbiome to microbial-based therapies in type 2-diabetes. *Infect. Genet. Evol.* **2020**, *81*, 104268.
36. Zafari, N.; Velayati, M.; Fahim, M.; et al. Role of gut bacterial and non-bacterial microbiome in alcohol-associated liver disease: Molecular mechanisms, biomarkers, and therapeutic prospective. *Life Sci.* **2022**,

305, 120760.
37. Mattner, J. Impact of Microbes on the Pathogenesis of Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC). *Int. J. Mol. Sci.* **2016**, *17*.
38. Chen, W.; Wei, Y.; Xiong, A.; et al. Comprehensive Analysis of Serum and Fecal Bile Acid Profiles and Interaction with Gut Microbiome in Primary Biliary Cholangitis. *Clin. Rev. Allergy Immunol.* **2020**, *58*, 25–38.
39. Usami, M.; Miyoshi, M.; Yamashita, H. Gut microbiome and host metabolism in liver cirrhosis. *World J. Gastroenterol.* **2015**, *21*, 11597–11608.
40. Rai, R.; Saraswat, V.A.; Dhiman, R.K. Gut microbiome: its role in hepatic encephalopathy. *J. Clin. Exp. Hepatol.* **2015**, *5*, S29–S36.
41. Won, S.M.; Oh, K.K.; Gupta, H.; et al. The Link between Gut Microbiome and Hepatic Encephalopathy. *Int. J. Mol. Sci.* **2022**, *23*.
42. Zhu, R.; Liu, L.; Zhang, G.; et al. The pathogenesis of gut microbiome in hepatic encephalopathy by the gut-liver-brain axis. *Biosci. Rep.* **2023**, *43*.
43. Stojic, J.; Kukla, M.; Grgurevic, I. The Intestinal Microbiome in the Development of Chronic Liver Disease: Current Status. *Diagnostics* **2023**, *13*, 2960.
44. Kalambokis, G.; Tsianos, E.V. Endotoxaemia in the pathogenesis of cytopenias in liver cirrhosis. Could oral antibiotics raise blood counts? *Med. Hypotheses* **2011**, *76*, 105–109.
45. Mancini, A.; Campagna, F.; Amodio, P.; et al. Gut:liver:brain axis: the microbial challenge in the hepatic encephalopathy. *Food Funct.* **2018**, *9*, 1373–1388.
46. Ding, J.H.; Jin, Z.; Yang, X.X.; et al. Role of gut microbiome via the gut-liver-brain axis in digestive diseases. *World J. Gastroenterol.* **2020**, *26*, 6141–6162.
47. Bellafante, D.; Gioia, S.; Faccioli, J.; et al. Old and New Precipitants in Hepatic Encephalopathy: A New Look at a Field in Continuous Evolution. *J. Clin. Med.* **2023**, *12*.
48. Kang, D.J.; Betrapally, N.S.; Ghosh, S.A.; et al. Gut microbiome drive the development of neuroinflammatory response in cirrhosis in mice. *Hepatology* **2016**, *64*, 1232–1248.
49. Bajaj, J.S.; Fagan, A.; White, M.B.; et al. Specific Gut and Salivary Microbiome Patterns Are Linked With Different Cognitive Testing Strategies in Minimal Hepatic Encephalopathy. *Am. J. Gastroenterol.* **2019**, *114*, 1080–1090.
50. Quigley, E.M.M.; Stanton, C.; Murphy, E.F. The gut microbiome and the liver. Pathophysiological and clinical implications. *J. Hepatol.* **2013**, *58*, 1020–1027.
51. Solé, C.; Guilly, S.; Da Silva, K.; et al. Alterations in Gut Microbiome in Cirrhosis as Assessed by Quantitative Metagenomics: Relationship With Acute-on-Chronic Liver Failure and Prognosis. *Gastroenterology* **2021**, *160*, 206–218.
52. Nie, G.; Zhang, H.; Xie, D.; et al. Liver cirrhosis and complications from the perspective of dysbiosis. *Front. Med.* **2023**, *10*, 1320015.
53. Agrinier, A.L.; Morissette, A.; Daoust, L.; et al. Camu-camu decreases hepatic steatosis and liver injury markers in overweight, hypertriglyceridemic individuals: A randomized crossover trial. *Cell Rep. Med.* **2024**, *5*, 101682.
54. Jin, Y.; Wang, X.; Chen, K.; et al. Silymarin decreases liver stiffness associated with gut microbiome in patients with metabolic dysfunction-associated steatotic liver disease: a randomized, double-blind, placebo-controlled trial. *Lipids Health Dis.* **2024**, *23*, 239.
55. Lin, J.H.; Lin, C.H.; Kuo, Y.W.; et al. Probiotic *Lactobacillus fermentum* TSF331, *Lactobacillus reuteri* TSR332, and *Lactobacillus plantarum* TSP05 improved liver function and uric acid management-A pilot study. *PLoS ONE* **2024**, *19*, e0307181.
56. Tian, S.; Lei, Y.; Zhao, F.; et al. Improving insulin resistance by sulforaphane via activating the *Bacteroides* and *Lactobacillus* SCFAs-GPR-GLP1 signal axis. *Food Funct.* **2024**, *15*, 8644–8660.
57. Reshef, N.; Gophna, U.; Reshef, L.; et al. Prebiotic Treatment in Patients with Nonalcoholic Fatty Liver Disease (NAFLD)-A Randomized Pilot Trial. *Nutrients* **2024**, *16*.
58. He, Y.; Chen, X.; Li, Y.; et al. Curcumin supplementation alleviates hepatic fat content associated with modulation of gut microbiome-dependent bile acid metabolism in patients with nonalcoholic simple fatty liver disease: a randomized controlled trial. *Am. J. Clin. Nutr.* **2024**, *120*, 66–79.
59. Liu, Q.; Li, X.; Pan, Y.; et al. Efficacy and safety of Qushi Huayu, a traditional Chinese medicine, in patients with nonalcoholic fatty liver disease in a randomized controlled trial. *Phytomedicine* **2024**, *130*, 155398.
60. Li, X.; Pan, C.; Ma, W.; et al. Effects of dietary supplementation of fish oil plus vitamin D(3) on gut microbiome and fecal metabolites, and their correlation with nonalcoholic fatty liver disease risk factors: a randomized

controlled trial. *Food Funct.* **2024**, *15*, 2616–2627.
61. Ni, Y.; Qian, L.; Siliceo, S.L.; et al. Resistant starch decreases intrahepatic triglycerides in patients with NAFLD via gut microbiome alterations. *Cell Metab.* **2023**, *35*, 1530–1547.
62. Gómez-Pérez, A.M.; Ruiz-Limón, P.; Salas-Salvadó, J.; et al. Gut microbiome in nonalcoholic fatty liver disease: a PREDIMED-Plus trial sub analysis. *Gut Microbes* **2023**, *15*, 2223339.
63. Escouto, G.S.; Port, G.Z.; Tovo, C.V.; et al. Probiotic Supplementation, Hepatic Fibrosis, and the Microbiome Profile in Patients with Nonalcoholic Steatohepatitis: A Randomized Controlled Trial. *J. Nutr.* **2023**, *153*, 1984–1993.
64. He, K.; Guo, L.L.; Tang, H.; et al. A Freshwater Fish-Based Diet Alleviates Liver Steatosis by Modulating Gut Microbiome and Metabolites: A Clinical Randomized Controlled Trial in Chinese Participants With Nonalcoholic Fatty Liver Disease. *Am. J. Gastroenterol.* **2022**, *117*, 1621–1631.
65. Chayanupatkul, M.; Sawatdee, W.; Chutaputti, A.; et al. The Efficacy of Oligonol in Nonalcoholic Fatty Liver Disease: A Randomized Double-Blinded Placebo-Controlled Trial. *J. Integr. Complement. Med.* **2022**, *28*, 904–908.
66. Xue, L.; Deng, Z.; Luo, W.; et al. Effect of Fecal Microbiome Transplantation on Non-Alcoholic Fatty Liver Disease: A Randomized Clinical Trial. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 759306.
67. Manzhalii, E.; Moyseyenko, V.; Kondratiuk, V.; et al. Effect of a specific *Escherichia coli* Nissle 1917 strain on minimal/mild hepatic encephalopathy treatment. *World J. Hepatol.* **2022**, *14*, 634–646.
68. Calabrese, F.M.; Disciglio, V.; Franco, I.; et al. A Low Glycemic Index Mediterranean Diet Combined with Aerobic Physical Activity Rearranges the Gut Microbiome Signature in NAFLD Patients. *Nutrients* **2022**, *14*.
69. Cheng, R.; Wang, L.; Le, S.; et al. A randomized controlled trial for response of microbiome network to exercise and diet intervention in patients with nonalcoholic fatty liver disease. *Nat. Commun.* **2022**, *13*, 2555.
70. Amadieu, C.; Coste, V.; Neyrinck, A.M.; et al. Restoring an adequate dietary fiber intake by inulin supplementation: a pilot study showing an impact on gut microbiome and sociability in alcohol use disorder patients. *Gut Microbes* **2022**, *14*, 2007042.
71. Mohamad Nor, M.H.; Ayob, N.; Mokhtar, N.M.; et al. The Effect of Probiotics (MCP(®) BCMC(®) Strains) on Hepatic Steatosis, Small Intestinal Mucosal Immune Function, and Intestinal Barrier in Patients with Non-Alcoholic Fatty Liver Disease. *Nutrients* **2021**, *13*.
72. Patel, V.C.; Lee, S.; McPhail, M.J.W.; et al. Rifaximin-α reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. *J. Hepatol.* **2022**, *76*, 332–342.
73. Amerikanou, C.; Kanoni, S.; Kaliora, A.C.; et al. Effect of Mastiha supplementation on NAFLD: The MAST4HEALTH Randomised, Controlled Trial. *Mol. Nutr. Food Res.* **2021**, *65*, e2001178.
74. Traussnigg, S.; Halilbasic, E.; Hofer, H.; et al. Open-label phase II study evaluating safety and efficacy of the non-steroidal farnesoid X receptor agonist PX-104 in non-alcoholic fatty liver disease. *Wien. Klin. Wochenschr.* **2021**, *133*, 441–451.
75. Bajaj, J.S.; Gavis, E.A.; Fagan, A.; et al. A Randomized Clinical Trial of Fecal Microbiome Transplant for Alcohol Use Disorder. *Hepatology* **2021**, *73*, 1688–1700.
76. Jian, C.; Luukkonen, P.; Sädevirta, S.; et al. Impact of short-term overfeeding of saturated or unsaturated fat or sugars on the gut microbiome in relation to liver fat in obese and overweight adults. *Clin. Nutr.* **2021**, *40*, 207–216.
77. Zhuo, L.; Xu, J.; You, N.; et al. Study on the new strategy and key techniques for accurate prevention and treatment of nonalcoholic steatohepatitis based on intestinal target bacteria. *Medicine* **2020**, *99*, e22867.
78. van Trijp, M.P.H.; Schutte, S.; et al. Minor Changes in the Composition and Function of the Gut Microbiome During a 12-Week Whole Grain Wheat or Refined Wheat Intervention Correlate with Liver Fat in Overweight and Obese Adults. *J. Nutr.* **2021**, *151*, 491–502.
79. Loomba, R.; Ling, L.; Dinh, D.M.; et al. The Commensal Microbe *Veillonella* as a Marker for Response to an FGF19 Analog in NASH. *Hepatology* **2021**, *73*, 126–143.
80. Quiroga, R.; Nistal, E.; Estébanez, B.; et al. Exercise training modulates the gut microbiome profile and impairs inflammatory signaling pathways in obese children. *Exp. Mol. Med.* **2020**, *52*, 1048–1061.
81. Craven, L.; Rahman, A.; Nair Parvathy, S.; et al. Allogenic Fecal Microbiome Transplantation in Patients With Nonalcoholic Fatty Liver Disease Improves Abnormal Small Intestinal Permeability: A Randomized Control Trial. *Am. J. Gastroenterol.* **2020**, *115*, 1055–1065.
82. Chong, C.Y.L.; Orr, D.; Plank, L.D.; et al. Randomised Double-Blind Placebo-Controlled Trial of Inulin with Metronidazole in Non-Alcoholic Fatty Liver Disease (NAFLD). *Nutrients* **2020**, *12*.
83. Scorletti, E.; Afolabi, P.R.; Miles, E.A.; et al. Synbiotics Alter Fecal Microbiomes, But Not Liver Fat or Fibrosis,

in a Randomized Trial of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* **2020**, *158*, 1597–1610.
84. Huber, Y.; Pfirrmann, D.; Gebhardt, I.; et al. Improvement of non-invasive markers of NAFLD from an individualised, web-based exercise program. *Aliment. Pharmacol. Ther.* **2019**, *50*, 930–939.
85. Chen, Y.; Feng, R.; Yang, X.; et al. Yogurt improves insulin resistance and liver fat in obese women with nonalcoholic fatty liver disease and metabolic syndrome: a randomized controlled trial. *Am. J. Clin. Nutr.* **2019**, *109*, 1611–1619.
86. Bajaj, J.S.; Salzman, N.H.; Acharya, C.; et al. Fecal Microbial Transplant Capsules Are Safe in Hepatic Encephalopathy: A Phase 1, Randomized, Placebo-Controlled Trial. *Hepatology* **2019**, *70*, 1690–1703.
87. Chambers, E. S.; Byrne, C. S.; Morrison, D. J.; et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. *Gut* **2019**, *68*, 1430–1438.
88. Ahn, S.B.; Jun, D.W.; Kang, B.K.; et al. Randomized, Double-blind, Placebo-controlled Study of a Multispecies Probiotic Mixture in Nonalcoholic Fatty Liver Disease. *Sci. Rep.* **2019**, *9*, 5688.
89. Allegretti, J.R.; Kassam, Z.; Carrellas, M.; et al. Fecal Microbiome Transplantation in Patients With Primary Sclerosing Cholangitis: A Pilot Clinical Trial. *Am. J. Gastroenterol.* **2019**, *114*, 1071–1079.
90. Chashmniam, S.; Mirhafez, S.R.; Dehabeh, M.; et al. A pilot study of the effect of phospholipid curcumin on serum metabolomic profile in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *Eur. J. Clin. Nutr.* **2019**, *73*, 4–1235.
91. Schutte, S.; Esser, D.; Hoevenaars, F.P.M.; et al. A 12-wk whole-grain wheat intervention protects against hepatic fat: the Graandioos study, a randomized trial in overweight subjects. *Am. J. Clin. Nutr.* **2018**, *108*, 1264–1274.
92. Tenorio-Jiménez, C.; Martínez-Ramírez, M.J.; Tercero-Lozano, M.; et al. Evaluation of the effect of *Lactobacillus reuteri* V3401 on biomarkers of inflammation, cardiovascular risk and liver steatosis in obese adults with metabolic syndrome: a randomized clinical trial (PROSIR). *BMC Complement. Altern. Med.* **2018**, *18*, 306.
93. Kobyliak, N.; Abenavoli, L.; Falalyeyeva, T.; et al. Beneficial effects of probiotic combination with omega-3 fatty acids in NAFLD: a randomized clinical study. *Minerva Med.* **2018**, *109*, 418–428.
94. Bajaj, J.S.; Matin, P.; White, M.B.; et al. Periodontal therapy favorably modulates the oral-gut-hepatic axis in cirrhosis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2018**, *315*, G824–G837.
95. Scorletti, E.; Afolabi, P.R.; Miles, E.A.; et al. Design and rationale of the INSYTE study: A randomised, placebo controlled study to test the efficacy of a synbiotic on liver fat, disease biomarkers and intestinal microbiome in non-alcoholic fatty liver disease. *Contemp. Clin. Trials* **2018**, *71*, 113–123.
96. Kobyliak, N.; Abenavoli, L.; Mykhalchyshyn, G.; et al. A Multi-strain Probiotic Reduces the Fatty Liver Index, Cytokines and Aminotransferase levels in NAFLD Patients: Evidence from a Randomized Clinical Trial. *J Gastrointest Liver Dis* **2018**, *27*, 41–49.
97. Manzhalii, E.; Virchenko, O.; Falalyeyeva, T.; et al. Treatment efficacy of a probiotic preparation for non-alcoholic steatohepatitis: A pilot trial. *J Dig Dis* **2017**, *18*, 698–703.
98. Sherf-Dagan, S.; Zelber-Sagi, S.; Zilberman-Schapira, G.; et al. Probiotics administration following sleeve gastrectomy surgery: a randomized double-blind trial. *Int J Obes* **2018**, *42*, 147–155.
99. Bajaj, J.S.; Kassam, Z.; Fagan, A.; et al. Fecal microbiome transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* **2017**, *66*, 1727–1738.
100. Ferolla, S.M.; Couto, C.A.; Costa-Silva, L.; et al. Beneficial Effect of Synbiotic Supplementation on Hepatic Steatosis and Anthropometric Parameters, But Not on Gut Permeability in a Population with Nonalcoholic Steatohepatitis. *Nutrients* **2016**, *8*, 1–11.
101. Lambert, J.E.; Parnell, J.A.; Eksteen, B.; et al. Gut microbiome manipulation with prebiotics in patients with non-alcoholic fatty liver disease: a randomized controlled trial protocol. *BMC Gastroenterol* **2015**, *15*, 169.
102. Engstler, A.J.; Aumiller, T.; Degen, C.; et al. Insulin resistance alters hepatic ethanol metabolism: studies in mice and children with non-alcoholic fatty liver disease. *Gut* **2016**, *65*, 1564–1571.
103. Kwak, D.S.; Jun, D.W.; Seo, J.G.; et al. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. *Eur J Gastroenterol Hepatol* **2014**, *26*, 1353–1359.
104. Alisi, A.; Bedogni, G.; Baviera, G.; et al. Randomised clinical trial: The beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* **2014**, *39*, 1276–1285.

105. Liu, W.Y.; Lu, D.J.; Du, X.M.; et al. Effect of aerobic exercise and low carbohydrate diet on pre-diabetic non-alcoholic fatty liver disease in postmenopausal women and middle aged men–the role of gut microbiome composition: study protocol for the AELC randomized controlled trial. *BMC Public Health* **2014**, *14*, 48.
106. Lunia, M.K.; Sharma, B.C.; Sharma, P.; et al. Probiotics prevent hepatic encephalopathy in patients with cirrhosis: a randomized controlled trial. *Clin Gastroenterol Hepatol* **2014**, *12*, 1003–1008.
107. Jayakumar, S.; Carbonneau, M.; Hotte, N.; et al. VSL#3® probiotic therapy does not reduce portal pressures in patients with decompensated cirrhosis. *Liver Int* **2013**, *33*, 1470–1477.
108. Zoghi, S.; Abbasi, A.; Heravi, F.; et al. The gut microbiome and celiac disease: Pathophysiology, current perspective and new therapeutic approaches. *Crit Rev Food Sci Nutr* **2022**, *64*, 1–21.
109. Hevia, A.; Delgado, S.; Margolles, A.; et al. Application of density gradient for the isolation of the fecal microbial stool component and the potential use thereof. *Sci Rep* **2015**, *5*, 16807.
110. Du, C.; Luo, Y.; Walsh, S.; et al. Oral Fecal Microbiome Transplant Capsules Are Safe and Effective for Recurrent *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol* **2021**, *55*, 300–308.
111. Mohan, B.P.; Loganathan, P.; Khan, S.R.; et al. Fecal microbiome transplant delivered via invasive routes in irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. *Indian J Gastroenterol* **2023**, *42*, 315–323.
112. Burz, S.D.; Monnoye, M.; Philippe, C.; et al. Fecal Microbiome Transplant from Human to Mice Gives Insights into the Role of the Gut Microbiome in Non-Alcoholic Fatty Liver Disease (NAFLD). *Microorganisms* **2021**, *9*, 1–14.
113. van Beurden, Y.H.; Nieuwdorp, M.; van de Berg, P.; et al. Current challenges in the treatment of severe *Clostridium difficile* infection: early treatment potential of fecal microbiome transplantation. *Therap Adv Gastroenterol* **2017**, *10*, 373–381.
114. Falconer, S.; Moss, E.; Andermann, T.; et al. Fecal Microbiome Transplant Is a Potentially Safe and Effective Treatment for *Clostridium Difficile* Infection in Hematopoietic Stem Cell Recipients. *Biol Blood Marrow Transplant* **2016**, *22*, S53–S54.
115. Porcari, S.; Severino, A.; Rondinella, D.; Bibbò, S.; et al. Fecal microbiome transplantation for recurrent *Clostridioides difficile* infection in patients with concurrent ulcerative colitis. *J Autoimmun* **2023**, *141*, 103033.
116. Belvoncikova, P.; Maronek, M.; Gardlik, R. Gut Dysbiosis and Fecal Microbiome Transplantation in Autoimmune Diseases. *Int J Mol Sci* **2022**, *23*, 1–19.
117. Feng, J.; Chen, Y.; Liu, Y.; et al. Efficacy and safety of fecal microbiome transplantation in the treatment of ulcerative colitis: a systematic review and meta-analysis. *Sci Rep* **2023**, *13*, 14494.
118. Airola, C.; Severino, A.; Porcari, S.; et al. Future Modulation of Gut Microbiome: From Eubiotics to FMT, Engineered Bacteria, and Phage Therapy. *Antibiotics* **2023**, *12*, 1–18.
119. Cammarota, G.; Ianiro, G.; Gasbarrini, A. Fecal microbiome transplantation for the treatment of *Clostridium difficile* infection: a systematic review. *J Clin Gastroenterol* **2014**, *48*, 693–702.
120. DeFilipp, Z.; Bloom, P.P.; Soto, M.T.; et al. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiome Transplant. *N Engl J Med* **2019**, *381*, 2043–2050.
121. Moayyedi, P.; Surette, M.G.; Kim, P.T.; et al. Fecal Microbiome Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* **2015**, *149*, 102–109.
122. Yu, E.W.; Gao, L.; Stastka, P.; et al. Fecal microbiota transplantation for the treatment of obesity and metabolic syndrome: A randomized double-blind placebo-controlled pilot trial. *PLOS Medicine* **2020**, *17*, e1003051.
123. Pérez-Montes de Oca, A.; Julián, M.T.; Ramos, A.; et al. Microbiome, Fiber, and NAFLD: Is There Any Connection? *Nutrients* **2020**, *12*, 1–14.
124. Zhou, X.; Wang, J.; Zhou, S.; et al. Efficacy of probiotics on nonalcoholic fatty liver disease: A meta-analysis. *Medicine* **2023**, *102*, e32734.
125. Wang, Y.; Wang, Y.; Sun, J. The clinical effect of probiotics on patients with non-alcoholic fatty liver disease: a meta-analysis. *Bioengineered* **2022**, *13*, 14960–14973.
126. Al-Muzafar, H.M.; Amin, K.A. Probiotic mixture improves fatty liver disease by virtue of its action on lipid profiles, leptin, and inflammatory biomarkers. *BMC Complement Altern Med* **2017**, *17*, 43.
127. Fasshauer, M.; Blüher, M. Adipokines in health and disease. *Trends Pharmacol Sci* **2015**, *36*, 461–470.
128. Polyzos, S.A.; Kountouras, J.; Mantzoros, C.S. Adipokines in nonalcoholic fatty liver disease. *Metabolism* **2016**, *65*, 1062–1079.
129. Behrouz, V.; Jazayeri, S.; Aryaeian, N.; et al. Effects of Probiotic and Prebiotic Supplementation on Leptin,

Adiponectin, and Glycemic Parameters in Non-alcoholic Fatty Liver Disease: A Randomized Clinical Trial. *Middle East J Dig Dis* **2017**, *9*, 150–157.
130. Paschos, P.; Paletas, K. Non alcoholic fatty liver disease and metabolic syndrome. *Hippokratia* **2009**, *13*, 9–19.
131. Yu, S.J.; Kim, W.; Kim, D.; et al. Visceral Obesity Predicts Significant Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Medicine* **2015**, *94*, e2159.
132. Choi, H.H.; Cho, Y.-S. Fecal Microbiome Transplantation: Current Applications, Effectiveness, and Future Perspectives. *Clin. Endosc.* **2016**, *49*, 257–265.
133. Schwenger, K.J.; Clermont-Dejean, N.; Allard, J.P. The role of the gut microbiome in chronic liver disease: the clinical evidence revised. *JHEP Rep.* **2019**, *1*, 214–226.
134. Lungosi, M.B.; Muzembo, B.A.; Mbendi, N.C.; et al. Assessing the prevalence of hepatitis B virus infection among health care workers in a referral hospital in Kisantu, Congo DR: a pilot study. *Ind Health* **2019**, *57*, 621–626.
135. Kassa, Y.; Million, Y.; Gedefie, A.; et al. Alteration of Gut Microbiome and Its Impact on Immune Response in Patients with Chronic HBV Infection: A Review. *Infect Drug Resist* **2021**, *14*, 2571–2578.
136. Gish, R.G.; Lok, A.S.; Chang, T.T.; et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology* **2007**, *133*, 1437–1444.
137. Tujios, S.; Stravitz, R.T.; Lee, W.M. Management of Acute Liver Failure: Update 2022. *Semin Liver Dis* **2022**, *42*, 362–378.
138. Chauhan, A.; Kumar, R.; Sharma, S.; et al. Fecal Microbiome Transplantation in Hepatitis B e Antigen-Positive Chronic Hepatitis B Patients: A Pilot Study. *Dig Dis Sci* **2021**, *66*, 873–880.
139. Ren, Y.D.; Ye, Z.S.; Yang, L.Z.; et al. Fecal microbiome transplantation induces hepatitis B virus e-antigen (HBeAg) clearance in patients with positive HBeAg after long-term antiviral therapy. *Hepatology* **2017**, *65*, 1765–1768.
140. Leylabadlo, H.E.; Kafil, H.S.; Farajnia, S.; et al. Gut microbiome in nonalcoholic fatty liver diseases with and without type-2 diabetes mellitus. *Eur J Gastroenterol Hepatol* **2021**, *33*, e548–e554.
141. Behzadi, E.; Hosseini, H.M.; Fooladi, A.A.I. The inhibitory impacts of *Lactobacillus rhamnosus* GG-derived extracellular vesicles on the growth of hepatic cancer cells. *Microb Pathog* **2017**, *110*, 1–6.