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Future Impact of Probiotic Therapy of Metabolic Disorder

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Abstract

Probiotics are live bacteria that of beneficial properties with other intestinal flora in maintaining digestive system and body health. There is a great association between obesity, intestinal inflammation and the development of diabetes, non-alcohol fatty liver disease and neurodegenerative disorder like Alzheimer disease. Yogurt is the principal sort of probiotic microorganism such as *Lactobacilli* and Bifid bacteria, the principal elements of producing bioactive nutrient compound important for maintaining intestinal homeostasis, impairing inflammation and glucose and fatty acid metabolism. It plays a great role in the metabolism of the body and decreasing the incidence of the development of metabolic diseases.

Keywords: Probiotic; Inflammation, Nonalcoholic fatty liver disease, Diabetes, Obesity, Neurodegenerative disorder

Probiotic definition and sources

Different terms of pro-, pre-, post-, dys-and synbiotics are known. Probiotics are live bacteria that of beneficial properties with other intestinal flora in maintaining health of digestive system. They are present in food stuffs such as yogurt, while prebiotics are found in whole grains, bananas, onions, garlic, honey and artichokes. Prebiotics are carbohydrates byproduct not digested in the human body and are of very important for nutrition of the living probiotics. These are indigestible food ingredients that promote the activity of probiotics in the gastrointestinal tract [1]. They include fructo-oligasaccharides, inulin, galactooligosaccharides, isomaltooligosaccharides, lactosucrose, glucooligosaccharides, sugar alcohols, and polysaccharides (e.g. resistant and modified starches) that are fermented in the caecum and colon by commensalism intestinal bacteria [2]. Postbiotics are biological active byproducts of dietary fibers including acetate, butyrate, and propionate, which categorized in short-chain fatty acids [3]. Dysbiotics means the decrease of useful bacteria and the increase of harmful bacteria. It contains both probiotics and prebiotics including oligofructose and probiotic bifid bacteria [4].

Dairy and fermented products are a good source of probiotics [5]. Milk fermentation has a past history in different regions of Mongolia or Africa [6]. Cheese contains moderate amounts of probiotic microorganisms *L. plantarum* strains have been determined in Italian, Argentinean and Bulgarian cheeses [7-9].

At birth, there is a detected sterile gastrointestinal tract and their microbiota is gradually increased after time via the contact of the breast with the external environment [10]. During infancy, the intestinal microbiota is composed of *bifidobacteria* and enterobacteria [11]. The anatomical structures of the small and large intestine exhibited variations in the intensity of mucous secreted by the goblet cells which act as bacterial insulator [12]. The human gastrointestinal tract possesses approximately 10^4 microorganisms/ml of luminal content, and over 5000 bacterial species. Most of the bacterial species, belong to the *bacteroidetes phyla*, composed mainly of Gram negative bacteria, and the *Firmicutes phyla*, composed mainly of Gram positive bacteria and attained about 90% [13,14].

Probiotics represent the main diet of mediterranean and middle eastern including fermented milk and vegetable products such as yogurt and pickles. Recently probiotic organisms as natural pharmaceutical agents are used in the treatment and prevention of disease and promoting longevity [15].

The gastrointestinal biota represents a good source of energy for the gut wall and immune stimulators throughout life [16,17]. It is also contributed to energy homeostasis, prevents mucosal infections and maintenance of an intact GI barrier [18] (Figure 1). The yogurt keep intestinal barrier function via maintaining localization of occludin and zona occludens protein 1 (ZO-1) at tight junctions of differentiated Caco-2 cells [19-20].

Probiotic and inflammation

Inflammation can occur when the pathogenic bacteria weaken the barrier function of the mucosa and infiltrated into the body and causes inflammation [21] (Barengolts et al. 2016). Probiotics is of great importance to the intestinal wall, promoting its permeability, bacterial translocation, endotoxemia and maintain the liver function from oxidative stress and inflammation [22-24] (Figure 1). Following

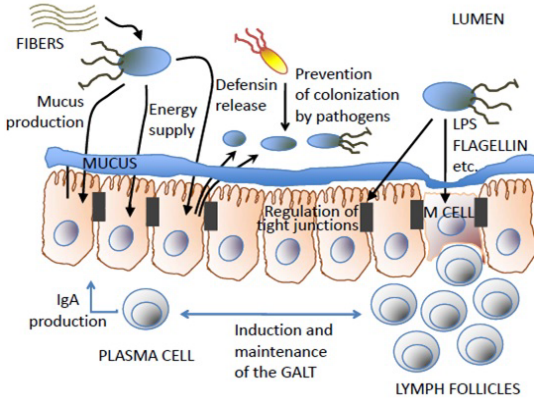

Figure 1: Intestinal microbiome promoting the gastrointestinal barrier via regulating mucus production in goblet cells, defensin release from Paneth cells, tight junction protein synthesis in normal epithelial cells and inhibit colonization of pathogens.

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DNA-based studies, *Lactobacillus* and *Bifidobacterium* are the main organisms of probiotics and yogurts are better sources such as bacterial species *L delbrueckii* subsp. *Bulgaricus* and *Streptococcus thermophilus* and *Bifidobacterium* [25]. *Bifidobacteria* comprises the main group of probiotic organisms. They are the main dietary supplements in Japan, which give promising health impacts on the colon [26]. They increased HDL cholesterol and decreasing total and LDL cholesterol levels in humans and animals [27]. Also, *bifidobacteria* supplementation suppressed inflammatory cytokine release, decreasing the inflammation that contributes to cardiovascular [28]. *Lactobacillus* and *Bifidobacterium* genera are the abundant bacterial flora used as food adjuvants [29,30]. Prebiotics are complex carbohydrates (i.e., dietary fiber) which exerts a neutral effect on body weight, decreased fasting and postprandial glucose, and improved insulin sensitivity and lipid profile. Some inflammation markers were reduced, reaching to 20-30% [21].

Administration of *Bifidobacterium lactis* BB-12 (B. lactis) and *Lactobacillus acidophilus* LA-5 (*L. acidophilus*) to patients with ulcerative colitis significantly increased IL-10, TGF-β, IFN-γ and TNF-α [31].

High fat diet caused intestinal dysbiosis resulting from the redistribution of bacteria especially in the intervillous spaces and crypts-associated with early physiopathological changes in the ileum, such as decreased antimicrobial peptides expression, impaired mucus secretion and thickened villi , and weak expression of tight junction proteins. After time, inflammatory signals (e.g. toll-like receptor-4 dependent) were activated, enhancing proinflammatory cytokines secretion in the small intestine. This exacerbated disruption of the mucus layer barrier and increase epithelial permeability of the small intestine, thereby creating an environment that facilitates bacterial infection (e.g. lipopolysaccharide, peptidoglycan and flagellin) and metabolites from the intestinal lumen (e.g. secondary bile acids) to the circulation and peripheral tissues (i.e. leaky gut), promoting the development of systemic inflammation, obesity, adiposity, insulin resistance and glucose intolerance preceding hyperglycemia [32].

In vitro studies revealed that the probiotic organisms decreased the expression of pro-inflammatory cytokines via promoting toll-like receptors. Probiotic administration improved the clinical symptoms, histological alterations, and mucus production in most of the evaluated animal studies [30].

Oral administration of *Bifidobacterium adolescentis* IM38 (2×10^9 CFU/mouse per day) for 6 weeks in obese mice decreased body and epididymal fat weight gain. These was carried out by suppressing the expression of interleukin (IL)-10, tight junction proteins, down regulated NF-κB activation and tumor necrosis factor expression in the colon. Also, IM38 inhibited its differentiation into helper T17 cells and reduced IL-17 levels in the colon of mice [33, 34] (Figure 2).

Probiotic and non-alcohol fatty liver

The prevalence of non-alcoholic fatty liver disease reached 20-30% all over the world [35]. It is characterized by increased liver lipid accumulation in obese children with insulin resistance leading to massive forms of inflammation and hepatic fibrosis leading to type 2 diabetes [36]. The disease started by hepatic damage, such as ballooning and inflammatory infiltrates [37] followed by increased accumulation of triglycerides within the hepatocytes due to de novo lipogenesis and impairing liver enzymes [38]. These led to alterations in glucose, fatty acid and lipoprotein metabolism associated with adipose tissue, hepatic, and systemic inflammation [39, 40]. Increased level of free fatty acids and chronic low-inflammation rate from visceral adipose tissue are the most predicted factors in the development of NAFLD. Increased release of adipokines from visceral adipose tissue and fatty

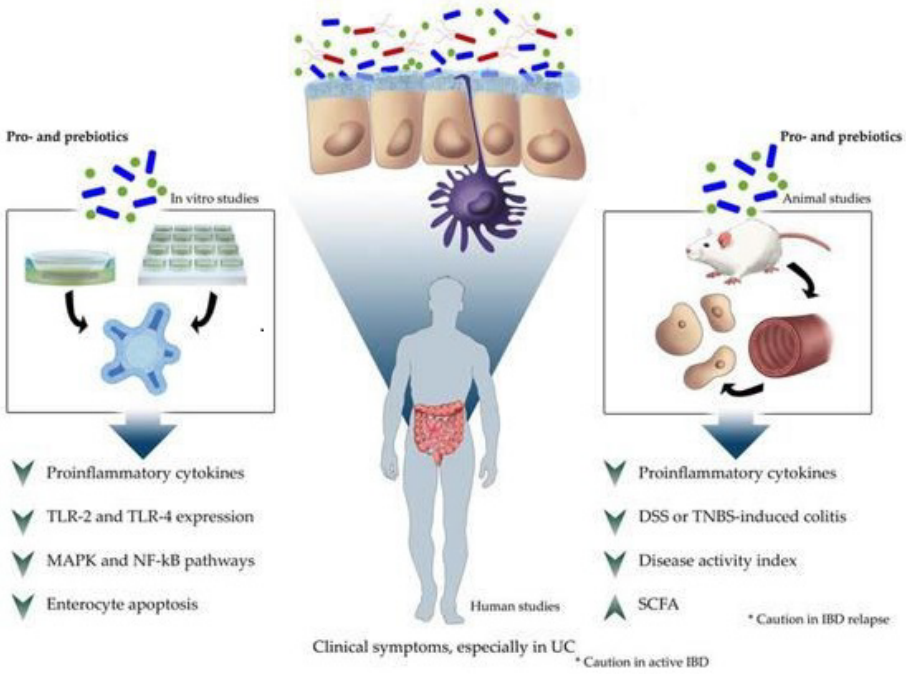

Figure 2: Diagram summarized the probiotic anti-inflammatory effects in intestinal chronic diseases. DSS, dextran sulfate sodium; IBD, inflammatory bowel disease; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-B; SCFA, short-chain fatty acids; TNBS, 2,4,6 trinitrobenzenesulfonic acid; TLR, toll-like receptor; UC, ulcerative colitis.

liver deposits stimulated inflammation via nuclear factor kappa B signaling pathways, which are also activated by free fatty acids, and contributed to insulin resistance [41, 42] (Figure 3).

Recently bile acids exerted signaling molecules and metabolic regulators that can activate nuclear receptors and G protein-coupled receptors to regulate hepatic lipid, glucose, and energy homeostasis, as well as its own synthesis and transport in the liver and intestine. The activation or modulation of bile acid signals promoted by bile acid receptors affects both insulin sensitivity and NAFLD pathogenesis [43]. It is known that steatosis may interfere with sinusoid microcirculation and hepatocellular clearance of microbial and stimulated hypertrophy of Kupffer cells. These have a great influence on Toll-like receptors, the pathogen sensors. TLRs are widely expressed on parenchymal and non-parenchymal cells in the liver, which play critical roles for the liver health [44].

Non-alcoholic steatohepatitis displayed increased macrophage infiltration and overexpression of inflammatory gene [45]. Different markers are associated with NAFLD such as increased peroxisome proliferator-activated receptor-γ co-activator, B-cell dysfunction and abnormal metabolism of mitochondria, lysosomes, rough endoplasmic reticulum and golgi complex [36].

There is a great association between gut flora and NAFLD increase of intestinal bacterial overgrowth, small bowel dysmotility, increased gut permeability, and decreased immunological defenses. These factors activated promote bacterial translocation from the gut to the systemic circulation, increasing the degree of infections and development of the disease [46, 47].

Obesity is a disease resulting from consumption of obesogenic foods (particularly those enriched in fat). These led to decrease of gut microbiota and increase intestinal barrier function increasing metabolic endotoxemia [48, 49], facilitating the development obesity-associated fatty liver disease.

The gut microbiota are associated with the disease via modulating energy homeostasis [50] by increased fermentation of carbohydrates to short chain fatty acids and accelerating de novo synthesis of triglycerides in the liver [51] managing choline metabolism (required for low-density lipoprotein synthesis and hepatic lipid export) [52]; bile acid homeostasis [53], elevated blood ethanol concentration [54] and bacteria-derived toxins [e.g., lipopolysaccharides (LPS)], which activate pro-inflammatory cytokine production.

Following quantitative polymerase chain reaction (qPCR) for bacterial determination in a 50 patients (17 controls, 11 patients with hepatic steatosis, and 22 patients with NASH), Mouzaki et al. [55] revealed that NASH patients had decreased fecal Bacteroidetes and increased Clostridium coccoides.

Animal studies revealed increased intestinal permeability in NAFLD, nonalcoholic steatohepatitis. and cirrhosis. This was associated with oxidative and inflammatory injury to the liver derived from the intestinal microbacteria. Bacterial translocation is associated with increased portal hypertension and hepatic encephalopathy in cirrhosis. By preventing bacterial adhesion and translocation, probiotics may have a role in the management of patients with NAFL, NASH, and cirrhosis [56].

Probiotic therapies of patients with NAFLD led to improvement of liver amino transferases, total-cholesterol, TNF-α and insulin resistance [57]. Also, the farnesoid X receptor, a nuclear transcriptional factor activated from bile acids chemically derived by the gut microbiota (GM) enzymes showed a great role in the disease [58]. Administration of 2 g of powder containing 5 X 109 colony-forming units of L. curvatus HY7601 and 5 X 109 of L. plantarum KY1032 each day for 12 week manage hypertriglyceridemic subjects and reduced plasma metabolites, fatty acid primary amides and lysophosphatidyl choline [59].

The gut microbiota composed of bacteria, having great value in food processing, digestion of complex indigestible polysaccharides and synthesis of vitamins [60]. It is also synthesize a wide range of bioactive metabolites serving inhibition of pathogens, metabolism of toxic compounds to modulation of host metabolism [61].

Following studies of a total of 535 children and adult with NAFLD Gao, et al. [62] reported that probiotics administration provided improvements in the outcomes of homeostasis, total cholesterol, high density lipoprotein, and tumor necrosis factor-α in NAFLD patients and triglyceride in Italian and Spanish patients. The gut microbiome represents a significant environmental factor contributing to NAFLD development and progression [63,64].

Probiotics are active microorganisms have a positive role in improving NAFLD. Following assay six studies with good validity and importance. Nursalim et al. [65] reported that probiotic is useful in reducing hepatic inflammation and liver aminotransferase, and liver fat content. However, further evidence is needed to show whether or

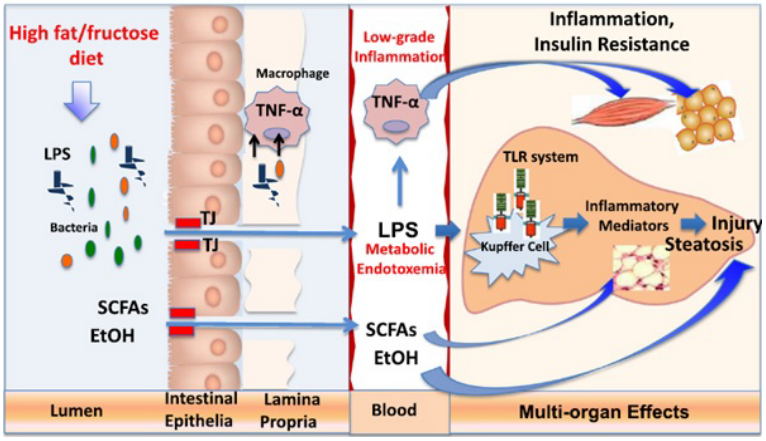

Figure 3: Gut microbiota and development of non-alcohol fatty liver disease. EtOH, ethanol; LPS, lipopolysaccharides; ROS, reactive oxygen species; SCFAs, short chain fatty acids; TJs, tight junctions; TLR, Toll like receptor; TNF-α, tumor-necrosis factor.

not probiotic is beneficial reducing cirrhosis progression and liver-related mortality [65,66].

There are bio products secreted by *Lactobacillus* and *Microbiota* derived metabolites, such as fatty acids and antioxidants, that could be used for precision medicine in the treatment of liver disease. Studying host-microbial interactions facilitated the discovery of novel therapeutic targets in the gut microbiota [67].

The immunoregulatory effects of probiotics may be beneficial in NAFLD treatment through promoting the intestinal microbiota; improve the epithelial barrier function and strengthen the intestinal wall decreasing its permeability; reduce the bacterial translocation and endotoxemia; improve the intestinal inflammation; and reduce oxidative and inflammatory liver damage [68].

Obesity

Obesity is one of the most public health disease of the 21st century especially increased prevalence among children and adolescents. It is associated with hypertension, dyslipidemia, chronic inflammation, and hyperinsulinemia and increasing the risk of death [69].

One of the main strategy is to overcome of the disease to adjustment of gut microbiota through dietary intervention, antibiotic application, the use of prebiotics and probiotics, bariatric surgery and faecal microbiota transplantation. Development of intestinal dysbiosis, shared in the development of obesity and metabolic disorders. Recently, there is a strategy of regulating pathways that increase energy expenditure, and reduce energy intake, and absorption and systemic inflammation. It is known that the metabolic disorders, such as diabetes, obesity, atherosclerosis are closely linked to lifestyle and diet especially intestinal microbiota. Although probiotics and prebiotic therapies are still obscure, the molecular mechanisms reported positive anti-obesity effects [70, 71] (Figure 4).

A study carried out on 75 healthy overweight and obese individuals consuming regular yogurt with a low-calorie diet or receiving probiotic yogurt (200g/day) with LCD and enriched by *Lactobacillus acidophilus* La5, *Bifidobacterium* BB12, and *Lactobacillus casei* DN001 108 colony-forming units/g. or without LCD for 8 weeks. The authors reported a reduction in both body mass index (BMI), fat percentage, leptin level and gene expression of ROR-γt [72].

Microbial dysbiosis led to the development of diabetes, obesity, atherosclerosis, and metabolic syndrome through activation of insulin resistance pathways. It is associated with the increase of harmful metabolites and changes to composition of bile acids occur via carbohydrate and protein fermentation [73,74]. Higher consumption of milk and yogurt and of milk and yogurt-based beverages were associated with decreased body fat, improved cardiovascular disease, and higher cardiorespiratory fitness [69].

Many studies are carried out on the next-generation probiotic bacteria (*Akkermansia*, *Bacteroides spp*, *Eubacterium halli*) and microbiota-derived molecules (membrane proteins, short-chain fatty acids) [75]. Probiotic and symbiotic dairy fermented products represent the future strategy to treat a variety of health disorders. Lactic acid bacteria possess anti-obesity and anti-diabetic in human subjects [76].

Bifidobacterium species (*B. longum*, *B. breve*, *B. bifidum*, *B. catenulatum* group, *B. infantis*, *B. adolescentis*, *B. angulatum* and *B. dentium*) were detected in 76 healthy full-term vaginally-born infants through the first three years of life [77]. Probiotic supplementation of either *B. longum* or a mixture of *B. longum* and *LcS bacteria* significantly reduced weight and triglycerides in the high fat diet groups. There is a detected depletion of leptin level, fat mass, adipocyte size and lipoprotein lipase expression, as well as increasing adiponectin and peroxisome proliferator-activated receptors-γ expression of high fat diet supplemented *B. longum* bacteria compared to those with other kinds of bacteria [78].

Administration of *L plantarum* and *L rhamnosus* with a hypocaloric diet as well as *L. plantarum* with *L curvatus*, *L gasseri*, *L amylovorus*, *L acidophilus* and *L casei* with phenolic compounds exhibited weight loss and help in obesity treatment [79].

High-fat diets led to a depletion of gut microbiota richness, increased *Firmicutes* to *Bacteroidetes* ratio. Saturated (SFA), monounsaturated (MUFA), polyunsaturated (PUFA) and conjugated linolenic fatty acids shared important pathways of immune system activation/inhibition with gut microbes, modulating obesogenic and proinflammatory profiles. These were carried out by increased intestinal permeability, systemic endotoxemia, and the activity of endocannabinoid system. Although the probiotic therapy represents a strategy to improve gut microbiota composition, it did not treat fat-induced dysbiosis [80].

Following assess the mixtures of whey milk - cow, sheep, goat at ratios of 60:20:20, respectively fermented for 24 hours, Sanchez-Moya, et al. [81] reported a significant increase of *Bifidobacterium* with cow, sheep and mixed whey and increased in the Lactobacillus group, particularly in obese donors. Supplementation of these whey can stimulate the growth of probiotic bacteria, enhancing short chain fatty acids production, which improved intestinal disorders and consequently prevent overweight, obesity and related diseases.

Imbalances in the gut microbiota are greatly associated with weight loss in overweight/obese adults and the pathogenesis of obesity. Prebiotics had a bifidogenic effect and increased butyrate producers, likely due to cross-feeding interactions, contributing to the gut barrier and improving metabolic outcomes [82].

Rats fed on high fat diet and a probiotic formulation containing 2 *Lactobacillus* strains (*L. acidophilus* LA1 and *L. rharmnosus* LR5), 3 *Bifidobacterium* (*B. bifidum* BF3, *B. lactis* BL3, and *B. longum* BG7), and *Streptococcus thermophilus* ST3 promoted growth of body weight and increased levels of bacteroidetes, *lactobacillus*, and *bifidobacterium*. There was a detected decrease of serum levels of the inflammatory cytokines and improved serum metabolites of lysophosphatidylcholine, lysophosphatidylethanolamine, phosphatidylcholine, and triacylglycerol [83].

Probiotic and cardiovascular disease

Cholesterol is important for insulate nerves, cell membranes and formation of hormones. Feeding on high fat diet led to the development of cardiovascular diseases including atherosclerosis, coronary heart disease and stroke [84].

Industrial food nutrients are absorbed in the proximal part of the small intestine and give no great important to the microbiota. Lack of healthy nutrition for gut microbiome developed disrupted microbiota, dysbiosis, increased inflammation, and the production and release of endotoxins through the different tissue barriers. Increased intake of advanced glycation and lipoxidation molecules, gluten and zein, and a reduced consumption of fruits and vegetables, enhanced inflammation, obesity and chronic diseases. On the other hand, probiotic therapy is promising. Phytotherapy with curcumin and resveratrol, and pre-, pro- and synbiotics offers similar health effects but free from its adverse effects [85].

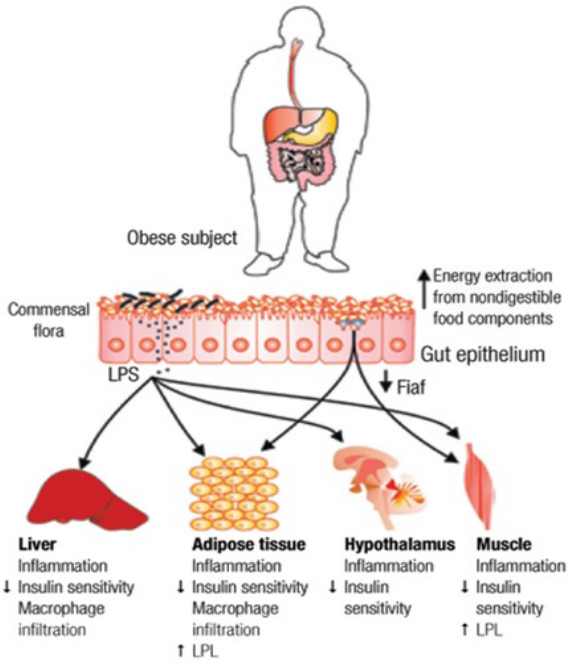

Figure 4: Chart illustrating the co-relation between obesity and gut flora. LPL, lipoprotein lipase; LPS, lipopolysaccharide.

Lactobacillus strains showed different mechanisms of decreasing the cholesterol level. Its hypocholesterolemic effect was attributed to their ability to bind to cholesterol in the small intestines. Reduction of hypercholesterolemia comes from dissociation of bile salt in the enterohepatic circulation by the enzyme bile salt hydrolase (BSH) through hydrolyzing the conjugated glycodeoxycholic acid and taurodeoxycholic acid, leading to the formation of dissociated glyco- and tauro-bile acids [86]. Oner et al. [87] reported that the BSH enzyme activities of human-derived lactic acid bacteria and *bifidobacteria* have the ability to decrease cholesterol level in *invitro* culture media based on cholesterol precipitation properties. Anandharaj and Sivasankari [88] isolated 6 strains of *Lactobacillus spp*. from 12 mother's milk isolates.HMI68 showed resistance to most of the antibiotics as well as antagonistic activity against the tested pathogens. The identified *Lactobacillus* strains reduced cholestrol metabolism. Dietary supplementation of yogurt containing fermented pepper juice (FPJY) to high fat and high cholesterol diet (HFCD) fed rat for 9 weeks led to increase serum HDL cholesterol level and decrease hepatic total cholesterol level associated with inhibit organ hypertrophy and accumulation of body fat [89].

Human subject with moderate hypercholesterolemia and supplemented Yogurt drink in combination with plant stanols (2-4 g/day) showed a statistically significant decrease in total cholesterol and low density lipoprotein cholesterol by 7.2% and 10.3% [90-92].

Supplementation of yoghurt containing *Bifidobacterium pseudocatenulatum* G4 or *B longum* BB536 to hypercholesterolemic rats for 8 weeks led to significantly depletion of plasma total cholesterol, low density lipoprotein -cholesterol and very-low-density lipoprotein cholesterol compared to hypercholesterolemic and healthy controlled groups [93].

Rat dietary supplemented hypercholesterolemic diet with soy yogurt fermented with *Enterococcus faecium* CRL 183 and isoflavones for 60 days exhibited significant decrease of total cholesterol level, significant increases in serum HDL-C concentration and marked reduction of atherosclerosis in the thoracic and abdominal aortas [94].

There is a great evidence that probiotic decrease low density lipoproteins (LDL) cholesterol and improve the LDL/high density lipoproteins (HDL) ratio, as well as lower blood pressure, inflammatory mediators, blood glucose levels and body mass index [95, 96].

From clinical and metaanalysis, administration of two synbiotics, L. acidophilus CHO-220 plus inulin and L. acidophilus plus fructo-oligosaccharides led a depletion of LDL-C and total cholesterol with a consequence of improving coronary heart disease [97].

Administration of the probiotic L rhamnosus GR-1 to rats with coronary artery occlusion exhibited a significant attenuation of left ventricular hypertrophy and gene expression of atrial natriuretic peptide and improved systolic and diastolic left ventricular function [98].

Probiotic and diabetes

Diabetes is of multifactorial origin, especially of altering the intestinal microbiota which enhance inflammatory responses, increase phosphorylation of serine residues in insulin receptor substrate-1 and reducing insulin sensitivity in type 2 diabetes. However, in type 1 diabetes, the depletion of adhesion proteins within the intestinal epithelium needs a greater immune response that may result in destruction of pancreatic β cells by CD8+ T-lymphocytes, and overexpressed interleukin-17, related to autoimmunity [99].

The gut microbiota distribution depends on the mode of delivery at birth, infant feeding, medications, antibiotics and the diet. Disrupted gut microbiota promotes intestinal inflammation and subsequent systemic low-grade inflammation, leading to the development of type 2 diabetes [100].

Type 2 diabetic patients are in need for ingestion of probiotics due suffering from dysbiosis. Intake of yogurt containing *L acidophilus* La-5 and *Bifidobacterium* animalis subsp lactis BB-12 (109 colony-

forming units/d, each) improved glycemic control of type 2 diabetes patients assessed by a significant decrease in fructosamine levels, hemoglobin A1c tended, TNF-α and resistin, total cholesterol and LDL-cholesterol and increase in acetic acid [101-103]. Postbiotics such as lipopolysaccharides, promote insulin resistance. Injection of bacterial cell wall-derived muramyl dipeptide led to a decrease of inflammation and reduced glucose intolerance in obese mice without causing weight loss or altering microbiome composition [104]. Intestinal dysbiosis, led to increased intestinal permeability and high circulating levels of lipopolysaccharides "Endotoxemia," the prediction of T2DM [105]. The gut microbiota is a complex community of bacteria affected by genetics, birth delivery, infant feeding, and the diet. It plays a great role in improving intestinal inflammation. Fermented milk products, such as yogurt, deliver a large number of lactic acid bacteria to the gastrointestinal tract which inhibit lipopolysaccharide production and increasing the tight junctions of gut epithelia cells [106]. Salas-Salvado et al. [107] reported decreased incidence of type 2 diabetes supplemented and modulation of glucose metabolism post yogurt administration.

Neurodegenerative diseases

Alzheimer's disease (AD). is disease characterized by impaired cognition and cerebral accumulation of amyloid-β peptides (Aβ). Microbiota dysbiosis increased permeability of the gut and blood-brain barrier leading to AD pathogenesis especially during aging. The gut microbiota secretes large amounts of amyloids and lipopolysaccharides, which modulated the signaling pathways and the production of proinflammatory cytokines related to AD [108, 109].

Probiotic biotherapies are promising of creating a healthy gut environment. The microbiota and its metabolites communicate to the host through a series of biochemical and functional improving the host homeostasis and health. The gastrointestinal tract communicates with the central nervous system through the gut-brain axis to support neuronal development. There are three ways that mediate the communication between the gut and the brain including direct neuronal communication, endocrine signaling mediators and the immune system. Probiotic may prevent ageing related to neurodegenerative disease via improving the decreased neurotransmitter levels, chronic inflammation, oxidative stress and apoptosis [110]. The gut-brain axis attached between the enteric nervous system (ENS) of the GI tract and the central nervous system (CNS) of the brain, via vagus nerve, positive diffusion and carrier by oxyhemoglobin. Amyloid precursor protein that forms amyloid beta plaques in AD is developed in the enteric nervous system nervous system by gut bacteria; Escherichia coli and *Salmonella enterica* altered the CNS function. Life style modifications are important in abberrant NO signaling in AD including NOS inhibitors, NMDA receptor antagonists channel modulators such as probiotics, and exercise [111].

Administration of probiotic to total thirty six of 32 APP/PS1 transgenic male mice besides running training for 20 week revealed improved the learning skills. The number of plaques in hippocampus were significantly decreased and the density of astrocytes around the plaques were increased. Also, exercise training and probiotic treatments delay inflammation, ameliorate oxidative stress, and decrease levels of beta amyloids, and delay the development of alzheimer disease [112].

A clinical trial conducted among 60 AD patients to assess the effects of probiotic supplementation on cognitive function and metabolic status. Supplementation of probiotic containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* (2×10^9 CFU/g for each) at dose of 200 ml/day for 12 weeks led to a significant improvement of plasma malondialdehyde, serum high-sensitivity C-reactive protein, insulin resistance, beta cell function, serum triglycerides and quantitative insulin sensitivity check [113].

Administration of SLAB51 probiotic formulation to mice model of AD of 3xTg-AD mice restored two impaired neuronal proteolytic pathways (the ubiquitin proteasome system and autophagy). Also, the probiotic formula led to improve cognition, decrease brain damage and depleted amyloid beta.

Conclusions and future trends

The incidence of diabetes, fatty liver, obesity, atherosclerosis, cardiovascular disease and neurodegenerative disorders are public health problem facing affected large rate of mortalities. The gut biota was altered as a result of the mentioned diseases and facilitated the widespread of pathogenic bacteria. This is of great importance for diagnosis and probiotic therapy. There is a great need to consume probiotic rich in *lactobacilli* microorganism and *Bifidobacterium* species to supply the body with the bioactive materials important for defense against inflammation and protection against the metabolic diseases.

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