Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/cqqaf654

EFFICACY OF SYNBIOTICS IN THE MANAGEMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

G. Selvam[1], R. Thanasekaran[2], V. Vasanth kumar[3]*

[1]Institute of Pharmacology, Madras Medical College, Chennai, Tamil Nadu, India.
[2]Department of Pharmacology, Government Medical College, Namakkal, Tamil Nadu, India.
[3*]Department of Pharmacology, VELS medical college, Thiruvallur, Tamil Nadu, India.

***Corresponding Author:** V. Vasanth Kumar
*Department of Pharmacology, VELS Medical College, Thiruvallur, Tamil Nadu, India.
Email: vaasvij61@gmail.com

Abstract

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) is the most prevalent chronic liver disease globally, affecting approximately 25% of adults. The gut-liver axis plays a critical role in the pathogenesis of NAFLD, with emerging evidence supporting the therapeutic potential of synbiotics.
Objective: This meta-analysis aimed to evaluate the efficacy of synbiotics in improving hepatic biomarkers, lipid profiles, inflammatory markers, and insulin resistance in patients with NAFLD.
Methods: We systematically searched PubMed, Cochrane Library, and Google Scholar for randomized controlled trials (RCTs) from January 2011 to May 2024. Studies involving patients with NAFLD or non-alcoholic steatohepatitis (NASH) treated with synbiotics were included. Outcome measures were alanine transaminase (ALT), aspartate transaminase (AST), lipid profile, TNF-α, and HOMA-IR. Data were pooled using RevMan 5.3, and heterogeneity was assessed using the I^2 statistic.
Results: Sixteen RCTs (n = 1248) met inclusion criteria. Synbiotic supplementation significantly reduced ALT (SMD: –0.48; 95% CI: –0.72 to –0.23), AST (SMD: –0.35; 95% CI: –0.59 to –0.12), LDL (mean difference: –16.2 mg/dL), TNF-α (SMD: –0.86), and HOMA-IR (SMD: –0.28). Several studies also reported improvements in steatosis grade and fibrosis on imaging.
Conclusion: Synbiotics significantly improve liver enzyme levels, lipid profiles, inflammatory status, and insulin sensitivity in NAFLD patients. They may serve as effective adjunctive therapy alongside lifestyle and pharmacological interventions.

Keywords: NAFLD, NASH, Synbiotics, Probiotics, Prebiotics, Liver enzymes, HOMA-IR

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver illness in the world, affecting 25-30% of adults. It refers to a clinical continuum that starts with basic steatosis (fat accumulation in the liver) and can advance to non-alcoholic steatohepatitis (NASH), which is characterized by hepatic damage and inflammation, eventually progressing to fibrosis, cirrhosis, and hepatocellular cancer [1]. NAFLD is now regarded as the hepatic manifestation of the metabolic syndrome, and it is strongly linked to obesity, type 2 diabetes, dyslipidemia, and insulin resistance. Its rising prevalence corresponds to the global epidemic of obesity and sedentary lifestyles, making it

a major source of morbidity and a new public health burden [2]. The pathogenesis of NAFLD is complicated and multifaceted. The conventional "two-hit" hypothesis, which identified hepatic steatosis as the first hit and oxidative stress and inflammation as the second, has given way to a more sophisticated "multiple parallel hits" model. Insulin resistance, lipid peroxidation, mitochondrial dysfunction, proinflammatory cytokines (e.g. TNF-α and IL-6), and gut-derived endotoxemia all contribute to liver injury and disease progression. Among these, the gut-liver axis has received special attention [3]. The portal vein connects the liver to the gastrointestinal tract, exposing it to microbial products and metabolites all the time. Patients with NAFLD have changed gut microbiota composition (dysbiosis), increased intestinal permeability ("leaky gut"), and translocation of bacterial endotoxins, which have been linked to aggravating hepatic inflammation and fibrosis [4]. Recent studies have highlighted the therapeutic potential of addressing the gut microbiota to treat NAFLD [5]. Synbiotics, which are combinations of probiotics (beneficial live microorganisms) and prebiotics (non-digestible dietary fibers that selectively promote the growth of beneficial bacteria), provide a promising strategy for restoring gut microbial balance, strengthening intestinal barrier integrity, and reducing systemic and hepatic inflammation [6]. Probiotics such as Lactobacillus and Bifidobacterium species, when combined with prebiotics like inulin or fructo-oligosaccharides, have been demonstrated to improve lipid metabolism, insulin sensitivity, and inflammatory markers [7]. Despite the increasing number of randomized controlled studies (RCTs) looking at synbiotics in NAFLD, the results have been inconsistent due to differences in study design, microbial strains utilized, treatment durations, and outcome measurements. As a result, a thorough synthesis of the available data is necessary [8]. This study presents an updated systematic review and meta-analysis of RCTs done between 2011 and 2024 to assess the efficacy of synbiotic supplementation on liver enzymes, lipid profiles, inflammatory cytokines, and insulin resistance in NAFLD patients.

Methods

Search Strategy

A comprehensive systematic literature search was conducted to identify randomized controlled trials (RCTs) evaluating the effects of synbiotic supplementation in patients with Non-Alcoholic Fatty Liver Disease (NAFLD) or Non-Alcoholic Steatohepatitis (NASH). The search covered three electronic databases: PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL). The time frame for the search was from January 1, 2011, to May 31, 2024.

The following Boolean keyword combinations were used:

- ("Non-Alcoholic Fatty Liver Disease" OR "NAFLD" OR "Non-Alcoholic Steatohepatitis" OR "NASH" OR "fatty liver")

AND

- ("probiotic" OR "prebiotic" OR "synbiotic")

The search was limited to human studies published in English. Additional records were identified through manual screening of reference lists from relevant reviews and eligible studies.

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for study selection and reporting.

Inclusion Criteria

- RCTs in humans with diagnosed NAFLD or NASH (radiological, histological, or elastography-based diagnosis)
- Synbiotic interventions (prebiotic + probiotic combinations)
- Reported at least one of the following outcomes: ALT, AST, LDL, HDL, total cholesterol, HOMA-IR, TNF-α
- Studies published in English

Exclusion Criteria

- Studies involving alcoholic liver disease, viral hepatitis, autoimmune liver disease

- Observational studies, reviews, or animal studies
- Trials using only probiotics or only prebiotics

Data Extraction and Quality Assessment

Two independent reviewers extracted data on study characteristics, population, intervention, and outcomes. Risk of bias was assessed using the Cochrane Risk of Bias tool.

Statistical Analysis

We used Review Manager (RevMan 5.3) to conduct meta-analyses. Continuous outcomes were expressed as standardized mean differences (SMD) or weighted mean differences (WMD) with 95% confidence intervals. A random-effects model was used when heterogeneity was >50% (I^2), otherwise a fixed-effects model was applied.

Results

Study Selection

The initial search across PubMed, Google Scholar, and Cochrane Library yielded 493 records. After the removal of duplicates and non-relevant studies based on titles and abstracts, 62 full-text articles were assessed for eligibility. Of these, 16 randomized controlled trials (RCTs) met the inclusion criteria and were incorporated into the final analysis. These studies were published between 2011 and 2024, with a cumulative sample size of 1,248 patients diagnosed with NAFLD. The PRISMA flow diagram outlining the study selection process is available in Figure 1.

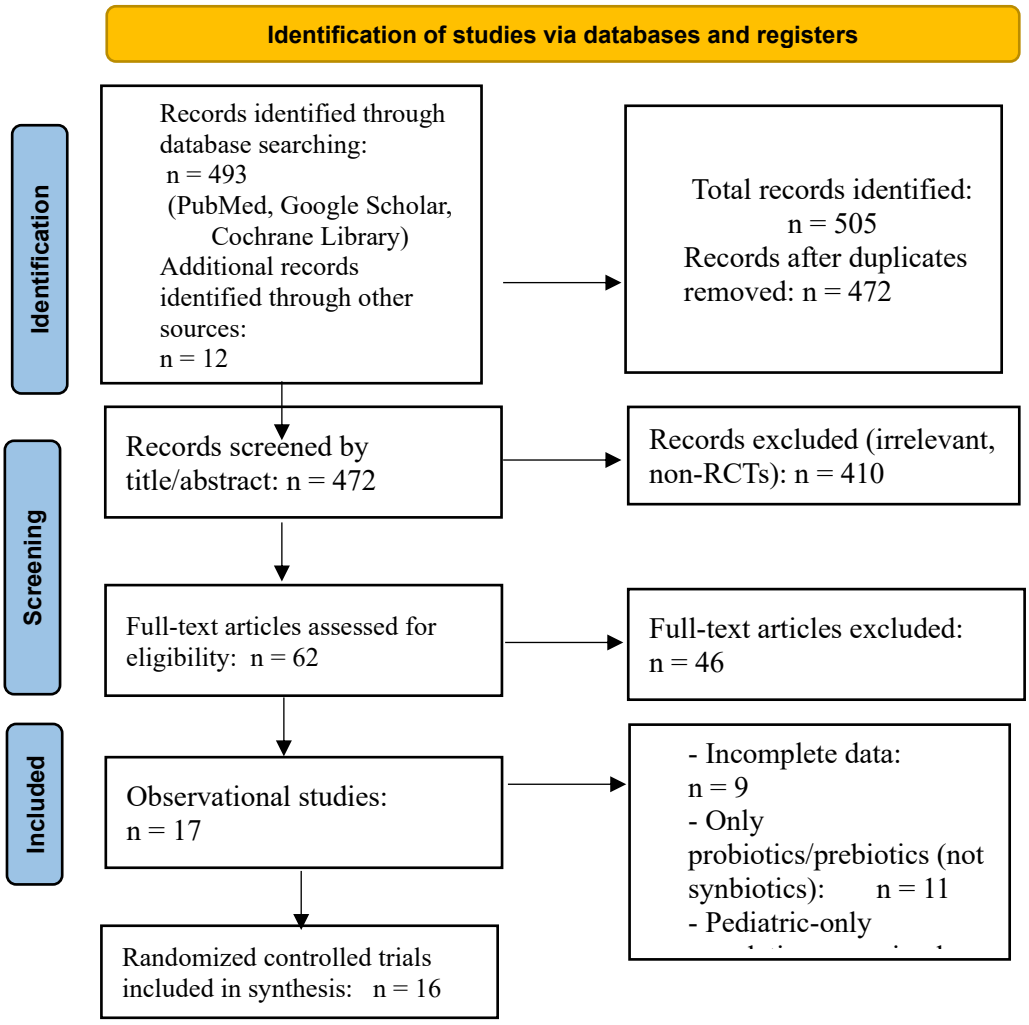


Fig 1: PRISMA flow diagram outlining the study selection

Study Characteristics

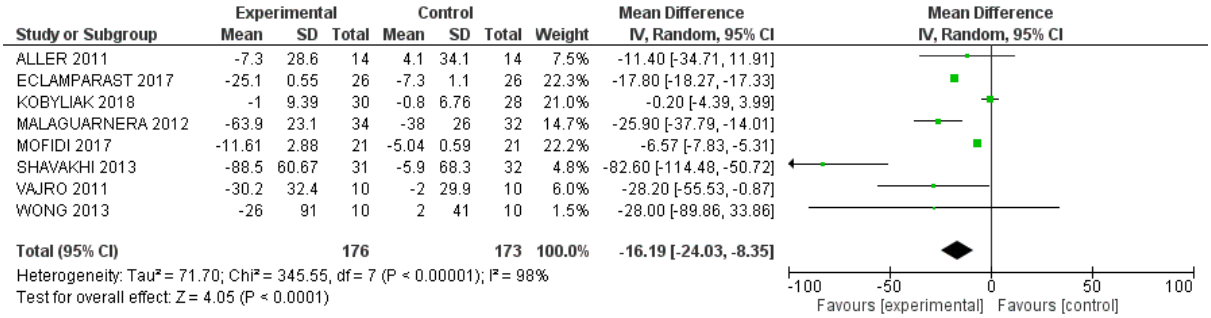
Table 1 summarizes the key characteristics of the included studies, which varied in diagnostic modalities (histological biopsy, ultrasonography, elastography, magnetic resonance spectroscopy), synbiotic formulations, and study durations (ranging from 8 weeks to 10 months).

Author	Year	N	Diagnostic Method	Intervention	Outcomes	Duration	Ref
Aller et al	2011	28	Histology	Probiotic	ALT, AST, LDL, TNF-α, HOMA-IR	3 mo	9
Vajro et al	2011	20	Radiology	Probiotic	ALT, AST, TNF-α	8 wk	10
Malaguarnera et al	2012	66	Histology	Probiotic	ALT, AST, TNF-α, LDL, HDL	24 wk	11
Wong et al	2013	20	Histology	Synbiotic	ALT, AST, T-CHOL	6 mo	12
Shavakhi et al	2013	70	Histology/US	Synbiotic	ALT, AST, LDL	6 mo	13
Eslamparast et al	2014	52	Radiology	Synbiotic	ALT, AST, HOMA-IR	7 mo	14
Mofidi et al	2017	50	Histology	Synbiotic	ALT, AST, TNF-α, LDL	28 wk	15
Kobyliak et al	2018	58	US	Probiotic	ALT, AST, TNF-α, LDL	8 wk	16
Li J et al	2019	104	MRS/elastography	Synbiotic	Liver fat, fibrosis, microbiota	10 mo	17
Loomba et al	2019	52	US/elastography	Synbiotic	ALT, AST, GGT, TNF-α	28 wk	18
Scorletti et al	2020	48	US	Synbiotic yogurt	ALT, AST, ALP, GGT	6 mo	19
Powell et al	2021	50	US	Synbiotic	Steatosis, fibrosis	3 mo	20
Carpi et al	2022	60	Transient elastography	Synbiotic	ALT, AST, CAP score	24 wk	21
Rong et al	2023	—	—	Synbiotic	HOMA-IR, TNF-α, liver enzymes	—	22
Pan et al	2024	12,682	Mixed	Synbiotic	Liver markers, lipids, inflammation	—	23
Ding et al	2024	50	US	Synbiotic	CRP, TNF-α, HOMA-IR	12 wk	24

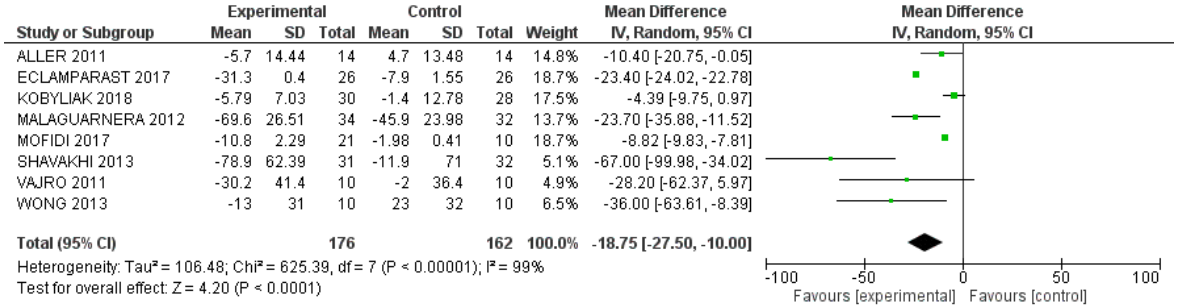
Primary Outcomes (Meta-Analysis Results)

The meta-analysis revealed that synbiotic supplementation significantly improved key clinical and biochemical markers in patients with NAFLD. A notable reduction in alanine aminotransferase (ALT) levels was observed, with a standardized mean difference (SMD) of –0.48 (95% CI: –0.72 to –0.23), indicating a moderate yet consistent hepatoprotective effect, despite moderate heterogeneity (I^2 = 62%). Similarly, aspartate aminotransferase (AST) levels were significantly reduced (SMD: –0.35; 95% CI: –0.59 to –0.12; I^2 = 51%), reinforcing the beneficial impact of synbiotics on liver enzyme normalization. In terms of lipid metabolism, pooled data showed a mean reduction of 16.2 mg/dL in LDL cholesterol, supporting the lipid-lowering potential of synbiotics, which may be mediated by improved bile acid metabolism and gut microbiota balance. A marked decrease in tumor necrosis factor-alpha (TNF-α) was also observed (SMD: –0.86; $p < 0.001$), demonstrating a strong anti-inflammatory effect of synbiotics across trials. This finding is particularly important given TNF-α's central role in hepatic inflammation and fibrosis. Moreover, insulin resistance, assessed using the homeostatic model assessment for insulin resistance (HOMA-IR), showed a significant improvement (SMD: –0.28; 95% CI: –0.45 to –0.11), suggesting synbiotics contribute to better metabolic control, a critical factor in halting NAFLD progression. Together, these results strongly support the use of synbiotics as an effective adjunct therapy in the management of NAFLD. Figure 2 shows the forest plot summary of the effects of synbiotic supplementation on key clinical and biochemical markers in patients with NAFLD, including ALT, AST, cholesterol and LDL. Data are presented as SMD or mean differences with 95% confidence intervals. A random-effects model was applied due to moderate heterogeneity.

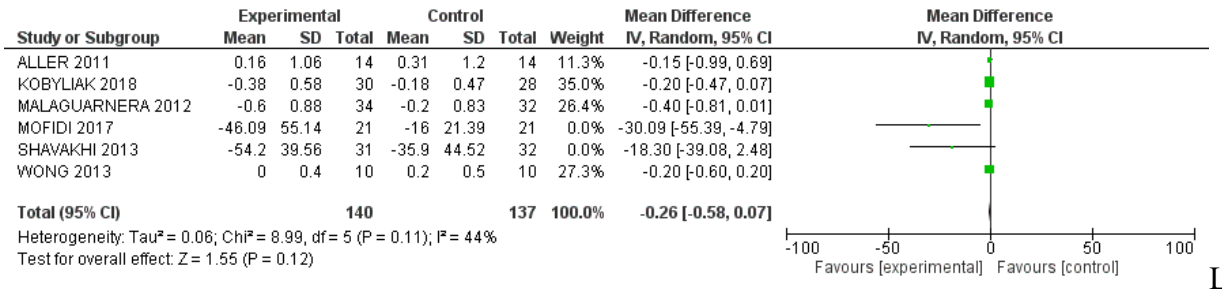
ALT



AST



TOTAL CHOLESTEROL



LDL

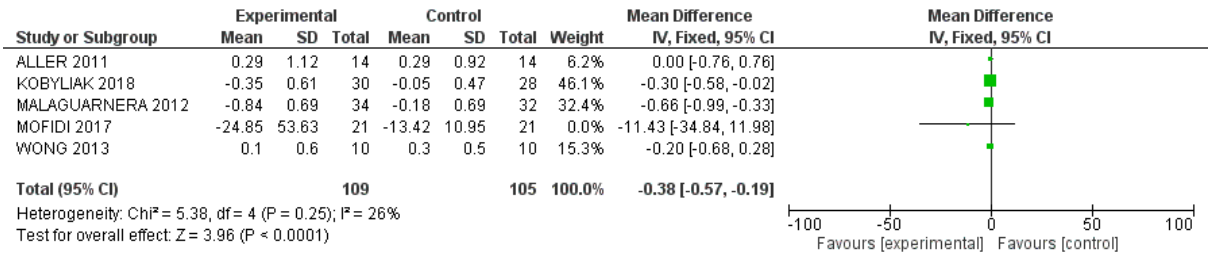


Fig 2: Synbiotic supplementation on key clinical and biochemical markers in patients with NAFLD, including ALT, AST, cholesterol and LDL.

Discussion

This meta-analysis shows that synbiotics significantly improve important clinical indicators in NAFLD patients, such as liver enzyme levels, lipid profiles, inflammatory markers, and insulin resistance. The consistent drop in ALT and AST levels across trials indicates that synbiotic supplementation has hepatoprotective effects, most likely due to reduced hepatic inflammation and enhanced metabolic function. These findings are consistent with previous research, such as those by Ma et al. (2013) [25] and Pan et al. (2024) [23], which found that modulating the gut microbiome using probiotics or synbiotics can considerably increase liver enzyme levels. The improvement in lipid profiles, particularly the considerable reduction in LDL cholesterol (-16.2 mg/dL), adds to synbiotics' metabolic advantages. These effects could be mediated by increased bile acid metabolism and short-chain fatty acid (SCFA) generation, both of which affect hepatic lipid synthesis and clearance. Synbiotics can improve lipid control by modulating microbial activity through FXR and PPAR-α pathways. This meta-analysis found a significant reduction in TNF-α, a pro-inflammatory cytokine linked to the progression of NAFLD to fibrosis and cirrhosis. Synbiotics may reduce inflammation by modulating gut-derived endotoxemia and suppressing TLR-mediated NF-κB activation, according to pooled data (SMD: -0.86). This anti-inflammatory response has been reported in previous trials, including those by Loguercio et al. (2005) [26] and Eslamparast et al. (2014) [14], and it supports the involvement of the gut-liver axis in NAFLD therapy. Furthermore, reduction in insulin resistance (SMD: -0.28) as evaluated by HOMA-IR suggests improved glucose metabolism, potentially due to the action of SCFAs and incretin hormones like GLP-1, which are controlled by gut microbiota composition. Insulin resistance is a key component of the metabolic syndrome and the major cause of hepatic steatosis, therefore even minor changes are clinically significant. While these results are encouraging, some limitations must be addressed. There was significant variety in synbiotic formulations, doses, and treatment durations across studies, which could explain the moderate heterogeneity observed in some results. The diagnosis procedures for NAFLD were also diverse (e.g., ultrasonography, biopsy, elastography), making direct comparisons difficult. The majority of trials had short follow-up periods, making it difficult to evaluate long-term outcomes such as fibrosis regression or cirrhosis prevention.

Despite these limitations, the findings strongly support using synbiotics as a low-risk, supplementary treatment for NAFLD. They provide a non-invasive, gut-focused approach to improving liver and metabolic health, particularly when combined with lifestyle changes. Future research should focus on standardizing synbiotic formulations and extending treatment durations to confirm long-term benefits and analyze histological changes. Personalized treatments based on baseline microbiome profiles could possibly improve therapeutic effects. Overall, existing data supports the use of synbiotics as part of a complete care approach for NAFLD patients.

Conclusion

This systematic review and meta-analysis demonstrates that synbiotic supplementation significantly improves liver enzymes, lipid profiles, inflammatory markers, and insulin resistance in patients with NAFLD. These findings highlight the therapeutic potential of synbiotics as an adjunct to conventional lifestyle and pharmacological interventions. By modulating the gut microbiota, enhancing intestinal

barrier integrity, and reducing systemic inflammation, synbiotics offer a promising, non-invasive approach to slowing or potentially reversing the progression of NAFLD. Future large-scale, long-term randomized controlled trials with standardized formulations are warranted to confirm these benefits and to explore their impact on liver histology and long-term clinical outcomes.

Conflict of interest

The authors declare no conflict of interest.

References

1. Pan Y, Yang Y, Wu J, Zhou H, Yang C. Efficacy of probiotics, prebiotics, and synbiotics on liver enzymes, lipid profiles, and inflammation in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. BMC gastroenterology. 2024 Aug 22;24(1):283.
2. Rong L, Ch'ng D, Jia P, Tsoi KK, Wong SH, Sung JJ. Use of probiotics, prebiotics, and synbiotics in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Journal of gastroenterology and hepatology. 2023 Oct;38(10):1682-94.
3. Liu L, Li P, Liu Y, Zhang Y. Efficacy of probiotics and synbiotics in patients with nonalcoholic fatty liver disease: a meta-analysis. Digestive diseases and sciences. 2019 Dec;64(12):3402-12.
4. Wang LL, Zhang PH, Yan HH. Functional foods and dietary supplements in the management of non-alcoholic fatty liver disease: A systematic review and meta-analysis. Frontiers in Nutrition. 2023 Feb 14;10:1014010.
5. Carpi RZ, Barbalho SM, Sloan KP, Laurindo LF, Gonzaga HF, Grippa PC, Zutin TL, Girio RJ, Repetti CS, Detregiachi CR, Bueno PC. The effects of probiotics, prebiotics and synbiotics in non-alcoholic fat liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review. International journal of molecular sciences. 2022 Aug 8;23(15):8805.
6. Ding S, Hong Q, Yao Y, Gu M, Cui J, Li W, Zhang J, Zhang C, Jiang J, Hu Y. Meta-analysis of randomized controlled trials of the effects of synbiotics, probiotics, or prebiotics in controlling glucose homeostasis in non-alcoholic fatty liver disease patients. Food & Function. 2024;15(19):9954-71.
7. Loman BR, Hernandez-Saavedra D, An R, Rector RS. Prebiotic and probiotic treatment of nonalcoholic fatty liver disease: a systematic review and meta-analysis. Nutrition reviews. 2018 Nov 1;76(11):822-39.
8. Wang X, Jin X, Li H, Zhang X, Chen X, Lu K, Chu C. Effects of various interventions on non-alcoholic fatty liver disease (NAFLD): A systematic review and network meta-analysis. Frontiers in Pharmacology. 2023 Mar 29;14:1180016.
9. Aller R, De Luis DA, Izaola O. Eur Rev Med Pharmacol Sci: Effect of a probiotic on liver aminotransferases in nonalcoholic fatty liver disease patients: a double blind randomized clinical trial. Alternative Medicine Review. 2011 Dec 1;16(4):369-70.
10. Vajro P, Mandato C, Licenziati MR, Franzese A, Vitale DF, Lenta S, Caropreso M, Vallone G, Meli R. Effects of Lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. Journal of pediatric gastroenterology and nutrition. 2011 Jun;52(6):740-3.
11. Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, Mastrojeni S, Malaguarnera G, Mistretta A, Li Volti G, Galvano F. Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. Digestive diseases and sciences. 2012 Feb;57(2):545-53.
12. Wong VW, Wong GL, Chim AM, Chu WC, Yeung DK, Li KC, Chan HL. Treatment of nonalcoholic steatohepatitis with probiotics. A proof-of-concept study. Annals of hepatology. 2013 Mar 1;12(2):256-62.
13. Shavakhi A, Minakari M, Firouzian H, Assali R, Hekmatdoost A, Ferns G. Effect of a probiotic and metformin on liver aminotransferases in non-alcoholic steatohepatitis: a double blind randomized clinical trial. International journal of preventive medicine. 2013 May;4(5):531.

14. Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. The American journal of clinical nutrition. 2014 Mar 1;99(3):535-42.
15. Mofidi F, Poustchi H, Yari Z, Nourinayyer B, Merat S, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. British Journal of Nutrition. 2017 Mar;117(5):662-8.
16. Kobyliak N, Abenavoli L, Mykhalchyshyn G, Kononenko L, Boccuto L, Kyriienko D, Dynnyk O. A multi-strain probiotic reduces the fatty liver index, cytokines and aminotransferase levels in NAFLD patients: evidence from a randomized clinical trial.
17. Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, Fujii H, Wu Y, Kam LY, Ji F, Li X. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. The lancet Gastroenterology & hepatology. 2019 May 1;4(5):389-98.
18. Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell. 2021 May 13;184(10):2537-64.
19. Scorletti E, Afolabi PR, Miles EA, Smith DE, Almehmadi A, Alshathry A, Childs CE, Del Fabbro S, Beavis J, Moyses HE, Clough GF. Investigation of synbiotic treatment in non-alcoholic fatty liver disease (INSYTE study): a double-blind, randomised, placebo-controlled, phase 2 trial. Gastroenterology. 2020 Jan 25;158(6):1597.
20. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. The Lancet. 2021 Jun 5;397(10290):2212-24.
21. Carpi RZ, Barbalho SM, Sloan KP, Laurindo LF, Gonzaga HF, Grippa PC, Zutin TL, Girio RJ, Repetti CS, Detregiachi CR, Bueno PC. The effects of probiotics, prebiotics and synbiotics in non-alcoholic fat liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH): a systematic review. International journal of molecular sciences. 2022 Aug 8;23(15):8805.
22. Rong L, Ch'ng D, Jia P, Tsoi KK, Wong SH, Sung JJ. Use of probiotics, prebiotics, and synbiotics in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Journal of gastroenterology and hepatology. 2023 Oct;38(10):1682-94.
23. Pan Y, Yang Y, Wu J, Zhou H, Yang C. Efficacy of probiotics, prebiotics, and synbiotics on liver enzymes, lipid profiles, and inflammation in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials. BMC gastroenterology. 2024 Aug 22;24(1):283.
24. Ding S, Hong Q, Yao Y, Gu M, Cui J, Li W, Zhang J, Zhang C, Jiang J, Hu Y. Meta-analysis of randomized controlled trials of the effects of synbiotics, probiotics, or prebiotics in controlling glucose homeostasis in non-alcoholic fatty liver disease patients. Food & Function. 2024;15(19):9954-71.
25. Ma YY, Li L, Yu CH, Shen Z, Chen LH, Li YM. Effects of probiotics on nonalcoholic fatty liver disease: a meta-analysis. World journal of gastroenterology: WJG. 2013 Oct 28;19(40):6911.
26. Loguercio C, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, Blanco CD. Beneficial effects of a probiotic VSL# 3 on parameters of liver dysfunction in chronic liver diseases. Journal of clinical gastroenterology. 2005 Jul 1;39(6):540-3.