Chapter 5
Probiotics and Prebiotics in Healthy Ageing

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Abstract Probiotics and prebiotics have been reported to be useful in maintaining health and ameliorating various disease conditions. This chapter provides insights into the beneficial role of various probiotics and prebiotics along with their probable mechanisms of action. Several pieces of evidence from clinical trials and *in-vitro* studies have been presented and discussed in this chapter specifically in relation to ageing, longevity and general well-being of an individual. Probiotics have been reported to significantly enhance the skin elasticity, moisture content and gloss with a reduction in wrinkle depth which are all aging related consequences. These biotics increase antioxidants levels with decreased hair loss, skin ulcers and age-related inflammation. It promotes the number of mitochondria in cell and extends the lifespan. Also, they display a beneficial role in the prevention of abdominal pain, diarrhoea, diabetes mellitus, infant colic, irritable bowel syndrome, *C. difficile* infection and ulcerative colitis. On the other hand, prebiotics is known for elevating the antioxidant enzyme levels thereby minimizing harmful reactive radicals and increase immuno-regulatory cytokines which may further impart double protection when given with the right combination of probiotics. The results from several studies reflect the potential of these biotics in various therapeutic interventions, albeit it is also recommended to the researcher's community to plan and execute active surveillance to understand other side effects associated with the usage of these biotics.

Keywords Probiotics · Prebiotics · Ageing · Health benefits · Mechanism · Safety issues

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5.1 Introduction

The microbiome comprises trillions of bacteria, viruses, and fungi in/on our body (Brody 2020; Wang et al. 2017). The microbes found in the cecum of our large intestine are referred to as the gut microbiome (Davani-Davari et al. 2019). This gut microbiome is home to over 100 trillion good micro-organisms that include 1000 species and more than 9000 strain of each species. The gut is also considered as the largest immune organ in the human body and a vital part of the endogenous host defense system. It is the home of more than 80% of the antibody-producing cells which is a little brain within the human body. Many of the gut microbiomes are distinct pathogenic and beneficial bacterial species (Brody 2020). This gut microbiota imparts many benefits to the host, through various physiological functions such as strengthening of gut integrity or shaping of the intestinal epithelium (Natividad and Verdu 2013; Thursby and Juge 2017), harvesting energy (den Besten et al. 2013; Thursby and Juge 2017), protecting against pathogens (Bäumler and Sperandio 2016; Thursby and Juge 2017), modulating the metabolic phenotype, regulating epithelial development (Wang et al. 2017), and influencing innate immunity (Gensollen et al. 2016; Thursby and Juge 2017; Wang et al. 2017). The gut microbiota starts colonizing right from birth and keeps on altering till the end of life. The modulation of gut microbiota from time to time depends upon the ages, sexes, races, diets of the host, illness, antibiotic treatments, environment, individual genetics, stress, hygiene sanitation practice followed, etc. (Arrieta et al. 2014; Thursby and Juge 2017; Wang et al. 2017).

Symbiotic relation of human and normal gut microbiota positively metabolizes non-digestible compounds, supplies essential nutrients, maintains energy homeostasis, prevents the colonization by opportunistic pathogens, and contributes to the formation of intestinal architecture enriching the long healthy lifespan (Round and Mazmanian 2009). These non-digestible foods are primarily dietary fibers such as cellulose and hemicellulose, which are commonly found in vegetables and can be digested by a specific species of *Bacteroides* (Larsbrink et al. 2014). Other non-digestible soluble fibers, for example fructooligosaccharides and galactooligosaccharides are utilized by beneficial microbes, such as *Lactobacillus* and *Bifidobacterium* (Goh and Klaenhammer 2015). As an end product, this gut microbiota produces short-chain fatty acids (SCFAs), such as acetic acids, propionic acids, and butyric acids (Duncan et al. 2009). These SCFAs are used as an energy source to the host intestinal epithelium, as well as are absorbed in the colon to serve various roles in regulating gut motility, inflammation, glucose homeostasis, and energy harvesting (Cani et al. 2013). Studies have been done to show the role of the gut microbiota in lipid and protein homeostasis, microbial synthesis of essential nutrients and vitamins such as folates, vitamin K, biotin, riboflavin (B2), cobalamin (B12), and possibly other B vitamins (Morowitz et al. 2011). Moreover, this gut-microbiota encourages the normal development of the humoral, cellular mucosal, innate immune systems of the host (Cebra 1999; Thaiss et al. 2016). Also gut microbiota leads to the normal development of gut-associated lymphoid tissue and antibody production (Round and

Mazmanian 2009) and inhibits the dendritic cells mediated T-helper cell (Th17) anti-inflammatory pathway (Magrone and Jirillo 2013).

However, with the modern lifestyle, there are changes in food habits, lack of physical activity and excess stress which has led to the fluctuations in the population of gut microbiota that culminates in various immune-mediated diseases. Moreover many life events experienced at an early age disrupt the microbiota which may result in the development of diseases later in life (Arrieta et al. 2014; Penders et al. 2007). Too much of gut bacteria will ferment more fiber into excess fatty acids which may get deposited in the liver and lead to "metabolic syndrome" that often leads to various conditions such as type 2 diabetes, heart diseases, and obesity. Reduction in the population count of anti-inflammatory gut bacteria may lead to inflammatory bowel diseases, including Crohn's disease and ulcerative colitis. On the contrary, when the population of inflammatory bacteria increases it may cause rheumatoid arthritis. Disorders of the CNS example—anxiety, depression, and autism spectrum disorder are also linked by the ecosystem of gut bacteria. Dysbiosis, i.e., imbalances in the ecosystem of gut bacteria may be the reason for the condition of colon cancer, chronic fatigue syndrome, etc. (Menees and Chey 2018; Nagy-Szakal et al. 2017).

In this chapter, we will discuss the various probiotic strains and prebiotics (non-digestible fibers) and their mechanisms of action as well as their health benefits specifically in relevance to aging and longevity. Various risks and safety-related issues related to the use of these biotics will also be discussed.

5.2 Probiotics

A healthy individual has 10 times more the number of gut microbiota in comparison to the number of cells present in the body. Four dominant phyla i.e. *Firmicutes, Bacteridetes, Proteobacteria* and *Actinobacteria* encompass different organisms of different genus and species. The phyla of *Firmicutes* include all organisms belonging to the genus *Lactobacilli*, *Staphylococcus* and *Clostridium* whereas *Proteobacteria* encompasses most of the pathogen like *Enterobacteria*, *Salmonella*, *Escherichia* and *Shigella* (Stojanov et al. 2020).The phylum called *Actinobacteria* includes *Bifidobacteria.* Many of these microbiotas are strategically associated with the gut epithelial lining called Gut Associated Lymphoid Tissue (GALT) which further serves as a habitat for 70% of all immunological active cells and also remains in constant communication with other immunologically active cells of the intestine (Belkaid and Hand 2014; Jandhyala et al. 2015).

There are specific probiotic strains known to display enhanced functionality, specifically *Lactobacillus* and *Bifidobacteria* and hence popularly called psychobiotics for their potential therapeutic benefits (Sarkar et al. 2016). A vast majority of probiotic bacteria belongs to the genus *Bifidobacteria* or *Lactobacilli* and within the genus, many bacterial species display different probiotic activities with a difference in the rate of survival and response. *Lactobacillus* are very popularly used as probiotics and are part of the lactic acid bacteria (LAB) family that converts hexose

sugars to lactic acid in the intestine thereby producing an acidic environment which inhibits the growth of several harmful bacterial species (Fayol-Messaoudi et al. 2005; Florou-Paneri et al. 2013). Further LAB family includes *Lactobacillus*, *Lactococcus*, *Enterococcus*, *Oenococcus*, *Pediococcus*, *Streptococcus* and *Leuconostoc* species and several other strains of the *Bifidobacterium* that are known for their resistive mechanisms to bile salts (Fijan 2014; Ruiz et al. 2013). Similarly a strain called *L. acidophilus* is resistant to bile acid and possess strong antimicrobial effect on other intestinal pathogens including fecal *E. coli* strains (Plaza-Diaz et al. 2019). *L. acidophilus* mainly ferments the non-digestible carbohydrate (include galactose, mannose, trehalose, saccharose and esculin), convert it into organic acids (lactic acid and acetic acid) and produce antibiotic substances (Lactocidin, Acidophilin, Acidolin, Lactocin B) (Nagpal et al. 2012). All these organisms together impart probiotic effect and influence the physiology of the individual.

5.2.1 Role of Probiotics in Aging, Longevity and Well Being

The microbiota and their metabolites in the gastrointestinal tract (GIT) system play a critical role in modulating gut-associated immune systems (Magrone and Jirillo 2013). There is a need for anti-aging and stress-reducing probiotics in all age groups. Particularly, in the elderly population due to gradual deterioration of their anatomy and physiological functions that leads to an imbalance in their gut microbiota ecosystem. This change in microbial composition mainly contributes to metabolic and inflammatory diseases such as irritable bowel disease, diabetes, cardiovascular disease, celiac diseases, food allergies, rheumatoid arthritis and colorectal cancer (Geier et al. 2006; Nagpal et al. 2018).

Moreover, the aging gut also contributes to the over-expression of proinflammatory cytokine IL-6, which significantly affects the function of the intestinal barrier and mucosal immune system (Nagpal et al. 2018). Further decrease in mucus secretion by these healthy bacteria causes changes in intestinal permeability which leads to the development of celiac disease, colorectal cancer, inflammatory bowel disease and even systemic as well as CNS disorders (Kho and Lal 2018). However, a healthy lifestyle with a customized nutritional diet including probiotics can protect against several age-related chronic diseases in elderly people (Landete et al. 2017).

The majority of probiotics inhabited in GIT are anaerobic and their mutualistic behavior possesses wild ranging metabolic activity in the maintenance of physiological functions, including intestinal homeostasis, digestion of complex carbohydrates, protection against pathogens, synthesis of essential nutrients and vitamins, and stimulation of the immune system (Gorbach 1996; Judkins et al. 2020). For example, many probiotics in the lower intestine tract ferment wide a variety of dietary fibers in food to produce SCFAsandother metabolites including acetate, propionate and butyrate that have a distinct role in promoting gut health. SCFA is also involved in controlling anorexigenic hormones by signaling to the gut via free fatty acid receptors (Lu et al. 2018). Acetate is mainly metabolized by the peripheral tissues and propionate is

gluconeogenic. Butyrate is the major energy source for the colonic epithelium that is significantly reduced in elderly people (Parada Venegas et al. 2019). The species called *F. Prausnitzii* and *Roseburia* notably involves in butyryl CoA: acetate CoA transferase route for butyrate formation (Shinohara et al. 2019). Moreover, butyrate can be generated from the LAB family in the colon from the lactate as a precursor. For example, *Bifidobacterium* species in combination with *A. hadrus* and *Eubacterium hallii* form butyrate in the host colon that confers several health benefits (Rivière et al. 2016). Studies also reveal that the supplementation of probiotics in the elderly population, with or without specific diet composition can improve the functionality of microbiota (Landete et al. 2017). In addition to this, a diet rich in phytoestrogens has benefited the aging population since they are pro-estrogenic and antioxidant in nature (Rietjens et al. 2017).

Lactobacillus species like *L. acidophilus*, *L. fermentum*, *L. reuteri* and *B. Bifidum* have been reported to up-regulate transforming growth factor beta (TGF-β), peroxisome proliferator activated receptor gamma (PPAR-γ) along with down-regulation of interleukin-1 (IL-1), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) in older patients with Parkinson's disease when supplemented for 12 weeks (Borzabadi et al. 2018). Probiotics supplementation has also been beneficial in older patients with osteoporosis. Treatment with Kefir fermented milk constituting *Leuconostoc* and *Lactobacillus* for 6 months was found to increase bone formation with elevated bone mineral density at the femoral neck and hip region (de Oliveira Leite et al. 2013; Tu et al. 2015). Further reports have suggested that probiotics can modulate serum hs-CRP levels, pain symptoms and may improve quality of life in patients with a history of knee osteoarthritis (Lei et al. 2017). Also in the same context, *L. casei* strain resulted in minimized pain and early recovery in wrist flexion and grip strength of elderly patients with distal radius fracture (Lei et al. 2016). Reports also point out the beneficial aspect of probiotics in relieving constipation issues. Bifidobacteria in yogurt has been reported to improve stool frequency (Tanaka and Shimosaka 1982). A commercially available *L. rhamnosus* LC705 and *Propionobacter freundreichii* mixture have been investigated to increase in defecation frequency of elderly subjects by 24% (Ouwehand et al. 2002). On the other hand, *B. subtitlis* which is an active ingredient of "natto" is proposed to be contributing to the long and healthy longevity of the Japanese population. At recommended doses *B. subtilis* in human food may decrease the rate of aging and stamp out disease because of the downregulation of insulin/IGF-1 signaling with enhancement of innate immunity (Ayala et al. 2017). More studies on various anti-aging properties of probiotics are represented in Table 5.1.

The probiotics in the gut ecosystem promise two major benefits that include immunomodulatory activity that alleviate many age-related pathologies as well as the formation of bioactive metabolites from dietary compounds (Hemarajata and Versalovic 2013). The immune and protective functions of the microbiota are mediated by different mechanisms. One of them is competition with the pathogen in the lumen and by enhancing the mucosal barrier (Bron et al. 2017; Plaza-Diaz et al. 2019). Microbiota stimulates the epithelium to secrete mucin and strengthen their tight junctions between cells (Takiishi et al. 2017). There are micro-organisms that

Table 5.1 Studies conducted on anti-ageing properties of probiotics

Sr.no	Strains	Models	Duration of exposure	Research finding	Reference
1	*Lactobacillus plantarum*	Humans	12 weeks	Significant enhancement in skin elasticity, reduction in the wrinkle depth associated with the improvement in skin moisture content and gloss	(Lee et al. 2015)
2	*Lactococcuslactis*	Mice strain (Senescence accelerated)	15 weeks	Elevated alpha interferon levels associated with minimised aging related skin thinning and expression of muscle degeneration gene. Increased expression levels of tight junction genes. Treated mice displayed considerably reduced senescence score	(Tsuji et al. 2018)
3	*Lactobacillus salivarius*	*C. elegans*	–	Increased antioxidant status of the model thereby extending the lifespan	(Zhao et al. 2013)
4	*Bacillus licheniformis*	*C. elegans*	–	Extended lifespan of the model organisms and proposed to be associated with the serotonin pathway	(Park et al. 2015)
5	*Lactococcuslactis*	Mice model (Senescence accelerated)	5 weeks	Extended lifespan associated with less consequences of senescence through activation of plasmacytoid dendritic cells	(Sugimura et al. 2018)

(continued)

Table 5.1 (continued)

Sr.no	Strains	Models	Duration of exposure	Research finding	Reference
6	*Lactococcuslactis*	(Senescence accelerated)	2–5 mo	Decreased hair loss, skin ulcers and number of *Staphylococcus* spp along with improved bone density	(Kimoto-Nira et al. 2007)
7	*Lactobacillus gasseri*	*C. elegans*	–	Elevated gene expression of skn-1 and numbers of mitochondria	(Nakagawa et al. 2016)
8	*B. bifidum, L. acidophilus* and *Ba. Coagulans*	Human Volunteers	–	Increasing saccharolytic fermentation and decreased inflammation associated with aging	(Liu et al. 2016)
9	*Lactobacillus* interventions alone or incombination with *Bifidobacterium, Bacillus coagulans*	364 healthy elderly subjects	3 to 12 weeks	Significantly increased NK cell activity	(Gui et al. 2020)
10	Human-origin probiotic cocktail containing 5 *Lactobacillus* and 5 *Enterococcus* strains	Mice model	–	Reduced leaky gut by increasing tight junctions, which in turn reduced inflammation. The action was attributed to increase bile salt hydrolase activity, which in turn increased taurine abundance in the gut that stimulated tight junctions and suppressed gut leakiness	(Ahmadi et al. 2020)

induce the immune system to secrete antibodies, specifically IgA. Whereas, other classes of micro-organisms modulates the cellular immune response in the gut by stimulating both Th1 and Th2 cell types (Yan and Polk 2011).

The composition of microbiota in the gut may affect brain function in adults, thereby having an impact on stress, anxiety, depression, and cognition. Evidences for

the effect of the brain on the gut microbiome can be found in studies documenting that parental, early-life and psychological stress changes the composition of the gut microbiota (Mohajeri et al. 2018). On the other hand, GIT physiology depends on the function of the gut including its motility, its sensation, diet, microbiota and immune function. Function of GITmicrobiota primarily proves beneficial in digestion and metabolic activities. Many of these bacteria synthesize vitamins along with the fermentation of non-digestible carbohydrates that reduce the pH of the gut and also metabolize carcinogens (Gorbach 1996; Judkins et al. 2020; Rowland 2000).

Furthermore, immune development, modulation and enhancement of gut barrier function are major components of gut microbiota. *Bifidobacterialactis* (strain Bp-12) was the first bacteria to achieve GRAS status from the US-FDA for use in infants from birth. The use of this *B. lactis* as oral probiotics by infants has a decade of safety record (Pham et al. 2017). There have been systematic reviews and clinical trials showing a group of babies growing adequately without having any severe side effects and considered safe by regulatory agencies (Sanders et al. 2010). There are reports on babies who have colic also expresses dysbiosis. Populations of children with colic are reported to harbor less *Lactobacilli* or have less diversity of bacteria in their gut ecosystem than babies who do not have colic. This unhealthy ecosystem has more coliform bacteria like *E. coli* which leads to an increase in gut inflammatory markers (Pham et al. 2017). Many reports explain the relationship between these symptoms of crying in colic and an abnormal gut ecosystem. Supplementation of *L. reuteri* increases the amount of *Lactobacilli* in the stools of babies and decrease of the presence of *E. coli* in the gut thereby improving the symptom of infantile colic along with the reduced frequency of functional regurgitation (Chau et al. 2015; Garofoli et al. 2014; Indrio et al. 2015; Savino et al. 2010). Also, *L. reuteri* supplementation significantly decreased the episodes and duration of diarrhea along with decreased respiratory tract infection in children compare with placebo (Gutierrez-Castrellon et al. 2014).

5.2.2 Incorporating Probiotics into Foods

The incorporation of probiotics in foods has decades of history and is added into several dairy and fermented foods to improve their structural and sensorial functionality. Although the techniques have matured over a period of time but their mechanism of action remains the same. These probiotics can be incorporated in fresh, refrigerated dairy products and a broader range of supplementation as an ingredient. However, the selection of compatible probiotic strain and incorporating into foods and most importantly keeping them alive throughout shelf life is a challenge for food biotechnologists. Besides fermented food products, one has to ensure that the food matrix will support probiotic growth. Furthermore, it is also necessary to ensure that the safety of incorporated probiotics does not adversely impact health as well as taste and texture of food during new product development.

These probiotic ingredients in food mainly are selected from *Lactobacillus* and *Bifidobacterium* genus due to their predominant inhabitance in human GI microbiota. A wild range of species in this genus has been used in food supplementation. Notably, some strains of those species have exhibited healthy probiotic attributes. For example, strain like *Bifidobacterium infantis, B. adolescentis, B. animalis subsp animalis, B. animalis subsp lactis, B. bifidum, B. longum, B. Breve* etc. are demonstrated to be effective probiotics in literature (O'Callaghan and van Sinderen 2016).

Phytoestrogens such as coumestans, ellagitannins, lignans, and isoflavones are similar to endogenous estrogen and have both anti-estrogenic and estrogenic effects. They are present in plants or foods derived from plants such as soya, cereals, vegetables, fruit etc. Phytoestrogens protect against various age-related chronic diseases such as cardiovascular and bone diseases, cancers, and cognitive function (Landete et al. 2017). These health benefits derived from phytoestrogens consumption are attributed to bioactive metabolites generated by gut bacteria (Bolca et al. 2013). Thus, the intake of a diet rich in isoflavones, lignans and ellagitannins in combination with selected probiotic bacteria may lead to the production of equol, enterolignans, and urolithins in the gut, respectively (Gaya et al. 2017; Romo-Vaquero et al. 2015; Shimada et al. 2010). This combination of bioactive-rich food with probiotics should be looked upon in amelioration, mitigation and prevention of aging-related pathologies. Nowadays, different bacteria such as *Butyribacterium methylotrophicum*, *Eubacterium callanderi*, and *Peptostreptococcus productus* and the strains *Eubacterium limosum*, *Ruminococcus productus*, *Clostridium scindens*, *Peptostreptococcus productus* SECO-Mt75m3, and *Eggerthellalenta* SECO-Mt75m2 have been involved are being used in the production of enterolignans which further protect from age-related diseases (Landeteetal 2017). Albeit direct anti-aging probiotic formulations are still to be explored, extensive research is being conducted to fortify various food products with probiotics that influence the health status, nutritional levels and well-being of a consumer.

Bifidobacteriumanimalis subsp. *lactis* which are included in LAB family are also used in the fermentation of milk due to their proteolytic activity. These probiotics are included in the dairy product for enhancing the sensorial property along with their proteolytic activity. Besides *Bifidobacterium* strain also induces immunoglobulin production that improved the nutritional value of food by assimilation of substrates not metabolized by the host (Maldonado Galdeano et al. 2019). Thus these probiotics with different functionality are used in combination to yield better results. For example *Lactobacillus delbrueckii* ssp and *Bulgaricus species* are used in combination for acid formation and the production of aroma substances such as acetaldehyde are popular (Chen et al. 2017). Similarly, for the production of yogurt optimum combination of *L. acidophilus*, *Bifidobacterium lactis* and *S. thermophiles* are used. The strain *S. thermophiles* also show a symbiotic relationship with *L. bulgaricus* in the yoghurt production. During yogurt production, there is increase in the acidity of the media and oxygen consumption which is favorable for the growth of *L. bulgaricus* that further forms valine, an essential growth component for *S. thermophilus*. In addition, these strains are also used in various starter cultures to produce fermented dairy products and cheese. Strain *L. casei* is also used to enhance the sensorial property

of traditional dairy products such as kefir and cheese (Horiuchi and Sasaki 2012). Studies have also shown the use of *L. rhamnosus* GG strain in dairy probiotic products marketed for infant formulations. This strain is indigenous to human intestinal flora and thus it has resistance to low pH values with superior adherence ability to the gastrointestinal tract. Another genus called *Enterococcus* are also present in a higher amount in dairy products and have been demonstrated to exhibit widespread technological properties owing to the production ability of bacteriocin (Banwo et al. 2013). Studies have also shown effective use of *E. faecium and L. gasseri* in diarrhea treatment and thus can serve as a possible alternative to the usage of antibiotics (Margreiter et al. 2006). As a probiotic, *E. faecium* have been used for reducing the absorption of cholesterol from the digestive system whereas *L. gasseri's* probiotic activity is attributed to its reducing fecal mutagenic enzyme (Kumar et al. 2012).

5.3 Prebiotics

In 1995, Gibson and Roberfroid defined prebiotics as "a non-digestible food ingredient that provides beneficial effects to host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" (Carlson et al. 2018). In other words, prebiotics is food source which remains undigested by host enzymes, but in the large intestine these are used by microbiota for nourishment. These substances should be selectively used by the host microorganisms and fermented by one or a few colonic bacteria that are beneficial. Also, it has to confer a health benefit which is a critical part because the health benefit has to be measurable and therefore confirmable. For example, a prebiotic called fructooligosaccharide (FOS) is used as a growth substrate for bifidobacteria and some other colonic bacteria as well (Rossi et al. 2005). FOS has been shown to improve calcium absorption, therefore has measurable health benefits (Whisner and Castillo 2018). Similarly, other carbohydrates with low digestibility are also being tested for health benefits which include mono-oligosaccharide (MOS), pectooligosaccharide (POS), galactooligosaccharide (GOS), and xylooligosaccharide (XOS) (Belorkar and Gupta 2016). Several other prebiotics such as inulin, oligofructose, lactulose, human milk oligosaccharide, arabinoxylan, resistant starch, polyphenol, etc. are being studied for their modes of action and health benefits. Recently clinical trial has been conducted using arabinoxylan oligosaccharide (AXOS) as an oral supplementation that reveals the increased total bacterial populations and fecal butyrate concentrations (Sanchez et al. 2009). The natural food sources of the prebiotics are wheat, onions, bananas, honey, garlic, berries, legumes, beans, peas, oats, jerusalem artichokes, asparagus, dandelion, apple skin, chicory root, and leeks. In contrast to fibers, such as cellulose, pectins, and xylans, which promote the growth of many microorganisms in the gut,

prebiotics such as fructooligosaccharides and galactooligosaccharides mainly stimulate the proliferation of *Lactobacillus* and *Bifidobacterium* ("Probiotics and Prebiotics | World Gastroenterology Organisation" 2018; Quigley 2019). Fructooligosaccharides are one of the most common prebiotics, whereas other non-digestible carbohydrates like non-starch polysaccharides, plant wall polysaccharides, and pectins, are not necessarily prebiotic agents, but are termed as dietary fibers. Thus all prebiotics are not fiber and all fibers are not prebiotics. The only thing common in both prebiotics and fibers is that both cannot be digested in the human small intestine and are fermented by the gut microbiota (Floch 2014).

5.3.1 Mechanism of Prebiotic Action

Understanding the mechanism of prebiotic action is very critical as probiotic bacteria use this prebiotics for their growth by fermenting them and releasing other metabolites as by-products. There are different routes for product formation which involve bacterial cross-feeding where the intermediate products are substrates for other bacteria (Blaak et al. 2020).

Production of SCFA by gut microorganisms from prebiotics and other substrates facilitates direct utilization of these prebiotics or complex carbohydrates that generate butyrate or propionate as beneficial SCFA. Further degradation of these complex compounds by short-chain fatty acid-producing bacteria or non-fermentative microorganisms can yield a different product. For example, Bifidobacteria can produce intermediate products such as lactate or even the short-chain fatty acid acetate that are then used by gut bacteria (Blaak et al. 2020). Moreover the antioxidant action of inulin-type fructans on colon mucosa and contractility is also reported. Inulin, through SCFA, can act as a scavenger of reactive oxygen species (ROS) and appears to resist cooking or digestion. Inulin can modulate responses to pathogenic bacterial lipopolysaccharide and protect the gut from inflammatory processes. This mode of inulin action is probably a defense mechanism against ROS by up-regulating colonic mucosal detoxification enzymes like glutathione S transferase thereby restoring the level of some important proteins involved in intestinal smooth muscle contraction (Guarino et al. 2020). However, the exact mechanisms by which inulin acts on intestinal muscle functions to exert direct and/or indirect response to colonic mucosa are not well understood. The various *in-vitro* effects of inulin-type prebiotics are documented not only to stimulate the antioxidant enzymes and scavenge reactive radicals but also to prevent lipid peroxidation in the stomach, replace vitamin C as dietary supplements and inhibit degradation of ascorbate (Busserolles et al. 2003; Kanner and Lapidot 2001; Miene et al. 2011; Phillips et al. 1995). β-GOS is also reported to exhibit immune-modulating function by increasing the immunoregulatory cytokine IL-10, with a significant reduction of IL-1β expression levels (Vulevic et al. 2015). GOS mixture is documented to increase the blood level of interleukin 8 (IL-8) and C-reactive protein and to improve Natural Killer (NK) cell activity as well (Vulevic et al. 2015). Another report indicates that supplementation

with GOS in mice improved lipid metabolism with significant enrichment of mouse microbiota (Cheng et al. 2018). LBA also has anti-inflammatory properties, and in a study on mice, it was demonstrated that its administration is associated with control of obesity and associated metabolic parameters. Lactulose on the other hand is reported to increase *Bifidobacterium* count (Bouhnik et al. 2004), but not Lactobacilli with low production of SCFAs. 5 g/day dose extends the correct balance among the microbial population and SCFAs production, while 10 g/day decreases butyrate production and increases acetate content (Bothe et al. 2017). XOS and soybean oligosaccharides increases the population of *Bifidobacteria*, *Lactobacilli*, butyrate fecal concentration and inhibit clostridium growth (Lecerf et al. 2012; Lin et al. 2016; Mäkeläinen et al. 2010). Polyphenols are also known to increase the growth of *Lactobacilli*, *Bifidobacterium*, *F. Prausnitzii* and reduce *Clostridium* growth (Okubo et al. 1992; Tzounis et al. 2011). It also inhibits pro-inflammatory mediators cyclooxygenase-2 (COX2), IL-6, TNF-α, Nuclear Factor kB (NFkB) and Vascular-Endothelial Growth Factor. Polyphenols have also been reported to reduce serum triacylglycerol and C- reactive protein (Guarino et al. 2020). Thus dietary intake of prebiotics seems to have a positive modulatory effect on intestinal microbiota by not only promoting the growth of good intestinal bacteria, but also by producing metabolites that are potentially protective of gut functionality.

5.3.2 The Health Benefits of Prebiotics

The health benefits of prebiotics need to be validated in controlled studies on the target subjects. This beneficial effect(s) are mainly categorized into local effects (gut targeted) or systemic effects (whole-body). There are three immediate local effects that prebiotics can have. First, prebiotics like dietary fiber contribute to fecal bulking and also increased transit rate through the colon that protecting the gut or the colonic epithelial cells from any toxic compounds that might have been ingested in the diet. Increased transit rate make sure that any such toxins move through the large intestine more quickly again protecting the gut cells. Second, bacterial fermentation of the prebiotic causes a lowering of the pH. This helps to inhibit the growth of pathogenic bacteria which donot generally grow in an acidic pH. Moreover it also improves calcium solubility and therefore uptake of calcium and influences bone health (Slavin 2013). SCFAs like butyrate, acetate and propionate are important energy sources for the gut epithelial cells which keep the gut healthy and help gut cell turnover (Parada Venegas et al. 2019). So these local effects have very specific health benefits. Furthermore, the European food safety authority (EFSA) has also given a positive opinion for the consumption of Native chicory inulin that increase stool frequency (Micka et al. 2017). Probiotics like GOS and FOS supplementation in infant formula reveals the increase in Bifidobacteria number (Vandenplas et al. 2014). Also, consumption of FOS and inulin resulted in increased in calcium absorption that improved bone health in adolescents and menopausal women (Whisner and Castillo 2018). The systemic effects of prebiotic fermentation by the gut microorganism have been

studied during clinical trials and have revealed metabolic and immunomodulatory functions (Hemarajata and Versalovic 2013). The effects are accomplished through fermentation by the gut bacteria and then through uptake of metabolites or interaction with the host. Food ingredients particularly diet as prebiotics are fermented by the gut microbiota into the SCFA that is used as an energy source by the epithelial cells. SCFA enters the liver through the bloodstream where most of it gets involved in gluconeogenesis (den Besten et al. 2013). Moreover, this SCFA also reaches other organs like brain, muscle and adipose tissue. SCFA may stimulate a particular effect through interaction with receptors present in these organs. For example G-protein-coupled receptors (GPR41/43) present in epithelial cells interact with SCFA and lead to the secretion of hormones PYY and GLP-1 which then reach the brain and lead to satiety (Koh et al. 2016). Similarly in adipose and muscle tissue SCFA lowers inflammation (Vinolo et al. 2011). A randomized double-blind trial suggests a fiber-containing yogurt sweetened with lactitol as a natural means of treating chronic constipation in elderly hospitalized subjects (Rajala et al. 1988). GOS relieves constipation in few but not all elderly people by ensuring an easy defecation process (Teuri and Korpela 1998). They suggested different people have different responses upon GOS ingestion. Another trial to investigate the repercussion of lactose or inulin on the bowel habits of constipated elderly patients revealed that inulin served as a better laxative effect than lactose and reduced functional constipation with mild discomfort (Kleessen et al. 1997). Furthermore, the consumption of oral supplementation with FOS and inulin for 12–13 weeks is reported to improve physical function, nutritional status, quality of life, as well as frailty degree (Jayanama and Theou 2020). Inulin with vitamin D is also reported to increase physical function, nutritional status and quality of life in a multicentric prospective observational study (Abizanda et al. 2015). Inulin with FOS enhanced handgrip strength and modulated Barthel index, body mass index along with frailty phenotype (Kleessen et al. 1997; Theou et al. 2019). The beneficial effect of GOS in increasing *Bifidobacteria, Lactobacillus, Enterococcus* with decrease in pathogenic organisms is also well established (Vulevic et al. 2015). This article also reports increased IL-10 levels with a decrease in IL-6, IL-1β, and TNF-α post GOS ingestion in a double-blind, cross-over, randomized controlled trial.

5.4 Risk and Safety Issues

Although probiotics have been used safely over a period of hundred years in the food and dairy industry, the safety outcomes have not yet been effectively reported during clinical trials. According to Marteau 2001, "the zero risk does not exist, and that acceptance of the concept that probiotics may not only have positive effects but potentially also side effects is important." A report by the Agency for Healthcare Research and Quality (AHRQ) on the safety of probiotics extended comprehensive literature on 622 organisms from 6 genera viz., *Bifidobacterium, Saccharomyces, Lactobacillus, Streptococcus, Enterobacillus and Bacillus* but did not provide conclusive evidence of risk and rather insinuated that the literature is not sufficiently equipped to claim the

safety nature of the probiotics with assurance (Hempel et al. 2011). Clinical trials in hospitalized children, hospitalized adults and immunocompromised subjects using various strains have revealed no toxic effects. Likewise, trials conducted in pregnant women, premature neonates, elderly people and patients with inflammatory bowel disease also showed no harmful repercussion of the probiotics (Doron and Snydman 2015). A report by World's Health Organisation (WHO) in 2002 suggested that probiotics may have four types of typical side effects like a) Systemic infections b) Excessive immune stimulation, c) detrimental metabolic activities and d) Transfer of genes FAO/WHO (2002). There exists a plethora of literature suggesting the side effects of the probiotic strains such as *S. boulardii, L. rhamnosus, B. subtilis, S. pyogenes, K. pneumonia, L. acidophilus, B. infantis, S. thermophilus, L. bulgaricus* during clinical trial. Some reports have revealed the occurrence of systemic infections caused by *S. boulardii* in subjects receiving treatment against fungemia and have reported complication such as fever spike, septic shock, contamination of central venous catheter, massive colonization by yeast and transmission of infection (Cesaro et al. 2000; Hennequin et al. 2000; Lherm et al. 2002; Muñoz et al. 2005; Perapoch et al. 2000). Munoz et al. 2005 have recommended that probiotics can prove to be critical specifically in immunosuppressed patients. A child with the short gut syndrome and a young man were reported with an incidence of bacteremia and endocarditis along with septic arthritis respectively owing to treatment with *L. rhamnosus* (De Groote et al. 2005; Presterl et al. 2001).On the other hand, nosocomial bacteremia and distinct septicemic episodes were recorded in subjects given with oral preparation of *B. Subtilis* (Oggioni et al. 1998; Richard et al. 1988). The organism caused severe immunodeficiency and persisted in the intestinal tract of 73 years old male with chronic lymphocytic leukemia (Oggioni et al. 1998). *Lactobacilli* strain was also reported to cause a systemic infection like bacteremia by Land et al. 2005.

In other reports, *S. pyogenes*, *L. rhamnosus, K. pneumonia* and other bacterial probiotic cocktail caused immunostimulation in monocytes, monocytes derived immature dendritic cells and bone marrow derived dendritic cells. *L. rhamnosus* caused moderate increase in the expression of cell-surface co-stimulatory molecules and chemokine response, whereas, *S. pyogenes* strongly induced maturation of monocyte derived dendritic cells (Veckman et al. 2004). *K. pneumoniae* induced Th1 immune responses via dendritic cells and differential response to various bacterial strains exist owing to differential modulation of dendritic cells (Braat et al. 2004). Probiotic cocktail was reported to modulate dendritic cell surface phenotype and cytokine release in granulocyte–macrophage (Drakes et al. 2004). A provoked D-lactic acidosis case was reported in a Chinese boy with short bowel syndrome upon probiotic (*L. acidophilus* and *B. infantis*) supplemention (KU et al. 2006). Furthermore, 61 pediatric patients when supplemented with *L. rhamnosus*, the zilch effect was observed in reducing the incidence of nosocomial infections and instead promoted the infection (Honeycutt et al. 2007). *L. acidophilus*, *B. lactis*, *S. thermophilus*and*L.bulgaricus* with oligofructose favorably altered the microbial composition of the upper gastrointestinal tract but had no effect on intestinal permeability (Jain et al. 2004).

Lactic acid bacteria possess plasmids containing genes conferring resistance to various antibiotics such as tetracycline, erythromycin, macrolide, chloramphenicol or lincosamide streptomycin, and streptogrammin. There are some reports that pediococcus and leuconostoc species can accept broad host range antibiotic resistance plasmids from lactococcus species. Conjugation transfer from enterococci to lactobacilli and lactococci can occur in the gut of animals as well as in vitro; however, the transfer to lactobacilli is quite rare (Doron and Snydman 2015). Lateral gene transfer between probiotic organisms to other organisms in the gut or other sites is possible though no clinical evidence of transfer of antimicrobial resistance has ever has been reported. This is particularly important to investigate as probiotics arecommonly used to rejuvenate the good microflora of gut post/during antibiotic treatment. Furthermore application of mono-strains or multi-strains need to be evaluated carefully for their synergistic modulatory role.

On the other hand, prebiotics are known to cause significant change in the gut microbiota composition, treat chronic constipation and facilitate easy defecation in elderly people. Prebiotics posse's better laxative potential and can improve nutritional status, physical function and quality of life of elderly subjects. Prebiotics are also reported to improve stool quality (pH, frequency and consistency) in children as well (Bozzi Cionci et al. 2018). It also reduced the risk of gastroenteritis and improves the general well-being of a person. Not many reports are available with respect to effect of prebiotics in elderly aged groups and thus more studies need to be undertaken for component characterization, functional characterization, product formulation and safety assessment using double blind, randomised-controlled human clinical trials.

5.5 Research Trends, Research Gaps and Future Perspective

Classical probiotics have shown promising effects on human gut microflora but there is always an urge to develop better strains followed by the improved selection process. Previous studies have lead to the possible next-generation probiotic strains like *Clostridium* clusters IV, XIVa and XVIII, *F. prausnitzii*, *Akkermansiamuciniphila, Bacteroidesuniformis*, *Bacteroidesfragilis*and *Eubacteriumhallii.* The next-generation probiotics were evaluated in preclinical trials and yielded positive outcomes of possessing modulatory roles in inflammatory and metabolic disorders. Extensive clinical trials can give information on the effective use of these next generation microbes in mono-strains or multi-strains based formulations against many age-related diseases. In addition, new techniques are required for the development of new probiotic products containing strains of human origin (El Hage et al. 2017). Other than next-generation microbes, postbiotics and paraprobiotics are the upcoming horizons in the field. Postbiotics and paraprobiotics are cell constituents, metabolic by-products and non-viable microbial cells, respectively that contribute in health improvement (Nataraj et al. 2020). They are made from many probiotic

strains and postbiotics by different inactivating methods. Various postbiotics include metabolic by products of living probiotic organisms such as vitamins, cell free supernatants, bio-surfactants, phenols (urolithins, equol, enterolactone, valerolactones, 8-prenylnaringenin and enterodiol) flavonoids (norathyriol, daidzein, desaminotyrosine, equoldaidzein), terpenoids (paeoniflorin, genipin, paeonimetabolin I, II, III and paeoni lactone glycosides) (Cortés-Martín et al. 2020; Wang et al. 2019). On the other hand, parabiotic include ruptured components of probiotic cells such as teichoic acids, muropeptides, pili, fimbriae, flagella, exopolysaccaride etc. (Chung et al. 2019; Shenderov 2013).

The use of such molecules in therapeutic studies provides an upper edge in understanding the molecular mechanisms of each purified cell component as using probiotics may yield confusing outcomes owing to complex bacterial structure. They have been linked to harbor immunomodulatory, anti-inflammatory, anti-hypertensive, hypocholesterolemic, anti-obesogenic, anti-proliferative, and antioxidant activities (Vallejo-Cordoba et al. 2020). Postbiotic preparations have also received patents as 1) anti-tumour agents, 2) bio-therapeutics for immunomodulation specific claims and feed additives for monogastric animals (Nataraj et al. 2020). These reports suggest the excellent potential of these molecules to boost host health by mitigation and prevention of the diseased condition. But their mechanism of action and elated signal transduction pathways are still unexplored and may be extensively researched by using of metatranscriptomic, metabolomic and metaproteomic approaches that may contribute in understanding their mechanism of action. Further their potential applications in the pharmaceutical and food industry can be revealed. Also, advancement in modern techniques and methods can lead to the production of bioengineered novel recombinant probiotics (Vallejo-Cordoba et al. 2020). More number of clinical trials authenticating the claims of these bioactive molecules may prove their direct therapeutic implications. Trials on subjects with low immune competence can unfold the tolerance status of these bioactive molecules by immunocompromised subjects. Stability related studies of para and postbiotics in in vitro and in vivo digestive conditions can prove beneficial in further exploring their health benefits.

There are still some important unanswered questions related to probiotics that need the urgent attention from researchers such as scientific validation of all claimed benefits by the definition of probiotics? There are very meagre reported meta-analyses, systematic reviews in comparison to the clinical trials conducted which reflects the inadequate comparison of these trials. Predominantly, the efficacy of probiotics is investigated widely in gastrointestinal diseases like antibiotic associated diarrhea, *Clostridium difficile* diarrhea, inflammatory bowel disease and necrotizing enterocolitis. Also, another major area of research is probiotic induced allergy and atopy. Despite of so much research, there are issues with understanding the efficacy of probiotics due to poor quality clinical trials, abysmal clinical trial reports and sufficiently evaluated safety reports. Moreover, Agency for Healthcare Research and Quality (2011) report complained about the inadequate literature to substantiate whether probiotics consumptions are safe, but still probiotics are being consumed by millions of people on daily basis further raising the concern.

5.6 Conclusion

Aging leads to several pathologies that may be directly or indirectly be associated with the imbalances of the gut microbiota and associated immune system. Moreover, intestine is considered to be the prime organ to enhance and improve the quality of life in age-related senescence process. These beneficial organisms residing in the gut may impart a powerful ameliorative effect in the prevention of age-associated health deterioration by its immunomodulatory activity. Reduction in proinflammatory status and age-related pathologies can be mitigated by adopting a healthy lifestyle along with a customized diet for elderly people. Probiotics possess excellent potential in preserving the integrity of the gut barrier and in evading infection. Prebiotics rich diet can facilitate the probiotics to exhibit their important function and may lead to the generation of equol, enterolignans, and urolithins, which are considered protective against chronic diseases related to aging. Although investigating the toxicological/safety aspect of probiotic and prebiotic is a pressing priority, their applications in treatment, prevention and amelioration of the diseases seem to be gaining popularity and have been reported to be beneficial by many researchers. The limited data expressed in the risk and safety section should not dishearten the investigator to promote the usage of good bacteria in different food products. Moreover, it is recommended to the researcher community to plan and execute active surveillance to understand infections and other side effects associated with the usage of these biotics. Also, it is important to investigate whether the probiotic usage is appropriate in subjects with low immune competence, short bowel syndrome, cardiac valve disease and central venous catheters.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

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