

# The effects of probiotic supplementation in Non-alcoholic Fatty Liver Disease: a literature review.

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**Abstract.** Non-alcoholic Fatty Liver Disease (NAFLD) is a metabolic disorder marked by fat accumulation in the liver, often linked to obesity and type II diabetes. With a global incidence of 47 cases per 1,000, NAFLD can lead to serious complications like cirrhosis and cardiovascular diseases if untreated. Current treatment options primarily focus on weight loss and lifestyle changes, which may not be feasible for many patients. Probiotics have emerged as potential alternative treatments due to their connection to gut health and the intestinal-liver axis. Given the recent focus on the microbiome, further investigation is needed to determine the effectiveness of probiotics, including optimal dosages and formulations, in treating NAFLD. This integrative literature review used the PubMed database and the Virtual Health Library (BVS) from May to September 2024. The search employed descriptors from Health Sciences and MeSH, using the terms “probiotics” AND “Non-alcoholic Fatty Liver Disease.” This review suggests that while probiotics alone may not significantly reduce NAFLD progression, their effectiveness improves when combined with prebiotics as symbiotics. Studies show that formulations containing *Lactobacillus* and *Bifidobacterium* with inulin can effectively reduce NAFLD markers. These findings highlight the need to integrate probiotics and symbiotics into NAFLD treatment plans, but more clinical trials are needed to continue to look for new approaches to manage this common metabolic disorder.

**Keywords.** Probiotics, Synbiotics, Non-alcoholic Fatty Liver Disease, Treatment, Prognosis.

## 1. Introduction

Non-alcoholic Fatty Liver Disease (NAFLD) is a metabolic disorder characterized by increased deposition of fat in the hepatocytes not caused by alcohol consumption and often associated with type II diabetes and obesity. It has been becoming increasingly relevant in the epidemiology of liver diseases, reaching an estimated global incidence of 47 cases per 1,000 population [1], and left untreated, can lead to complications such as non-alcoholic steatohepatitis, cirrhosis, hepatocellular carcinoma, cardiovascular diseases, and chronic kidney disease [2]. Even with this critical situation, the current treatment guidelines are limited. They include weight loss, a healthy diet, and constant exercise [3], which are not optimal options considering that the patients who develop this disease usually already have problems managing these aspects of their lifestyle. As such, it becomes important to increase the spectrum of possible treatments for this condition.

Probiotics, defined by the World Health Organization (WHO) as live microorganisms that, when administered in adequate quantities, can improve the patient's health [4], have gained ground in the medical field in recent years as an alternative treatment for various health conditions. The revolution in their use is due not only to the increase in scientific research but also to the growing awareness of the importance of the microbiome.[5]

The relationship between this type of treatment and Non-Alcoholic Fatty Liver Disease was thought of because, during recent studies on the intestinal microbiota, the intestinal-liver axis was described, a concept that refers to the complex interactions between the intestines and the liver, highlighting how gut health can significantly influence liver function and overall metabolism. This axis impacts the maintenance of homeostasis and acts in various physiological processes, including digestion, immune response, and metabolism. For example, the intestinal microbiota produces short-chain fatty acids (SCFAs) derived from fiber fermentation. They

have anti-inflammatory properties and can influence liver metabolism [6]. Another important discovery was that some bacterial endotoxins can trigger inflammatory responses in the liver, contributing to cirrhosis and hepatitis [7]. Considering these examples, it is possible to infer that an unbalanced microbiota could be a trigger for NAFLD, and an intervention in this dysbiosis could have a positive impact on the treatment of this disease.

As the study of the microbiome and how it impacts other body functions is relatively new, probiotics as an alternative treatment need to be reviewed to stipulate if enough clinical trials have been done to determine optimal dosages, types, and the effectiveness of such an approach.

## 2. Research Methods

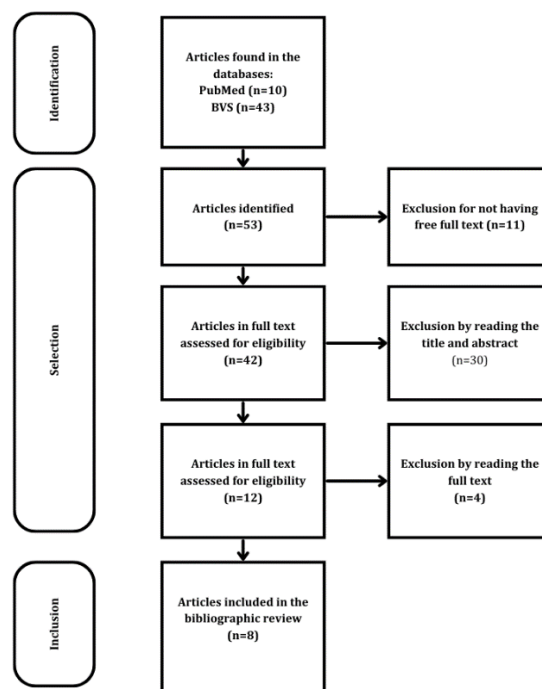
This is an integrative literature review study carried out using research tools from the Pubmed database and the Virtual Health Library (BVS) from May to September 2024. The descriptors defined by the Descriptors in Health Sciences and Medical Subject Headings (DeCS/MeSH), with the search strategy used in these bases: “probiotics” AND “Non-alcoholic Fatty Liver Disease”.

As a result, articles published in the last 5 years were included in both databases, with no language filters being used. Furthermore, only articles with full text available based on clinical trials and randomized clinical trials were filtered. After reading the titles and abstracts, duplicate articles and those that did not address the main topic were excluded. Then, the selected works were read in full, excluding those that did not respond to the main objective of this review. In view of the above, the others were elected to compose this review.

## 3. Results

The search and selection processes for the texts included in the review are organized in the flowchart (Figure 1). The 11 selected articles are organized in the table (Table 1).

**Figure 1:** Article selection flow diagram.



Source: Elaborated by the author (2024).

**Table 1:** Studies included in the article are enumerated and classified according to the title and author of the publication.

Number	Title	Author
1	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	Mohamad Hizami Mohamad Nor
2	A randomised placebo-controlled trial of VSL#3@ probiotic on biomarkers of cardiovascular risk and liver injury in non-alcoholic fatty liver disease	Pui Lin Chong
3	A Specifically Tailored Multistrain Probiotic and Micronutrient Mixture Affects Nonalcoholic Fatty Liver Disease—Related Markers in	Crommen Silke

	Patients with Obesity after Mini Gastric Bypass Surgery		
4	Probiotic Supplementation, Hepatic Fibrosis, and the Microbiota Profile in Patients with Nonalcoholic Steatohepatitis: A Randomized Controlled Trial	Giselle Escouto	S
5	The effects of synbiotics on the liver steatosis, inflammation, and gut microbiome of metabolic dysfunction-associated liver disease patients-randomized trial	Miloš Mitrović	
6	Effects of probiotic and prebiotic supplementation on metabolic parameters, liver aminotransferases, and systemic inflammation in nonalcoholic fatty liver disease: A randomized clinical trial	Vahideh Behrouz	
7	The effects of Bacillus coagulans supplementation in patients with non-alcoholic fatty liver disease: A randomized, placebo-controlled, clinical trial	Khadijeh Abhari	
8	Randomized, Double-blind, Placebo-controlled Study of a Multispecies Probiotic Mixture in Nonalcoholic Fatty Liver Disease	Sang Bong Ahn	

Source: Elaborated by the author (2024).

Table 2 presents the main results of each article included in the review about the impacts of probiotics in managing non-alcoholic fatty liver disease.

**Table 2:** Main results of each article

Number	Results
1	Participants received either probiotics (MCP® BCMC® strains) with six Lactobacillus and Bifidobacterium species at 30 billion CFU or a placebo for six months. The results show no significance between the use of probiotics and a reduction in hepatic steatosis, fibrosis levels, and liver enzymes. The results show relevance in the probiotic's ability to support mucosal immune function and safeguard NAFLD patients from heightened intestinal permeability.
2	Patients with NAFLD were divided into groups so that each group could receive two sachets of the probiotic VSL#3® or placebo twice daily for ten weeks. No significance was found between this probiotic and the reduction of NAFLD markers.
3	Patients were given either a tailored multistrain probiotic powder with a specific micronutrient blend (Pro+SM) or a control treatment comprising a placebo and a basic micronutrient mix (Con+BM) with lower doses for 12 weeks post-hospital discharge. The difference in ALAT serum concentrations did not differ between groups. There was significance in the Pro+SM group, where the intervention reduced NAFLD fibrosis score, visceral adiposity index, and serum ASAT. The probiotic contained Lactobacillus acidophilus, Bifidobacterium breve, B. longum, L. delbrueckii susp. bulgaricus, L. helveticus, L. plantarum, L. rhamnosus, L. casei, Lactococcus lactis susp. lactis, and Streptococcus thermophiles (15 × 10 <sup>9</sup> CFU/4 g).
4	Patients with nonalcoholic steatohepatitis (NASH) were assigned to groups to receive PROs (Lactobacillus acidophilus 1 × 10 <sup>9</sup> colony forming units and Bifidobacterium lactis 1 × 10 <sup>9</sup> colony forming units) or a placebo, daily dosage for six months. There was a reduction in the AST to Platelet Ratio Index of the PROs group, but later analysis showed no significance. The conclusion was that, alone, probiotics don't impact the treatment of NASH.
5	People with Metabolic Dysfunction-associated Liver Disease (MASLD) were divided into groups to receive a synbiotic with 64x10 <sup>9</sup> CFU

of *Lactobacillus* and *Bifidobacterium* and 6.4g of inulin or a placebo for 12 weeks. The use of the symbiotic was associated with significantly decreased liver steatosis and decreased levels of high-sensitive C-reactive protein, results that show that this approach could be effective in MASLD treatment.

- 6 Patients with NAFLD were recruited and assigned to one of three groups to receive either probiotic capsule + placebo of prebiotic (probiotic group), oligofructose + placebo of probiotic (prebiotic group), or placebo of probiotic + placebo of prebiotic (control group) for 12 weeks. The results show that Probiotic supplementation reduced triglycerides, ALT, AST, GGT, and alkaline phosphatase compared to the control group. The prebiotic group showed significant differences in serum triglycerides, total and LDL cholesterol, ALT, AST, and GGT compared to placebo. The probiotic was administered twice a day and was composed of 5 billion of five bacterial strains (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bifidobacterium breve*).
- 7 Patients received a symbiotic supplementation with 109 spores of *Bacillus coagulans* (GBI-30) plus inulin or placebo for 12 weeks. Serum alanine aminotransferase and gamma-glutamyltransferase, serum tumor necrosis factor-alpha, and hepatic steatosis were decreased significantly more in the synbiotic group than in the placebo group. In conclusion, the use of symbiotics with lifestyle modifications is better than only treating NAFLD with lifestyle modifications.
- 8 This study administered a probiotic that contained six probiotic agents (*Lactobacillus acidophilus*, *L. rhamnosus*, *L. paracasei*, *Pediococcus pentosaceus*, *Bifidobacterium lactis*, and *B. Breve*) for 12 weeks. The results showed that the reduced triglyceride levels and intrahepatic fat were not associated with the probiotic treatment but with changes in body weight during the trial.

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Source: Elaborated by the author (2024).

## 4. Discussion

When looking for alternative treatments for Non-alcoholic Fatty Liver Disease, the idea to use probiotics, supplements of live microorganisms, to manage this disease came from the critical role that imbalance of the gut microbial community plays in the progression of NAFLD.

Despite the initial hypothesis, most of the results of this review show that, alone, probiotics don't have a significant impact in lowering NAFLD development. An exception to this statement was the Behrouz treatment, which showed reduced triglycerides, ALT, AST, GGT, and alkaline phosphatase compared to the control group. [13]

Although probiotics did not have the effectiveness expected, this does not mean that they should not be used in the management of NAFLD, only that they have better benefits when associated with a healthy lifestyle or prebiotics.

Symbiotics are a combination of prebiotics and probiotics. Prebiotics serve as food for probiotics, helping to increase their viability and colonization in the intestines. Because of this, this synergy can result in more pronounced effects in modulating the intestinal microbiota and promoting digestive health [16]. Considering this idea, the symbiotic approach proposed by Mitrović [12], of 64x10<sup>9</sup> CFU of *Lactobacillus* and *Bifidobacterium* and 6.4g of inulin for 12 weeks and the conduct proposed by Abhari [14], of 10<sup>9</sup> spores of *Bacillus coagulans* (GBI-30) plus inulin or placebo for 12 weeks were successful in obtaining significant results in decreasing NAFLD markers.

Finally, Silke [10] did show relevance in the use of a probiotic that contained *Lactobacillus acidophilus*, *Bifidobacterium breve*, *B. longum*, *L. delbrueckii* susp. *bulgaricus*, *L. helveticus*, *L. plantarum*, *L. rhamnosus*, *L. casei*, *Lactococcus lactis* susp. *lactis*, and *Streptococcus thermophiles* (15 × 10<sup>9</sup> CFU/4 g) for 12 weeks, but only when in association with a change in diet, concluding that this could also be an optimal combination for managing NAFLD.

## 5. Conclusion

The research in this review indicates that while probiotics alone may not substantially mitigate the progression of NAFLD, their effectiveness can be enhanced when combined with prebiotics in the form of symbiotics. Noteworthy studies have demonstrated that specific symbiotic formulations, such as those containing *Lactobacillus* and *Bifidobacterium* alongside inulin, can yield promising results in reducing NAFLD markers.

Ultimately, the findings show the importance of integrating probiotics and symbiotics into the treatment plan for NAFLD. As research evolves, a more nuanced understanding of the microbiome's

role in liver health may pave the way for innovative therapies, offering hope for better management of NAFLD and improving patient outcomes. Further clinical trials are necessary to establish optimal dosages and formulations, but the potential of these interventions marks an exciting frontier in the fight against this increasingly common metabolic disorder.

## 6. References

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