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Review Article

Synbiotic Efficacy as Therapeutic Approach in Human Disease: A Review

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ABSTRACT

In combatting the increase in healthcare costs, at present, one of the preventive approaches to medicine has been developed with the upliftment of new synbiotic products. Synbiotic is the synergistic effect of probiotics and prebiotics which exert multiple beneficial effects and have been increasingly used in preventing or treating human diseases since the last ten years. Several trials have reported that synbiotic therapy could help in the treatment of human disease prevention. PubMed, Science Direct, and Google Scholar were searched by keywords 'prebiotic', 'probiotic', and 'synbiotic' for relevant literature from 2000 to 2020. A total of 58 articles were selected and revised. This paper evaluates the effect of synbiotic supplementation on different diseases, for instance, obesity, insulin resistance syndrome, diabetes, and non-alcoholic fatty liver disease. The progressive knowledge on the outcome of synbiotic supplementation on health, recent trends and developments in this field are summarised. However, further research is required to understand the mechanism of how synbiotics affect in different diseases.

Keywords: Diabetes, obesity, prebiotic, probiotic, synbiotic

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INTRODUCTION

Synbiotic supplementation has significant effects in gut environment and human immunity system compared with the consumption of probiotic or prebiotic alone (Frece et al., 2009). Considerable evidence indicated the important function of synbiotics in human metabolic regulation

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(Tajabadi-Ebrahimi et al., 2017). The modulation can be performed through the oral administration of good bacteria, such as *Lactobacillus* and *Bifidobacterium*, which are commonly known as probiotics. The appropriate intake of prebiotics, which are mainly indigestible oligosaccharides, results in a positive improvement in the formation of gut microbiota including unique functional properties (Tajabadi-Ebrahimi et al., 2017). Synbiotics mainly consist of probiotics and prebiotics with synergistic effects only. Synbiotics have diverse forms and are consumed as ingredients of yogurt or fermented milk, cheese, synbiotic juice and bread (Singh et al., 2011). By altering the gut microbiota probiotics and prebiotics, type 2 diabetes mellitus (T2DM) and cardiovascular diseases may be affected through the regulation of insulin signalling pathway and decrease the cholesterol level as well (Yoo & Kim, 2016). According to Ipar et al. (2015), the serum total cholesterol and total oxidative stress levels are significantly reduced after a synbiotic intervention in a study group.

An altered gut microbiota is linked with hypertension, which leads to the development of chronic kidney disease (CKD) (Yang et al., 2018). The intestinal microbes can be deliberated as best suitable candidate for the treatment and prevention of several diseases, such as weight loss regimens and weight management (Heiss, 2018). Moreover, human gut microbes are linked with various health conditions including respiratory tract infections (RTIs) via the gut–lung axis. Studies have reported that synbiotic therapy could help prevent RTIs (Chan et al., 2020). The findings of random clinical intervention trials using synbiotic supplementation in obesity, insulin resistance syndrome (IRS), T2DM, and non-alcoholic fatty liver disease (NAFLD) have been summarized in Table 1. Diet containing high protein and less carbohydrate is often efficiently followed during weight loss program but has been linked with the decrement of beneficial bacteria inside the body (Russell et al., 2011). These diets induce protein fermentation with metabolic by-product formation by the gut microbiota and can trigger inflammation in the colon (Yao et al., 2016). The synbiotic dietary intervention aims to correct the breakdown of upset gut microbiota found in obese people and improve health conditions by facilitating the weight reduction process (Anhê et al., 2015; Martinez et al., 2017). The structure of gut microbiota can influence the environmental factors and cause intrahepatic fat accumulation (Çakır et al., 2017). Consequently, the modulated interaction between liver and microbes has become the principle objective in the maintenance of NAFLD (Quigley, 2015). The incident of bacterial overgrowth in small intestinal can alter intestinal integrity and play a significant role in the pathogenesis of NAFLD. This situation can be regulated by modulating synbiotic content on the human diet (dos Santos et al., 2019; Mehal, 2013). A graphical representation of synbiotic effect on obesity, NAFLD, IRS and T2DM is reflected in Figure 1 (Sáez-Lara et al., 2016).

Table 1
Summarized information of random clinical trial intervention of synbiotics in obesity, insulin resistance syndrome, type 2 diabetes mellitus, and non-alcoholic fatty liver disease

Subjects	Dose/Strain/Prebiotics	Time	Outcomes	References
		Obesity		
153 men and women with obesity	*Lactobacillus rhamnosus* CGMCC1.3724, 6×10^8 CFU, with inulin	36 weeks	Reduces leptin and increase in Lachnospiraceae	Sanchez et al. (2014)
High BMI containing 73 children and adolescents	*Lactobacillus casei*, *L. rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *B. longum*, *Lactobacillus bulgaricus*, containing FOS	8 weeks	Reduction in BMI z-score and waist circumference	Sáez-Lara et al. (2016)
77 overweight children	*Lactobacillus acidophilus*, *L. rhamnosus*, *Bifidobacterium bifidum*, *B. longum*, *Enterococcus faecium*, including FOS	4 weeks	Alteration of anthropometric measurements, reduction in TC, LDL-C, and serum level of oxidative stress	Ipar et al. (2015)
		Insulin resistance syndrome		
IRS (38 subjects)	*Lactobacillus casei*, *L. rhamnosus*, *S. thermophilus*, *B. breve*, *L. acidophilus*, *B. longum, L. bulgaricus*, with FOS	28 weeks	Fasting blood sugar level and insulin resistance level improved remarkably	Sáez-Lara et al. (2016)
		Type 2 diabetes		
54 T2DM patients Age- 35 to 70 years	*Lactobacillus acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. longum*, *B. breve*, *S. thermophilus*, 10^9 CFU, including 100 mg FOS	8 weeks	Improved TGL plasma level, HOMA-IR, and decreased CRP in serum level	Sáez-Lara et al. (2016)
81 patients (T2DM)	*Lactobacillus sporogenes*, 1×10^8 CFU with 0.07 g inulin in per gram	8 weeks	Remarkable reduction of serum insulin level, HOMA-IR, and assessment of homeostatic model β-cell function	Tajadadi-Ebrahimi et al. (2014)
78 T2DM patients	*Lactobacillus sporogenes*, 1×10^8 CFU including 0.07 g inulin in per gram	8 weeks	Serum lipid profile reduction especially TAG, TC/HDL-C with a significant increase in HDL-C serum level	Tajadadi-Ebrahimi et al. (2014)
20 T2DM patients	*Lactobacillus acidophilus* 10^8 CFU/mL, *B. bifidum* 10^8 CFU/mL, and oligofructose (2g)	2 weeks	Raised HDL-C level with decreasing fasting glycemia	Moroti et al. (2012)

Table 1 *(continue)*

Subjects	Dose/Strain/Prebiotics	Time	Outcomes	References
		Non-alcoholic fatty liver disease		
20 study patients with NASH	*Lactobacillus plantarum*, *Lactobacillus delbrueckii* spp., *L. bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *B. bifidum*, and inulin	26 weeks	Reduction in intrahepatic triacylglycerol content (IHTG)	Sáez-Lara et al. (2016)
NAFLD individuals (52 adults)	*Lactobacillus casei*, *S. thermophilus*, *B. breve*, *L. rhamnosus*, *L. acidophilus*, *B. longum*, *L. bulgaricus*, with FOS	30 weeks	Prohibition of NF-$_{k}$B and decreased TNF-α	Eslamparast et al. (2014a)

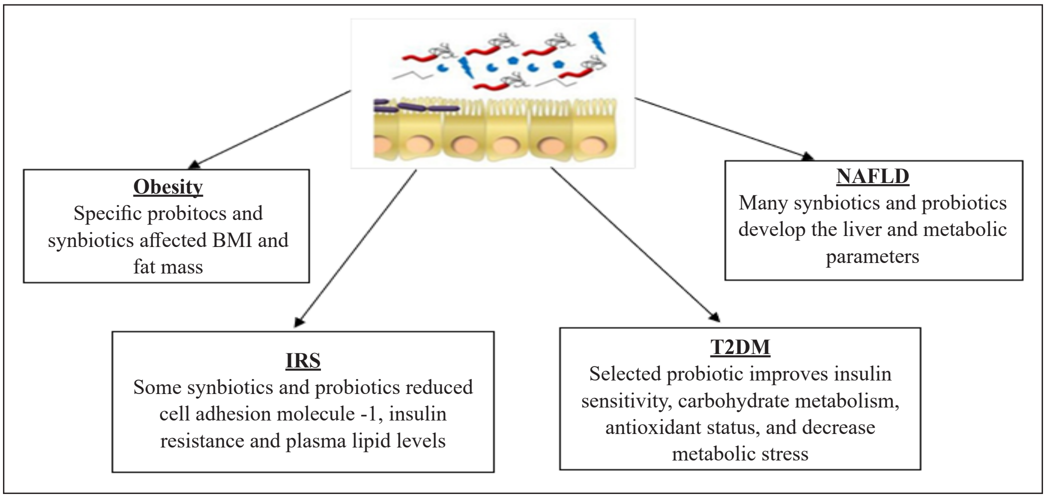

Figure 1. Graphical representation of synbiotic effect in obesity, insulin resistance syndrome, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (Sáez-Lara et al., 2016)

EFFECTS OF SYNBIOTICS ON OBESITY

The intestinal microbiota affects energy balance in the human body and *Eubacteria rectale*, *Lactobacillus*, *Blautia coccoides*, and *Bifidobacterium* bacteria are associated with obesity (Sáez-Lara et al., 2016). The developed gut manipulating field can be valuable to the promotion of therapeutic strategies for managing obese problem and related metabolic diseases. Synbiotic supplementation can result in the proper balance in the gut microbiota and thus have advantageous effects, such as fat storage reduction, peptide secretion, glucose and insulin metabolism development, inflammatory biomarker, and body weight reduction (Rabiei, 2019). Enteroendocrine cells (EEC) in the gastrointestinal tract regulate gut motility and peptide hormone secretion to control food consumption and insulin production (Covasa et al., 2019).

Gut microbiota produces active signaling molecules like short-chain fatty acids (SCFAs) by the fermentation process of dietary fibers. The interaction between gut microbes and G protein-coupled receptors (GPCRs) affects insulin sensitivity and regulate energy metabolism. Transient changes in the gut ecosystem disrupt the host physiology and increase the risk of developing metabolic disorders including low-grade inflammation (Boulangé et al., 2016). The effect of supplementation with *Lactobacillus rhamnosus* (CGMCC1.3724), oligofructose, and inulin was investigated in obese men and women subjected to a 24-week weight loss program (Sanchez et al., 2014). The results showed that *L. rhamnosus* could induce weight loss in women with a remarkable decrease in fat mass and the abundance of bacteria (Lachnospiraceae) in the faeces from Firmicutes phylum family, a taxonomic group that is related to obesity. In brief, supplementation with selected synbiotics can reduce body mass index (BMI), body fat percentage, and serum leptin levels in women with a growing level of Lachnospiraceae family in their faeces. In children, treatment with synbiotics shows the reduction of BMI z-score, waist circumference (WC), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and triacylglycerol (TAG) serum levels (Sáez-Lara et al., 2016). Results observed from another study in obese children showed a dramatic reduction in BMI score, WC, and the risk factors of the cardiometabolic conditions such as TC, LDL-C, and TAG, after the intake of synbiotics (Zarrati et al., 2014). Furthermore, a protein-rich, less carbohydrate and restricted-energy diet can be efficiently utilized to reduce the excess weight of an obese person (Noakes et al., 2005). In the large intestine, microbial breakdown of proteins is considered as the principle reason for generating genotoxic and cancer related metabolites, such as N-nitroso compounds and ammonia (Hinai et al., 2019). Evidence from the previous study revealed that the synbiotic food could alter the microbial composition and exerts beneficial effects on weight loss and maintenance (Ferrarese et al., 2018). A 3-month intervention using synbiotic supplementation with four strains of *Bifidobacterium* and *Lactobacillus acidophilus* and galactooligosaccharides significantly increased the abundance of the probiotic group in intestinal *Bifidobacterium* (Sergeev et al., 2020). In this study, significant modulation of the intestinal microbiota with a decrease in *Prevotella* and *Gardnerella* genera were observed after having this intervention.

EFFECTS OF SYNBIOTICS ON INSULIN RESISTANCE SYNDROME, TYPE 2 DIABETES MELLITUS AND CORONARY HEART DISEASES

Insulin Resistance Syndrome

There are an increasing number of people with IRS, in which individuals are suffering from hypertension, obesity, glucose intolerance, and dyslipidemia. Synbiotic supplementation can decrease plasma fasting insulin and triglyceride concentrations (Asemi et al., 2014). However, IRS can increase the overall morbidity and mortality rate of cardiovascular diseases (Hong et al., 2014). Visceral adipose tissues increase free fatty acid flux due to low insulin sensitivity, inhibit the activity of insulin-sensitive tissues, and can be allied with the development of diabetes mellitus (Sáez-Lara et al., 2016). Synbiotic capsules containing fructooligosaccharide (FOS) with preselected strains significantly alleviate the insulin resistance and improve the fasting blood sugar level of patients with IRS (Eslamparast et al., 2014b). In another study, IRS patients were treated with synbiotic capsules consisting of seven strains and fructooligosaccharide with placebo capsules for the investigation of lipid profile and insulin resistance (Sáez-Lara et al., 2016). The results exhibited a significant improvement of the fasting blood sugar and insulin level in synbiotic group compared to control group (Eslamparast et al., 2014b). Probiotics decrease cell adhesion molecule-1 levels; for instance, *Lactobacillus plantarum* reduces TC, glucose and homocysteine levels in postmenopausal women (Plaza-Diaz et al., 2019). Prebiotic and probiotic mixtures alleviate insulin resistance and high-density lipoprotein (HDL) and decrease the TAG and TC levels in individuals with IRS (Sáez-Lara et al., 2016).

Type 2 Diabetes Mellitus

The salutary effects of synbiotic on metabolic activity were reported beforehand in patients with NAFLD, gestational diabetes mellitus, T2DM, and non-obese T2DM (Farrokhian et al., 2019). Evidence from a new study suggested that the structure of gut microbes is associated with T2DM development (Han & Lin, 2014). A translucent relationship was found between T2DM and compositional alteration in patients with T2DM, whose intestinal microbiotas had a decreased amount of Firmicutes and high amounts of Bacteroidetes and Proteobacteria (Sáez-Lara et al., 2016). The outcome of synbiotic bread consumption contributes to decrease insulin level, serum lipid profile (TAG, TC/HDL), homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment cell function, and to rise high-density lipoprotein cholesterol (HDL-C) level comparing to control bread consumption (Sáez-Lara et al., 2016; Tajadadi-Ebrahimi et al., 2014). The administration of probiotic mixture shows significant improvement in their lipid profile, decreasing total cholesterol (TC), LDL-C level, and increasing insulin sensitivity (Sáez-Lara et al., 2016). Lastly, a diet (for 24 weeks) containing *Bifidobacterium longum* with fructooligosaccharides results in a significant reduction in HOMA-IR in people with non-alcoholic steatohepatitis (Malaguarnera et al, 2012).

Coronary Heart Diseases

The outbreak of T2DM has significantly increased world-wide; in addition, the risk for coronary heart diseases (CHDs) has increased twofold (Farrag et al., 2013). Differences in intestinal microflora of diabetic and non-diabetic patients and between lean and obese subjects are significant with respect to composition and function (Larsen et al., 2010; Turnbaugh et al., 2009). In patients with T2DM, impaired insulin metabolism can influence individuals with CHD and dyslipidemia (Gaede et al., 2003). Consequently, parameters for glucose homeostasis and lipid profile control can successfully reduce the morbidity and mortality rate of T2DM and CHD patients (Chillarón et al., 2014). The supplementation of synbiotic capsule for 84 days showed significant upshot on diabetic patients with CHD, particularly on their serum insulin and HDL-cholesterol levels (Tajabadi-Ebrahimi et al., 2017). Synbiotic consumption can promote insulin function by providing beneficial effects on hepatic insulin signalling and decreasing the phosphorylation of insulin receptor (substrate-1) and inflammatory cytokine production (Raso et al., 2014). Through the assembly of good bacteria in the intestinal microbiota, synbiotics can suppress the growth of Gram-negative bacteria in the inner lining of the intestinal tract and decrease the disposal of pathogens in the bloodstream by maintaining the unity of the mucosal barrier (Kellow et al., 2014). A study was conducted on patients with T2DM but without previous histories of CHD. After consuming the food full of *Lactobacillus sporogenes* and inulin for six weeks, the patients showed not much difference in lipid profile but showed difference in serum triglyceride level (Asemi et al., 2014). Following the food consumption consisting *L. sporogenes* (1×10 colony-forming-unit (CFU) with inulin 0.04g in per gram for nine weeks, a pregnant woman in good health expressed a drastic reduction in serum triglyceride and low-density lipoprotein cholesterol level (Taghizadeh et al., 2014). In another study synbiotic food containing *L. sporogenes* (27×10^7 CFU) with inulin (1.1g) for 42 days intervention in diabetic patients showed a promising decrease in the serum level (Asemi et al., 2014). However, new therapeutical strategies by modulating the gut microbiota can be a useful invention to reduce the vulnerability of CHD (DiRienz, 2014).

EFFECTS OF SYNBIOTICS IN NON-ALCOHOLIC FATTY LIVER DISEASE

NAFLD is a state when an excess amount of fat accumulated in the liver and correlated to obesity (Vajro et al., 2012). Results from synbiotic cases showed lower fat production in the liver and tumour necrosis factor (TNF) to restrain NAFLD development (Sáez-Lara et al., 2016). A clinical trial on study patients expressed that those consumed synbiotic yogurts for twenty-four weeks have improved the lipid profile, glycaemic variables, liver enzyme, oxidative stress, gut peptide concentrations, steatosis, and adipokine concentrations. However, no significant changes observed in insulin and HDL cholesterol levels (Bakhshimoghaddam et al., 2018). This study was conducted on synbiotic supplementation that included seven probiotic strains and fructooligosaccharide for 28 weeks. This intervention was performed on adult patients with NAFLD, who subsequently showed lifestyle modification that is superior to that of the non-synbiotic group (Eslamparast et al., 2014a). Synbiotic supplementation can control inflammatory markers and reduce BMI and waist circumference. This effect was observed after 14 weeks of treatment and was maintained till the treatment was completed. In another study, steatosis in rats that received synbiotic supplementation was alleviated (dos Santos et al., 2019). An experimental study model of hypercholesterolemia involving prebiotic and probiotic supplementations showed significant changes in the gene expression of toll-like receptor 4 (TLR-4), nuclear factor kappa B (NF-$_k$B) and tumour necrosis factor α (TNF-α) (Gurry, 2017). Prebiotic and synbiotic supplementations can increase TLR-4 and NF-$_k$B levels. TNF-α raised only in those rats treated with prebiotics; moreover, the potential immunomodulatory function of prebiotics also found on monocytes and T cells (Capitán-Cañadas et al., 2014). A 4-month synbiotic intervention involving a change in lifestyle patterns decreased nearly two-third of sonographic grade in children with fatty liver disease (Çakır et al., 2017). This study also observed that fatty liver condition was alleviated after an increase in LDL level in synbiotic-supplemented children (Hernandez-Rodas et al., 2015). High LDL level is the risk factor of cardiovascular disease in NAFLD patients and reduction in LDL level after synbiotic supplementation mitigates the complications for fatty liver and cardiovascular diseases (Katsiki et al., 2016).

EFFECTS OF SYNBIOTICS IN RESPIRATORY TRACT INFECTIONS

According to World Health Organization (WHO) (2018), RTIs have various clinical symptoms, including the normal flu, rhinitis, nasopharyngitis, bronchitis, inflammation of the epiglottis, laryngitis, inflammation of the trachea and bronchi, pneumonia, upper, and lower RTIs. Apart from providing the synergistic effects of probiotics and prebiotics in immunity system, synbiotics may be essential to nutritional strategies for managing global problems associated with respiratory infections and abuse of antibiotics on RTIs (Markowiak, 2017). Synbiotic intervention decreases the outbreak and ratio of RTI cases by 16% (Chan et al., 2020). Moreover, their potential beneficial effects against this disease may be imposed to their anti-inflammatory function that was discovered in gastrointestinal diseases (Gurry, 2017).

EFFECTS OF SYNBIOTICS IN CHRONIC KIDNEY DISEASE

CKD is advanced and irretrievable damage of the kidney function, which requires dialysis or kidney transplant after developing to the last stage (Kocełak et al., 2012). The study shows that a synbiotic supplement of 500 mg two times a day for 42 days could lessen the level of urea nitrogen in blood of stage 3 or 4 CKD patients (Dehghani et al., 2016). CKD changes the formation and function of intestinal microbiota and illustrates a dysbiotic state with hostile consequences (Yang et al., 2018). Toxic solutes, such as trimethylamine-N-oxide, ρ-cresol sulphate (PCS), and indoxyl sulphate (IS) reduce the micronutrients that help to mitigate systemic inflammation, CKD development, and complications of cardiovascular disease (Niwa, 2011; Vaziri, 2016). The findings of the study expose that synbiotic therapy considerably decreases serum PCS and IS levels in study patients who have not received antibiotics (Nakabayashi et al., 2011).

CONCLUSION

The present review focuses on the synbiotic efficacy as a therapeutic approach in the treatment of diseases such as obesity, IRS, T2DM, and NAFLD. Recent findings have noted that synbiotic consumption along with changing lifestyle may help in patients with NAFLD and promote serum lipid levels in T2DM patients. Scientific evidence from other studies showed a dramatic reduction in abdominal adiposity, IRS, and BMI in patients with obesity who undergone synbiotic interventions. Moreover, the availability of beneficial bacteria for modulating gut microbes demonstrates a tremendous contribution in mitigating the risk factors of chronic disease. This study provides an opportunity to design advanced dietary intervention with synbiotic supplementation as a new therapeutic approach to treat diseases such as metabolic syndrome, NAFLD, diabetes, CKD, obesity, and many more. Without a doubt, further research is required to analyse the superlative dose-response effect, follow up experiment, and long-term intervention effects of synbiotics for the betterment of human life.

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