ACTA SCIENTIARUM POLONORUM
Acta Sci. Pol. Technol. Aliment. 21(1) 2022, 53–66
www.food.actapol.net pISSN 1644-0730 eISSN 1898-9594 http://dx.doi.org/10.17306/J.AFS.2022.1013

ORIGINAL PAPER

Received: 16.10.2021
Accepted: 3.01.2022

THE ROLE OF PROBIOTICS ON SLOWING DOWN THE AGING PROCESS

Pınar Şanlibaba[1], Zehra Tuğçe Toprak[1], Başar Uymaz Tezel[2]✉

[1]Department of Food Engineering, Engineering Faculty, Ankara University
50th Year Settlement, 06830 Gölbaşı, Ankara, **Turkey**
[2]Bayramiç Vocational School, Çanakkale Onsekiz Mart University
17700 Bayramiç, Çanakkale, **Turkey**

ABSTRACT

The gastrointestinal (GI) microbiota is one of the most complex ecosystems in nature that are mainly comprised of bacteria and other microbes like fungi, protozoa, and viruses. More than 1000 bacterial species have been reported in the gut microbiome, of which most of these species belong to *Firmicutes* (31.1%), *Proteobacteria* (29.5%), *Actinobacteria* (25.9%), or *Bacteroidetes* (7.1%) phylum. A symbiotic relationship, which plays a critical role in host health, exists between intestinal microflora and its host. With aging, the intestinal microbiota profile changes are observed, generally characterized by the decrease in biodiversity, carriage of commensals, and enrichment of opportunistic pathogens. The dysbiosis associated with aging in the gut microbiota increases the risk of several diseases. Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" and play crucial functions in improving gut health and disease in all age groups, particularly the elderly induvial. This review focuses on the promising effects of probiotics on slowing down the aging process, treating age-related diseases, and improving the quality of life in light of the current clinical studies.

Keywords: probiotic, microbiota, gut, aging, elderly

INTRODUCTION

Intestinal microbiota, one of the most complex ecosystems in nature, hosts between 10^{13} and 10^{14} microorganisms. Although, initially this number is believed to be at least 10 times higher than the number of human cells (Vyas and Ranganathan, 2012), the recent findings indicate that there are approximately equal microbial and human cells (Anwar et al., 2021; Sender et al., 2016). The total weight of these microorganisms is 1–2 kg, similar to the weight of the human brain (Foster et al., 2017). Even if only 20% of the intestinal microflora is characterized, a significant variation is observed wherein hundreds of different types of microorganisms participate (Jensen et al., 2017). Consisting of a predominant bacterial ecosystem, the intestinal microbiota includes archaea, protozoa, eukaryotic and bacterial viruses (bacteriophages), fungi, and helminth parasites (Foster et al., 2017). More than 1000 bacterial species have been reported in the gut microbiome, of which at least 160 species can be observed in each person, and a significant number of them colonize in the lower intestinal tract (10^{11}–10^{12} cells/g). While most of these species belong to *Firmicutes* (31.1%), *Proteobacteria* (29.5%), *Actinobacteria* (25.9%), or *Bacteroidetes* (7.1%) phylum, the others are included in *Verrucomicrobia*, *Fusobacteria*, *Cyanobacteria*, or *Spirochaetes* phylum. The number

✉buymaz@comu.edu.tr, https://orcid.org/000-0002-4156-8861, +90 286 773 2512/139, fax +90 286 773 2513

© Copyright by Wydawnictwo Uniwersytetu Przyrodniczego w Poznaniu
(cc) BY-NC

of anaerobic bacteria in the intestinal ecosystem is two to three times higher than that of facultative anaerobic and aerobic bacteria. The two dominant phylotypes, *Firmicutes* and *Bacteroidetes*, include *Lactobacillus* sp., *Clostridium* sp., *Enterococcus* sp., and *Bacteroides* sp. (Jensen et al., 2017).

A symbiotic relationship exists between intestinal microflora and its host, which includes supporting metabolic functions, regulating angiogenesis, activating the enteric nervous system, maintaining intestinal motility, contributing to the development of immune tolerance, and preserving mucosal barrier function (Cheng et al., 2019). Epidemiological studies on the relationships between changes in intestinal microflora diversity, structure, or function in the early stages of life and disease development later in life revealed that a correct establishment of the host-flora relationship is essential for immune system development (Akçelik et al., 2020; Jensen et al., 2017). The correct establishment of this relationship, which plays a critical role in host health, is closely associated with various factors such as genetic, mode of birth, gender, diet, age, physical activity, stress, environmental factors, various diseases, and antibiotic usage. Therefore, the microbiota has reached a critical position where it needs to be defined as a new organ. This has led to increasing scientific attention to the microbiota (Akçelik et al., 2020).

Disruptions in the composition and metabolic capacities of microbial communities are known as dysbiosis or dysbacteriosis that deteriorates not only the relationships between microorganisms but also the interaction between these microorganisms and their hosts. Although most of the factors that play a role in dysbiosis are still unknown, several internal and external factors such as the method of birth, exposure to disinfectants, household cleaners and other chemicals at young ages, diet, antibiotic usage, and stress may be considered. Dysbiosis is typically initiated with the combined effects of these factors, and its severity may increase or decrease depending on personal predispositions, particularly genetic predispositions (Akçelik et al., 2020). Although the microbial balance (normal microflora) cannot be defined and the causes of dysbiosis cannot be definitively stated, dysbiosis can be expressed as the loss of beneficial microorganisms, proliferation of potentially harmful microorganisms, and/or loss of general microbial diversity (Olesen and Alm, 2016). Dysbiosis causes intestinal diseases, such as inflammatory bowel syndrome, irritable bowel syndrome, and colorectal cancer, and other crucial diseases such as allergy, asthma, obesity, nonalcoholic fatty liver diseases, cardiovascular diseases (CVD), and even neuropsychiatric diseases (Akçelik et al., 2020; Olesen and Alm, 2016; Vyas and Ranganathan, 2012).

The composition of the gut microbiota is shaped by host cells using multiple control mechanisms which act as habitat filters and by host behaviors such as diet selection. Among the several approaches to positive modulation of intestinal microflora, the probiotic approach is prominent, which began with the pioneering work of Nobel Prize-winning scientist Elie Metchnikoff (Akçelik et al., 2020). The new term probiosis (the modulation of intestinal microbiota using probiotics) could be a promising approach for the prevention and treatment of diseases (Vyas and Ranganathan, 2012).

According to the definition of Food and Agriculture Organization of the United Nations and the World Health Organization, probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014). Most of the probiotic microorganisms belong to the lactic acid bacteria (LAB) group, such as *Lactobacillus* spp., *Leuconostoc* spp., *Lactococcus* spp., *Pediococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. In addition to *Saccharomyces boulardii*, an eukaryotic microorganism, other bacterial species such as *Bifidobacterium* spp., *Bacillus* spp., *Escherichia coli*, and *Clostridium butyricum* have been described in detail regarding their probiotic properties in Table 1.

The ancient history of LAB in the fermentation and preservation of foods may be explained by their ability to metabolize different carbon sources, their widespread tolerance to various stress environments, and their "generally recognized as safe" (GRAS) status for human and animal consumption (Akçelik and Akçelik 2020; Oniszczuk et al., 2021). A wide variety of fermented foods such as yogurt, kefir, tempeh, sauerkraut, and kimchi are potential sources for isolating probiotic microorganisms.

Thanks to some outstanding properties, probiotics have beneficial effects on host health, which are demonstrated by clinical studies, such as anti-pathogenicity,

Table 1. Microorganisms used as probiotics

Microbial groups	Genus	Species
Lactic acid bacteria	*Lactobacillus* spp.	*Lb. acidophilus*, *Lb. amylovorus*, *Lb. brevis*, *Lb. bulgaricus*, *Lb. casei*, *Lb. cellobiosus*, *Lb. crispatus*, *Lb. curvatus*, *Lb. fermentum*, *Lb. gallinarum*, *Lb. helveticus*, *Lb. johnsonii*, *Lb. lactis*, *Lb. paracasei*, *Lb. plantarum*, *Lb. reuteri*, *Lb. rhamnosus*, *Lb. delbrueckii* ssp. *bulgaricus*
	Streptococcus spp.	*Str. salivaris* ssp. *thermophiles*
	Lactococcus spp.	*Lactococcus lactis* ssp. *cremoris*
	Leuconostoc spp.	*Leuconostoc mesenteroides*
	Pediococcus spp.	*Pediococcus pentosaceus*, *P. acidilactici*
	Enterococcus spp.	*Ent. faecium*, *Ent. faecalis*
Bifidobacteria	*Bifidobacteria* spp.	*B. adolescentis*, *B. animalis*, *B. bifidum*, *B. breve*, *B. essensis*, *B. infantis*, *B. longum*, *B. laterosporum*, *B. thermophilum*
Propionibacteria	*Propionibacteria* spp.	*Propionibacteria acidipropionici*, *P. freudenreichii*, *P. jensenii*, *P. thoenii*
Spore forming bacteria	*Bacillus* spp.	*Bacillus alcalophilus*, *B. cereus*, *B. clausii*, *B. coagulans*, *B. subtilis*
Other bacteria	*Escherichia* spp.	*Escherichia coli*
	Sporolactobacillus spp.	*Sporolactobacillus inulinus*
Yeast	*Saccharomyces* spp.	*Saccharomyces cerevisiae* (*boulardii*)

Source: adopted from Anadón et al. (2016).

antidiabetic, anti-obesity, anti-inflammatory, anticarcinogenic, and anti-allergic activities (Gao et al., 2019; Tezel Uymaz and Uymaz, 2020). For the mentioned effects, probiotics must chemically or physically inhibit the growth of pathogenic bacteria through immune, hormonal, and neuronal manipulations and must stimulate the growth of useful microorganisms (Oniszczuk et al., 2021). Probiotics are reported to be associated with vitamin synthesis, stimulation of the immune system, protection of the intestinal barrier defense system, metabolism of carcinogens, prevention of pathogenic microbial colonization, production of short-chain fatty acids (SCFAs) for enterocyte energy, and potentially lowering levels of neurotoxic components (Logan and Katzman, 2005). Probiotics can communicate with the host through the microbiota-gut-brain axis, including the immune, neuroendocrine, and neural pathways that affect the brain and host behavior (Liang et al., 2015). In addition, the gut microbiota can potentially convert some dietary components such as polyphenols into metabolically more suitable forms. Because of the positive changes in the intestinal microbiota composition, the metabolic balance and cardiovascular health of humans are maintained (Gao et al., 2019; Tezel Uymaz and Uymaz, 2020).

The intestinal microbiota profile changes sharply in elderly individuals compared with healthy adults, and these changes occur gradually over time, with no chronological threshold defined (Jackson et al., 2016; Şireli et al., 2020). The intestinal microecosystem of the elderly is generally characterized by the decrease in biodiversity, carriage of commensals, and enrichment of opportunistic pathogens (Rondanelli et al., 2015). The mentioned changes could be because of various reasons associated with aging, such as deterioration of chewing function, taste, and saliva production (Ni et al., 2019). On the other hand, gastric acid production and GI transit duration slow down, causing constipation. In addition, the rate of impairment of these biological functions is affected by factors such as lifestyle, malnutrition, weakness, and inflammations of the elderly (Cancello et al., 2019; Şireli et al., 2020).

The dysbiosis of harmonious relationship in the gut microbiota associated with aging or different reasons is associated with several diseases, including type 2 diabetes, inflammatory bowel diseases, and colorectal cancer (Ferretti et al., 2018). Studies have revealed that therapeutic approaches targeting the microbiota are promising in treating age-related metabolic and neurodegenerative diseases (Asl et al., 2019). This study aimed to summarize the use of probiotics in treating age-related diseases in the light of the current clinical studies. In this study, the effects of probiotics on slowing down the aging process and improving the quality of life will also be discussed.

THE CHANGES IN GUT MICROBIOTA COMPOSITION IN ELDERLY

Changes in the intestinal microbiota composition at different ages are summarized in Table 2 (Duncan and Flint, 2013).

The first microbial colonization commences during and early after birth. Several crucial factors affect the infant microbiota composition, including delivery type, gestational age at birth, feeding mode (breastfeeding or formula), and antibiotics use (Ferretti et al., 2018). Among these factors, the type of birth is crucial in identifying the precursor bacterial species in the microbial colonization of infants. Babies born by vaginal delivery are colonized first by maternal vaginal and fecal bacteria; therefore, lactobacilli and *Prevotella* species are predominant (Hardy et al., 2013). Those born by cesarean section are first exposed to bacteria originating from the hospital environment (Hardy et al., 2013); they are reported to develop a different microbiota with abnormal short-term immune responses and the risk of developing immune diseases in the longer term (Dinan et al., 2013).

The feeding mode of the newborn is another essential factor that affects microbial colonization. Breast milk includes free human milk oligosaccharides, fermented by infant gut microbiota. Human milk oligosaccharides represent a pool of more than 45 different linear or branched oligosaccharides, consisting of 3–15 carbohydrate units, including glucose, galactose, N-acetylglucosamine, fucose, and sialic acid (Thomson et al., 2018; Walker, 2013). This oligosaccharide composition of human milk, depending on the genetic variability, is crucial for forming a healthy microbiome dominated by *Bifidobacterium* species in the infant gut microbiome (Díaz and Garrido, 2020). Moreover, normal colonization with the species occurs if the baby is only breastfed during the first six months. *Bifidobacterium* genomes include a large set of genes for using carbohydrates. *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, and *Bifidobacterium breve* can use human milk oligosaccharides, particularly infant-derived ones (Thomson et al., 2018). The members of genus *Bifidobacterium* play a critical role in the barrier effect, immune system stimulation, and are associated with certain beneficial health effects (Arboleya et al., 2016). In the newborn, breast milk is a continuous source of commensals such as *Lactobacillus acidophilus* and *Lactobacillus gasseri* and *Bifidobacterium* species. Hardy et al. (2013) stated that diarrhea, allergies, and inflammatory diseases are less common in breastfed babies. The gut of formula-fed babies is characterized by a crucial amount of bifidobacteria and an increased amount of *Firmicutes* and *Bacteroides*, *Clostridium difficile*, *Bifidobacterium adolescentis*, and certain *Proteobacteria*

Table 2. Changes in gut microbiota composition at different ages

Fetus	Baby	Child	Adult	Elderly
Generally sterile	**Breastfed:** *Bifidobacteria* usually dominate **Bottle-fed:** more diverse with more *Bacteroidetes* and less *Bifidobacteria*	Increase in biodiversity following weaning and intake of solids	**Dominant phyla:** *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* **Less dominant phyla:** *Proteobacteria*, *Verrucomicrobia*	**Compared to healthy adults:** decrease in *Firmicutes* and *Bifidobacteria*; increase in *Bacteroidetes* and *Proteobacteria*

Source: adopted from Duncan and Flint (2013).

species. Eventually, by 12 to 18 months, the baby's gut is completely colonized with microorganisms involving more than 1000 separate species. During these months, if antibiotic treatment is administered, the timing and nature of colonization change negatively (Walker, 2013). After this period, only minor changes occur, and the child has an adult-like microbiota by approximately three years of age. At the phylum level, the intestinal microbiota is made up of 80–90% *Firmicutes* (species such as *Lactobacillus*, *Clostridium*, and *Enterococcus*) and *Bacteroidetes* (species such as *Bacteroides*; Arboleya et al., 2016).

Although the rate of bifidobacteria reaches up to 90% of the total colon microbiota in the first 12 months of life in breastfed infants, it decreases over time to 5% in adulthood and even below in the elderly (Rivière et al., 2016). In adulthood (aged <65 years), the composition of gut microbiota at the species level is comparatively stable. The adult gut is inhabited by 10^{13} to 10^{14} microorganisms (Dinan et al., 2013). The dominant bacterial phyla in healthy adults are *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*, whereas *Proteobacteria* and *Verrucomicrobia* are present in lower amounts. One of the most abundant species in the healthy gut is *Faecalibacterium prausnitzii*, which shows potent anti-inflammatory activities. Typically, *B. adolescentis* and *B. longum* dominate the adult intestinal microbiota. In addition, the gut community can contain organisms that can have adverse effects through their metabolic outputs and gene products. Therefore, the balance between benefit and harm for the host depends on the overall state of the microbial community, including its distribution, diversity, species composition, and metabolic outputs (Duncan and Flint, 2013; Rivière et al., 2016).

Aging is associated with intestinal imbalance, dysbiosis, increased intestinal permeability, and leaky gut that enables the transition of endotoxins, some microorganisms, and other microbial metabolites into the blood circulation system (Singh et al., 2020). In addition, the changes observed in the gut microbiota of older adults can be caused by various factors, including the decrease in general health status with malnutrition and an increased need for drugs, particularly antibiotics. Table 3 summarizes aging-related changes in the gut microbiota profile.

Rondanelli et al. (2015) have demonstrated that the elderly typically show a decline in numbers of *Bifidobacterium* and *Firmicutes* species and an increase in *Enterobacteriaceae* and *Bacteroidetes* compared with the adult population. Although *B. adolescentis*, *Bifidobacterium catenulatum*, and *B. longum* are highly

Table 3. Aging-related changes in the gut microbiota profile

Aging-related changes in the gut microbiota profile	Results	Mechanism
Decrease in biodiversity	increased diarrhea risk related to *Cl. difficile*	reduction in *Cl. difficile* colonization resistance
Enterobacteriaceae proliferation	increased in the inflammatory response increased in the probability of metastatic colorectal cancer development	excessive endotoxin production
Reduction in butyrate producer bacteria	weakening in the colon epithelium increased in the inflammatory response increased colorectal cancer risk	decreased in: • protective and trophic function of butyrate in colon epithelium • reduction in anti-inflammatory effects of butyrate • reduction in anti-neoplastic effects of butyrate
Colonization with toxin-producer *E. coli*, *Helicobacter pylori*, and *B. fragilis*	increased colorectal cancer risk	due to toxins, deterioration in control of the: • cell cycle • regulation and growth • DNA damage

Source: adapted from Biagi et al. (2017).

dominant bifidobacteria species in the elderly, their diversity and abundance significantly decrease with aging. Although this is associated with reduced adhesion to the gut mucosa, it is unclear whether this was because of changes in the microbiota or the mucus structure (Arboleya et al., 2016). Moreover, SCFAs--producing saccharolytic bacteria from the *Lachnospiraceae* and *Ruminococcaceae* families are reduced. SCFAs have essential functions such as maintaining epithelial barrier integrity, metabolic regulation, immune functioning, and modulation of neuronal activity (Cancello et al., 2019). This aged-associated microbiota profile played a central role in systemic inflammation during the aging process (Ni et al., 2019). On the other hand, facultative anaerobes, including opportunistic pathogens, such as enterobacteria, enterococci, streptococci, and staphylococci, increase by advancing age. Levels of *Clostridium* cluster XIV and *Faecalibacterium prausnitzii*, the primary producers of butyrate, also decrease in the elderly (Rondanelli et al., 2015; Singh et al., 2020). However, according to the age of individuals and geographic location, these results may differ from each other. Members of the *Clostridium* cluster XIVa have been reported to decline in the elderly and centenarians from Japan, Finland, and Italy. In contrast, an opposing trend has been reported from Germany in individuals above 60 years of age. Increasing levels of *Bacteroidetes* have been reported in the elderly from several countries, including Germany, Austria, Finland, and Ireland; however, these results differed among the elderly and centenarians in Italy (Bedani et al., 2016).

The extended use of antibiotics in the elderly has a detrimental effect on the gut microbiota composition, reducing the bacterial diversity (Arboleya et al., 2016). For example, the treatment for *C. difficile*-associated diarrhea includes the use of broad-spectrum antibiotics such as metronidazole and vancomycin. Although broad-spectrum antibiotic therapy mainly affects the target pathogen bacteria, it also affects up to 33% of the gut microbial population. Moreover, there is a personalized effect on the gut microbiota can be mentioned (Rea et al., 2012). The antibiotic treatment decreases the number of the *Bacteroides* group, changes its composition, and decreases the number of *Bifidobacterium* spp., *Clostridium* spp., *Desulfovibrio* spp., and *Faecalibacterium* spp. (O'Sullivan et al., 2013). After antibiotic treatment, virulent strains of *C. difficile* can colonize the gut and synthesize toxins, shedding spores and causing illnesses, ranging from mild diarrhea to fulminant relapsing diarrhea and pseudomembranous colitis (Rupnik et al., 2009). During the use of antibiotics, strategies aimed at restoring the microbiota have been studied, particularly the use of probiotics to adjust the dysbiosis in the bifidobacteria population and the change in gut microbiota after antibiotic treatment. O'Sullivan et al. (2013) have studied the effect of antibiotic therapy on the composition of the gut microbiota in elderly Irish individuals (aged ≥65 years). A total of 42 of 185 elderly individuals were treated with at least one antibiotic for one month. *Bifidobacterium* spp. numbers were noted to significantly decrease, whereas *Lactobacillus* spp. and *Enterobacteriaceae* levels remain unaffected in individuals treated with antibiotics compared with those not given antibiotics.

THE EFFECTS OF PROBIOTICS IN ELDERLY

Lactobacillus, *Bifidobacterium*, and *Saccharomyces* are known as probiotics, which show beneficial health effects by restoring the balance of gut microflora. Probiotics play crucial functions in improving gut health and disease in all age groups, particularly the elderly. The dysbiosis of gut microbiota has been associated with inflammatory and metabolic disorders, including inflammatory bowel disease, diabetes, irritable bowel disease, colorectal cancer, CVD, and frailty (Duncan and Flint, 2013).

Increasing evidence has demonstrated the beneficial effects of probiotics in the elderly, which include protection against pathogens, strengthening barrier functions, regulating immune response, preventing GI diseases, and reducing inflammation and oxidative stress. Therefore, probiotics can be used as preventive and/or therapeutic agents against diseases. However, the available clinical evidence is still minimal to draw any certain conclusions regarding the benefit of probiotics in the elderly (Ni et al., 2019). The studies conducted to test the effect of probiotic administration on microbiota composition and therapeutic outcomes in certain diseases in the elderly population have been summarized in Table 4.

Table 4. Review of the recent articles on the effects of probiotic administration on microbiota composition and therapeutic outcomes in certain diseases in the elderly

Pathology	Subjects *n*; age	Probiotics	Results	References
1	2	3	4	5
Alzheimer's disease (AD)	60; 60–95 years	probiotic milk containing *Lb. casei*, *Lb. acidophilus*, *B. bifidum*, and *Lb. fermentum*; 200 mL/day for 12 weeks	decreased the plasma malondialdehyde (MDA) and high sensitivity C-reactive protein (hs-CRP) levels	Akbari et al. (2016)
	30 mice; 2 months old	cow's milk fermented with *Lb. fermentum* LAB9 or *Lb. casei* LABPC; 10^9 CFU/0.2 mL for 28 days	increased antioxidant levels, learning and memory behavior decreased the levels of acetylcholinesterase (AChE), MDA, and pro-inflammatory cytokines	Musa et al. (2017)
	64 mice; 8-week-old	probiotic formulation SLAB51 (*Str. thermophilus*, *B. longum*, *B. infantis*, *B. breve*, *Lb. plantarum*, *Lb. acidophilus*, *Lb. paracasei*, *Lb. delbrueckii* subsp. *bulgaricus*, *Lb. brevis*); 200 bn bacteria/kg/day for 16 weeks	reduced the oxidative stress associated with AD	Bonfili et al. (2018)
Parkinson's disease	40; 76.05 ±2.09 years	60 mg per tablet of two lactic bacteria tablets: *Lb. acidophilus* and *B. infantis*; 2 times/day for three months	improved abdominal pain and bloating	Georgescu et al. (2016)
	20 mice; 7-week-old	probiotic cocktail containing *Lb. rhamnosus* GG, *B. animalis lactis*, and *Lb. acidophilus*; 2×10^6 CFU/day for 30 days	increased butyrate level and improved neurodegeneration	Srivastav et al. (2019)
	60; 50–90 years	a probiotic combination of *B. bifidum*, *Lb. acidophilus*, *Lb. reuteri* and *Lb. fermentum*; 8–10^9 CFU/day for 12 weeks	decreased score on the Unified Parkinson's Disease Rating Scale (UPDRS) reduced hs-CRP and MDA levels increased glutathione (GSH) levels decreased insulin levels	Tamtaji et al. (2019)
Mental disorders	38; 66–78 years	a sachet containing lyophilized powder of *B. longum* subsp. *longum* BB536, *B. longum* subsp. *infantis* M-63, *B. breve* M-16V and *B. breve* B-3; 1.25×10^{10} CFU/day for 12 weeks	decreased depression anxiety scores	Inoue et al. (2018)
Cognitive dysfunction	63; ≥65 years	probiotics containing *B. bifidum* BGN4 and *B. longum* BORI; 1×10^9 CFU/day for 12 weeks	decreased the relative abundance of *Eubacterium*, *Clostridiales*, *Allisonella*, and *Prevotellaceae*, advancement in mental flexibility testing and stress score increased the brain-derived neurotrophic factor (BDNF) level, improving brain functions	Kim et al. (2021)

Table 4 – cont.

1	2	3	4	5
Osteoporosis	24 ovariectomized rats; 10-week-old	*B. longum*; 10^8–10^9 CFU/mL; once a day for 16 weeks	alleviated bone loss and increased bone mass density	Parvaneh et al. (2015)
	417; ≥65 years	*Lb. casei* Shirota; for four months	speeded functional improvement, accelerated the fracture healing process	Lei et al. (2016)
	70; 75 to 80 years	*Lb. reuteri* 6475; 10^{10} CFU/day for 12 months	declined bone loss	Nilsson et al. (2018)
Obesity	20; ≥65 years	a probiotic mix (*Str. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *Lb. acidophilus, Lb. plantarum*, *Lb. paracasei, Lb. delbrueckii* subsp. *bulgaricus*); 450 billion bacteria for two weeks combined with Mediterranean diet	decreased oxidative stress and the weight of subjects	Cancello et al. (2019)
Cardiovascular diseases	26 clinical trials; 2 meta-analyses	*Lb. reuteri* NCIMB 30242, *Ent. faecium*, and the combination of *Lb. acidophilus* La5 and *B. lactis* Bb12; ranged from 2×10^7–2×10^{13} CFU/day; duration ranged from 4 weeks to 10 weeks	remarkably reduced low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) improving other coronary heart disease risk factors	DiRienzo (2014)
	1971; 19–85 years	*Lb. acidophilus*, *B. lactis*, and *Lb. plantarum* strains; ranged from approximately 10^6–10^{11} CFU/day; duration ranged from one week to 24 weeks	reduced serum TC was significantly	Wang et al. (2018)
	60; 18–65 years	*Lb. reuteri* V3401; 5×10^9 CFU/day for 12 weeks	reduced risk of cardiovascular disease	Tenorio-Jiménez et al. (2018)
	47; 45–75 years	*B. bifidum* TMC3115; for three weeks	lower plasma TC and LDL-C levels increased *Firmicutes*, *Bacteroides* and *Actinobacteria* reduced *Proteobacteria* and *Fusobacteria*	Wang et al. (2019)

The intestinal microbiota is known to play a crucial role in the pathogenesis of Parkinson's disease (PD). More than 70% of patients with PD suffer from gut dysfunction (Sharma et al., 2019). According to the study conducted by Scheperjans et al. (2015), the abundance of *Prevotellaceae* in feces of patients with PD decreased by 77.6% compared with the control group. The relative abundance of *Prevotellaceae* of 6.5% or less had 86.1% sensitivity and 38.9% specificity for PD. Moreover, the relative abundance of *Enterobacteriaceae* was positively associated with the severity of postural instability and gait difficulty. The changes in GI microbiota and excessive neuroinflammation in the gut of the patients with PD cause nonmotor symptoms such as constipation. Constipation is the most common complication reported in several patients with PD (Sharma et al., 2019). Furthermore, the increased risk of constipation will cause autonomic dysfunction of GI system permeability in PD (Postuma et al., 2013). The therapies based on modulating the gut microbiome to prevent or stop the progression of PD pathologies, such as probiotics,

improve the symptoms of constipation (Cheng et al., 2019; Srivastav et al., 2019). In a study conducted by Georgescu et al. (2016), 20 out of 40 randomly selected patients with PD (mean age, 76.05 ±2.09 years) received trimebutine 200 mg three times daily. The other 20 patients received probiotics (60 mg per tablet of two lactic bacteria tablets: *Lb. acidophilus* and *B. infantis*) two times per day for three months. According to the results, the administration of probiotics improved abdominal pain and bloating, similar to that with trimebutine.

The gut-brain axis is a bidirectional relation between the gut and brain. It refers to the relationship between the gut microbiota and age-related neurodegenerative diseases, such as Alzheimer's disease (AD) and mood disorders (including depression and anxiety; Kim et al., 2021). Alzheimer's disease – AD is one of the most common chronic neurodegenerative disorders in the elderly characterized by cognitive and memory impairments (Cheng et al., 2019). In 2016, Akbari and research team reported the first study to evaluate the beneficial effects of probiotic supplementation on the biomarkers of oxidative stress, cognitive function, inflammation, and metabolic status in patients with AD. In this randomized, double-blind, controlled study, patients with AD received 200 mL/day of probiotic milk containing *Lactobacillus casei*, *Lb. acidophilus*, *B. bifidum* and *Lb. fermentum* for 12 weeks. The plasma malondialdehyde and high-sensitivity C-reactive protein levels decreased in patients with AD treated with probiotics compared with the control group. According to the study conducted by Musa et al. (2017), the treatment with cow's milk fermented with *Lb. fermentum* LAB9 or *Lb. casei* LABPC increases antioxidant levels, learning, and memory behavior in mice. In addition, the levels of acetylcholinesterase, malondialdehyde, and proinflammatory cytokines are reduced in the probiotic group compared with the control group. The administration of the probiotic formulation SLAB51 (*Streptococcus thermophilus* [*Str. thermophilus*], *B. longum*, *B. infantis*, *B. breve*, *Lb. plantarum*, *Lb. acidophilus*, *Lb. paracasei*, *Lb. delbrueckii* subsp. *bulgaricus*, *Lb. brevis*) on transgenic AD mice ($n = 64$) for 16 weeks (200 bn bacteria/kg/day) crucially reduced AD-related oxidative stress (Bonfili et al., 2018). Asl et al. (2019) administered an encapsulated probiotic supplement consisting of *Lb. acidophilus*, *B. bifidum*, and *B. longum* (each capsule contains 500 mg of bacterial mixture with a total of 15×10^9 colony-forming units [CFU]) for 56 days to rats with AD. Spatial learning and memory were assessed in the Morris water maze. The probiotic treatment improved maze navigation compared to other rats. Essentially, it has been reported to restore long-term potentiation, one of the candidate mechanisms through which long-lasting memories are consolidated.

Probiotics have been suggested to improve cognitive dysfunction and mental disorder in patients and experimental animal models through the gut-brain axis. *Lactobacillus* strains such as *Lactobacillus odontolyticus* and *Lb. plantarum* secrete acetylcholine, the principal neurotransmitter in the human brain (Cheng et al., 2019). *Saccharomyces*, *Escherichia*, and *Bacillus* secrete norepinephrine; *Streptococcus*, *Enterococcus*, *Candida*, and *Escherichia* secrete serotonin, whereas *Serratia* and *Bacillus* have the potential to secrete dopamine. All these neurotransmitters are known to play a crucial role in mental health (Fond et al., 2015). On the other hand, it is still unclear whether probiotics have a beneficial role in the brain function of healthy elderly (Sharon et al., 2016). In a randomized, double-blind, placebo-controlled trial, 38 healthy elderly individuals (aged 66–78 years) were given a combination of *Bifidobacterium* spp. supplementation (*B. longum* subsp. *longum* BB536, *B. longum* subsp. *infantis* M-63, *B. breve* M-16V, and *B. breve* B-3) and moderate resistance training for 12 weeks. The probiotic group had a significant decrease in depression anxiety scores (Inoue et al., 2018). In a randomized, double-blind, and placebo-controlled, multicenter trial to evaluate the effects of probiotics on cognition and mood, 63 healthy older adults (aged ≥65 years) consumed either placebo or probiotics containing *B. bifidum* BGN4 and *B. longum* BORI for 12 weeks. At the genus level, crucial changes in the gut microbial composition were detected in the probiotic group. The relative abundance of inflammation-inducing gut bacteria (*Eubacterium*, *Clostridiales*, *Allisonella*, and *Prevotellaceae*) decreased significantly at week 12 with probiotic use. Older people using probiotics showed more advancement in mental flexibility testing and stress score. The brain-derived neurotrophic factor (BDNF) level, known to be extremely

crucial for learning, memory processes, and stress, remarkably increased in the probiotic group compared with the placebo group. Moreover, the decrease in the relative abundance of *Eubacterium* and *Clostridiales* in the gut with probiotic administration is associated with the increase in the serum BDNF, thus improving brain functions (Kim et al., 2021).

Probiotics may be a promising new application for bone loss and the prevention of osteoporosis. Osteoporosis is a disease that occurs with the loss of bone density and deterioration of bone microstructure, resulting in decreased bone strength and increased fracture risk (Collins et al., 2017). Osteoporotic fractures affect one in two women and one in five men after 50 years of age (Lorentzon and Cummings, 2015). Parvaneh et al. (2015) found positive results in their study on the effectiveness of the probiotic, *B. longum*, in protecting rats from ovariectomized (OVX)-induced bone loss. In the survey, OVX rats were used to mimic menopausal conditions in women with estrogen deficiency. Bone loss was found to be alleviated and bone mass density to be increased in OVX rats receiving *B. longum* (10^8–10^9 CFU/mL) once a day for 16 weeks, starting from two weeks after surgery. In a double-blind placebo-controlled clinical trial involving 417 older patients with an acute distal radius fracture, *Lb. casei* Shirota speeded functional improvement. The treatment outcomes of patients receiving probiotics at month 4 were at comparable levels with those receiving placebo at month 6, suggesting that probiotics may accelerate the fracture healing process (Lei et al., 2016). A randomized, placebo-controlled, double-blind, clinical trial using *Lb. reuteri* 6475 (10^{10} CFU/day) indicated that probiotic strain could decrease bone loss in older women (75 to 80 years old) with low bone mineral density (Nilsson et al., 2018).

In vitro, *in vivo*, and human clinical studies are available on the association of probiotic supplementation with obesity (Sivamaruthi et al., 2019). In a study, 20 elderly obese women (aged ≥65 years) received a hypocaloric Mediterranean diet administered alone for two weeks and a diet enriched with a probiotic mix for the following next two weeks (it contains *Str. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *Lb. acidophilus*, *Lb. plantarum*, *Lb. paracasei*, *Lb. delbrueckii* subsp. *bulgaricus*). The addition of probiotics to the diet further decreased oxidative stress. Moreover, it increased the relative abundance of Akkermansia, a mucin degrader with beneficial effects on host metabolism. The weight of individuals decreased further, and oxidative stress markers improved. These findings suggest that the combined use of the balanced Mediterranean diet and probiotics, even in the short term, may have significant beneficial effects on the intestinal microbiota and risk profile in individuals with high cardiometabolic risk, such as older obese people (Cancello et al., 2019).

Changes in the intestinal microbiota could affect lipid and glucose metabolism and insulin activities. In recent years, the increasing frequency of metabolic diseases such as obesity, hyperglycemia, and dyslipidemia resulted in a higher incidence of CVD (Aggarwal et al., 2013). Epidemiological studies have supported the relationship between total cholesterol (TC) and increased cardiovascular risk. As an alternative application, probiotic treatment has shown a beneficial effect in TC regulation (Wang et al., 2018). However, an unhealthy diet is a primary factor for CVD morbidity. Intestinal bacteria can produce diet-derived metabolic products that can affect the cardiovascular situation of a person. For example, the circulating levels of branched-chain amino acid metabolites, histidine, and tryptophan are associated with vascular disease and insulin resistance. The gut microbiome plays an essential role in CVD in several ways. On the other hand, little is known regarding the function of probiotic administrations in preventing and treating CVD (Oniszczuk et al., 2021). Moreover, pathogenic bacteria such as *Campylobacter*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, and species of genus *Candida* are highly abundant in the intestine in patients with chronic heart failure compared with the control group (Pasini et al., 2016). Cui et al. (2018) observed essential differences in the composition of the intestinal microbiota between patients with chronic heart failure and the control group. Notably, *Faecalibacterium prausnitzii* decreased and *Ruminococcus gnavus* increased in patients with chronic heart failure.

DiRienzo (2014) reported a remarkable reduction in the level of low-density lipoprotein-cholesterol (LDL-C) for *Lb. reuteri* NCIMB 30242, *Enterococcus faecium (Ent. faecium)*, and the combination of *Lb. acidophilus* La5 and *Bifidobacterium lactis* Bb12

in a study of 26 clinical trials and two meta-analyses. *Lb. reuteri* NCIMB 30242, which has GRAS status, has been shown to remarkably reduce LDL-C and TC, improving other coronary heart disease risk factors. A total of 32 randomized controlled studies including 1971 patients were examined. Serum TC was found to significantly reduce in the probiotic group compared with the control group. Particularly, *Lb. acidophilus*, *B. lactis* and *Lb. plantarum* strains have significant effects (Wang et al., 2018). Tenorio-Jiménez et al. (2018) observed the association between the consumption of *Lb. reuteri* V3401 for 12 weeks and reduced CVD risk in adults aged 18 to 65 years with insulin resistance syndrome. Another study showed that patients with mild hyperglycemia and dyslipidemia (aged 45–75 years) who consumed *B. bifidum* TMC3115 strain for three weeks have significantly lower plasma TC and LDL-C levels. *Firmicutes*, *Bacteroides*, and *Actinobacteria* increased with the use of TMC3115, whereas *Proteobacteria* and *Fusobacteria* reduced. Serum triglycerides values correlated negatively with the proportions of *Bacteroidetes* and *Bacteroides*. *Proteobacteria* proportion positively and meaningfully correlated with fasting blood glucose level (Wang et al., 2019).

No clear information exists on how long probiotics should be administered to benefit from their positive effects. In general, the duration of probiotic consumption in studies varies between two and eight weeks. Gao et al. (2019) studied the long-term (more than six months) modulatory effect of probiotics on the intestinal microbiota in individuals aged 30–85 years. The consumption of probiotics (*B. longum*, *Lb. acidophilus*, and *Ent. faecalis*) contributed to a crucial profile alteration in the relative abundance of the intestinal microbiota. In addition, *Flavobacterium*, *Brochothrix*, and *Bifidobacterium* contribute at the genus level in the long-term group. Another critical piece of information from studies was that the relative abundance of *Bifidobacterium* was 11 times higher in the long-term group than in the short-term group. Conversely, a decline in the relative abundance of *Enterococcus* was observed in the long-term group. These findings suggest that the long-term intake of probiotics induces essential changes in the gut microbiota structure and increases the composition of beneficial microorganisms and thus can help maintain host health.

CONCLUSION

Probiotics could be a promising approach to prevent and/or treat diseases in the elderly where traditional treatments have failed. Evidence states that protecting the gut microbial balance during aging is compulsory for healthy late life. Probiotic intake induces significant changes in the gut microbiota structure and increases the composition of beneficial microorganisms and thus may help maintain the health of the elderly host. On the other hand, older people are typically defined by weakened immune systems, gut dysbiosis, and/or impaired intestinal barriers, which require careful consideration of the safety associated with the deliberate consumption of probiotics. Further clinical studies with more individuals and long-term interventions are needed to provide evidence that probiotics have health-promoting properties in the general population of the elderly.

REFERENCES

Aggarwal, J., Swami, G., Kumar, M. (2013). Probiotics and their effects on metabolic diseases: an update. J. Clin. Diagnostic Res., 7(1), 173. https://doi.org/10.7860/JCDR/2012/5004.2701

Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O. R., ..., Salami, M. (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Front. Aging Neurosci., 8, 256. https://doi.org/10.3389/fnagi.2016.00256

Akçelik, N., Akçelik, M., (2020). Probiyotik Mikroorganizmalar I: Laktik Asit Bakterileri (LAB) [Probiotic microorganisms I: Lactic acid bacteria (LAB)]. In M. Akçelik, N. Akçelik, P. Şanlıbaba, B. Tezel Uymaz (Eds.), Probiyotik Yüzyılı (pp. 40–66). Gazi Kitabevi [in Turkish].

Akçelik, N., Akçelik, M., Tezel Uymaz, B., Şanlıbaba, P., Şimşek, Ö. (2020). İnsan Bağırsak Mikrobiyotasının Disbiyozu ve Probiyotikler Aracılığı ile Modülasyonu. In M. Akçelik, N. Akçelik, P. Şanlıbaba, B. Tezel Uymaz (Eds.), Probiyotik Yüzyılı (pp. 643–677). Gazi Kitabevi [in Turkish].

Anadón, A., Martínez-Larrańaga, M. R., Ares, I., Martínez, M. A. (2016). Probiotics: Safety and toxicity considerations. In R. C. Gupta (Ed.), Nutraceuticals (pp. 777–798). Academic Press.

Anwar, H., Iftikhar, A., Muzaffar, H., Almatroudi, A., Allemailem, K. S., Navaid, S., ..., Khurshid, M. (2021).

Biodiversity of gut microbiota: Impact of various host and environmental factors. BioMed Res. Intl., e5575245. https://doi.org/10.1155/2021/5575245

Arboleya, S., Watkins, C., Stanton, C., Ross, R. P. (2016). Gut bifidobacteria populations in human health and aging. Front. Microbiol., 7, 1204. https://doi.org/10.3389/fmicb.2016.01204

Asl, Z. R., Sepehri, G., Salami, M. (2019). Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. Behav. Brain Res., 376, 112183. https://doi.org/10.1016/j.bbr.2019.112183

Bedani, R., Saad, S. M. I., Sivieri, K. (2016). Potential benefits of probiotics, prebiotics, and synbiotics on the intestinal microbiota of the elderly. In R. R. Watson, V. R. Preedy (Eds.), Probiotics, prebiotics, and synbiotics (pp. 525–538). Academic Press. https://doi.org/10.1016/B978-0-12-802189-7.00037-X

Biagi, E., Rampelli, S., Turroni, S., Quercia, S., Candela, M., Brigidi, P. (2017). The gut microbiota of centenarians: Signatures of longevity in the gut microbiota profile. Mech. Ageing Dev., 165 (Part B), 180–184. https://doi.org/10.1016/j.mad.2016.12.013

Bonfili, L., Cecarini, V., Cuccioloni, M., Angeletti, M., Berardi, S., Scarpona, S., ..., Eleuteri, A. M. (2018). SLAB51 probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. Mol. Neurobiol., 55(10), 7987–8000. https://doi.org/10.1007/s12035-018-0973-4

Cancello, R., Turroni, S., Rampelli, S., Cattaldo, S., Candela, M., Cattani, L., ..., Invitti, C. (2019). Effect of short-term dietary intervention and probiotic mix supplementation on the gut microbiota of elderly obese women. Nutrients, 11(12), 3011. https://doi.org/10.3390/nu11123011

Cheng, L. H., Liu, Y. W., Wu, C. C., Wang, S., Tsai, Y. C. (2019). Psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders. J. Food Drug Anal., 27(3), 632–648. https://doi.org/10.1016/j.jfda.2019.01.002

Collins, F. L., Rios-Arce, N. D., Schepper, J. D., Parameswaran, N., McCabe, L. R. (2017). The potential of probiotics as a therapy for osteoporosis. Microbiol. Spectr., 5(4), 5–4. https://doi.org/10.1128/microbiolspec.BAD-0015-2016

Cui, X., Ye, L., Li, J., Jin, L., Wang, W., Li, S., ..., Cai, J. (2018). Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients. Sci. Rep., 8(1), 1–15. https://doi.org/10.1038/s41598-017-18756-2

Díaz, R., Garrido, D. (2020). Recent advances in the infant gut microbiome and health. In J. Faintuch, S. Faintuch (Eds.), Precision medicine for investigators, practitioners and providers (pp. 33–38). Academic Press. https://doi.org/10.1016/B978-0-12-819178-1.00004-6

Dinan, T. G., Stanton, C., Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. Biol. Psychiat., 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

DiRienzo, D. B. (2014). Effect of probiotics on biomarkers of cardiovascular disease: implications for heart-healthy diets. Nutr. Rev., 72(1), 18–29. https://doi.org/10.1111/nure.12084

Duncan, S. H., Flint, H. J. (2013). Probiotics and prebiotics and health in ageing populations. Maturitas, 75(1), 44–50. https://doi.org/10.1016/j.maturitas.2013.02.004

Ferretti, P., Pasolli, E., Tett, A., Asnicar, F., Gorfer, V., Fedi, S., ..., Segata, N. (2018). Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. Cell Host Microbe, 24(1), 133–145. https://doi.org/10.1016/j.chom.2018.06.005

Fond, G., Boukouaci, W., Chevalier, G., Regnault, A., Eberl, G., Hamdani, N., ..., Leboyer, M. (2015). The "psychomicrobiotic": Targeting microbiota in major psychiatric disorders: A systematic review. Pathol. Biol., 63(1), 35–42. https://doi.org/10.1016/j.patbio.2014.10.003

Foster, J. A., Rinaman, L., Cryan, J. F. (2017). Stress and the gut-brain axis: Regulation by the microbiome. Neurobiol. Stress, 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Gao, R., Zhang, X., Huang, L., Shen, R., Qin, H. (2019). Gut microbiota alteration after long-term consumption of probiotics in the elderly. Probiot. Antimicrob. Prot., 11(2), 655–666. https://doi.org/10.1007/s12602-018-9403-1

Georgescu, D., Ancusa, O. E., Georgescu, L. A., Ionit, I., Reisz, D. (2016). Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: Is there hope? Clin. Interv. Aging, 11(11), 1601–1608. https://doi.org/10.2147/CIA.S106284

Hardy, H., Harris, J., Lyon, E., Beal, J., Foey, A. D. (2013). Probiotics, prebiotics and immunomodulation of gut mucosal defences: homeostasis and immunopathology. Nutrients, 5(6), 1869–1912. https://doi.org/10.3390/nu5061869

Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., ..., Sanders, M. E. (2014). The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the

term probiotic. Nat. Rev. Gastroenterol. Hepatol., 11(8), 506–514. https://doi.org/10.1038/nrgastro.2014.66

Inoue, T., Kobayashi, Y., Mori, N., Sakagawa, M., Xiao, J. Z., Moritani, T., ..., Nagai, N. (2018). Effect of combined bifidobacteria supplementation and resistance training on cognitive function, body composition and bowel habits of healthy elderly subjects. Benef. Microb., 9(6), 843–853. https://doi.org/10.3920/BM2017.0193

Jackson, M. A., Jeffery, I. B., Beaumont, M., Bell, J. T., Clark, A. G., Ley, R. E., ..., Steves, C. J. (2016). Signatures of early frailty in the gut microbiota. Genome Med., 8(1), 8. https://doi.org/10.1186/s13073-016-0262-7

Jensen, E. T., Bertelsen, R. J., Ringel-Kulka, T. (2017). Microbiota of the gastrointestinal tract in infancy. In M. Floch, Y. Ringel, W. A. Walker (Eds.), The microbiota in gastrointestinal pathophysiology (pp. 27–35). Academic Press.

Kim, C. S., Cha, L., Sim, M., Jung, S., Chun, W. Y., Baik, H. W., Shin, D. M. (2021). Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling elderly: A randomized, double-blind, placebo-controlled, multicenter trial. J. Gerontol., Biol. Sci. Med. Sci., 76(1), 32–40. https://doi.org/10.1093/gerona/glaa090

Lei, M., Hua, L. M., Wang, D. W. (2016). The effect of probiotic treatment on elderly patients with distal radius fracture: a prospective double-blind, placebo-controlled randomized clinical trial. Benef. Microb., 7(5), 631–637. https://doi.org/10.3920/BM2016.0067

Liang, S., Wang, T., Hu, X., Luo, J., Li, W., Wu, X., ..., Jin, F. (2015). Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience, 310, 561–577. https://doi.org/10.1016/j.neuroscience.2015.09.033

Logan, A. C., Katzman, M. (2005). Major depressive disorder: Probiotics may be an adjuvant therapy. Med. Hypothes., 64(3), 533–538. https://doi.org/10.1016/j.mehy.2004.08.019

Lorentzon, M., Cummings, S. R. (2015). Osteoporosis: the evolution of a diagnosis. J. Intern. Med., 277(6), 650–661. https://doi.org/10.1111/joim.12369

Musa, N. H., Mani, V., Lim, S. M., Vidyadaran, S., Majeed, A. B. A., Ramasamy, K. (2017). Lactobacilli-fermented cow's milk attenuated lipopolysaccharide-induced neuroinflammation and memory impairment in vitro and in vivo. J. Dairy Res., 84(4), 488–495. https://doi.org/10.1017/S0022029917000620

Ni, Y., Yang, X., Zheng, L., Wang, Z., Wu, L., Jiang, J., Fu, Z. (2019). *Lactobacillus* and *Bifidobacterium* improves physiological function and cognitive ability in aged mice by the regulation of gut microbiota. Mol. Nutr. Food Res., 63(22), 1900603. https://doi.org/10.1002/mnfr.201900603

Nilsson, A. G., Sundh, D., Bäckhed, F., Lorentzon, M. (2018). *Lactobacillus reuteri* reduces bone loss in older women with low bone mineral density: a randomized, placebo-controlled, double-blind, clinical trial. J. Intern. Med., 284(3), 307–317. https://doi.org/10.1111/joim.12805

Olesen, S. W., Alm, E. J. (2016). Dysbiosis is not an answer. Nat. Microbiol., 1, 16228–16232. https://doi.org/10.1038/nmicrobiol.2016.228

Oniszczuk, A., Oniszczuk, T., Gancarz, M., Szymańska, J. (2021). Role of gut microbiota, probiotics and prebiotics in the cardiovascular diseases. Molecules, 26(4), 1172. https://doi.org/10.3390/molecules26041172

O'Sullivan, O., Coakley, M., Lakshminarayanan, B., Conde, S., Claesson, M. J., Cusack, S., ..., Ross, R. P. (2013). Alterations in intestinal microbiota of elderly Irish subjects post-antibiotic therapy. J. Antimicrob. Chemother., 68(1), 214–221. https://doi.org/10.1093/jac/dks348

Parvaneh, K., Ebrahimi, M., Sabran, M. R., Karimi, G., Hwei, A. N. M., Abdul-Majeed, S., ..., Jamaluddin, R. (2015). Probiotics (*Bifidobacterium longum*) increase bone mass density and upregulate *Sparc* and *Bmp-2* genes in rats with bone loss resulting from ovariectomy. BioMed Res. Int., 2015, 897639. https://doi.org/10.1155/2015/897639

Pasini, E., Aquilani, R., Testa, C., Baiardi, P., Angioletti, S., Boschi, F., ..., Dioguardi, F. (2016). Pathogenic gut flora in patients with chronic heart failure. JACC: Heart Fail., 4(3), 220–227. https://doi.org/10.1016/j.jchf.2015.10.009

Postuma, R. B., Gagnon, J. F., Pelletier, A., Montplaisir, J. (2013). Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies. Mov. Disord., 28(5), 597–604. https://doi.org/10.1002/mds.25445

Rea, M. C., O'Sullivan, O., Shanahan, F., O'Toole, P. W., Stanton, C., Ross, R. P., Hill, C. (2012). *Clostridium difficile* carriage in elderly subjects and associated changes in the intestinal microbiota. J. Clin. Microbiol., 50(3), 867–875. https://doi.org/10.1128/JCM.05176-11

Rivière, A., Selak, M., Lantin, D., Leroy, F., De Vuyst, L. (2016). Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Front. Microbiol., 7, 979. https://doi.org/10.3389/fmicb.2016.00979

Rondanelli, M., Giacosa, A., Faliva, M. A., Perna, S., Allieri, F., Castellazzi, A. M. (2015). Review on microbiota and effectiveness of probiotics use in older. World J. Clin. Cases, 3(2), 156–162. https://doi.org/10.12998/wjcc.v3.i2.156

Rupnik, M., Wilcox, M. H., Gerding, D. N. (2009). *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. Nat. Rev. Microbiol., 7(7), 526–536. https://doi.org/10.1038/nrmicro2164

Sender, R., Fuchs, S., Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. PLoS Biol., 14(8), e1002533. https://doi.org/10.1371/journal.pbio.1002533

Scheperjans, F., Aho, V., Pereira, P. A. B., Koskinen, K., Paulin, L., Pekkonen, E., ..., Auvinen, P. (2015). Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov. Disord., 30(3), 350–358. https://doi.org/10.1002/mds.26069

Sharma, S., Awasthi, A., Singh, S. (2019). Altered gut microbiota and intestinal permeability in Parkinson's disease: Pathological highlight to management. Neurosci. Lett., 712, 134516. https://doi.org/10.1016/j.neulet.2019.134516

Sharon, G., Sampson, T. R., Geschwind, D. H., Mazmanian, S. K. (2016). The central nervous system and the gut microbiome. Cell, 167(4), 915–932. https://doi.org/10.1016/j.cell.2016.10.027

Singh, B., Catanzaro, R., Mal, G., Gautam, S. K., He, F., Yadav, H., ..., Marotta, F. (2020). Gut microbiota and aging: Targets and anti-aging interventions. In Suresh I. S. Rattan (Ed.), Encyclopedia of biomedical gerontology (pp. 185–198). Academic Press. https://doi.org/10.1016/B978-0-12-801238-3.62181-5

Sivamaruthi, B. S., Kesika, P., Suganthy, N., Chaiyasut, C. (2019). A review on role of microbiome in obesity and anti-obesity properties of probiotic supplements. BioMed Res. Int., 2019, 3291367. https://doi.org/10.1155/2019/3291367

Srivastav, S., Neupane, S., Bhurtel, S., Katila, N., Maharjan, S., Choi, H., ..., Choi, D. Y. (2019). Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity. J. Nutr. Biochem., 69, 73–86. https://doi.org/10.1016/j.jnutbio.2019.03.021

Şireli, T. U., Yurdakök-Dikmen, B., Filazi, A., Şahin, D. (2020). Yetişkin ve Yaşlıların Beslenmesinde Probiyotik Gıdalar. In M. Akçelik, N. Akçelik, P. Şanlıbaba, B. Tezel Uymaz (Eds.), Probiyotik Yüzyılı (pp. 455–490). Gazi Kitabevi [in Turkish].

Tamtaji, O. R., Taghizadeh, M., Kakhaki, R. D., Kouchaki, E., Bahmani, F., Borzabadi, S., ..., Asemi, Z. (2019). Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin. Nutr., 38(3), 1031–1035. https://doi.org/10.1016/j.clnu.2018.05.018

Tenorio-Jiménez, C., Martínez-Ramírez, M. J., Tercero-Lozano, M., Arraiza-Irigoyen, C., Del Castillo-Codes, I., Olza, ..., Gomez-Llorente, C. (2018). Evaluation of the effect of *Lactobacillus reuteri* V3401 on biomarkers of inflammation, cardiovascular risk and liver steatosis in obese adults with metabolic syndrome: A randomized clinical trial (PROSIR). BMC Compl. Altern. Med., 18(1), 1–8. https://doi.org/10.1186/s12906-018-2371-x

Tezel Uymaz B., Uymaz B. (2020). Probiyotiklerin Sağlık Üzerine Etkileri. In M. Akçelik, N. Akçelik, P. Şanlıbaba, B. Tezel Uymaz (Eds.), Probiyotik Yüzyılı (pp. 181–223). Gazi Kitabevi [in Turkish].

Thomson, P., Medina, D. A., Garrido, D. (2018). Human milk oligosaccharides and infant gut bifidobacteria: Molecular strategies for their utilization. Food Microbiol., 75, 37–46. https://doi.org/10.1016/j.fm.2017.09.001

Walker, W. A. (2013). Initial intestinal colonization in the human infant and immune homeostasis. Ann. Nutr. Metab., 63(Suppl. 2), 8–15. https://doi.org/10.1159/000354907

Wang, L., Guo, M. J., Gao, Q., Yang, J. F., Yang, L., Pang, X. L., Jiang, X. J. (2018). The effects of probiotics on total cholesterol: A meta-analysis of randomized controlled trials. Medicine, 97(5), e9679. https://doi.org/10.1097/MD.0000000000009679

Wang, K., Yu, X., Li, Y., Guo, Y., Ge, L., Pu, F., ..., Li, M. (2019). *Bifidobacterium bifidum* TMC3115 can characteristically influence glucose and lipid profile and intestinal microbiota in the middle-aged and elderly. Probiot. Antimicrob. Prot., 11(4), 1182–1194. https://doi.org/10.1007/s12602-018-9441-8

Vyas, U., Ranganathan, N. (2012). Probiotics, prebiotics, and synbiotics: gut and beyond. Gastroenterol. Res. Pract., 2012, ID 872716. https://doi.org/10.1155/2012/872716