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The Role of Probiotics in Managing Metabolic-Associated Fatty Liver Disease: An Updated Review

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Abstract

Metabolic-associated fatty liver disease (MAFLD) has become a very significant health problem worldwide, characterized by hepatic steatosis and systemic metabolic disturbances. Grasping the complex interaction between the intestine and liver, referred to as the gut-liver axis, is crucial to decipher the pathogenesis of MAFLD and identify potential therapeutic targets. Probiotics, which are live microorganisms offering health benefits, have garnered attention for their potential in treating MAFLD. A literature search in PubMed and Google Scholar using "MAFLD," "NAFLD," "probiotics," and "gut microbiota" yielded 642 studies; 32 clinical trials met the inclusion criteria for the final analysis. This review encapsulates the current knowledge of MAFLD pathophysiology, emphasizing the role of the gut-liver axis, and assesses the clinical evidence supporting probiotic treatments for MAFLD. The mechanisms of action of probiotics are explored, including their ability to modulate gut microbiota composition, enhance epithelial barrier function, and influence the immune response. Various randomized controlled trials have shown that probiotics are effective in enhancing several aspects of MAFLD, such as liver enzymes, lipid profiles, body mass index, insulin sensitivity, or even histological efficacy. However, mixed results have been reported in some clinical trials, highlighting the need for further research to optimize probiotic interventions. Future investigations should focus on standardized protocols, personalized approaches and exploring synergistic combinations with other therapeutic modalities to maximize the potential of probiotics in the treatment of MAFLD.

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Introduction

The medical term metabolic-associated fatty liver disease (MAFLD) was coined in 2020 by an international consensus to delineate fatty liver disease correlated with a systemic metabolic condition.[1] Like the earlier term non-alcoholic fatty liver disease (NAFLD), MAFLD describes a liver condition that is part of a broader multisystemic disease with heterogeneous causes, symptoms, course and consequences.[2] The development of MAFLD is strongly linked to insulin resistance (IR), obesity, and lack of physical activity, along with genetic and epigenetic factors contributing to the development and progression of liver fat accumulation and damage.[3] Diagnosis requires evidence of hepatic steatosis, which can be confirmed through histology, imaging tests, or blood biomarkers, along with at least either of the following requirements: overweight/obesity, type 2 diabetes mellitus (T2DM), or indicators of dysregulated metabolism.[4] MAFLD pathogenesis is complicated, affecting multiple organs and interacting with environmental factors, obesity, microbiota changes, and genetic predispositions.[1] A pathophysiological model rooted in the 'two-hit hypothesis' was described in 1998.[5] The initial hit prompts fat buildup in hepatocytes, while the subsequent hit induces oxidative stress, escalating inflammation and potentially culminating in fibrosis over time. Nevertheless, the mechanism appears increasingly intricate, with the "multiple hit" hypothesis emerging as a more viable explanation.[6] Implementing effective treatment at an early stage can prevent the development of other health complications. IR is the main factor that causes lipotoxicity, endoplasmic reticulum stress, impaired autophagy, and ultimately hepatocyte damage and death. This accelerates the condition by causing liver inflammation, activating hepatic stellate cells, and increasing fibrogenesis.[7] MAFLD affects between 17% and 51% of adults worldwide, with a prevalence of 50.7% in overweight or obese adults in the general population.[6] Nevertheless, MAFLD-induced abnormalities extend beyond the liver to affect other organs. These patients face heightened risks of complications, including heart and vascular disease, renal disease, obstructive sleep apnea syndrome, osteoporosis, neurological and endocrine disorders.[6] Given the increasing global prevalence of MAFLD, there is a pressing need for safe and effective treatments to manage this condition, because available treatment is limited and mainly focuses on lifestyle interventions. Despite the appearance of drugs that improve the metabolic profile, such as semaglutide, many patients cannot afford its use due to its high cost.

Probiotics are live microorganisms which, when consumed in sufficient quantities, provide a health benefit to the host by supporting the balance of microorganisms in the gut.[8] Probiotics could be a cheap and readily available therapeutic option for people suffering from MAFLD. This review aims to comprehensively evaluate the potential role of probiotics in the treatment of MAFLD by summarizing the current knowledge of the gut-liver axis and the pathophysiology of MAFLD. The main objective is to analyze the clinical evidence for the efficacy of probiotic interventions in improving hepatic steatosis, inflammation and metabolic parameters associated with MAFLD.

Materials and Methods

A comprehensive literature search was conducted in PubMed and Google Scholar electronic databases to search all published literature from inception to March 2024 for relevant studies. The search terms included "MAFLD", NAFLD", "probiotics" and "gut microbiota". We included studies that met the following inclusion criteria: (1) articles written in the English language, (2) clinical trials investigating the association between MAFLD/NAFLD and probiotics, and (3) studies with human participants. A total of 642 studies were found in the initial search. 32 studies that m*et a*ll three inclusion criteria were included in the final analysis (Table 1).

Gut-liver axis in MAFLD

The gut-liver axis refers to the connection between the gut, the microbiome and the liver, which includes signals from genetic, environmental and dietary factors. The portal vein facilitates bidirectional transportation between the intestines and the liver. Substances from the gut are conveyed to the liver, while bile and antibodies are released into the intestine. The integrity of the intestinal mucosal and vascular barrier is crucial in the gut-liver axis, as it prevents the spread of microbes and toxins while facilitating the circulation of nutrients to reach the liver.[9] Under normal circumstances, the balance

of the gut-liver axis is preserved by healthy intestinal barriers and practical immune functions in the liver, which work together to prevent the movement of bacteria and their metabolites.[10] The first theory stating that the connection between the intestine and liver can cause the development of various diseases was put forward by Llewellyn Jones in 1890. The theory was based on autointoxication by intestinal bacteria.[8]

Table 1: An overview of clinical trials on effects of probiotics for MAFLD/NAFLD patients.

Authors, Year and Reference	Sample size	Probiotic genera	Duration of Study
Aller *et al*. (2011)[28]	28	*Lactobacillus* and *Streptococcus*	3 months
Vajro *et al*. (2011)[36]	20	*Lactobacillus*	8 weeks
Malaguarner *et al*. (2012)[52]	66	*Bifidobacterium*	24 weeks
Wong *et al*. (2013)[38]	20	*Lactobacillus* and *Bifidobacterium*	6 months
Alisi *et al*. (2014) [46]	48	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	4 months
Nabavi *et al*. (2014) [29]	72	*Lactobacillus* and *Bifidobacterium*	8 weeks
Eslamparast *et al*. (2014) [30]	52	*Lactobacillus* and *Bifidobacterium*	28 weeks
Miccheli *et al*. (2015) [39]	31	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	4 months
Asgharian *et al*. (2016) [40]	80	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	8 weeks
Sepideh *et al*. (2016) [50]	42	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	8 weeks
Ferolla *et al*. (2016) [45]	50	*Lactobacillus*	3 months
Famouri *et al*. (2017)[33]	64	*Lactobacillus* and *Bifidobacterium*	12 weeks
Mofidi *et al*. (2017) [51]	50	*Lactobacillus* and *Bifidobacterium*	28 weeks
Manzhalii *et al*. (2017) [43]	75	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	12 weeks
Asgharian *et al*. (2017) [44]	80	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	8 weeks
Kobyliak *et al*. (2018) [32]	58	*Bifidobacterium*, *Lactobacillus*, *Lactococcus* and *Propionibacterium*	8 weeks
Kobyliak *et al*. (2018) [58]	48	*Bifidobacterium*, *Lactobacillus*, *Lactococcus* and *Propionibacterium*	8 weeks
Javadi *et al*. (2018) [48]	75	*Lactobacillus* and *Bifidobacterium*	3 months
Ahn *et al*. (2019) [42]	68	*Lactobacillus*, Pediococcus and Bifdobacterium	12 weeks
Duseja *et al*. (2019) [37]	39	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	1 year
Chen *et al*. (2019) [47]	100	Whole-fat liquid yogurt and regular whole milk – No data	24 weeks
Scorletti *et al*. (2020)[65]	104	*Bifidobacterium*	1 year
Behrouz *et al*. (2020) [34]	111	*Lactobacillus* and *Bifidobacterium*	12 weeks
Abhari *et al*. (2020) [35]	53	Bacillus	12 weeks
Chong *et al*. (2021) [61]	35	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	10 weeks
Nor *et al*. (2021) [64]	32	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	6 months

Crommen *et al*. (2022) [59]	60	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	12 weeks
Rodrigo *et al*. (2022) [62]	84	Bacillus, *Bifidobacterium*, *Lactobacillus* and *Streptococcus*	6 months
Derosa *et al*. (2022) [49]	60	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	3 months
Barcelos *et al*. (2023) [63]	46	*Lactobacillus* and *Bifidobacterium*	24 weeks
Ayob *et al*. (2023) [60]	30	*Lactobacillus* and *Bifidobacterium*	6 months
Alam *et al*. (2024) [53]	100	*Lactobacillus*, *Bifidobacterium* and *Streptococcus*	6 months

Clinical evidence describes the disturbance of the gut-liver axis in many intestinal and liver diseases. Understanding the complicated metabolic interaction between the gut and liver in health and disease may play a significant role in targeted therapies.[11] A high-fat diet changes the microbiome, weakens both the intestinal and gut vascular barriers, and allows bacterial products to enter through the portal vein, making the liver vulnerable. There is an increase in intestinal inflammation factors like tumor necrosis factor (TNF-α) and interferon γ (IFN-γ) and a decrease in regulatory T-cells. The increased fecal secondary bile acids and decreased intestinal farnesoid X receptor (FXR) signaling can also be observed in patients with MAFLD. There is also a change in intestinal bacterial metabolites – an increase of intestinal trimethylamine, branched-chain and aromatic amino acids, and blood ethanol and a decrease of intestinal short-chain fatty acids and blood choline.[9]

Gut Microbiota and MAFLD

The human microbiota, commonly called the "hidden organ," provides more than 150 genetic data than the human genome. Microbiota refers to the live microorganisms in a particular habitat, such as the mouth and intestines. The gut microbiota comprises six genera: *Firmicutes, Actinobacteria, Bacteroidetes, Fusobacteria, Proteobacteria and Verrucomicrobia. Firmicutes and Bacteroidetes* are the two primary genera.[12] The human gastrointestinal tract hosts over 100 trillion microorganisms, outnumbering somatic cells by about ten to one.[3] Recently, the role of gut microbiota in the development of MAFLD has attracted significant attention.[13] According to reports, MAFLD may be associated with small intestinal bacterial overgrowth (SIBO), characterized by an increase in the number and/or changes in the type of bacteria in the upper gastrointestinal tract caused by the failure of several endogenous mechanisms.[14] Analysis of the gut microbiota can be used to predict the severity of MAFLD. *Bacteroides* are independently and positively associated with nonalcoholic steatohepatitis (NASH), and *Ruminococcus* accumulation similarly correlates with fibrosis stage.[15] Different results from a study conducted in Asia noted that the ratio of Firmicutes to Bacteroidetes was similar among patients with NAFLD or NASH and healthy controls, and the diversity model was distinct from what is observed in Western countries.[16] Deletion of Interleukin-17 (IL-17) may also affect NAFLD/NASH progression by disturbing the gut microbiota composition, exhibiting overgrowth of *Enterococcaceae*, and inhibiting the growth of *Oscillospira*.[17] Elevated intestinal permeability could play a role in the onset of NASH. The portal vein and liver may become the destination of some pro-inflammatory chemicals from the gut flora. For instance, individuals with NASH had higher blood levels of lipopolysaccharide-binding protein (LPS) than those with NAFLD.[18]

Multiple scientific studies have shown that there are several potential microbiota-related therapeutic targets for MAFLD. Diet and weight loss may have an influence on gut dysbiosis and restoration of gut homeostasis. Caffeine consumption is believed to protect against NASH and its progression. Regular exercise has been found to increase presence of *Verrucomicrobia* and reduce the population of *Proteobacteria*. Some antibiotics such as norfloxacin and neomycin can improve liver function by altering the microbiota and are responsible for bacterial translocation.[19] Low-carbohydrate diets (LCD) and ketogenic diets (KD) have been found to significantly alter the gut microbiota and affect the populations of *Actinobacteria, Bacteroidetes, Firmicutes and Bifidobacterium.* The production

of β-hydroxybutyrate during a KD is associated with a decrease in *Bifidobacterium* abundance. In addition, the gut microbiota associated with a KD has been observed to decrease proinflammatory Th17 cells, indicating a potential anti-inflammatory benefit. A Mediterranean diet strengthens the intestinal barrier, reduces inflammation and reduces harmful bacteria such as *Escherichia* and *Shigella.*[19]

Potential Role of Probiotics in MAFLD

Probiotics are typically present in fermented foods such as yogurt, buttermilk, or kimchi and are also available as dietary supplements.[20] The beneficial impacts of probiotics encompass averting constipation and antibiotic-associated diarrhea (ADD), harmonizing the intestinal microflora, reducing cholesterol levels, improving conditions such as hypertension, diabetes, lactose intolerance, and gastrointestinal ailments, fortifying the immune system, and diminishing the likelihood of various cancers.[21] For an organism to be classified as a probiotic, it must meet the following standards: It should be derived from the same species as its intended host, demonstrate a measurable positive impact on the host, be non-pathogenic, be capable of surviving passage through the gastrointestinal tract and during storage, a substantial quantity of viable bacteria should endure for extended periods.[22]

Probiotics exert their effects through diverse mechanisms, such as bolstering epithelial barrier function, outcompeting pathogenic microorganisms, generating antimicrobial peptides, and regulating the immune system.[20] In the contemporary probiotics industry, the primary microorganisms utilized continue to hail from the genera *Lactobacillus* and *Bifidobacterium*, alongside *Streptococcus thermophilus, Lactococcus spp., E. coli Nissle* 1917, and the yeast *Saccharomyces boulardii.* Although certain health-promoting mechanisms, such as the formation of bile salt hydrolases, are shared across multiple probiotic genera and species, other attributes may exhibit species-specific or strain-specific variations. Additionally, certain beneficial effects may necessitate collaborative interactions among different strains.[23] Prebiotics and synbiotics are increasingly recognized for their potential benefits in mitigating liver damage. Prebiotics are selectively fermented components that promote specific transformations in the composition and activity of the gastrointestinal microbiota, thereby enhancing host healthiness. Synbiotics, on the other hand, are blends of probiotics and prebiotics.[24] Manipulation of the intestine microbiota by administration of probiotics has been proposed as a potential strategy for treating MAFLD. Previous studies have demonstrated that treatment with probiotics alleviates the symptoms of MAFLD in animal models.[3,25,26] Rabbits exposed to a high cholesterol diet (HCD) showed upregulation of lipoprotein and hepatic lipase and cholesteryl ester transfer protein (CETP) gene expression. However, administration of probiotics reversed the HCD-induced changes in gene expression. In addition, the administration of probiotics led to an improvement in liver function tests, antioxidant and peroxide levels and lipid profiles in rabbits.[25]

Several clinical studies have explored probiotics in MAFLD, and the results are promising, improving various aspects of MAFLD, including hepatic steatosis, inflammation, liver function, and metabolic parameters. In a cross-sectional study involving 24,389 Chinese adults, it was observed that increased yogurt consumption correlated dose-dependently with a reduced incidence of newly diagnosed NAFLD.[27] However, the main problem with assessing the impact of probiotics in the prevention and treatment of NAFLD/MAFLD is that clinical trials had variable sample sizes, used different strains of probiotics, and used various parameters to assess the study results.

The first randomized clinical trial (RCT) was conducted by Aller *et al*. in 2011.[28] The patients in the study group received a tablet containing 500 million *Streptococcus thermophilus* and *Lactobacillus bulgaricus* daily for three months. The intake of probiotics was associated with an improvement in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT). Elevated levels of liver enzymes, such as ALT and AST, are often associated with liver inflammation and damage.

In the study by Nabavi *et al*., a decrease in ALT, AST, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) was observed compared to the control group.[29] For eight weeks, the patients in the intervention group received 300 g of probiotic yogurt

with *Lactobacillus, Streptococcus,* enriched with *Bifidobacterium* every day. In another RCT, 52 patients with NAFLD who ate a healthy diet and exercise regularly were given either symbiotic capsules or a placebo twice a day for 28 weeks. The symbiotic group demonstrated significant reductions in liver function tests, chronic inflammation parameters and fibrosis scores in transient elastography compared to the placebo group.[30] In a different RCT, the intervention groups consumed 300 g of synbiotic yogurt containing 10^8 CFU of *Bifidobacterium animalis*/ml and 1.5 g of inulin or conventional yogurt daily, while also being encouraged to maintain a healthy lifestyle. They were consuming the synbiotic for 24 weeks and adhering to a healthy lifestyle. It led to statistically and clinically significant improvements in liver steatosis, ALT, AST, alkaline phosphatase (ALP) and GGT, while insulin and high-density lipoprotein (HDL) cholesterol levels did not change.[31] RCT from Ukraine involved patients with DMT2 and NAFLD. The first group received the multi-probiotic "Symbiter", and the second group was given a placebo for eight weeks. The study showed that the fatty liver index measured by Shear Wave Elastography (SWE) in the probiotic group was significantly lowered, and there was a slight but not noteworthy reduction in liver stiffness (LS). Decreased serum AST and GGT levels were found. Markers of chronic inflammation also changed, and the level of TNF-α and IL-6 increased.[32] In a study carried out by Famouri *et al*, it was observed that patients with NAFLD experienced improvements in their lipid profiles, even in the absence of any meaningful changes in their weight and body mass index (BMI).[33] In the many RCTs that used different probiotic species, a reduction in ALT, AST, and other liver enzymes and lipid profiles was also observed compared to the control group.[34–39] Symbiotic supplementation can also lead to significant changes in steatosis, which are noticeable on ultrasound but not associated with changes in laboratory parameters.[40]

Currently, weight loss is the most effective treatment for NAFLD and is recommended in all national and international guidelines.[41] Some RCTs have shown that the use of probiotics can lead to weight loss and a reduction in BMI in patients with MAFLD.[42–48] In one study, a short 12-week course of a probiotic cocktail and fructooligosaccharides together with a low-calorie diet not only led to a reduction in BMI, but also to a reduction in ALT, AST, and TC levels and liver stiffness.[43] In addition, Asgharian *et al*. found an improvement in the lipid profile and body composition in patients with NAFLD. In this RCT conducted in Iran, participants in the intervention group received a synbiotic preparation containing seven probiotic bacterial species and fructooligosaccharides for eight weeks.[44] Another study of 50 patients diagnosed with NASH by biopsy who received 10^8 CFU of Lactobacillus reuteri twice daily along with 4 g of partially hydrolysed guar gum and inulin over a three-month period showed a decrease in the severity of hepatic steatosis and improvements in certain metabolic indicators associated with NASH, including body weight, BMI, waist circumference (WC) and serum uric acid levels.[45] Reduction in fatty liver in patients with NASH was also observed after 6 months of taking the probiotic formula Lepicol. The intrahepatic triglyceride content (IHTG) and the AST level in the serum decreased significantly in the probiotic group.[38]

In the first clinical trial with VSL#3, the researchers were able to demonstrate that short-term supplementation with VSL#3 significantly improved hepatic steatosis and BMI in children with NAFLD.[46] In 2022, Derosa *et al*. however, observed no changes in BMI, WC, fasting glucose (FPG), TC, LDL, HDL and adiponectin (ADN) in adult patients taking VSL#3 for three months.[49] Regardless, GGT and AST/ALT ratio were significantly decreased in the VSL#3 group compared to the placebo group. In addition, all patients experienced an improvement or resolution of hepatic steatosis.

Moreover, probiotics have demonstrated potential benefits in metabolic parameters associated with MAFLD. Multiple researchers have demonstrated that adding probiotics to a patient's diet can enhance insulin sensitivity and blood glucose levels. The study by Sepideh *et al*. demonstrated that the intake of probiotics improved the glycemic index while also lowering fasting blood sugar and inflammatory indicators.[50] Similarly, in the study by Mofidini *et al*., the group taking symbiotics showed a reduction in FPG, IR, TG, and most inflammatory mediators and, in addition, in Fibroscan, a significant decrease of hepatic steatosis and fibrosis was observed.[51] In addition, supplementing with

Bifidobacterium longum with *Fructooligosaccharides* alongside lifestyle modifications for treating NASH significantly decreases IR, TNF-α, c-reactive protein (CRP), as well as serum AST levels, serum endotoxin, steatosis, and the NASH activity index.[52] The Fibroscan research with controlled attenuated parameter (CAP) showed that non-obese NAFLD patients who received probiotic supplementation experienced a more significant improvement in steatosis compared to obese patients, regardless of BMI changes.[53]

Combining probiotics with omega-3 polyunsaturated fatty acids (n-3 PUFA) shows potential benefits due to their antioxidant and anti-inflammatory properties.[54,55] Previous studies have demonstrated improvements in biochemical aspects and alleviation of hepatic steatosis in NAFLD with n-3 PUFA supplementation.[54,56,57] In RCT involving 48 patients with NAFLD and DMT2, those receiving Symbiter Omega, a combination of probiotics, flax, and wheat germ oil, for eight weeks experienced a significant decrease in fatty liver index (FLI) measured by SWE. The combination of probiotics and omega-3 supplementation also reduced serum GGT, TG, and TC levels.[58] At the same time, no changes were observed in the placebo group. Furthermore, the addition of a specially selected blend of probiotics to micronutrients in obese patients after mini gastric bypass surgery resulted in a more significant decrease in AST, NAFLD fibrosis score, TG, and visceral obesity index compared to those taking the basic micronutrient blend after 12 weeks of supplementation.[59]

Duseja *et al*. conducted the first human study demonstrating the histological efficacy of a multistrain probiotic in biopsy-confirmed NAFLD patients.[37] In this double-blind trial, patients with NAFLD were randomly assigned to one of three groups: lifestyle modifications, an oral multistrain probiotic, or an identical placebo, for a duration of one year. NAFLD Activity Score (NAS) showed a significant improvement in the probiotic group, with notable enhancements in hepatocyte ballooning and hepatic fibrosis. Additionally, patients in the probiotic group experienced reduced levels of ALT, leptin, TNF-α, IL-1β, and IL-6.

Probiotics consisting of various *Lactobacillus and Bifidobacterium* species have been shown to alter gut permeability, inflammatory cytokines, and intestinal microbiota in NAFLD patients. Nonetheless, this study found no statistically significant improvement in biochemical blood parameters.[60]

Some clinical studies suggest that probiotics may not effectively treat fatty liver in MAFLD. In the first study to assess the impact of VSL#3 on acoustic structure quantification (ASQ) in NAFLD patients, Chong *et al*. found no significant differences in cardiovascular risk biomarkers and liver damage markers, such as the NAFLD fibrosis risk score or Fibrosis-4 (FIB-4) score. However, the limited sample size and brief duration of VSL#3 treatment may have affected these results.[61] Similarly, in the study by Rodrigo *et al*., a 6-month probiotic treatment in children was not better than a structured diet and physical activity.[62] Oral supplementation with a probiotic mix for 24 weeks did not lead to any clinically significant changes in body mass index or laboratory parameters, including lipid and glucose profiles.[63] Another RCT revealed that liver steatosis, fibrosis, and activity scores, as well as biochemical blood tests, showed no significant improvement in the group taking probiotic sachets (MCP® BCMC® strains) over six months. However, probiotics seemed to maintain the stability of mucosal immune function, as indicated by a reduction in CD8+ T-cell expression in the placebo group but not in the probiotic group.[64] In study with 104 patients, 55 patients were given symbiotic agents - *Fructooligosaccharides* plus *Bifidobacterium animalis subspecies lactis* BB-12, while 49 patients were given a placebo for 10-14 months.[65]

Similarly, a 2022 meta-analysis revealed that probiotic supplementation positively impacts lipid metabolism, reduces IR, and regulates the body's immunity. Additionally, it was found to improve the levels of key liver enzymes and lipoproteins, such as ALT, AST, GGT, LDL, HDL, and TG, thereby slowing down the progression of liver diseases.[66] Zhu *et al*. concluded that new-generation probiotics (NGP) offer similar therapeutic benefits to traditional probiotics while also directly affecting gene expression in hepatic antioxidant pathways. They emphasized the need to develop personalized treatment plans for NGPs tailored to each patient's specific pathological features and intestinal microbiota composition.[67]

Conclusion

In contemporary society, characterized by incessant haste and a pervasive scarcity of time, a considerable segment of the populace is adopting a lax approach toward dietary and lifestyle practices. Consequently, there has been an alarming proliferation of obesity and DMT2, precipitating a burgeoning epidemic of metabolic disorders, notably including MAFLD.

MAFLD not only affects the liver but also poses significant risks for various systemic complications, underlining the importance of effective therapeutic interventions. Dysregulation of the gut-liver axis plays a significant part in the pathogenesis of MAFLD. Alterations in the gut microbiota profile, intestinal barrier function, and immune functions contribute to the progression of hepatic steatosis and inflammation. Understanding these intricate interactions sheds light on potential targeted therapies for MAFLD. As live microorganisms confer health benefits, probiotics have emerged as promising candidates for MAFLD management. Clinical evidence suggests that probiotic supplementation can ameliorate inflammatory parameters like CRP, TNF-α or IL-6, liver enzymes, lipid profiles, and insulin sensitivity. Mechanisms of action include regulation of gut microbiota composition, improvement of epithelial barrier function, and immune system modulation. Probiotic supplementation, either alone or in combination with prebiotics or synbiotics, has shown significant improvements in histological markers, inflammatory cytokines and results of liver imaging tests like Fibroscan. Despite promising findings, some studies have reported varying results concerning the effectiveness of probiotics in MAFLD treatment. Probiotic strains, dosage, treatment duration, and patient characteristics may influence outcomes.

Probiotics could be potential safe adjunctive therapy for MAFLD. Future research should focus on standardized protocols, personalized approaches, and exploring combinations with other therapeutic modalities. Additionally, investigating the effects of probiotics on gut microbiota-host interactions and systemic metabolic pathways will enhance our understanding of MAFLD pathogenesis and treatment options.

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The authors declare no conflict of interest.

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Authors' Contribution

Conceptualisation: AB, AR, SS; literature search and data analysis: AB, AR; writing, original draft preparation: AB, AR; writing, review and editing: SS, RJ; supervision: SS, RJ. All authors read and approved the final manuscript.

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