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Review

A review of synbiotic efficacy in non-alcoholic fatty liver disease as a therapeutic approach

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ABSTRACT

According to recent epidemiological studies, non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the worldwide. Pathophysiological pathways and mechanisms involved in NAFLD are not fully clear, but Inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia are among the main causes of NAFLD. There is still no standard drug for the treatment of NAFLD. Diet modification, weight loss and physical activity are considered as the main treatment line for this disease. It has been shown that gut microbiota imbalance is associated with the main factors causing of NAFLD. Synbiotics, which have positive effects on the balance of gut microbiota, are a combination of prebiotics and probiotics. It is believed that the consumption of synbiotics can help to treatment of NAFLD through effect on gut microbiota and subsequently improving the risk factors of this disease. The purpose of this review is to investigate the effects of synbiotics on the main causes of NAFLD based on existing evidence, especially the clinical effects of synbiotics supplementation in patients with NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive accumulation of fat in the liver (more than 5% of the liver weight) of non-alcoholic individuals (alcohol consumption <10 g/d) [1]. Non-alcoholic fatty liver disease involves simple steatosis to non-alcoholic steatohepatitis (NASH) and ultimately can lead to fibrosis, cirrhosis and hepatocellular carcinoma [2]. Currently, the prevalence of NAFLD is ~25% in worldwide, which is rising rapidly [3]. The mechanisms involved in the pathogenesis of NAFLD are not fully clear; but inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia are the main risk factors for this disease [1,4–6]. Many studies have been conducted to treating NAFLD, but there is still no approved drug in this field [7]. Currently, diet modification, weight loss and physical activity are on the standard line of NAFLD treatment [8,9].

Several studies have shown that the gut microbiota status is associated with pathogenesis of NAFLD through mechanisms such as releasing lipopolysaccharide (LPS), increasing the production of ethanol, and activating inflammatory cytokines in the luminal epithelial cells as well as liver macrophages [10,11]. Also, it has been shown that change in the composition of gut microbiota (dysbiosis) is correlated with obesity, inflammation, and metabolic syndrome [12], and consequently dysbiosis can play an important role in liver diseases, including NAFLD (Fig. 1).

Prebiotics are indigestible carbohydrates that can have a positive effect on host health by changing the composition and activity of the gut microbiota [13]. Probiotics are also known as non-pathogenic living microorganisms, that in sufficient quantities, they can affect the host's health by modifying the gut microbiota [14]. Synbiotics are the combination of prebiotics and probiotics [15]. Accordingly, it was suggested that synbiotic with the effect on gut microbiota can facilitate the treatment of NAFLD by improving the main factors causing of this disease. Several randomized clinical trials (RCTs) were also conducted to investigate this issue (see Table 1). We decided to review the effects of synbiotic on the main causative factors of NAFLD based on existing evidence among NAFLD patients.

2. Effects of synbiotics on inflammation

Inflammation is one of the important factors that can contribute

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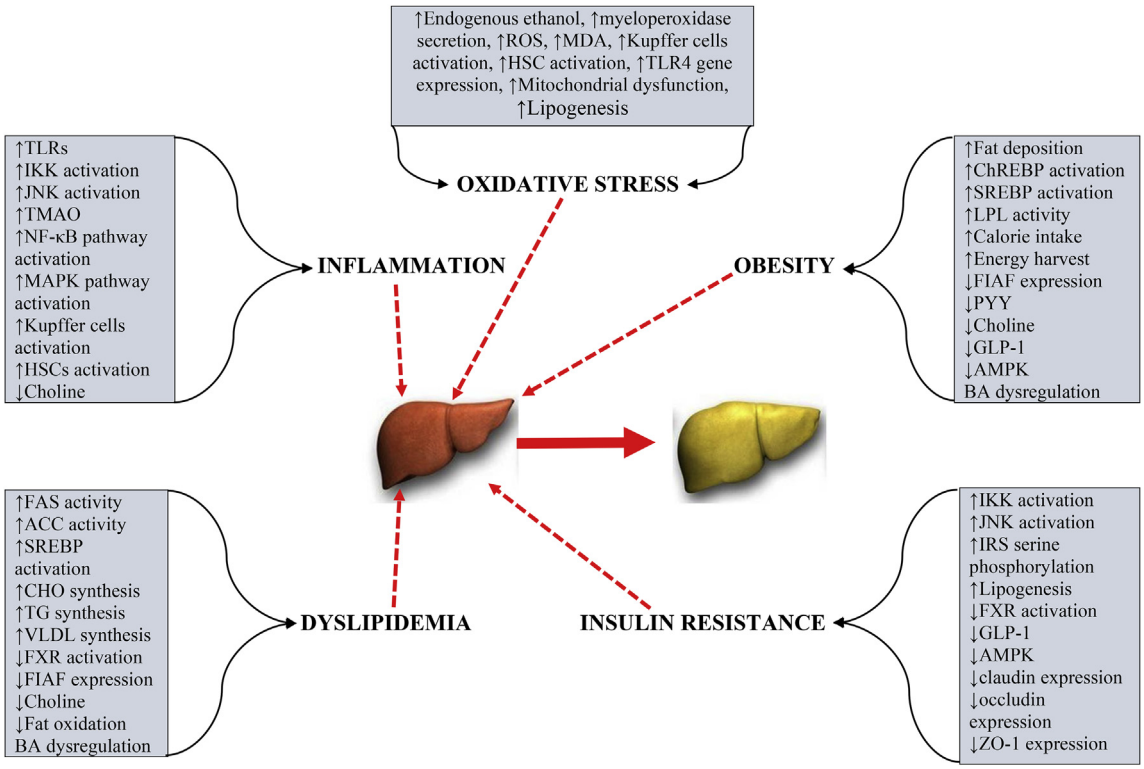

Fig. 1. Overview of the role of gut microbiota dysbiosis on NAFLD development. ChREBP: carbohydrate-responsive element-binding protein, SREBP: sterol regulatory element-binding protein, LPL: lipoprotein lipase, FIAF: fasting-induced adipocyte factor, SCFA: short-chain fatty acid, GLP-1: glucagon-like peptide-1, PYY: peptide YY, AMPK: adenosine monophosphate activated protein kinase, BA: bile acid, ROS: Reactive oxygen species, MDA: malondialdehyde, TLRs: toll-like receptors, IKK: IκB kinase, JNK: c-Jun-N-terminal kinases, TMAO: trimethylamine N-Oxide, MAPK: Mitogen-activated protein kinase, NF-κb: Nuclear factor-κb, HSCs: hepatic stellate cells, IRS: insulin receptor substrate, FXR: farnesoid X receptor, ZO-1: zonula occludens-1, FAS: fatty acid synthase, ACC: acetyl-coA carboxylase, CHO: cholesterol, TG: triglyceride, VLDL: Very low-density lipoprotein.

to the pathogenesis of NAFLD through mechanisms such as increasing the activation of the nuclear factor κ-B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, increasing the activity of kupffer cells and mitochondrial dysfunction [16]. Studies have shown that the severity of NAFLD is directly related to levels of inflammatory markers such as Tumor Necrosis Factor alpha (TNF-α) and C-reactive protein (CRP) [17,18]. Lipopolysaccharides (LPSs) derived from the extracellular membrane of intestinal Gram-negative bacteria, can induce a chronic inflammatory process and consequently lead to obesity and insulin resistance [19]. Also, lipopolysaccharides increase the release of pro-inflammatory cytokines [20]. It has been observed that change in the gut microbiota composition is associated with a change in the concentration of LPSs [19]. As a result, it seems logical that the use of synbiotic can change the gut microbiota, improves inflammation and subsequently reduces NAFLD severity. Several RCTs have evaluated the effects of synbiotic supplementation on inflammatory markers in NAFLD patients.

In the study of Eslamparast et al. [21] after 28 weeks, inflammatory markers including tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (Hs-CRP) and NF-κB p65 were significantly reduced in synbiotic group compared with placebo group. The relatively long duration of the study and evaluating NF-κB activity in peripheral blood mononuclear cell (PBMC) are important advantages of this RCT. In another study that conducted by Malaguarnera et al. [22] synbiotic group (*Bifidobacterium longum* with fructooligosaccharide (FOS) and lifestyle modification) versus the control group (placebo and lifestyle modification) showed significant differences in the TNF-α and CRP status after 24-week intervention. In the study of Mofidi et al. [23] after 28-week intervention, CRP and NF-κB reduced significantly in synbiotic group compared to placebo group; however, there was no significant difference between two groups in the TNF-α level. Some strengths of this study are the relatively long duration of the study, evaluating NF-κB activity in PBMC. In the study that conducted by Asgharian et al. [24] synbiotic supplementation did not significantly improve CRP levels. Intervention duration of this study is much shorter (8 weeks) than other RCTs mentioned and this can because of differences. Also, the results of other RCTs in this field [25,26] confirm the improvement of inflammation markers after synbiotic supplementation. As a result, there is strong evidence that synbiotics are beneficial for attenuating inflammation among NAFLD patients.

3. Effects of synbiotics on insulin resistance

Although the mechanisms of NAFLD pathogenesis are not fully clear, insulin resistance seems to play a pivotal role in this regard [27,28]. In the "two-hit" theory of NAFLD pathogenesis, insulin resistance is considered as part of the "first-hit" [5]. Also, the effectiveness of insulin resistance in the pathogenesis of NAFLD occurs through mechanisms such as increased activation of sterol regulatory element-bindings (SREBPs) and carbohydrate-responsive element-binding protein (ChREBP) as well as increased lipogenesis [16]. Studies have shown that insulin sensitivity decreases in the level of muscle, adipose tissue and liver in the NAFLD patients [29–31]. Dysbiosis through several mechanisms, in particular effect on insulin resistance, can influence in the pathogenesis of NAFLD and in this issue it has been shown that LPS levels are directly related to insulin resistance [19,32,33]. As a

Table 1
Randomized controlled trials that evaluated the effect of synbiotic on NAFLD patients.

Reference	Population	Study design	Duration	Outcomes related to our study	findings
Eslamparast et al. [21]	52	Intervention group: 2 synbiotic capsules (Protexin) that contained 200 million CFU of 7 strains (Lactobacillus casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacteriu breve, L. acidophilus, B. longum, and L. bulgaricus) and prebiotic (fructooligosaccharide) and probiotic cultures (magnesium stearate [source: mineral and vegetable] vegetable capsule [hydroxypropyl methyl cellulose]) (n = 26) Control group: placebo (n = 26)	28 week	Hs-CRP, TNF-α, NF-κB, HOMA-IR, BMI, WHR	Hs-CRP(↓), TNF-α(↓), NF-κB (↓), HOMA-IR(↓), BMI(−), WHR(−)
Malaguarnera et al. [22]	63	Intervention group: Bifidobacterium longum and fructooligosaccharide (Zirfos, Alfa Wassermann) + lifestyle modification (n = 34) Control group: Placebo + lifestyle modification (n = 29)	24 week	Hs-CRP, TNF-α, HOMA-IR, LDL, TC, TG, HDL	Hs-CRP(↓), TNF-α(↓), HOMA-IR(↓), LDL(↓), TC(−), TG(−), HDL(−)
Mofidi et al. [23]	50	Intervention group: Daily 2 synbiotic capsule that each capsule (Protexin; Probiotics International Ltd) contained 200 million bacteria of seven strains (Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum and Lactobacillus bulgaricus) and prebiotic (125 mg fructo-oligosaccharide) and probiotic cultures (magnesium stearate (source: mineral and vegetable) and a vegetable capsule (hydroxypropylmethyl cellulose)) (n = 25) Control group: Placebo (n = 25)	28 week	Hs-CRP, TNF-α, NF-κB, HOMA-IR, QUICKI, TC, TG, LDL, HDL	Hs-CRP(↓), TNF-α(−), NF-κB(↓), HOMA-IR(↓), QUICKI(↑), TC(−), TG(↓), LDL(−), HDL(−)
Asgharian et al. [24]	74	Intervention group: 500-mg synbiotic capsule (Familact containing 7 species of probiotic bacteria (L. casei, L. acidophilus, L. rhamnosus, L. bulgaricus, B. breve, B. longum, S. thermophilus) and fructooligosaccharides, (n = 38) Control group: placebo (n = 36)	8 week	Hs-CRP, BMI, Weight	Hs-CRP(−), BMI(−), Weight(↓)
Javadi et al. [25]	75	Intervention group1: probiotic (B.L and L.A: 2×10^7 CFU/day) + placebo (n = 20) Intervention group2: inulin + placebo (n = 19) Intervention group3: probiotic (B.L and L.A: 2×10^7 CFU/day) + inulin (n = 17) Control group: Placebo + placebo (n = 19)	3 month	Hs-CRP, TNF-α, IL-6, TAC, MDA, WHR, FM, FFM, BMI, WC, Weight	Hs-CRP(↓), TNF-α(↓), IL-6(−), TAC(↑), MDA(−), WHR(−), FM(−), FFM(−), BMI(↓), WC(↓), Weight(↓)
Bakhshimoghaddam et al. [26]	102	Intervention group 1: 300 g synbiotic yogurt (starter cultures of Streptococcus thermophilus and Lactobacillus delbrueckii subsp. Bulgaricus +10^8 CFUs Bifidobacterium animalis subsp. lactis (BB-12)/mL as a probiotic and 1.5 g inulin as a prebiotic) (n = 34) Intervention group 2: 300 g conventional yogurt (starter cultures of Streptococcus thermophilus and Lactobacillus delbrueckii subsp. Bulgaricus) (n = 34) Control group: Placebo (n = 34)	24 week	CTRP-5, HOMA-IR, QUICKI, TAC, TOS, TC, TG, LDL, HDL	CTRP-5(↑), HOMA-IR(↓), QUICKI(↑), TAC(↑), TOS(↓), TC(↓), TG(↓), LDL(↓), HDL(−)
ekhlasi et al. [44]	60	Intervention group 1: 2 synbiotic capsules/d (Protexin Probiotics International Ltd.) that contained L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. longum, L. bulgaricus (2 _ 10^8 CFU/g per capsule) and fructooligosaccharide + placebo (n = 15) Intervention group 2: alpha tocopherol + placebo (n = 15) Intervention group 3: synbiotic + alpha tocopherol (n = 15) Control group: Placebo + placebo (n = 15)	8 week	TNF-α, NO, BMI, WC, Weight	TNF-α(↓), NO(−), BMI(−), WC(−), Weight(−)
Sayari et al. [50]	138	Intervention group: sitagliptin (50 mg daily) + synbiotic (Each synbiotic capsule (Familakt) contained 10^9 colony forming unit (CFU) of 7 strains of friendly bacteria (Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Streptococcus thermophilus) and prebiotic (fructooligosaccharide) and probiotic cultures (magnesium stearate [source: mineral and vegetable] vegetable capsule [hydroxypropyl methylcellulose]))(n = 70) Control group: sitagliptin (50 mg daily) + Placebo (n = 68)	16 week	BMI, Weight, TC, LDL, TG, HDL	BMI(−), Weight(−), TC(↓), LDL(↓), TG(−), HDL(−)
Ferolla et al. [51]	50	Intervention group 1: Lactobacillus reuteri with guar gum and inulin and healthy balanced nutritional counseling (n = 27) Control group: nutritional counseling alone (n = 23)	3 month	BMI, WC, Weight, TC, TG, LDL, HDL, VLDL,	BMI(↓), WC(↓), Weight(↓), TC(−), TG(−), LDL(−), HDL(−), VLDL(−)

NAFLD: Non-Alcoholic Fatty Liver Disease, TNF-α: Tumor Necrosis Factor alpha, Hs-CRP: High-sensitivity C-reactive protein, NF- κB: nuclear factor κ-B, IL-6: interleukin-6, CTRP-5: C1q/TNF-related protein 5, TAC: Total Antioxidant Capacity, NO: Nitric Oxide, TOS: Total Oxidant Status. MDA: Malondialdehyde, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, QUICKI: Quantitative Insulin Sensitivity Check Index, BMI: Body Mass Index, WC: Waist Circumference, WHR: Waist-Hip Ratio, FM: Fat Mass, FFM: Fat Free Mass, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, VLDL: Very Low-Density Lipoprotein, TG: Triglyceride, TC: Total Cholesterol, (↓): Significant Decrease, (↑): Significant Increase, (−): no significant difference.

result, it seems by focusing on the balance of gut microbiota and the use of synbiotics can help to improve NAFLD. In some RCTs, the effect of synbiotic supplementation on insulin resistance among NAFLD patients has been evaluated.

In the study of Malaguarnera et al. [22] after 24-week intervention, synbiotic group (*Bifidobacterium longum* with FOS and lifestyle modification) compared with placebo group (placebo and lifestyle modification) showed a significant reduce in HOMA-IR. In another study that conducted by Bakhshimoghaddam et al. [26] at the end of 24-week treatment period, the synbiotic group showed significantly greater decreases in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and a significantly greater increase in Quantitative Insulin Sensitivity Check Index (QUICKI) compared with control group; However, HOMA-IR and QUICKI differences between synbiotic and conventional groups were not significant. Patients in this study were divided into three groups including synbiotic group (300 g synbiotic yogurt), conventional group (300 g conventional yogurt) and control group. Also, in the study of Eslamparast et al. [21] after 28-week treatment, HOMA-IR reduced significantly in the synbiotic group compared with placebo group. Nonetheless, after 28-week intervention, there was no significant difference in HOMA-IR and QUICKI between synbiotic and placebo groups in the study of Mofidi et al. [23] It should be noted that most of these RCTs used fasting values for glucose and insulin to assess IR, while euglycemic clamp technique or intravenous glucose tolerance testing could measure insulin sensitivity more accurately [34]. In general, there are promising results in this regard, but the improvement of insulin resistance through synbiotic supplementation in NAFLD patients can't be fully confirmed. The need for further studies is felt.

4. Effects of synbiotics on oxidative stress

Non-alcoholic fatty liver disease is a multi-cause disease, and oxidative stress plays an important role in the pathogenesis of this disease [35,36]. According to the “two-hit” theory of NAFLD pathogenesis, oxidative stress is known as the “second-hit” [5]. Oxidative stress through mechanisms such as increasing reactive oxygen species (ROS), lipid peroxidation, activation of kupffer cells and mitochondrial dysfunction contributes in the pathogenesis of NAFLD [16]. Levels of ROS and lipid peroxidation products in NAFLD patients are increased compared with healthy people [37]. Also, it has been shown that levels of lipid peroxidation products have a direct correlate with the severity of NAFLD [38–40]. Endogenous ethanol and its derived compounds (acetaldehyde and acetate) produce in gut microbiota and increase production of ROS by kupffer cells and hepatic stellate cells (HSCs) [41,42]. Also, ROS along with LPSs increase the gene expression of Toll-like receptor 4 (TLR4) [43]. It seems that use the synbiotics through changing the gut microbiota, decreased the production of ROS and lipid peroxidation products and subsequently help to improve the NAFLD by attenuating the pathogenic mechanisms of oxidative stress. The effect of Synbiotic on oxidative stress status in NAFLD patients has been investigated in some RCTs.

In the study of Bakhshimoghaddam et al. [26] that had three groups (synbiotic, conventional and control groups), after 24 weeks, total oxidant status (TOS) reduced significantly and total antioxidant capacity (TAC) significantly increased in the synbiotic group compared with control group. In this study, the differences between the synbiotic and conventional groups were significant only in the case of serum TOS, and there were no differences between synbiotic and conventional groups in serum TAC. The important advantage of this RCT was evaluating the effects of synbiotic in the form of food. In the study of Javadi et al. [25] probiotic and probiotic + prebiotic groups compared with prebiotic and placebo groups, showed significantly greater increases in serum TAC; however, the mean of malondialdehyde (MDA) were not significantly different among four groups including three intervention (probiotic, prebiotic and probiotic + prebiotic groups) and one control groups after 3 months. Short intervention duration of this RCT compared with most other RCTs in this field can considered as limitation. Also, in the study that conducted by Ekhlasi et al. [44] No significant differences were observed in nitric oxide (NO) status between synbiotic and placebo groups. Patients in this study were divided into four groups including synbiotic, alpha-tocopherol, synbiotic + alpha-tocopherol and placebo groups. Short follow-up duration of this RCT is an important limitation. There are contradictory results in this regard. In order to better conclusion, further studies are needed with well-controlled methods.

5. Effects of synbiotics on obesity

The high prevalence of NAFLD in obese people indicates the importance of considering obesity as one of the most important factors associated with this disease [45]. Obesity seems to play an important role in the onset of the development of steatosis and in the progression to NASH [46]. Obesity is also a main contributor to the progression of insulin resistance and inflammation that affects the pathogenesis of NAFLD [6]. Early studies showed that gut microbiota can affect caloric intake, intestinal absorption and energy balance [47,48]. Also, specific microbial species are associated with a decrease or increase in weight, and it was found that the higher proportions of Bacteroidetes species relative to Firmicutes species was associated with a leaner status [48,49]. Considering the ability of synbiotics to change the gut microbiota, the idea that synbiotic, by weight reduction, improves NAFLD, seems logical. Some RCTs examined the effect of synbiotic supplementation on obesity in NAFLD patients.

In the study of Eslamparast et al. [21] after 28 weeks, body mass index (BMI) and waist-hip ratio (WHR) were decreased in synbiotic and placebo groups; however, no significant differences were observed between the two groups. In another study, after 16 weeks, Sayari et al. [50] observed that weight and BMI decreased in two groups including sitagliptin + synbiotic and sitagliptin + placebo, but the differences between these groups were not significant. In the study of Javadi et al. [25] at the end of study, no significant differences in some anthropometric indices such as WHR, fat mass (FM) and fat free mass (FFM) between groups was observed; however waist circumference (WC), BMI and weight significantly reduced in intervention groups (probiotic, prebiotic and probiotic + prebiotic groups) compared with control group. It should be noted that after the end of this study, BMI, WC and weight were not significantly different among the intervention groups. In the study of Ferolla et al. [51] after the three-month synbiotic supplementation, the study group also presented a reduction of the anthropometric parameters such as BMI, WC and body weight; but these anthropometric parameters remained relatively unchanged in control group. In another study that conducted by Ekhlasi et al. [44] after synbiotic supplementation for 8 weeks, no significant differences were observed between synbiotic and control groups in indices such as BMI, WC, and weight. Also, in the study of Asgharian et al. [24] after 8 weeks, there was no significant change in BMI in both study groups, but weight significantly reduces in synbiotic group compared with placebo group. More results from these RCTs are not consistent with results of primary studies that suggest positive effects of synbiotics on the improvement of obesity.

6. Effects of synbiotics on dyslipidemia

Intrahepatic lipid accumulation along with insulin resistance is known as the "first-hit" in the "two-hit" theory of NAFLD pathogenesis [5]. Lipid metabolism abnormalities such as increased lipolysis, Liver free fatty acid (FFA) uptake and very-low density lipoprotein (VLDL) synthesis as well as reduced FFA oxidation and Triglyceride (TG) export, leads to intrahepatic lipid accumulation [52,53]. Also, these changes in lipid metabolism contribute to the pathogenesis of NAFLD by increasing adipokines production, inflammation and oxidative stress [54–57]. Several studies have shown the association between gut microbiota and lipid profile levels (As indicators of lipid metabolism) [58–61]. As a result, it is logical that the use of synbiotics can improve NAFLD by improving lipid profile status and correcting lipid metabolism. The effect of synbiotic supplementation on lipid profile among NAFLD patients in some RCTs was investigated.

In the study of Ferolla et al. [51] after 3 months, no significant changes were observed in any of the lipid profile indicators, such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and very low-density lipoprotein cholesterol (VLDL-c) in the synbiotic group. In another study that conducted by Malaguarnera et al. [22] after the end of 24-week treatment period, there was no significant difference between synbiotic group (*Bifidobacterium longum* with FOS and lifestyle modification) and placebo group (placebo and lifestyle modification) in HDL-c, TG and TC levels, but there was a significant difference in LDL-c in synbiotic group versus placebo group. Also in the study of Mofidi et al. [23] after 28 weeks, differences in TC, LDL-c and HDL-c levels between two groups were not significant, and the differences between two groups were significant only in the case of TG. In this RCT, the effect of synbiotic evaluated among lean patients with NAFLD. In the study of Bakhshimoghaddam et al. [26] after 28 weeks, the synbiotic group showed a significantly greater decrease in TC, TG and LDL-c serum levels compared with control group; however, in this study, only TC and TG levels, decreased significantly in the synbiotic group (300 g synbiotic yogurt) compared with the conventional group (300 g conventional yogurt). Also in the study of Sayari et al. [50] after the end of 16-week treatment period, cholesterol and LDL levels significantly reduced in sitagliptin + synbiotic group compared with sitagliptin + placebo; but, there was no significant difference between both groups in HDL and TG levels. Given the contradictory results in this regard, further studies are needed in order to correct conclusion.

7. Conclusion

Recent evidence suggests the benefit effects of using prebiotics and probiotics on inflammation, insulin resistance and metabolic syndrome. Based on this, it seems reasonable to assume that synbiotics can improve the main causes of NAFLD. The present review focuses on the clinical effects of using synbiotics to improve the causes of NAFLD. Evidence suggests that receiving synbiotic can improve inflammation among NAFLD patients. Also, it seems the use of synbiotic lead to improve insulin resistance, although further studies with more accurate measurement methods are needed. Concerning oxidative stress and dyslipidemia, the results are inconsistent and further studies, in order to correct conclusions is required. But, in the context of obesity, more studies, especially RCTs with longer intervention period have shown that Synbiotic can't lead to significant improve in anthropometric indices among NAFLD patients. This is in contradiction with previous studies that believed that gut microbiota modification is an important factor in weight loss. Of course, this adverse result may be due to the inappropriate method design of some RCTs, low sample size, diversity, and doses of synbiotic.

For the design of future RCTs, it is better to consider higher accuracy methods for measurement of parameters, prebiotic dietary intake, higher sample sizes, gut microbiota evaluation and using effective dose of synbiotic.

Based on this review, also it is expected that the use of synbiotic improve NAFLD severity. In order to better conclusion about NAFLD and synbiotic, it is necessary to review the results of studies that have evaluated the effect of synbiotic consumption on NAFLD status indicators such as liver enzymes and NAFLD severity.

Conflicts of interest

We have no conflicts of interest to disclose.

References

[1] Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American association for the study of liver diseases, American college of gastroenterology, and the American gastroenterological association. Hepatology 2012;55(6):2005–23.

[2] Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006;43(2 Suppl 1):S99–112.

[3] Araújo AR, Rosso N, Bedogni G, Tiribelli C, Bellentani S. Global epidemiology of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis: what we need in the future. Liver Int. 2018;38(Suppl 1):47–51.

[4] McCullough A, Hoofnagle JH, Sanyal AJ, Lavine JE, Brunt EM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362(18):1675–85.

[5] Day CP, James OFW. Steatohepatitis: a tale of two "Hits"? Gastroenterology 1998;114(4):842–5.

[6] Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the dionysos nutrition and liver study. Hepatology 2005;42(1):44–52.

[7] Tomasiewicz K, Flisiak R, Halota W, Jaroszewicz J, Lebensztejn D, Lisik W, et al. Recommendations for the management of non-alcoholic fatty liver disease (NAFLD). Clin Exp Hepatol. 2018;4(3):153–7.

[8] Zelber-Sagi S, Godos J, Salomone F. Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials. Ther. Adv. Gastroenterol. 2016;9(3):392–407.

[9] Geier A, Rau M. Emerging therapies for NASH - the future is now. Expert Rev Clin Pharmacol. 2017;10(5):467–9.

[10] Miele L, Valenza V, La Torre G, Montalto M, Cammarota G, Ricci R, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. Hepatology 2009;49(6):1877–87.

[11] Gratz SW, Mykkanen H, El-Nezami HS. Probiotics and gut health: a special focus on liver diseases. World J Gastroenterol. 2010;16(4):403–10.

[12] Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016;8(1):42.

[13] Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, et al. Prebiotic effects: metabolic and health benefits. Br J Nutr. 2010;104(Suppl 2):S1–63.

[14] Rijkers GT, de Vos WM, Brummer R-J, Morelli L, Corthier G, Marteau P. Health benefits and health claims of probiotics: bridging science and marketing. Br J Nutr. 2011;106(9):1291–6.

[15] Parnell JA, Raman M, Rioux KP, Reimer RA. The potential role of prebiotic fibre for treatment and management of non-alcoholic fatty liver disease and associated obesity and insulin resistance. Liver Int. 2012;32(5):701–11.

[16] Sangouni AA, Ghavamzadeh S, Jamalzehi A. A narrative review on effects of vitamin D on main risk factors and severity of Non-Alcoholic Fatty Liver Disease. Diabetes Metab. Syndrome Clin. Res. Rev. 2019;13(3):2260–5.

[17] Manco M, Marcellini M, Giannone G, Nobili V. Correlation of serum TNF-α levels and histologic liver injury scores in pediatric nonalcoholic fatty liver disease. Am J Clin Pathol. 2007;127(6):954–60.

[18] Abiru S, Migita K, Maeda Y, Daikoku M, Ito M, Ohata K, et al. Serum cytokine and soluble cytokine receptor levels in patients with non-alcoholic steatohepatitis. Liver Int. 2006;26(1):39–45.

[19] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56(7):1761–72.

[20] Medzhitov R, Horng T. Transcriptional control of the inflammatory response. Nat Rev. Immunol. 2009;9(10):692–703.

[21] 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. Am J Clin Nutr. 2014;99(3):535–42.

[22] Malaguarnera M, Vacante M, Antic T, Giordano M, Chisari G, Acquaviva R, et al. Bifidobacterium longum with fructo-oligosaccharides in patients with non alcoholic steatohepatitis. Dig Dis Sci. 2012;57(2):545–53.
[23] Mofidi F, Poustchi H, Yari Z, Nourinayyer B, Merat S, Sharafkhah M, et al. Synbiotic supplementation in lean patients with non-alcoholic fatty liver disease: a pilot, randomised, double-blind, placebo-controlled, clinical trial. Br J Nutr. 2017;117(5):662–8.
[24] Asgharian A, Askari G, Esmailzade A, Feizi A, Mohammadi V. The effect of symbiotic supplementation on liver enzymes, c-reactive protein and ultrasound findings in patients with non-alcoholic fatty liver disease: a clinical trial. Int J Prev Med. 2016;7:59.
[25] Javadi L, Khoshbaten M, Safaiyan A, Ghavami M, Abbasi MM, Gargari BP. Pro- and prebiotic effects on oxidative stress and inflammatory markers in non-alcoholic fatty liver disease. Asia Pac J Clin Nutr. 2018;27(5):1031–9.
[26] Bakhshimoghaddam F, Shateri K, Sina M, Hashemian M, Alizadeh M. Daily consumption of synbiotic yogurt decreases liver steatosis in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. J Nutr. 2018;148(8):1276–84.
[27] Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology 2002;35(2):367–72.
[28] Farrell GC. Signalling links in the liver: knitting SOCS with fat and inflammation. J Hepatol. 2005;43(1):193–6.
[29] Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia 2005;48(4):634–42.
[30] Lomonaco R, Ortiz-Lopez C, Orsak B, Webb A, Hardies J, Darland C, et al. Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease. Hepatology 2012;55(5):1389–97.
[31] Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y, Berria R, et al. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology 2007;133(2):496–506.
[32] Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. Mol Asp Med. 2013;34(1):39–58.
[33] He X, Ji G, Jia W, Li H. Gut microbiota and nonalcoholic fatty liver disease: insights on mechanism and application of metabolomics. Int J Mol Sci. 2016;17(3):300.
[34] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol Metab. 1979;237(3):E214–23.
[35] Ashraf NU, Sheikh TA. Endoplasmic reticulum stress and Oxidative stress in the pathogenesis of Non-alcoholic fatty liver disease. Free Radic Res. 2015;49(12):1405–18.
[36] Albano E, Mottaran E, Occhino G, Reale E, Vidali M. Review article: role of oxidative stress in the progression of non-alcoholic steatosis. Aliment Pharmacol Ther. 2005;22(Suppl 2):71–3.
[37] Videla LA1, Rodrigo R, Orellana M, Fernandez V, Tapia G, Quiñones L, et al. Oxidative stress-related parameters in the liver of non-alcoholic fatty liver disease patients. Clin Sci. 2004;106(3):261–8.
[38] Zein CO, Lopez R, Fu X, Kirwan JP, Yerian LM, McCullough AJ, et al. Pentoxifylline decreases oxidized lipid products in nonalcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. Hepatology 2012;56(4):1291–9.
[39] Rolo AP, Teodoro JS, Palmeira CM. Role of oxidative stress in the pathogenesis of nonalcoholic steatohepatitis. Free Radic Biol Med. 2012;52(1):59–69.
[40] Matsuzawa N, Takamura T, Kurita S, Misu H, Ota T, Ando H, et al. Lipid-induced oxidative stress causes steatohepatitis in mice fed an atherogenic diet. Hepatology 2007;46(5):1392–403.
[41] Setshedi M, Wands JR, De La Monte SM. Acetaldehyde adducts in alcoholic liver disease. Oxidative Med. Cell. Longev. 2010;3(3):178–85.
[42] Su GL. Lipopolysaccharides in liver injury: molecular mechanisms of Kupffer cell activation. Am J Physiol Liver Physiol. 2002;283(2):G256–65.
[43] Gustot T, Lemmers A, Moreno C, Nagy N, Quertinmont E, Nicaise C, et al. Differential liver sensitization to toll-like receptor pathways in mice with alcoholic fatty liver. Hepatology 2006;43(5):989–1000.
[44] Ekhlasi G, Zarrati M, Agah S, Hosseini AF, Hosseini S, Shidfar S, et al. Effects of symbiotic and vitamin E supplementation on blood pressure, nitric oxide and inflammatory factors in non-alcoholic fatty liver disease. EXCLI J. 2017;16:278–90.
[45] Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, et al. Prevalence of and risk factors for hepatic steatosis in northern Italy. Ann Intern Med. 2000;132(2):112–7.
[46] Polyzos SA, Kountouras J, Mantzoros CS. Adipose tissue, obesity and non-alcoholic fatty liver disease. Minerva Endocrinol. 2017;42(2):92–108.
[47] Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr. 2011;94(1):58–65.
[48] Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006;444(7122):1027–31.
[49] Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. A core gut microbiome in obese and lean twins. Nature 2009;457(7228):480–4.
[50] Sayari S, Neishaboori H, Jameshorani M. Combined effects of synbiotic and sitagliptin versus sitagliptin alone in patients with nonalcoholic fatty liver disease. Clin Mol Hepatol. 2018;24(3):331–8.
[51] Ferolla SM, Couto CA, Costa-Silva L, Armiliato GNA, Pereira CAS, Martins FS, et al. Beneficial effect of synbiotic supplementation on hepatic steatosis and anthropometric parameters, but not on gut permeability in a population with nonalcoholic steatohepatitis. Nutrients 2016;8(7):397.
[52] Ress C, Kaser S. Mechanisms of intrahepatic triglyceride accumulation. World J Gastroenterol. 2016;22(4):1664–73.
[53] Almeda-Valdes P, Altamirano-Barrera A, Méndez-Sánchez N. Insights in non-alcoholic fatty liver disease pathophysiology with lipidomic analyses. Ann Hepatol. 2015;14(4):567–9.
[54] Polyzos SA, Kountouras J, Mantzoros CS. Adipokines in nonalcoholic fatty liver disease. Metab Clin Exp. 2016;65(8):1062–79.
[55] Polyzos SA, Aronis KN, Kountouras J, Raptis DD, Vasiloglou MF, Mantzoros CS. Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Diabetologia 2016;59(1):30–43.
[56] Zeng L, Tang WJ, Yin JJ, Zhou BJ. Signal transductions and nonalcoholic fatty liver: a mini-review. Int J Clin Exp Med. 2014;7(7):1624–31.
[57] Bekaert M, Verhelst X, Geerts A, Lapauw B, Calders P. Association of recently described adipokines with liver histology in biopsy-proven non-alcoholic fatty liver disease: a systematic review. Obes Rev. 2016;17(1):68–80.
[58] Fu J, Bonder MJ, Cenit MC, Tigchelaar EF, Maatman A, Dekens JAM, et al. The gut microbiome contributes to a substantial proportion of the variation in blood lipids. Circ Res. 2015;117(9):817–24.
[59] Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500(7464):541–6.
[60] Velagapudi VR, Hezaveh R, Reigstad CS, Gopalacharyulu P, Yetukuri L, Islam S, et al. The gut microbiota modulates host energy and lipid metabolism in mice. J Lipid Res. 2010;51(5):1101–12.
[61] Rabot S, Membrez M, Bruneau A, Gérard P, Harach T, Moser M, et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. FASEB J. 2010;24(12):4948–59.