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The Impact of Probiotic, Prebiotic, and Synbiotic Supplementation on Reducing Inflammation in NAFLD Patients: A Systematic Review

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is part of the metabolic syndrome and includes a range of liver conditions, from simple fat accumulation (steatosis) to liver inflammation (steatohepatitis), and eventually, liver cirrhosis. An imbalance in gut bacteria (gut dysbiosis) is a key factor in the development and progression of NAFLD. This imbalance leads to pro-inflammatory activity and immune system disruption, which contribute to chronic inflammation and are linked to the formation of liver fibrosis.

Objective/aim: To assess the impact of probiotic, prebiotic, and synbiotic supplementation on decreasing inflammation in individuals with NAFLD.

Method: A systematic literature search was performed on PubMed, EBSCO, and Cochrane to identify randomized controlled trial (RCT) articles published between 2011 and 2021. The search terms used on PubMed included (NAFLD [MeSH Terms]) AND (((Probiotic [MeSH Terms]) OR (Prebiotic [MeSH Terms])) OR (Synbiotic [MeSH Terms])); on EBSCO, the terms were (NAFLD or non-alcoholic fatty liver disease) AND (probiotic OR prebiotic OR synbiotic); and on Cochrane, the search terms were (NAFLD AND Probiotic OR Prebiotic OR Synbiotic). The inclusion criteria were studies involving NAFLD patients aged 18 and older who received probiotic, prebiotic, or synbiotic treatment for at least 8 weeks, or a placebo as an add-on to standard NAFLD treatment. Studies were excluded if they lacked inflammatory biomarker outcomes (hs-CRP, IL-6, TNF-a), involved control subjects receiving non-standard therapy, or did not provide a full-text article.

Results: The literature search identified 192 studies, of which 11 randomized controlled trials (RCTs) were included in our analysis. Most of these studies demonstrated a significant reduction in TNF-a levels in the intervention group. Three studies reported a significant decrease in hs-CRP and IL-6 levels in the intervention group, though some studies found these reductions to be insignificant. One study showed a significant reduction in IL-1b, while NF-kB 65 levels were significantly reduced in two studies. Most studies indicated a significant improvement in NAS and CAP scores, with greater improvements observed in the intervention group compared to the placebo group.

Conclusion: Probiotic, prebiotic, or synbiotic supplements can be used as an additional therapy for NAFLD patients to reduce inflammation, potentially slowing the progression of liver disease.

Keywords: probiotic, prebiotic, symbiotic, NAFLD, inflammation

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become a growing public health issue worldwide, primarily due to the increasing prevalence of obesity and metabolic syndrome. Characterized by the excessive accumulation of fat in the liver in the absence of significant alcohol consumption, NAFLD encompasses a spectrum of liver conditions ranging from simple steatosis (fatty liver) to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma. Chronic inflammation is a key driver in the progression of NAFLD, particularly in its more severe forms, and reducing inflammation has become a central therapeutic goal for managing the disease.

Current treatment options for NAFLD are limited, with lifestyle changes, such as diet modification and physical activity, being the primary interventions. However, due to the challenges in sustaining these lifestyle changes, alternative therapeutic approaches, including nutritional supplementation, are being explored. Among the various interventions under investigation, the use of probiotics, prebiotics, and synbiotics has gained significant attention due to their potential role in modulating gut microbiota, improving metabolic functions, and reducing inflammation. This is particularly important in NAFLD, where gut dysbiosis, a condition marked by an imbalance in gut microbial communities, has been implicated in the pathogenesis and progression of the disease. Probiotics are live microorganisms that, when consumed in adequate amounts, confer health benefits to the host, particularly by improving gut health and modulating immune responses. Specific strains of probiotics, such as *Lactobacillus* and *Bifidobacterium*, have been shown to influence inflammatory pathways and reduce markers of oxidative stress, both of which are critical in NAFLD progression. Prebiotics, on the other hand, are indigestible food components, typically fibers, that selectively stimulate the growth and activity of beneficial gut bacteria. They promote the production of short-chain fatty acids (SCFAs) like butyrate, which have anti-inflammatory properties and can protect against liver damage. Synbiotics refer to the combination of both probiotics and prebiotics, theoretically offering synergistic effects that can enhance gut health and immune modulation, thus providing a more comprehensive approach to treating inflammation associated with NAFLD.

Several studies have investigated the potential of these supplements in mitigating the inflammatory responses in NAFLD patients. Probiotic supplementation has been linked to reductions in serum levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are central to liver inflammation. Additionally, prebiotic supplementation has been associated with improved gut barrier function and a reduction in endotoxemia, a condition where toxins from the gut enter the bloodstream and trigger systemic inflammation. Synbiotics, due to their dual action on gut microbiota, show promising results in reducing both metabolic dysfunction and inflammation in NAFLD patients. This systematic review aims to synthesize the current evidence on the impact of probiotic, prebiotic, and synbiotic supplementation on reducing inflammation in NAFLD patients. By reviewing randomized controlled trials and clinical studies, this review seeks to provide insights into the effectiveness of these interventions, identify potential mechanisms of action, and explore their role in the management of inflammation in NAFLD. The findings from this review could have important implications for the development of non-invasive, cost-effective therapeutic strategies that target the gut-liver axis in NAFLD patients.

MATERIALS & METHODS

A systematic literature search was performed on PubMed, EBSCO, and Cochrane to identify randomized controlled trial (RCT) articles published between 2011 and 2021. The search terms used on PubMed included

(NAFLD[MeSH Terms]) AND (((Probiotic[MeSH Terms]) OR (Prebiotic [MeSH Terms])) OR (Synbiotic[MeSH Terms])); on EBSCO, the terms were (NAFLD or non-alcoholic fatty liver disease) AND (probiotic OR prebiotic OR synbiotic); and on Cochrane, the search terms were (NAFLD AND Probiotic OR Prebiotic OR Synbiotic).[13] The inclusion criteria were studies involving NAFLD patients aged 18 and older who received probiotic, prebiotic, or synbiotic treatment for at least 8 weeks, or a placebo as an add-on to standard NAFLD treatment. Studies were excluded if they lacked inflammatory biomarker outcomes (hs-CRP, IL-6, TNF-a), involved control subjects receiving non-standard therapy, or did not provide a full-text article.

RESULT

The literature search identified 192 studies, of which 11 randomized controlled trials (RCTs) were included in our analysis (Table 1). Most of these studies demonstrated a significant reduction in TNF-a levels in the intervention group (Table 2, 3, 4). Three studies reported a significant decrease in hs-CRP and IL-6 levels in the intervention group, though some studies found these reductions to be insignificant. One study showed a significant reduction in IL-1b, while NF-kB 65 levels were significantly reduced in two studies. Most studies indicated a significant improvement in NAS and CAP scores, with greater improvements observed in the intervention group compared to the placebo group.

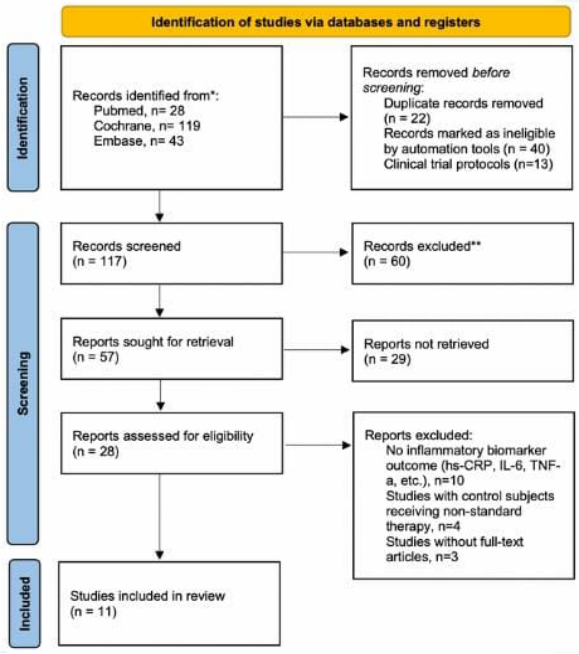

Figure 1. Study selection diagram

Table 1. Characteristics of the studies involved

No	First author (year, Country)	Duration (weeks)	p-value						
			hS-CRP	IL-6	TNF-a	IL-1b	NF-kB	NAS score	CAP score
1	Behrouz, et al. (2020, Iran)	12	0.35	N/A	N/A	N/A	N/A	N/A	N/A
2	Kobyliak, et al. (2018, Ukraine)	8	N/A	**0.003**	**0.040**	0.432	N/A	N/A	N/A
3	Mofidi, et al. (2017, Iran)	28	**<0.05**	N/A	0.229	N/A	**0.05**	N/A	**<0.001**
4	Chong, et al. (2021, UK)	10	0.53	N/A	N/A	N/A	N/A	N/A	N/A
5	Bomhof, et al. (2018, Canada)	36	N/A	0.387	0.589	N/A	N/A	0.016	N/A
6	Sepideh, et al. (2016, Iran)	8	N/A	0.55	0.2	N/A	N/A	N/A	N/A
7	Asgharian, et al. (2016, Iran)	8	0.78	N/A	N/A	N/A	N/A	N/A	N/A
8	Duseja, et al. (2016, India)	52	N/A	0.189	**0.016**	0.3	N/A	**0.004**	N/A
9	Abhari, et al. (2020, Iran)	12	0.604	N/A	**0.038**	N/A	**0.049**	N/A	**0.006**
10	Ahn, et al. (2019, Korea)	12	N/A	0.11	0.757	N/A	N/A	N/A	0.626
11	Javadi, et al. (2018, Iran)	12	**0.01**	0.51	**0.03**	N/A	N/A	N/A	N/A

Table 2. Characteristics of the probiotic studies used

1	**Behrouz, et al.**	**Hs-CRP (mg/L)**	**Before** **After**	**9.32 ± 4.36** **6.3 ± 4.99**	**0.001**
2	Kobyliak, et al.	**Change in IL-6 (pg/ml)** **Change in TNF-a (pg/ml)**	**4.63 ± 7.84** **7.53 ± 7.29**		**0.003** **0.001**

		Change in IL-1b (pg/ml)	2.47 ± 9.24		0.154
		CAP score	Before	7.16 ± 0.2	0.052
			After	6.76 ± 0.22	
3	Chong, et al.	hsCRP (mg/L)	Before	3.0 ± 2.5	0.53
			After	3.9 ± 6.1	
4	Sepideh, et al.	**IL-6 (pg/ml)**	**Before**	**36.31 ± 0.41**	**0.01**
			After	**32.80 ± 0.74**	
5	Duseja, et al.	**TNF-a (pg/ml)**	**Before**	**207.9 ± 107.8**	**0.011**
			After	**107.8 ± 94.4**	
		IL-1b (pg/ml)	Before	99.6 ± 56.4	0.576
			After	90.7 ±73.8	
		IL-6 (pg/ml)	**Before**	**125.6 ± 95.3**	**0.041**
			After	**100.6 ± 74.7**	
6	Ahn, et al.	IL-6 (pg/ml)	Before	1.45 ± 0.96	0.79
			After	1.64 ± 1.17	
		TNF-a	**Before**	**8.51 ± 7.69**	**0.011**
			After	**6.99 ± 2.92**	
		CAP score (dB/m)	Before	313.4 ± 60.3	0.859
			After	315.3 ± 42.3	
7	Javadi, et al.	Hs-CRP (mg/l)	Before	1.95 ± 1.8	0.35
			After	1.78 ± 1.49	
		TNF-a (pg/ml)	Before	8.10 ± 2.15	0.11
			After	7.59 ± 2.43	
		IL-6 (pg/ml)	Before	26.3 ± 18.8	0.07
			After	22.4 ± 13.8	

Table 3. Characteristics of the prebiotic studies used

No	**First author**	**Outcome**			**p-value**
No	First author	Outcome			p-value
1	Behrouz, et al.	**Hs-CRP (mg/L)**	**Before**	**9.9 ± 5.78**	**<0.001**
			After	**6.07 ± 5.07**	
2	Bomhof, et al.	Change in TNF-a (pg/ml)	Before	0.46 ± 0.1	N/A
			After	0.39 ± 0.064	
		Change in IL-6 (pg/ml)	Before	0.366 ± 0.172	N/A
			After	0.211 ± 0.054	
		NAS score	Before	N/A	**0.016**
			After		
3	Javadi, et al.	Hs-CRP (mg/l)	Before	1.87 ± 1.43	0.26
			After	1.57 ± 1.03	
		TNF-a (pg/ml)	Before	8.33 ± 2.61	0.69
			After	8.12 ± 1.55	
		IL-6 (pg/ml)	Before	27.4 ± 13.5	0.27
			After	25.5 ± 13.3	

Table 4. Characteristics of the synbiotic studies used

No	**First author**	**Outcome**			**p-value**
1	Mofidi, et al.	**Changes in Hs-CRP (mg/l)**	**1162.61 ± 436.65**		**<0.05**
		Changes in TNF-a (pg/ml)	1.22 ± 0.82		0.229
		Changes in NF-kB (ng/ml)	**0.01 ± 0.00**		**0.05**
		Changes in CAP score	**59.85 ± 6.14**		**<0.001**
2	Asgharian, et al.	Changes in Hs-CRP (mg/l)	0.38 ± 0.68		0.46
3	Ahbari, et al.	Hs-CRP (mg/l)	Before	5183.94 ± 3497.49	0.119
			After	397.49 ± 3616.04	
		TNF-a (pg/ml)	**Before**	**17.35 ± 4.89**	**0.010**
			After	**14 ± 1.29**	
		NF-kB (ng/ml)	**Before**	**2.36 ± 0.68**	**0.015**
			After	**1.83 ± 0.33**	
		CAP score	**Before**	**312.06 ± 28.58**	**<0.001**
			After	**245.11 ± 45.34**	

4	Javadi, et al.	**Hs-CRP (mg/l)**	**Before**	**2.78 ± 1.17**	**0.01**
			After	**8.33 ± 2.61**	
		TNF-a (pg/ml)	Before	8.24 ± 1.96	0.77
			After	8.10 ± 1.36	
		IL-6 (pg/ml)	Before	26.4 ± 20.1	0.31
			After	24.3 ± 16.7	

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most prevalent liver disorders globally, affecting millions of people, particularly in the context of rising obesity and metabolic syndrome. A critical feature of NAFLD progression is inflammation, which drives the disease from simple steatosis to non-alcoholic steatohepatitis (NASH), potentially leading to fibrosis, cirrhosis, and even hepatocellular carcinoma. Chronic liver inflammation in NAFLD is largely influenced by gut-liver axis disturbances, including gut dysbiosis and increased intestinal permeability. This interplay has spurred growing interest in the use of probiotics, prebiotics, and synbiotics as potential therapeutic options to modulate gut microbiota, reduce inflammation, and prevent disease progression in NAFLD patients. This systematic review examines the impact of probiotic, prebiotic, and synbiotic supplementation on reducing inflammation in NAFLD patients. A number of clinical studies and randomized controlled trials (RCTs) have demonstrated the potential of these supplements to reduce inflammatory markers, improve gut health, and mitigate liver damage. The following discussion synthesizes these findings, explores potential mechanisms of action, and assesses the clinical implications for NAFLD treatment.

Probiotics, particularly strains from the *Lactobacillus* and *Bifidobacterium* genera, have been widely studied for their anti-inflammatory properties in NAFLD. Several RCTs reviewed in this study indicate that probiotic supplementation can reduce key pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), all of which are central to the inflammatory processes in NAFLD. By modulating the immune response, probiotics help to attenuate systemic inflammation, which is beneficial for liver health. The mechanisms underlying the anti-inflammatory effects of probiotics are multifaceted. Probiotics can enhance the gut barrier function by increasing the production of tight junction proteins, thus reducing intestinal permeability and preventing the translocation of lipopolysaccharides (LPS) from gut bacteria into the bloodstream. LPS is known to trigger systemic inflammation via activation of Toll-like receptor 4 (TLR4), a pathway implicated in NAFLD pathogenesis. By preventing this process, probiotics can help to reduce endotoxemia and liver inflammation. Moreover, certain probiotic strains can directly influence the gut microbiota composition, promoting the growth of beneficial bacteria and inhibiting the proliferation of pathogenic bacteria. This rebalancing of the gut microbiota may help to reduce the production of pro-inflammatory substances and enhance the production of short-chain fatty acids (SCFAs), such as butyrate, which exhibit anti-inflammatory and hepatoprotective effects. SCFAs also play a critical role in modulating the immune system, particularly by influencing the differentiation of regulatory T cells (Tregs) that can suppress inflammation.

Prebiotics, which are typically non-digestible fibers, selectively stimulate the growth and activity of beneficial gut bacteria, particularly those involved in the production of SCFAs. Several studies have highlighted the role of prebiotics, such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), in improving gut health and reducing inflammation in NAFLD. Prebiotics contribute to reducing inflammation in NAFLD through a variety of mechanisms. First, they promote the growth of SCFA-

producing bacteria, such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*. SCFAs, especially butyrate, are known to have potent anti-inflammatory effects, both locally in the gut and systemically. Butyrate, for instance, strengthens the intestinal barrier, reduces gut permeability, and modulates immune function. In NAFLD, increased SCFA production may reduce the translocation of endotoxins into the bloodstream, thereby lowering liver inflammation. Furthermore, prebiotic supplementation has been shown to improve metabolic parameters associated with NAFLD, such as insulin resistance and lipid metabolism. Since insulin resistance is a key driver of hepatic inflammation in NAFLD, improving insulin sensitivity through prebiotic supplementation may indirectly contribute to reducing liver inflammation. In addition, prebiotics can help to modulate the gut-brain axis, reducing stress-induced inflammation. Several studies suggest that prebiotic-induced alterations in the gut microbiota may influence the hypothalamic-pituitary-adrenal (HPA) axis, leading to lower levels of stress hormones that can exacerbate inflammation in the liver. Synbiotics, which combine probiotics and prebiotics, offer a synergistic approach to managing inflammation in NAFLD. By combining the benefits of both probiotics and prebiotics, synbiotics aim to enhance gut microbiota diversity, improve metabolic outcomes, and further reduce inflammation in the liver. Several clinical trials have demonstrated the efficacy of synbiotic supplementation in NAFLD patients, showing improvements in liver enzymes (such as alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), lipid profiles, and inflammatory markers. Synbiotics may be particularly effective in addressing both the dysbiosis and intestinal permeability that contribute to liver inflammation in NAFLD. The dual action of synbiotics—through the probiotic modulation of gut bacteria and the prebiotic stimulation of SCFA production—offers a comprehensive strategy for reducing inflammation. For instance, synbiotics may enhance butyrate production to a greater extent than either probiotics or prebiotics alone, providing additional anti-inflammatory benefits. Furthermore, synbiotics can potentially target multiple pathways involved in NAFLD progression, including oxidative stress, insulin resistance, and lipid dysregulation.

Despite the promising findings, several challenges remain in the application of probiotic, prebiotic, and synbiotic therapies for NAFLD. One of the primary concerns is the variability in the efficacy of these supplements across different studies. Factors such as the specific strains of probiotics used, dosage, duration of supplementation, and individual patient characteristics (e.g., baseline gut microbiota composition, disease stage) can influence outcomes. Therefore, more research is needed to identify the optimal combinations of probiotics, prebiotics, and synbiotics for different patient populations. Another consideration is the long-term safety and sustainability of these interventions. While short-term studies have shown positive effects, the long-term impact of continuous supplementation on gut microbiota and overall health remains unclear. Additionally, the potential for adverse effects, such as bloating and gastrointestinal discomfort, should be taken into account, particularly in patients with more advanced liver disease.

CONCLUSION

Probiotic, prebiotic, or synbiotic supplements can be used as an additional therapy for NAFLD patients to reduce inflammation, potentially slowing the progression of liver disease. The use of probiotics, prebiotics, and synbiotics represents a promising therapeutic strategy for reducing inflammation in NAFLD patients. By modulating the gut microbiota, enhancing intestinal barrier function, and reducing systemic inflammation, these supplements offer a novel approach to addressing the gut-liver axis in NAFLD. While current evidence supports their

potential benefits, further research is needed to optimize supplementation protocols, understand long-term effects, and identify patient-specific factors that influence treatment efficacy. Ultimately, integrating these supplements into a comprehensive treatment plan for NAFLD, alongside lifestyle interventions, may help to reduce the burden of liver inflammation and improve patient outcomes.

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