The Egyptian Journal of Hospital Medicine (April 2025) Vol. 99, Page 1838-1844

Exploring the Role of Gut Microbiome-Targeted Therapies in Non-Alcoholic Fatty Liver Disease: A Systematic Review

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ABSTRACT

Background: Modification of the gut microbiota may be a novel therapeutic target for nonalcoholic fatty liver disease (NAFLD), according to earlier research that demonstrated the encouraging benefits of gut microbiome-targeted therapeutics (MTTs).

Aim: This meta-analysis study aimed to determine the impact of microbiome-targeted therapies on NAFLD patients, highlighting similarities and differences in reported clinical outcomes.

Methods: A search across PubMed, Scopus, Web of Science, and the Cochrane Library for: Microbiome-targeted treatments, probiotics, synbiotics, and prebiotics for randomized controlled trials (RCTs) that included individuals with non-alcoholic fatty liver disease (NAFLD) and compared MTT to normal care or a placebo.

Results: The meta-analysis, including seven studies with a total of 430 participants, found that probiotics, synbiotics, and other pharmacological agents like rifaximin and sitagliptin-synbiotics demonstrated varying degrees of efficacy in improving liver function, reducing inflammatory markers, and managing associated comorbidities. Probiotic treatments, while generally safe, well-tolerated, and cost-effective, have shown promising results in reducing liver enzymes, improving insulin resistance, and modulating inflammatory cytokines. Synbiotics, particularly when combined with sitagliptin, have been found to produce superior results in managing glycemic control and lipoprotein levels compared to placebo treatments. Similarly, rifaximin therapy has demonstrated significant reductions in endotoxin levels, proinflammatory cytokines, and liver fat scores, highlighting its potential as an adjunctive treatment for nonalcoholic steatohepatitis (NASH).

Conclusion: Although encouraging, larger-scale studies with longer follow-up times are needed to fully investigate the therapeutic utility of probiotics, synbiotics, and adjuvant therapies in order to develop clear clinical guidelines for their application in the therapy of NASH and NAFLD.

Keywords: Non-alcoholic fatty liver disease, Probiotics, Synbiotics, Fecal microbiota transplantation, Microbiome-targeted therapy, liver function,inflammatory markers.

INTRODUCTION

The presence of at least 5% hepatic steatosis without common secondary causes such as chronic viral hepatitis, autoimmune hepatitis, congenital hepatic disorders, excessive alcohol consumption, or long-term use of steatosis-inducing medications is known as non-alcoholic fatty liver disease (NAFLD) [(1)]. Globally, the prevalence of NAFLD, which is predicted to overtake all other causes of liver transplants by 2030, is rising due in large part to the obesity pandemic, which is also raising healthcare costs [(2)].

More than half as many people now have NAFLD worldwide in recent decades, from 25.3% between 1990 and 2006 to 38.0% between 2016 and 2019, which is consistent with the growth in type 2 diabetes (T2D) and obesity [(3)]. For the majority of people, NAFLD is associated with comorbid conditions such obesity, insulin resistance, beta cell dysfunction, type 2 diabetes, and dyslipidemia [(4)]. Uncertainty surrounds the strong correlations between NAFLD and associated mortality-causing comorbidities, which may include persistent low-grade inflammation [(2)].

Trillions of intricate microorganisms coexist peacefully with the human body in the gut, where they aid in the regulation of digestion, immunity, metabolism, and nutrient absorption [(5)]. By dysregulating host metabolism and immunology, alterations in the gut flora's composition or function can contribute to the onset and progression of a number of illnesses [(6, 7)]. Targeting the gut microbiota is a viable treatment approach, since preclinical research has demonstrated that it can delay the onset of NASH, reduce liver inflammation, and prevent the development of obesity and hepatic steatosis [(8–10)].

Several types of microbiome-targeted therapeutics (MTTs) have been proposed as ways to alter the gut microbiome, including probiotics, synbiotics, antibiotics, and fecal microbiota transplantation (FMT) [(11)]. A probiotic is a culture of live bacteria that, when taken in sufficient quantities, may help the human host's health. Probiotics and prebiotics are combined to form synbiotics. Prebiotics are made up of fermentable dietary fibers, such as fructo-oligosaccharides and inulin, which help probiotics grow and survive. The process of FMT involves taking stool from a healthy donor and giving it to a patient by a variety of delivery methods, such as enema, nasogastric tube, and colonoscopy [(12, 13)].

A recent development in the management of nonalcoholic fatty liver disease (NAFLD) is the use of microbiome-targeted treatments. Even though this

Received: 17/11/2024
Accepted: 16/01/2025

subject has been the subject of many studies, more thorough investigation and assessment are still needed to determine the clinical effectiveness of these treatments as well as their biological mechanisms of action. By comparing and contrasting reported clinical outcomes. The purpose of this comprehensive study was to determine how patients with non-alcoholic fatty liver disease responded to microbiome-targeted therapy.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines **(Figure 1)**.

Search strategy: A comprehensive literature search was conducted to locate relevant studies. NAFLD or NASH and "probiotics", "synbiotics", "FMT", "gut microbiota", "MTT" and ("liver function–related parameters" OR "ALT", "AST", "steatosis" and "fibrosis" and "insulin resistance" were included in the search method, which employed a combination of Medical Subject Headings (MeSH) phrases and keywords that included "inflammatory markers." The search was limited to English-language publications in peer-reviewed journals, regardless of the year of publication. In order to find more studies, manual searches of the reference lists of pertinent publications were also conducted.

Inclusion Criteria: Studies that satisfied the following requirements were accepted: (1) Randomized controlled trials (RCTs) and double-blind placebo-controlled studies, (2) Studies comprised intervention measures (experiment group) that were administered MTTs, such as prebiotics, synbiotics, antibiotics, and other pharmacological agents like rifaximin and sitagliptin-synbiotics, (3) Studies examined patients with NAFLD, which was defined by either liver histology or non-invasive imaging modality (MRI, ultrasound, or elastography). (4) Research where a comparison group (control group) received therapy with a placebo, standard care, and additional MTTs that differed from the experiment group, (5) Research where the treatment follow-up period was at least four weeks and (5) Research presenting quantifiable results (e.g., inflammatory indicators, BMI, liver enzymes)

Exclusion Criteria: The studies were excluded based on the following criteria: (1) The study that did not collect complete text, (2) Autoimmune hepatitis, liver cancer, hepatitis, and other causes of hepatitis steatosis or fibrosis in people, (3) Non-randomized studies, case reports, or reviews, and (4) publications written in languages other than English and animal studies.

Data extraction: To assess its applicability, two researchers independently evaluated the abstracts and titles of every publication produced. After carefully reviewing every experiment that was found, we made the decision to include or exclude it. Additionally, the data were separately extracted by researchers and entered into a standardized data extraction form. On choices about the inclusion of research and data extraction, the two reviewers came to an agreement. When differences were found, a third researcher had the last say over who is eligible for the trial and how to retrieve data.

RESULTS

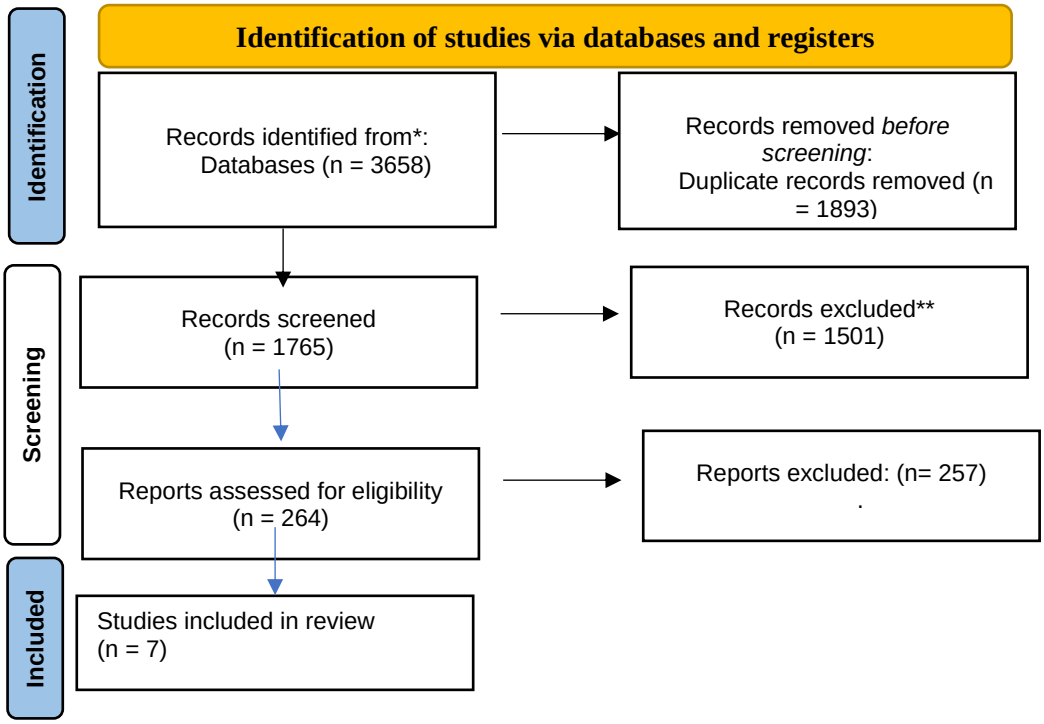

Figure (1): PRISMA flow chart for study selection process.

Tables (1), (2) and (3) showed the demographic and clinical characteristics as well as the interventions and control groups of the included studies. Also, the key outcomes and clinical findings of therapeutic interventions.

Table (1): Demographic and clinical characteristics of included studies

Study ID	Year	Study Location	Study Design	Sample Size	Age	Gender Distribution	Patient`s Body mass index (BMI)
Monem *et al.* [14]	2017	Egypt	Randomized controlled study	30	E= 44.20 ± 5.51 C= 44.33 ± 5.62	E= 9 (60%) male and 6 (40%) female C= 8 (53.3%) male and 7 (46.7%) female	E= 32.56 ± 1.19 C= 33.05 ± 1.27
Sayari *et al.* [15]	2018	Iran	Randomized, double blind trial	138	E= 42.48±11.41 C= 43.42±11.65	E= 35.7% were female and 64.3% were male C= 44.1% were female and 55.9% were male	E= 29.72±3.62 C= 29.54±3.71
Abdel-Razik *et al.* [16]	2018	Egypt	Multicentric, double-blind, randomized, placebo-controlled study	50	E= 40.2 ± 9.88 C= 38.4 ± 9.21	E= 18 female and 9 male C= 16 female and 7 male	E= 33.3 ± 7.45 C= 32.8 ± 7.35
Abhari *et al.* [17]	2020	Iran	Randomized, double-blind, placebo-controlled clinical trial	53	E= 47.7 ± 11.4 C= 46.7 ± 12.4	E= 14 (61%) male and 9 (39%) female C= 11 (50%) male and 11 (50%) female	E= 32.2 ± 6.72 C= 33.6 ± 5.06
Sadrkabir *et al.* [18]	2020	Iran	Randomized clinical trial	61	E= 43.26±11.42 C= 43.72±10.76	E= 22 (66.7%) male and 11 (33.3%) female C= 18 (64.3%) male and 10 (35.7%) female	E=31.87±5.4 C= 30.83±4.6
Escouto *et al.* [19]	2023	Canada	Double-blind, placebo-controlled clinical trial	48	E= median age of 58 y C= median age of 57 y	E= 20 (87.0%) female while C= 18 (72.0%) female	Both E and C groups showed median BMI of 31.6 kg/ m2
Abd El Hamid *et al.* [20]	2024	Egypt	Double-arm randomized controlled trial	50	E= 45.72 ±8.9 C= 46.48 ±11.60	E= 7 (28%) male and 18 (72%) female. C= 8 (32%) male and 17 (68%) female	E= 33.88 ±7.43 C= 31.21 ±3.32

E: Experimental group; C: Control group,

*Age and BMI are reported as presented in the original studies (mean ± SD or median), without transformation.

Table (2): Interventions and control groups in included studies

Study ID	Intervention (experimental group)	Comparison (Control group)	Duration
Monem *et al.* [14]	Probiotics (Acidophilus capsule (Lactobacillus acidophilus)	Control group (who did not receive probiotics)	One month
Sayari *et al.* [15]	Sitagliptin 50 mg daily plus synbiotic (one capsule per day)	Sitagliptin 50 mg daily plus placebo (one capsule per day)	16 weeks
Abdel-Razik *et al.* [16]	Rifaximin Therapy	Placebo	6 months
Abhari *et al.* [17]	Synbiotic containing B. coagulans and inulin	Placebo capsule	12 weeks
Sadrkabir *et al.* [18]	GeriLact	Placebo	60 days.
Escouto *et al.* [19]	Probiotics (PROs) (Lactobacillus acidophilus and Bifidobacterium lactis)	Placebo	6 month.
Abd El Hamid *et al.* [20]	Probiotic group received lifestyle modification instructions along with daily probiotic supplementation	Standard Treatment group received low-fat diet and lifestyle modification instructions only	12 weeks,

Table (3): Key outcomes and clinical findings of therapeutic interventions

Study ID	Main Findings	Outcome
Monem *et al.* [14]	There was significant decrease in liver enzymes (ALT and AST) and no statistically significant other laboratory findings. Also, there was relief for dyspepsia in some patients.	Probiotics treatment is effective, safe, well-tolerated, inexpensive, appropriate for long-term use, and optimally, works at multiple levels to downregulate inflammatory mediators, and therefore, probiotics could be an option in the treatment of NASH
Sayari *et al.* [15]	The mean change in FBS with sitagliptin-placebo from baseline was -10.47±5.77 mg/dL, and that with sitagliptin-synbiotic was -13.52±4.16 mg/dL (P<0.001). The mean change in cholesterol (Chol) was -8.34±28.83 mg/dL with sitagliptin-placebo and -21.25±15.50 mg/dL with sitagliptinsynbiotic (P=0.029). The administration of sitagliptin-placebo induced an increase of 6.13±27.04 mg/dL in low density lipoprotein (LDL), whereas sitagliptin-synbiotic induced a decrease of 14.92±15.85 mg/dL in LDL (P<0.001). However, the sitagliptin-synbiotic group showed a significant improvement in aspartate aminotransferase (AST) level compared to the sitagliptin-placebo group (P=0.018).	Sitagliptin-synbiotic produced greater improvement in FBS, AST, Chol, and LDL compared to sitagliptin alone in patients with NAFLD
Abdel-Razik *et al.* [16]	After 6 months of rifaximin therapy, patients with NASH showed a significant reduction in homeostatic model assessment, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, endotoxin, toll-like receptor-4, IL-6, tumor necrosis factor-α, CK-18, and NAFLD-liver fat score (all P<0.05), but no changes in the lipid profile; moreover, there was a mild non-statistically significant reduction of BMI. However, in the placebo group, there was no significant difference in these variables at baseline and after therapy	Rifaximin therapy appears to be effective and safe in modifying NASH through reduction of serum endotoxin and improvement of insulin resistance, proinflammatory cytokines, CK-18, and NAFLD-liver fat score.
Abhari *et al.* [17]	At the end of their study, serum alanine aminotransferase and g glutamine transaminase decreased significantly more in synbiotic group compared to placebo group (p= 0.001, and p= 0.004, respectively). Synbiotic supplementation significantly reduced serum tumor necrosis factor-a (p= 0.03) and nuclear factor-kB activity (p= 0.04). Moreover, hepatic steatosis reduced significantly more in synbiotic group compared to placebo group (p < 0.001).	12 weeks supplementation with B. coagulans plus inulin is beneficial for treatment of NAFLD and its related inflammation without any significant effects on related cardiovascular risk factors
Sadrkabir *et al.* [18]	In the GeriLact group, there was a significant decrease in ALT (p=0.002) and AST (p<0.001) levels, while the placebo group showed a significant decrease only in ALT level (p=0.01). There was a significant decrease in cholesterol levels in the intervention group compared to the placebo group (p=0.01), but there were no significant changes in FBS, triglycerides, LDL, and HDL levels between the two groups. The fatty liver grade was improved by 63.6% in the intervention group and by 46.4% in the placebo group.	Probiotics caused significant improvement in ALT, AST, and cholesterol levels but had no effects on FBS, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Overall, treatment with GeriLact was found to be effective, safe, with low cost and well-tolerated in the long term use by the patients.
Escouto *et al.* [19]	The AST to Platelet Ratio Index (APRI) score was the primary outcome that decreased over time in the PRO group. Aspartate aminotransferase presented a statistically significant result in the group-moment interaction analyses. Liver fibrosis, steatosis, and inflammatory activity presented no statistically significant differences between the groups. No major shifts in gut microbiota composition were identified between groups after PRO treatment.	Patients with NASH who received PRO supplementation for 6 mo presented improvement in the APRI score after treatment. This result draw attention to clinical practice and suggest that supplementation with PROs alone is not sufficient to improve enzymatic liver markers, inflammatory parameters, and gut microbiota in patients with NASH.
Abd El Hamid *et al.* [20]	The study found a statistically significant difference in liver enzymes (ALT and AST) and BMI in the probiotic group before and after intervention. However, there was no significant difference in NAFLD fibrosis score between the two groups.	Short-term probiotic treatment resulted in improvements in ALT, AST, and BMI in the probiotic group, but did not significantly affect NAFLD fibrosis score.

DISCUSSION

Nonalcoholic steatohepatitis (NASH), a more severe manifestation of the illness, is one of the histopathologic abnormalities that fall under the umbrella of non-alcoholic fatty liver disease (NAFLD), which affects both adults and children. The correlation between NASH and cirrhosis, hepatocellular carcinoma, and liver-related mortality highlights the detrimental consequences of overeating and the metabolic syndrome on liver function [(21)]. There is growing interest in using MTTs to treat NAFLD because of preclinical data showing a substantial correlation between the gut microbiota and the disease.

The impact of gut microbiome-targeted treatments, particularly probiotics, synbiotics, and antibiotic-based methods, on liver-related outcomes in patients with NAFLD was assessed in this comprehensive review. The results demonstrated that substantial changes in lipid levels (total cholesterol and LDL) were recorded in the majority of the included trials, and liver function markers (ALT and AST) following the use of microbiota-targeted therapies, particularly synbiotics [(15)].

Despite these reported improvements, **Abd El Hamid *et al.*** [(20)] demonstrated that, in terms of NAFLD fibrosis score, 12-week probiotic treatment does not perform better than standard treatment. Furthermore, **Escouto *et al.*** [(19)] noted that improving inflammatory parameters, gut microbiota, and enzymatic liver indicators in NASH patients requires more than just taking PRO supplements. This could highlight the importance of considering additional aspects in addition to taking medication, like: Losing weight and leading a healthy lifestyle are still effective ways to prevent and treat NAFLD. Research suggests that losing 10% of body weight can improve liver steatosis and fibrosis in NASH patients and lower liver damage levels [(22)].

Furthermore, a number of studies have demonstrated decreases in inflammatory markers and fasting blood sugar levels [(15, 18)]. Most of these outcomes showed statistically significant differences, and they were more noticeable in the intervention groups than in the placebo or usual care groups. These results align with earlier meta-analyses. **Song *et al.*** [(23)], studied the effects of antibiotics, fecal microbiota transplants, probiotics, synbiotics, and prebiotics on liver enzymes, metabolic impacts, and liver-specific factors in patients with NAFLD. They suggested that probiotics and synbiotics could help NAFLD patients with hepatic steatosis and fibrosis, lower enzyme levels, and greatly enhance liver function. Similarly, **Amini-Salehi *et al.*** [(24)] investigated the effects of probiotics, prebiotics, and synbiotics on liver enzymes in the NAFLD population and demonstrated that hepatic damage in NAFLD patients may be treated with therapies that target the gut microbiota.

Limitations: Our study had certain limitations. First, there was variation in treatment duration, which could lead to clinical heterogeneity. We did not perform a dose subgroup analysis because of the small number of included studies, which could have impacted the accuracy of the findings. Second, the statistical reliability was diminished because all of the included studies had small sample sizes. Third, the findings might have been impacted by the absence of long-term follow-up data.

RECOMMENDATIONS

In light of these limitations, more research is required to better identify the ideal bacterial strains, treatment duration, and dose of treatments for the NAFLD population that target the gut microbiota. It is also suggested that future study conduct multi-large sample studies to clarify the precise efficacy of MTTs in the treatment of NAFLD and long-term follow-up RCT studies to collect reliable data. To improve the precision of the study findings, the intervention measures must be made clear. Last but not least, common side effects including nausea, diarrhea, and stomach pain should be mentioned since they could prevent MTTs from being used widely.

CONCLUSION

The potential benefits of various treatments for the management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis are insightfully revealed by this comprehensive review. While probiotics, synbiotics, and other pharmaceuticals such as rifaximin and sitagliptin-synbiotics appear to be generally effective in enhancing liver function, lowering inflammatory markers, and controlling related comorbidities, but the effectiveness of each intervention varies. Therefore, in order to develop clear therapeutic guidelines for their usage in the management of NASH and NAFLD, more research should be investigated through larger-scale trials with longer follow-up periods.

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