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New perspectives on probiotics in health and disease

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Abstract

The gut microbiota continues to fascinate scientists in many realms when it is considered that humans contain 90% bacteria. Correlations between changes in composition and activity of the gut microbiota and common disorders such as cancer, hypertension, hypercholesterolemia, inflammatory bowel diseases, obesity, oral health, *etc.* have been proposed. What is the real role of probiotics, prebiotics and synbiotics in influencing a healthy microbiota? Both *in vitro* evidences and *in vivo* clinical data have supported some of these new health claims, while recent molecular advancement has provided strong indications to support and justify the hypotheses. However, probiotics validity and health claims have continuously been rejected on the basis of "biomarker deficiency". To battle the increase in health care costs, a preventive approach to medicine with the development of probiotics and prebiotics or symbiotic products is being advanced. This review discusses the potential beneficial effects of probiotics in preventing and treating certain diseases as well as current and future perspectives of probiotic research.

Keywords: Probiotic; Heath benefits; Bile salt hydrolase; Dysbiosis; Microbiome

1. Introduction

Food fermentation and the consumption of fermented foods date far beyond human civilization. The transition from hunting and gathering to an agricultural lifestyle might have contributed to the further development of these food fermentations that are now practiced on industrial scales. However, human interactions with probiotics are more intimate and have a much longer history than the historic food fermentations. All parts of the human body such as the skin, oral cavity, gastrointestinal tract, and vaginal cavity are inhabited by trillions of microbes [1,2]. At birth, the human gut is sterile but colonized immediately after birth [3]. Factors such as the type of delivery (vaginal birth *versus* cesarean section) and the type of diet (breast feeding *versus* formula feeding) affect the colonization patterns [4]. The pioneer microbes that 'infest' the gut make permanent adaptations and determine the physiological, immune, metabolic and behavioral development and also influence future disease susceptibility [132]. Age and life style are some causes of many disease conditions since they contribute to alterations in the microbial flora in the body [5]. Recent studies have demonstrated that bacterial community composition is considerably altered in diseases such as obesity and periodontal disease, with healthy subjects usually exhibiting distinct, diverse and temporally stable bacterial populations at these sites when compared with patients displaying disease symptoms [6]. As consumers become aware of the impact of what they eat on their health, they tend to search for functional foods. Attention has been paid to prevention of diseases than cure and hence, probiotic containing foods are abundant on the market.

2. Diseases and disorders caused by alterations in the human gut microbiota

It is evident that prenatal maternal exposure influences postnatal microbial colonization [3] and this plays pivotal roles in gut-associated lymphoid tissue (GALT) development [7], specific aspects of immune system development [8,9] and the

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Table 1
Diseases and disorders caused by alterations in the gut microbiome.

Disease/disorder	Potential role of the microbiome	Recent findings
Atopy and asthma	• Pre- and postnatal microbial exposures influence immune development [3]. • Mode of delivery and nutrient uptake influence GI community development and protection against subsequent atopic disease development [13].	• Infants born by cesarean section are more often colonized with *Staphylococcus*, *Corynebacterium* and *Propionibacterium* and less with bifidobacteria and lactobacilli while vaginally delivered infants are colonized with *Lactobacillus*, *Prevotella* or *Sneathia* [14]. • *Streptococcus*, *Clostridium* species, *Bacillus subtilis*, *Bacteroides vulgatus* and *Veillonella parvula* are predominant in formula fed infants making them prone to allergic and autoimmune diseases [15].
Candida infection	• Depletion of gut microbiota permits *Candida albicans* proliferation and infection [131].	• Depletion of the gut microbiome through antibiotic administration is associated with increased *C. albicans* abundance and infection [131].
Celiac disease	• The GI of celiac disease patients contain large populations of Gram negative bacteria compared to healthy individuals [130].	• Pediatric celiac disease patients have significantly higher numbers of *Bacteroides*, *Staphylococcus*, *Salmonella*, *Shighella* and *Klebsiella* relative to healthy subjects [130]. • The ratio of *Lactobacillus–Bifidobacterium* species to *Bacteroides–E. coli* was lower for celiac disease patients [16].
Colorectal cancer	• High abundances *of Bacteroides* spp. and *Clostridium* spp. are present in the GI of CC patents [17].	• Overall bacterial diversity increased for CC patients compared with healthy controls [18]. • Microbial butyrate production causes apoptosis of CC cells [18].
Type I diabetes	• Interaction between the gut community and innate immune system may be a predisposing factor for diabetes [19]. • The microbiome plays a role in the development of insulin resistance [20].	• Metabolic profiling reveals a contribution of gut microbiota to fatty liver phenotype in insulin-resistant mice [20]. • The intestinal microbiota interacts with environmental factors and susceptible genetic factors, contributing to the development of diabetes [21].
Type II diabetes	• Gut microbiome dysbiosis is critical for pathogenesis [22].	• Low levels of *Roseburia intestinalis* and *Faecalibacterium prausnitzii* in the microbiome of Type II diabetics [22]. • Type II diabetes and obesity are highly influenced by gut microbiome [23]. • Gut microbiota may contribute to insulin sensitivity and cause low-grade systemic inflammation [20].
HIV	• Gut microbiome dysbiosis may be critical for pathogenesis [24].	• An important relationship exists between altered mucosal bacterial communities and intestinal inflammation during chronic HIV-1 infection [25]. • HIV-1-infected subjects had increased abundances of Proteobacteria and decreased abundances of Firmicutes compared with uninfected donors [24].
IBD	• Composition of gut microbiota contributes to inflammation [3]. • Treg-promoting organisms are depleted; overgrowth of bacteria that induce proinflammatory Th17 cell populations [26].	**Crohn's disease (IBDC)** • IBDC patients have high levels of Enterobacteriaceae, Pasteurellacaea, Veillonellaceae, and Fusobacteriaceae, and decreased abundance in Erysipelotrichales, Bacteroidales, and Clostridiales [27]. • IBDC patients have abnormal increase in antimicrobial dual oxidase (DUOX2) expression with increasing numbers of proteobacteria [28] • Fecal samples of CD patients have increased levels of *Bacteroides fragilis* (*B. fragilis*) reletive to control samples [129]. • An overall decrease in microbial diversity is observed in CD patients [128]. • CD patients have significant alterations in oxidative stress pathways, as well as decreased carbohydrate metabolism and amino acid biosynthesis in favor of nutrient transport and uptake [128]. • CD patients have leucine, isoleucine, valine, lysine, alanine, tyrosine, phenylalanine, glycine, glutamate, and aspartate malabsorption [29]. • Microbial diversity lower when compared with healthy individuals [29]. **Ulcerative colitis (IBDU)** • Lower levels of Bifidobacteria and *Clostridium leptum* [30] reported relative to healthy individuals. • TRUC gut microbiomes with active colitis has a reduced potential for both carbohydrate and energy metabolism and an enhanced potential for flagellar assembly, tetrathionate respiration and benzoate degradation [31].
IBS	• Disturbances of mucosa-associated bacteria may be important in the pathogenesis of IBS symptoms [32].	• Abnormal detection of hydrogen and methane in patients' breath suggests changes in bacterial fermentation [33]. • In children, a fecal microbiome with increased percentage of *Haemophilus parainfluenzae as well as* bacterial taxa from the genus *Alistipes characterizes IBS* [32].
Gastroenteritis	• Pathogenic species capitalize on GI microbial community disruption to elicit infection [34].	• *Helicobacter pylori* capitalizes on host disruption of GI microbiome to induce persistent inflammatory infiltration and can cause gastropathy and cancer [35].

Table 1 (*Continued*)

Disease/disorder	Potential role of the microbiome	Recent findings
NEC	• The interactions of a predisposing genetic background, an immature intestinal barrier and a conducive microbial environment in neonates play critical roles in pathogenesis [36]. • The absence of *Propionibacterium* in the first week of birth and the dominance of *Staphylococcus* and *Enterococcus indicate a* risk of NEC [37].	• There is lower bacteria diversity in all preterm infants, particularly NEC infants [127]. • NEC patients had higher abundance of Gammaproteobacteria in the GI tract [127]. • Lower bacterial diversity may favor certain dominant organisms, which proliferate with the administration of antibiotics [36].
Obesity	• Gastrointestinal microbiota impact adiposity *via* interactions with epithelial and endocrine cells [38]. • Differential energy harvest capacity by microbiota may be a mechanism for the increased adiposity in obese mice [39].	• Obese patients may depend on interspecies transfer of H_2 between archaea and bacteria to improve energy uptake [40]. • Obese individuals exhibit lower abundance of Bacteroidetes and a higher abundance of Firmicutes compared with lean people [41]. • The ratio of Bacteroidetes and Firmicutes reverts back to a composition similar to that of lean subjects following a diet and exercise regime [42].
Rheumatoid arthritis	• Microbiome may be a causative agent underlying certain rheumatic diseases like ankylosing spondylitis and rheumatoid arthritis [43]. • Treg-promoting organisms depleted; overgrowth of bacteria that induce Th17 cell populations, leading to inflammation [26].	• Patients with rheumatoid arthritis had high numbers of *P. intermedia*, *P. gingivalis* and *Prevotella nigrescens* indicating the presence of the chromosomal DNA of periodontal disease-associated bacteria in the sera and synovial fluid of the patients [44]. • *P. gingivalis* could be involved in rheumatoid arthritis by generating citrullinated proteins of itself as well as human antigen and the immune response to them [45].

CC: colon cancer; GI: gastrointestinal; IBD: inflammatory bowel disease; IBDC: irritable bowel disease-Crohn's disease; IBDU: irritable bowel disease-ulcerative colitis; IBS: Irritable bowel syndrome; NEC: necrotizing enterocolitis; CD: Crohns' disease; TRUC: *T-bet*$^{-/-}$ *Rag2*$^{-/-}$ ulcerative colitis.

integrity of the mucosal barrier [10]. Therefore the development of the gut microbiota in the early stages of life may be linked to future disease susceptibility. Many studies have associated diseases such as Inflammatory bowel disease [3], obesity [6] colon cancer [11] and some allergies [9] to alterations in the gut microbiome (Table 1). In many instances, there is an imbalance in the population densities of gut microbiota (dysbiosis) and this results in an overgrowth of pathogenic microbes. In obesity, the altered microbial population is associated with a shift in function of the cells, resulting in increased energy harvest from ingested food; unexpended excess energy is deposited as adipose tissue [12].

3. Probiotics and probiotic selection criteria

Probiotics are live microorganisms which, when administered in adequate amounts, confer health effects on the host and prebiotics are non-digestible food ingredients that stimulate the growth and or activity of probiotics [125]. Though some non-living cells may have probiotic properties [46,47] living cells tend to function better. The stomach is highly acidic due to the presence of HCl. Therefore, one of the first barriers probiotics must endure is the gastric acidity of the stomach as well as the bile in the upper digestive tract before they get to the small intestines [35]. Many types of bacteria have probiotic properties, however, the most documented groups comprise of lactic acid bacteria (LAB) and bifidobacteria. While *L. casei* and *Lactobacillus acidophilus* survive in the acidic conditions of artificial gastric juice at pH 3.0 at 37 °C, *Lactobacillus delbruekii* ssp. *bulgaricus* does not. Strains of *Bifidobacterium* vary in their ability to survive transit through the stomach. The initial screening and selection of probiotics also include testing of the phenotype and genotype

Table 2
Properties and benefits of good probiotic strains.

Properties	Benefits
• Resistance to pancreatic enzymes, acid and bile	Survival of passage through the intestinal tract
• Adhesion to the intestinal mucosa	Immune modulation; pathogen exclusion; enhance healing of damaged mucosa; prolonged transient colonization
• Human origin	Species-dependent health effects and maintained viability
• Production of antimicrobial substrates	Antagonism against pathogenic microorganisms
• Documented health effects	Proposed health effects are "true"; clinically validated and documented health effects of minimum effective dosage in products
• Health	The assessment and proof of a 'GRAS' strain, with a previous 'history of safe use' and safety in food; non-pathogenic even in immunocompromised hosts
• Good technology properties	Strain stability; production at large scale; oxygen tolerance

Adapted from Lee et al. [35].

stability, including plasmid stability; intestinal epithelial adhesion properties; protein and carbohydrate utilization patterns; production of antimicrobial substances; antibiotic resistance patterns; ability to inhibit known pathogens, spoilage organisms, or both; and immunogenicity [124]. Table 2 shows the properties and benefits of good probiotic strains. It is necessary that probiotic strains survive, proliferate and colonize their specific locations. They must neither be pathogenic nor trigger allergic response in the host. However, they may serve as adjuvants to stimulate the immune system against pathogens. Practically and for commercialization purposes, probiotics must

be easily culturable on a large scale and must resist technological manipulations such as heating and low oxygen conditions in packages.

4. Functional genomics of LAB

Recently, the number of sequenced LAB genomes has increased exponentially and the genomic data from several LAB species and strains are available to give a better understanding of their gene content, their properties and their roles in human health and food fermentation [48]. The most important LAB used as starters in dairy fermentations are *Lactococcus lactis*, *Streptococcus thermophilus*, *L. delbruekii* subsp. *bulgaricus*, while in some cases also some *Leuconostoc* or other *Lactobacillus* spp. are used [49]. Because LAB do not contain a functional respiratory system, they obtain energy by substrate level phosphorylation. They use either the homofermentative pathway to virtually produce only lactate or the heterofermentative pathway to produce large amounts of CO_2, and ethanol in addition to lactate. LAB compete with other bacteria based on their rapid growth and their lactic acid production in their habitats. Luesink et al. [50] have reported that the main factor controlling sugar degradation in LAB is the catabolite control protein CcpA which acts as a transcriptional activator of the lactic acid synthesis (*las*) operon with the order *pfk-pyk-ldh*. In many LAB, the *ccpA* gene is colocated with the prolidase-encoding pepQ gene but divergently transcribed from each other, indicating a link between carbon and nitrogen metabolism [2]. Of all the nitrogen control systems present in LAB, GlnR and CodY are the most studied. All LAB genomes posses GlnR but CodY is only present in *Lactocccus*, *Streptococcus* and *Enterococcus* spp. GlnR is involved in controlling the import of nitrogenous compounds and the synthesis of intracellular ammonia under high nitrogen concentrations [51], while CodY controls the proteolytic system of *L. lactis* and particularly the cell-wall proteinase (PrtP), the key enzyme in milk degradation [52].

5. Mechanism of action of probiotics

The actual mechanism of action of probiotics has not been clearly understood, however, documented results are those obtained from animal models and *in vitro* experiments. One mode of action of probiotics may be an improvement of the barrier functions of the gut mucosa (Fig. 1). Several strains of *Lactobacillus* and *Bifidobacterium* as well as structural components, and microbial-produced metabolites are able to stimulate epithelial cell signaling pathways [53]. The Nuclear Factor Kappa-Light-Chain-Enhancer of activated B cells (NF-kB) pathway is modulated by probiotics at many different levels with effects seen on I Kappa B protein (IKB) degradation and ubiquitination [123], proteosome function [122] and nuclear-cytoplasmic movement of RelA through a PPAR-gamma dependent pathway. Some probiotics such as *S. thermophilus* and *L. acidophilus* alter the expression of tight junction proteins and/or their localization in both *in vivo* and *in vitro* models [54]. *Lactobacillus plantarum* MB452 has been shown to alter expression levels of genes coding for occludin, tubulin, proteasome and certain cytoskeleton anchoring proteins [55]. Other probiotics boost gut barrier function through increased production of cytoprotective molecules such as heat-shock proteins. In addition, probiotics are able to prevent cytokine and oxidant-induced epithelial damage thereby promoting cell survival [121].

Probiotics may also modulate the immune system functions. For instance, *L. acidophilus* has been found to modulate toll-like receptors and the proteoglycan recognition proteins of enterocytes, leading to activation of dendric cells and lymphocytes T-helper 1 responds. The resulting stimulation of lymphocytes T-helper 1 cytokines can suppress lymphocyte T-helper 2 responses which provoke the atopic issues [120]. By this mechanism, the probiotics such as *L. acidophilus*, and *Rhamnococcus* GG decrease skin sensitivity in children and can reduce disorders like eczema [56,57]. Another possible mechanism of action of probiotics may be their ability to suppress the growth of pathogenic bacteria by producing broad spectrum bacteriocins [58]. Probiotics such as *B. infantis* Y1, *L. acidophilus* MB 443, *L. plantarum* MB 452, *L. paracasei* MB 451, *L. bulgaricus* MB453 inhibit pathogens from binding to gut cell walls and also produce short chain fatty acids (SCFA) which decrease the pH of the gut to selectively favor the growth of desirable microbes [118,119]. Some strains of lactobacilli express human mucus-binding pili, which would enhance their ability for colonization [117].

6. Health effects of probiotics

Though many human and animal studies have proved the health effects of probiotic consumption [59–61,103], health authorities have only approved claims on (a) lactose intolerance and lactose digestion and (b) cholesterol reduction mostly because of biomarker deficiency. Probiotics research is still in the early stages, and far more studies need to be conducted to determine the health benefits and safety of probiotics.

6.1. Cholesterol reducing ability

Cholesterol plays a vital role in many functions of the body, such as in the synthesis of steroidal hormones, but excessive cholesterol in the blood causes arterial clogging and increases the risk of heart disease and/or stroke. The risk of heart attack is three times higher in those with hypercholesterolemia, compared to those who have normal blood lipid profiles [115]. The cholesterol reducing ability of probiotics has been extensively reviewed by Ishimwe et al. [62]. In a randomized, double-blind, placebo-controlled, and parallel-designed study, *L. acidophilus* CHO-220 and inulin was administered to thirty-two hypercholesterolemic men and women. After 12 weeks, their plasma total cholesterol and low-density lipoprotein (LDL)-cholesterol reduced by 7.84 and 9.27%, respectively [63]. Many hypotheses have been proposed for the mechanism by which probiotics lower cholesterol levels. The hypothesis include deconjugation of bile *via* bile salt hydrolase [111], binding of cholesterol to probiotic cellular surface and incorporation of cholesterol molecules into the probiotic cellular membrane, production of short-chain fatty acids from oligosaccharides, co-precipitation of cholesterol with deconjugated bile [64] and cholesterol

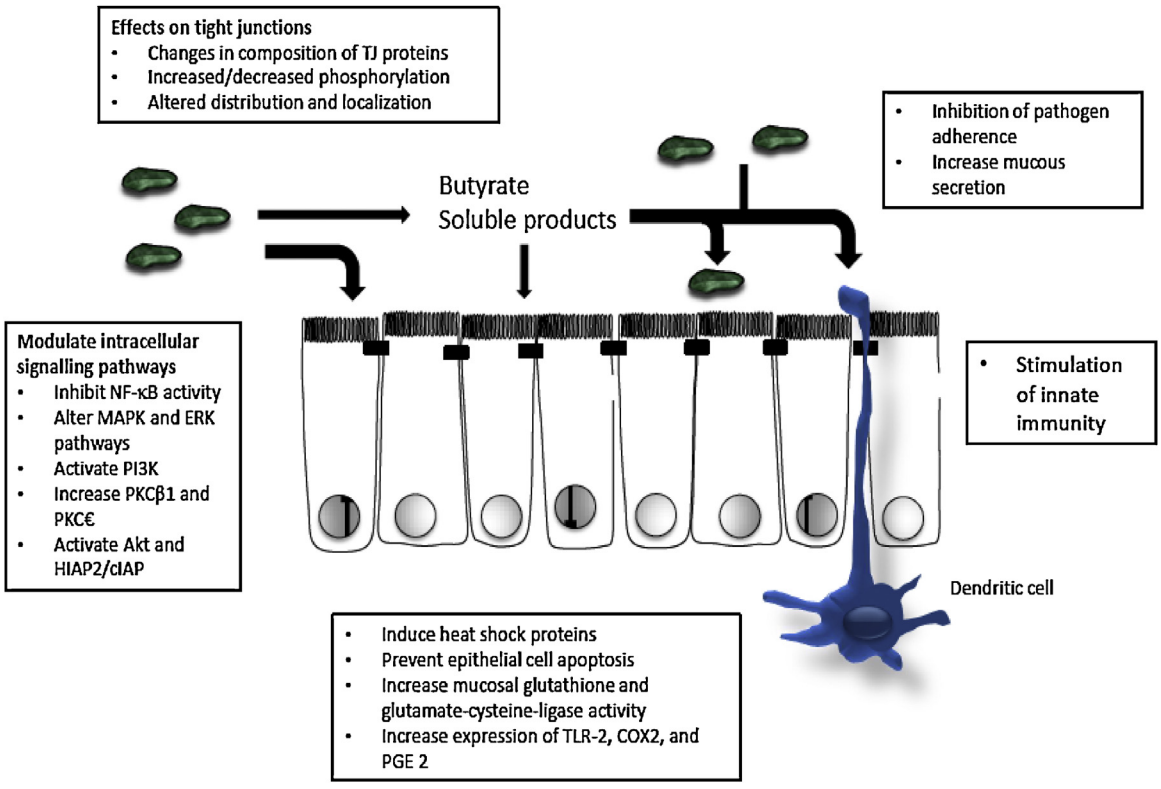

Fig. 1. An overview of mechanisms involved in probiotic-induced enhancement of epithelial barrier function. These include direct modulation of epithelial cell signaling pathways and tight junctions, as well as effects on microbial ecology, innate and adaptive immune function [116].

conversion to coprostanolin [114]. Among all the hypothesis, the bile salt hydroxylase theory is most popular. Liver hepatocytes produce bile salts which enhance dietary cholesterol and fat transport across the intestinal epithelium. The primary bile acids conjugate with either glycine to form glycocholic acid (cholylglycine) or taurine to form taurocholic acid. Since the conjugated bile salts are very soluble, most of them enter into enterohepatic circulation after absorption [113] resulting in an accumulation in the blood. Studies have shown that many *Bifidobacterium and Lactobacillus* species produce bile salt hydrolase (BSH) which cleaves amide bonds between bile acids and their conjugates [65,112]. Probiotics BSH may therefore hydrolyze conjugated bile acids to liberate free primary bile acids which are less efficiently reabsorbed from the intestinal lumen and excreted in feces [111,112]. Such probiotics containing active BSH increase the production of bile salts from cholesterol in their colonized area, thus reducing cholesterol associated problems. Some *Lactobacillus* species such as *L. acidophilus* possess protease-sensitive receptors on their cell surface with which they bind tightly to exogenous cholesterol or phosphatidylcholine vesicles and incorporate them into their cell membranes [64,111]. Bacteria such as *Sterolibacterium denitrificans* produce cholesterol dehydrogenase/isomerase which catalyzes the conversion of cholesterol to cholest-4-en-3-one which is converted into coprostanol and excreted in feces [63]. Since probiotic cholesterol lowering ability is strain specific [62], strains that exhibit excellent properties still need to be identified. Secondary bile acids have been reported to disrupt DNA repair pathway and cause oxidative stress in epithelial cells [66]. This thus calls for more research on how BSH producing probiotics may prevent risks such as sepsis or colon cancer due to the secondary bile salts [67].

6.2. *Urogenital and vaginal health*

The dominant microflora in a healthy human vagina is a variety of *Lactobacillus* species which play essential roles in protecting women from genital infections. An alteration in the population of lactobacilli can result in microbial imbalance in the vagina, causing a quantitative and qualitative shift from normally occurring lactobacilli to a mixed microflora dominated by anaerobic bacteria such as *Gardnerella vaginalis*, *Bacteroides*, *Prevotella*, and *Mobiluncus* species [68]. Such a condition is termed bacterial vaginosis. Infections that involve urogenital microbial flora imbalance such as yeast vaginitis, candidiasis, bacterial vaginosis, and urinary tract infection can be recurrent [35]. Current available antimicrobial treatments can often lead to diarrhea, super infections, depression and even renal failure. Moreover, antimicrobial resistance tends to decrease the effectiveness of this therapy over time. Lactobacilli have been shown to produce biosurfactants and collagen-binding proteins that inhibit pathogen adhesion to cells. This may account for why the vaginal mucosa is dominated by lactobacilli making it less receptive to pathogens [69]. Cell to cell communication could also be a mechanism by which probiotics stimulate mucus production which serves as a barrier to pathogens and also signaling the anti-inflammatory cytokine production [70]. Falagas et al. [71] observed that lactobacilli can inhibit the growth of

Candida albicans and its adherence on the vaginal epithelium in small sample sizes. Presently, the only strains clinically shown to have an effect are *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* [72], when administered intra-vaginally once weekly or twice daily orally, reduced recurrences of UTI and restored a normal lactobacilli dominated vaginal flora in patients [73]. A recent study on the role of probiotics in a woman's urogenital health confirms that supplemental probiotics containing *L. rhamnosus* GR-1 and *L. reuteri* promote the colonization of beneficial microbiota and may help to support overall vaginal health [110]. Daily oral intake of *L. rhamnosus* and *Lactobacillus fermentum* have also been shown to modify the vaginal flora [74]. Though many properties required by probiotics to confer urogenital protection have been identified, yet evidence of their expression *in vivo* is scanty. To make this approach successful, proper selection of strains, proof of concept, and efficacy must accompany products used in patients.

6.3. Oral health

The human mouth harbors diverse microbiomes in the human body such as viruses, fungi, protozoa, archaea and bacteria. The bacteria cause two common diseases namely dental caries (tooth decay) and the periodontal (gum) diseases [75]. The balance of all these microorganisms can easily be disturbed and a prevalence of pathogenic organisms can lead to different oral health problems such as dental caries, periodontitis, and halitosis [76]. Although the evidence for periodontitis is less than dental caries, the use of probiotics to manage the oral microflora appears to be an effective method to control oral conditions [109].

Probiotics marketed for oral health include species of *Lactobacillus* and *Bifidobacterium* [77]. Many studies have shown that they can reduce oral levels of the cariogenic species *Streptococcus mutans* [78,79,108]. *Streptococcus salivarius* K12 has also been identified to produces bacteriocins against pathogens such as *Streptococcus pyogenes* and *Streptococcus pneumonia*, and prevents recurrent pharyngitis, otitis media, and tonsillitis [80,81]. In a double-blind, placebo-controlled trial administration of *S. salivarius* K12 reduced the occurrence of plaque and reduced levels of *S. mutans* in subjects [82]. Species such as *Streptococcus uberis* and *Streptococcus oralis* also suppress periodontal pathogens [83]. Probiotics was effective on halitosis and prevented the production of volatile sulfur compounds. In addition, Vivekananda et al. [107] observed a reduction in gingivitis and gum bleeding after *L. reuteri* administration. The mechanism by which these probiotics colonize and affect the oral cavity is needed to better understand how they improve oral health.

6.4. Lactose intolerance

Lactose is an important nutrient in all mammalian neonates that almost all have the ability to digest lactose to glucose and galactose for a variable time after birth. In most human populations, lactase activity decreases during mid-childhood (about five years of age), resulting in low levels from that age onwards. However, some people retain high levels of activity throughout adult life. In humans, inheritance of lactase persistent (LP: adults retain ability to digest lactose) is dominant and lactase-non persistent (LNP: adults lose ability to digest lactose) is recessive [104]. When milk is ingested and the small intestine fails to produce enough lactase, Lactose intolerance (LI) or lactose malabsorption occurs. Colonic bacteria then metabolize unabsorbed lactose producing hydrogen, methane and short chain fatty acids [106]. Lactose intolerance is determined by blood glucose concentrations, and breath hydrogen test following ingestion of a lactose load. Also, a genetic detection of C/T polymorphism at −13,910 upstream of LPH (lactase-phlorizin hydrolase) gene can also be used. Lactose maldigestion may be classified as primary type (hypolactasia) or secondary type. Primary maldigestion is due to an autosomal recessive condition which results in reduced lactase activities in the intestine [104]. On the other hand, secondary-type lactose maldigestion is thought to be due to a loss of small intestinal mucosa. Symptoms of lactose intolerance include abdominal pain, bloating, flatulence and diarrhea, but the cause may be multifactorial. In humans, a decline in intestinal lactase cannot be reversed by consuming lactose regular. Lactose ingestion and digestion have several effects on health. People with lactose intolerance may avoid milk consumption and other dairy products, take lactase tablets or take probiotic supplements to manage the condition. Another approach to manage lactose intolerance is to increase the lactose load steadily in one's diet. This aids the colon to adapt slowly. Since lactase from intestinal brush border is not an inducible enzyme, the reduction in symptoms may be explained by colonic adaptation [102].

Microbial β-galactosidase in yogurt is known to survive gastric passage and support lactose digestion. Ibrahim and O'Sullivan [84] observed that overproducing β-galactosidase mutants improved symptoms of lactose malabsorption and milk containing *L. acidophilus* also aids lactose absorption in LI patients [126]. Probiotic supplementation can also alter the amount of colonic microbiota and alleviate symptoms in lactose-intolerant subjects [101]. Alterations in colonic microbiota by the supplementation might be one of the factors that alleviate lactose intolerance. Prebiotics are nondigestible (by the host) food ingredients that have a beneficial effect through their selective metabolism in the intestinal tract [103]. A wide range of prebiotics have been isolated from plant materials, including β-glucans from oats, inulin from chicory root, many types of oligosaccharides from lactose, starch, xylose, *etc.* The combination of probiotics and prebiotic (called synbiotics) also increases effectiveness of probiotic preparations for therapeutic use [103]. Prebiotics may also be effective in LI management and treatment [104,105] since they support the growth of probiotics.

7. Future perspectives

From general gut health, to immune support, skin health, cholesterol control, maybe even sensorimotor behaviors, the research thus continues to build. Over the past decade, there has been extensive work in animal models on how probiotics and prebiotics modulate host metabolism. Studies with animal models

have shown that the gut microbiota can regulate inflammation, adiposity, satiety, energy expenditure and glucose metabolism. As more knowledge on the mechanisms from *in vivo* experiments is unraveling, there is a growing need to translate the results into humans. However, there are very few good, double-blind, placebo-controlled clinical trials that can prove causality of pro- and prebiotics on modulating human metabolism [62]. At present, high-quality human trials have demonstrated the potential for gut microbiota in manipulating and preventing or treating disease such as hypercholesterolemia and obesity [12,85,86]. Cholesterol lowering effects of fermented dairy products and encapsulated bile salt hydrolase (BSH) were reported in animal trials, with a reduction of 58% serum cholesterol level in rats by oral feeding of encapsulated BSH [87]. Though cholesterol reducing probiotic *L. reuteri* NCIMB 30242 (Micropharma, Canada) has been on the market as the first recognized biomaker of disease, in human trials, however, there are mixed outcomes [88,89]. This therefore calls for more work to carry out to identify strains with excellent activities as well as their mechanism of action. Lebeer et al. [90] have reported an increase in anti-inflammatory activity when lipoteichoic acid is removed from lactobacilli cell walls and this opens a new door to unraveling the mechanism by which probiotics work. Specific bacterial strains can therefore be genetically modified to study their mechanisms of action. Some animal studies have revealed that probiotics produce bioactive compounds which significantly contribute to functionality within the gastrointestinal tract [91]. *Bifidobacterium breve*, *B. bifidum*, *B. pseudolongum* and *Lactobacillus* convert linoleic acid (LA) into conjugated linoleic acid, CLA [92,93] which suppresses multistage carcinogenesis at different sites [94]. *Lactobacillus helveticus* and *Bifidobacterium longum* have also been reported to produce and respond to mammalian serotonin [95] and affect behavior modulation [96,97]. The ability of these bacteria to produce as well as respond to neurochemicals substantiates the potential of probiotics to influence psychological health and general behavior as observed by Hsiao et al. [98] and Tillisch et al. [99]. It is therefore probable that modulating the gut microbiota with such biotherapeutics may target stress-related CNS disorders, including stress-induced cognitive deficits [100]. However, elucidation of mechanisms and substantiation of animal studies in humans remain essential research goals.

Conflict of interest

The authors declare no conflict of interest.

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