



LITERATUR REVIEW: THE ROLE OF PROBIOTICS IN PREVENTING AGING

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ABSTRACT

Aging is a complex biological process characterized by progressive functional decline of organs and tissues, largely driven by oxidative stress, chronic inflammation, and cellular senescence. Recent evidence suggests that age-related gut microbiota dysbiosis contributes significantly to inflammaging and oxidative damage, accelerating the aging process. Probiotics have emerged as potential gerobiotics due to their antioxidant, anti-inflammatory, and microbiota-modulating properties. This literature review aims to evaluate the role of probiotics in preventing and delaying the aging process through modulation of gut microbiota, oxidative stress reduction, and regulation of inflammatory. A narrative literature review was conducted using scientific publications from 2012 to 2023 obtained from NCBI (PubMed), ScienceDirect, and Google Scholar databases. Articles were selected based on relevance to probiotics, gut microbiota, oxidative stress, inflammation, and aging mechanisms. A total of 300 articles were identified from PubMed (n = 120), Science Direct (n = 95), and Google Scholar (n = 85). After removing duplicates, 235 articles were screened. 45 full text articles were assessed for eligibility, and 11 studies were included in the quantitative synthesis. The reviewed studies indicate that probiotics, particularly strains from the genera *Lactobacillus*, exert anti-aging effects by reducing reactive oxygen species (ROS), enhancing endogenous antioxidant enzymes (SOD, CAT, GPx), regulating inflammatory pathways (NF-κB, cytokines), activating Nrf2 signaling, maintaining intestinal barrier integrity, and restoring gut microbiota balance. Several probiotic strains were shown to delay telomere shortening, suppress cellular senescence markers, and improve metabolic. Probiotics play a significant role in preventing aging by modulating gut microbiota composition, reducing oxidative stress, and suppressing chronic inflammation. These findings support the potential application of probiotics as gerobiotics to promote healthy aging and extend health span.

Keywords: aging; preventing; probiotics; role

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INTRODUCTION

Globally, the number of people over 65 years old is 617 million (8.5%) and this number is expected to grow to 1.6 billion by 2050. The world is facing the problem of an aging population, with around 10% of people worldwide aged 65 years or older in 2020. By 2030 and 2050, the proportion of this age group is projected to be 12% and 16% respectively (Mohabbat & Arazi, 2024) (2022). The 2018 Riskesdas data shows that Indonesia experienced an increase in the number of elderly people, from 18 million people (7.56%) in 2010 to 25.9 million people (9.7%) in 2019 and is expected to continue to increase where in 2035 it will be 48.2 million people (15.77%) (Riskesdas, 2018).

An increase in the elderly population will increase the risk of age-related pathologies due to the aging process so that the prevalence of aging-related diseases also increases. According to the National Council on Aging, about 80% of older people have at least one chronic disease, and 77%

have at least two chronic diseases (Tsai et al., 2021). In the aging process, changes in organ structure and function occur, Reactive Oxygen Species (ROS) are thought to play a major role in skin aging (Kumalasari, 2022). The imbalance between ROS and the body's antioxidants results in oxidative stress, which is one of the most intrinsic factors associated with aging (Gupta et al., 2024). Aging results from the accumulation of oxidative damage due to excess ROS, which are generated from aerobic metabolism. ROS cause damage to lipids, proteins, and DNA and also affect cellular aging. (Kumalasari, 2022)

In recent years, aging has also been linked to gut microbiome homeostasis (Tsai et al., 2021; Ren et al., 2023). The gut microbiota participates in the aging process mainly through the regulation of oxidative stress, immune response, and metabolism (Fang et al., 2021). The composition of the gut microbiota changes with age (Lephart & Naftolin, 2020; Woo & Kim, 2024). Reduced numbers and diversity/composition of microbiota in elderly people have been associated with various disease pathogenesis (Ren et al., 2023). Probiotics are live microorganisms that can provide health benefits to consumers, when given in sufficient quantities (Sharma & Padwad, 2020). The most widely used microorganisms as probiotics are strains of lactic acid bacteria (LAB) (Tawaran et al., 2016). Probiotic bacteria secrete various bioactive metabolites in the gut and are absorbed into the circulation through passive and active mechanisms, allowing cellular modulating effects at sites far from the gut (Sharma & Padwad, 2020). Probiotics have been recognized to have many beneficial effects on health, including their antioxidant activity and their ability to prevent and reverse the toxic effects caused by ROS. The antioxidant activity of probiotics is supported by several mechanisms: probiotics possess their own antioxidant enzymes, such as SOD; probiotics produce various types of metabolites with antioxidant activity, such as GSH, butyrate, and folate; probiotics can enhance their host's SOD, GPx, and CAT; probiotics can modulate signaling pathways, namely Nrf2 activation, a key regulator of antioxidant responses; probiotics inhibit the activity of ROS-producing enzymes, such as NOX (Azzimonti et al., 2023; Ren et al., 2023). Because of the role of the gut microbiome in health, many functional foods use probiotics as active ingredients (Carvalho et al., 2023). Research in the field of gerobiotics is also constantly evolving to find specific probiotic strains that are able to reduce the physiological aging process and improve the health span of the host (Tsai, et al., 2021) This literature review aims to analyse the biological mechanisms of probiotics in influencing the ageing process.

## **METHOD**

The literature review was conducted by searching for scientific publications from the period 2012-2023 using the NCBI, Scindirect and Google Scholar databases. A total of 300 articles were identified through database searches. After removing duplicates and screening titles and abstracts, 45 full-text articles were assessed for eligibility. Finally, 11 studies met the inclusion criteria and were included in the qualitative synthesis.

## **RESULT**

### **Study Selection**

A total of 300 articles were identified from PubMed (n = 120), Science Direct (n = 95), and Google Scholar (n = 85). After removing duplicates, 235 articles were screened. 45 full text articles were assessed for eligibility, and 11 studies were included in the quantitative synthesis. A total of 300 articles were initially identified through electronic database searches, including PubMed (n = 120), ScienceDirect (n = 95), and Google Scholar (n = 85). After removing 65 duplicate records, 235 unique articles remained and were screened based on their titles and abstracts. During the screening process, 190 articles were excluded because they did not meet the inclusion criteria, such as irrelevance to the research topic, inappropriate study design, or insufficient outcome data. As a result, 45 full-text articles were retrieved and assessed for eligibility. 35 articles were excluded after full-text evaluation due to reasons including mismatch with the study objectives, lack of relevant outcome measures, or insufficient methodological quality. Ultimately, 11 studies met all the inclusion criteria and were included in the qualitative synthesis of this review.

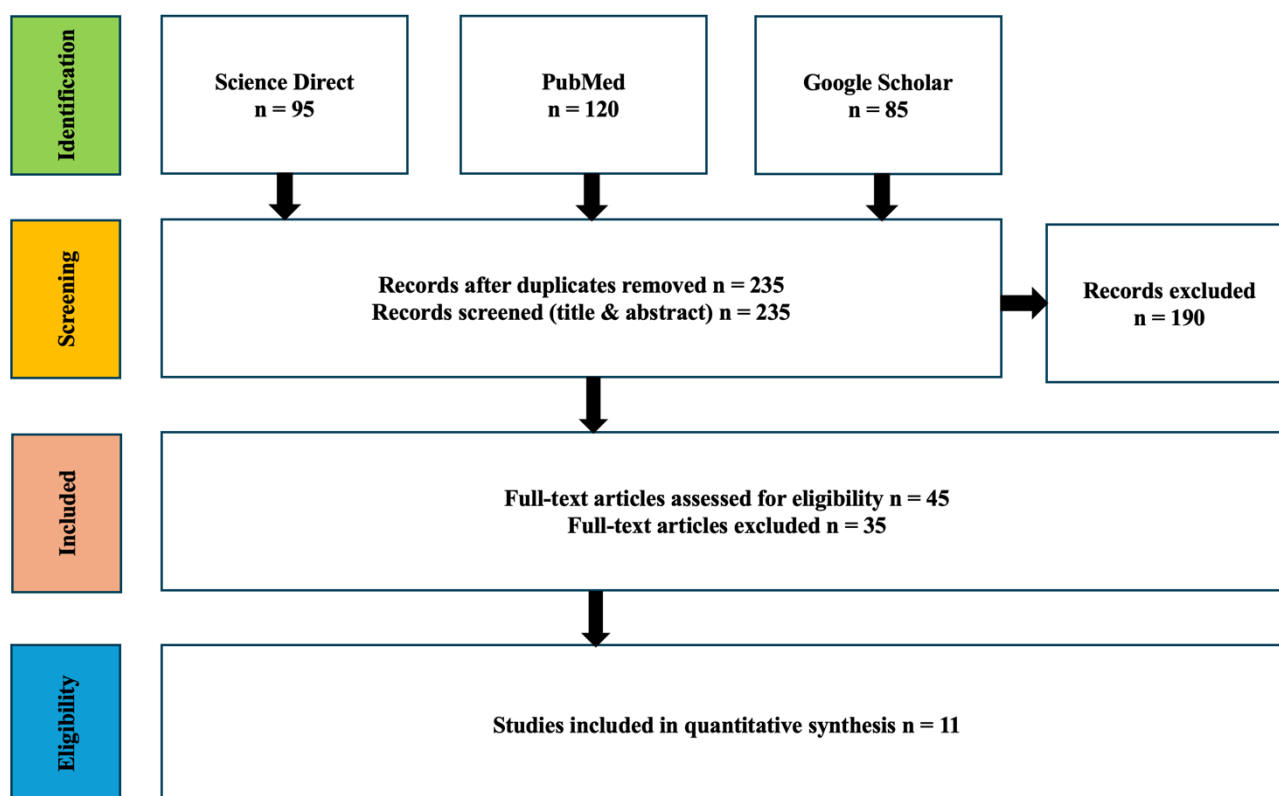


Figure 1. Flow diagram of the study selection process.

### Collating, Summarising, and Reporting the Results

The selected studies were collated and systematically organized to enable structured synthesis of the available evidence. Data from the included articles were extracted using a standardized data extraction form, which captured key information such as author and year of publication, study design, population or experimental model, probiotic strains investigated, intervention characteristics, and main outcomes relevant to the study objectives. The extracted data were then summarized descriptively to identify patterns and trends across studies. Given the heterogeneity in study designs, models, and outcome measures, a narrative synthesis approach was applied rather than a quantitative meta-analysis. The included studies were grouped according to study type (in vivo, in vitro, and review studies) and primary outcome domains, including antioxidant activity, anti-inflammatory effects, modulation of gut microbiota, and markers related to aging processes. Finally, the results were reported in a structured manner using tables and narrative descriptions. A summary table was developed to present the characteristics of the included studies, while the main findings were described thematically to highlight consistencies and differences among studies. This approach facilitated a comprehensive understanding of the current evidence and allowed identification of research gaps and directions for future studies.

Tabel 1.

#### Summary of Included Studies

No	Article Title	Researcher	Year	Location	Purpose	Method	Sample	instrument	Results
1.	Evaluation of the Anti-Aging Effects of a Probiotic Combination Isolated From Centenarians in a SAMP8 Mouse Model	Fang Xin, Mengyun Yue , Wei Jing , Yun Wang et all,	2021	Tiong kok	Anti-aging effects of probiotic combination using the senescence-accelerated mouse model, SAMP8.	Experimental animal	SAMP8 mice are a rapidly aging mouse model, and SAMR1 mice are a normal aging model, and 3-month-old male mice.	L. fermentum SX0718, L. casei SX1107, B. longum SX-1326, and L. animalis SX-0582. From the feces of 7 centenarians from Centenarian Village in Ganzhou Bacteria -	The combination of probiotics can inhibit TLR4/NFkB and upregulate Sirt1 expression to protect hippocampal neurons.

No	Article Title	Researcher	Year	Location	Purpose	Method	Sample	instrument	Results
								Western Blot (Sirt 1; 1:1000; Cell Signaling Technology (Santa Cruz Biotechnology)).	
2	Lactobacilli modulated AMPK activity and prevented telomere shortening in ageing rats	Lew L.C, Hor Y.Y M.H. Jaafar, A.S.Y. Lau, J.S. Ong, L.O. Chuah , K.P. Yap, G. Azzam, A. Azlan and Liong M.T	2019	Malaysia	Evaluating the anti-aging effects of lactobacilli (long telomeres, peroxidation, plasma lipids, liver AMPK expression, in the model old mouse (induced by a high-fat diet)	Experimental animal	Male Sprague Dawley rats 8 weeks	Strain identification: 16S rRNA gene sequencing. - mRNA expression by real-time RT-PCR - Telomere length measured by RT-PCR	Administration of <i>L. plantarum</i> DR7, <i>L. fermentum</i> DR9, and <i>L. reuteri</i> 8513 resulted in telomere shortening, increased expression of AMPK subunit- $\alpha$ 1, and plasma lipid peroxidation.
3	Lactobacillus fermentum JX306 Restrains D-galactose-induced Oxidative Stress of Mice through its Antioxidant Activity	Zhang Di, Chuang Zhang, Li Shi Rui, et al	2020	Taian, China	To observe the effect of <i>L. fermentum</i> JX306 on MDA, GSH, and TOC levels, as well as the expression of antioxidant genes in an old rat model induced by D-galactose.	Experimental animal	Mouse Male	(MDA), (SOD), (GSH-Px), and antioxidant capacity (T-AOC) were determined in serum, liver, and kidney samples using ELISA. - The transcription of antioxidant-related genes Prdx1, Gsr, Gpx, and TR3 in the liver was measured using RT-PCR.	<i>L. fermentum</i> JX306 $\downarrow$ (MDA) (GSH-Px), and total antioxidant capacity (TOC) in serum, kidneys, and liver - $\uparrow$ transcription of antioxidant-related enzyme genes, (Prdx1), (Gsr) (Gpx1), (TR3).
4	Antioxidant Effect of Lactobacillus fermentum CQPC04-Fermented Soy Milk on D-Galactose-Induced Oxidative Aging Mice	Zhou Xianrong Hang-hang Du, Jiang Meiqing Zhou Chaolekan g, et al	2021	Chongqing	Exploring the effects of fermented milk on D-galactose-induced mouse models (oxidative aging).	Experimental animal	Healthy female mice (7 weeks old)	- mRNA expression of related genes in mouse liver and spleen skin Examined by RT-PCR.	Fermented soy milk - $\uparrow$ expression of Cu/Zn-SOD, Mn-SOD, GSH-Px, (TIMP1), (TIMP2) - $\downarrow$ expression of matrix (MMP1) (MMP9) in skin tissue.
5	Lactobacillus plantarum KSFY06 on d-galactose induced oxidation and aging in Kunming mice	Fang Li, Guangbin Huang Fang Tan, Ruokun Yi, Xianrong Zhou, Jianfei Mu, Xin Zhao	2019		Observing the effect of <i>L. plantarum</i> KSFY06 on In the network of aging mice.	Experimental animal	Kunming (KM) male mice, 6 weeks old, weighing 20-25	-SOD, GSH, GSH-Px, CAT, and MDA activities in serum and liver, a colorimetric test is performed, antioxidant gene expression with (qPCR), histopathological analysis of skin, liver, and spleen after H&E staining	Strain <i>L. fermentum</i> KSFY06 $\uparrow$ activity of (SOD), (GSH-Px), (CAT), (GSH) in serum and liver of aging mice, $\downarrow$ (MDA) analysis by PA showed $\downarrow$ damage to the liver, spleen, and skin of mice - $\uparrow$ expression of SOD1, SOD2, CAT, eNOS, nNOS, and iNOS in aging mice.
6	Cell-Free Culture	Kumar	2019		Assessing the	Experimental	Murine	-Bacterial	<i>L. fermentum</i> $\downarrow$

No	Article Title	Researcher	Year	Location	Purpose	Method	Sample	instrument	Results
	Supernatant of Probiotic Lactobacillus fermentum Protects Against H2O2-Induced Premature Senescence by Suppressing ROS-Akt-mTOR Axis in Murine Preadipocytes	Ravi, Anamika Sharma, Mahesh Gupta, Yogendra Padwad, Rohit Sharma			anti-aging potential of probiotic Lfermentum secretory metabolites on H2O2-induced 3T3-L1 preadipocyte cells.	ental cell line invitro.	preadipocyte cell line, 3T3-L1	species were identified using the 16s rRNA gene. -β-galactosidase activity (SA-β-gal) (K802; Biovision, USA, blue color development). - Intracellular ROS were measured using H2O2 and DCFDA dye. - Expression of p53, p21, and p16 genes was determined by qRT-PCR.	phosphorylates the PI3K/Akt/mTOR pathway, ↓ senescence markers p53, p21WAF1, SA-β-gal, p38MAPK, iNOS, cox-2, ROS, NF-κB, and DNA damage response.
7	Orally Administrated Lactobacillus pentosus var. plantarum C29 Ameliorates Age Dependent Colitis by Inhibiting the Nuclear Factor-Kappa B Signaling Pathway via the Regulation of Lipopolysaccharide Production by Gut Microbiota	Jin-Ju Jeong1‡, Kyung-Ah Kim1‡, Se-Eun Jang1,2, Jae-Yeon Wool, Myung Joo Han2, DongHyun Kim	2018	Korea	Observing the effect of LAB anti-inflammatory and anti-aging L. plantarum C29 on old Fischer rats	Experim ental	Fischer 344 rat age (age, 16 months)	- TNF-α, IL-1β, IL-4, IL-6 kit ELISA - Plasma (MDA) was determined using thiobarbituric acid (TBARS). - Gene expression was measured by RT-PCR.	- L. plantarum C29 can ↓NF-κB, AP1, MAPK - ↓ expression of (TNF) α, IL-6 (NF-κB), (AP1), - ↓ expression of aging markers p16 and p53 in the colon of old mice, ↑ expression of SIRT 1, ↓ gut microbial LPS and plasma LPS and ROS levels.
8.	Lactobacillus plantarum AR501 Alleviates the Oxidative Stress of D-Galactose-Induced Aging Mice Liver by Upregulation of Nrf2-Mediated Antioxidant Enzyme Expression	Lin Xiangna, Yongjun Xia, Guangqian Wang, Zhiqiang Xiong, Hui Zhang, Fengxi Lai, and Lianzhong A	2018		To determine the antioxidant effect of BAL on hepatotoxicity in D-galactose-induced aged rats	Experim ental	Male ICR mice (20±2 g)	- L. plantarum was identified using 16S rDNA. - Gene expression analysis was performed using quantitative real-time PCR. - The activities of ALT, AST, catalase (CAT), GSH-Px, SOD, and TBARS, and GSH spectrophotometry were measured	L. plantarum AR501 ↑ gene expression (Nrf2), glutathione reductase, glutathione S-transferase, and NAD(P)H genes in the livers of old mice.
9	Lactobacillus fermentum HFY06 attenuates D-galactose-induced oxidative stress and inf	F, Huang H, Wu Y, Lu Z, Zhou X, Tan F, Zhao X (2021)	2021		Investigating the effects of Lactobacillus fermentum HFY06 on D-galactose-induced aging mice.	Experim ental	Kunming male mice	Quantitative PCR, Western blot analysis	Lactobacillus fermentum HFY06 upregulated the expression of Nrf2, γ-GCS, NOS1, NOS3, SOD1, SOD2, and CAT in liver and brain tissues, increased serum SOD, GSH, CAT, and MDA levels, and decreased IL-6, IL-1β, TNF-α, and IFN-γ. L. fermentum

No	Article Title	Researcher	Year	Location	Purpose	Method	Sample	instrument	Results
									HFY06 can prevent aging or reduce oxidative stress.
10	Antioxidant Effect of Soymilk Fermented by Lactobacillus plantarum HFY01 on D-Galactose-Induced Premature Aging Mouse Mode	Li Chong, Fan Yang, Shuang Li, Zhou Xianron, Kun-Young Park Xin Zhaoand Huazhi Liu	2021	Chong qing, Tiong kok	To investigate the antioxidant effects of fermented soybean milk by Lactobacillus plantarum HFY01 on D-galactose-induced aging in mice.	Experimental	66-week-old female Kunming mice	Analisis histologi hati dan kulit diwarnai dengan hematoxylin-eosin (H&E), trikrom Masson	-LP- HFY01-DR ↑glutathione, catalase, SOD, (GSH-Px) ↓(MDA) in the liver, brain, and serum - ↑ gene expression of (Cu/Zn-SOD, SOD1 (Mn-SOD, SOD2), GSH, and GSH-Px in the liver, spleen, and skin LP-HFY01-DR ↑ antioxidant capacity in D-galactose-induced premature aging mice
11	Antioxidant Activity of Lactobacillus Plantarum NJAU-01 in an Animal Model of Aging.” <i>BMC Microbiology</i> 21(1):1–9. doi:10.1186/s12866-021-02248-	Ge, Qingfeng, Bo Yang, et al.	2021		to explore the potential role of an antioxidant strain, Lactobacillus plantarum NJAU-01 in regulating D-galactose-induced subacute senescence of mice.	Experimental	KM mice (female, 4 weeks old, weighing 18–20 g	- Total antioxidant capacity (ABTS method, SOD (WST method) GSH-PX dan CAT dgn Colorimetric method MDA (TBA method)	L. plantarum NJAU-01 ↑ (T-AOC), (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) and ↓ MDA serum, heart and liver.

## DISCUSSION

### Aging

Aging is a complex and multifaceted process that leads to a decline in organ and tissue function. Phenotypically, the aging process is associated with several indicators at the molecular, cellular and physiological levels, namely changes in genomic stability, decreased telomere length, loss of proteostasis, overall decline in cellular and subcellular function, deregulation of the signal system (Zeppa et al., 2023). Aging is a biological process characterized by various risk factors (neurodegenerative diseases, cardiovascular diseases, cancer, metabolic syndrome, poor immune system, and directly affects the appearance of the skin) (Mumtaz et al., 2023). Some of the fundamental biological processes that occur in aging and are cellular and molecular indicators are: (Tsai, et al., 2021; Zeppa et al., 2023).

### Intestinal Microbiome

The gut microbiota is a highly complex and diverse ecosystem of microorganisms that live in the gastrointestinal tract (Bairamian et al., 2022). A microbiome refers to the genome present in a particular environment, meaning a microorganism with the accumulation of all its genetic material (i.e. DNA and RNA) (Pessemier et al., 2021). The gut microbiome produces short-chain fatty acids (SCFAs); secondary bile acids; cortisol; and neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, dopamine, and tryptophan. Certain gut microbiomes can also respond to hormones secreted by their host. The balance between beneficial and pathogenic bacteria in the gut contributes to the maintenance of health and homeostatic microbiota in the gut (Ren et al., 2023;

Zeppa et al., 2023). Some of these gut microbes have anti- or pro-inflammatory properties. Microbial strains with anti-inflammatory properties increase the production of short-chain fatty acids (SCFA). SCFAs (butyrate, acetate, propionate, etc.) regulate energy metabolism and act as immunomodulators to maintain anti-inflammatory/proinflammatory balance (Clark et al., 2015). The microbial flora associated with increased SCFA production includes *Lactobacillus*. Gut microbes play three important roles from birth: protecting the host, performing metabolic activities, and contributing to the development and regulation of the immune system. However, the microbial composition of the gut can be altered by a variety of factors, including an individual's lifestyle, aging, age, race, antibiotic use, and degree of disease (Woo & Kim, 2024) (Woolery-Lloyd et al., 2023).

### **Microbial Dybiosis**

Gut microbes play three important roles from birth: protecting the host, performing metabolic activities, and contributing to the development and regulation of the immune system. However, the microbial composition of the gut can be altered by a variety of factors, including an individual's lifestyle, antibiotic use, aging and degree of disease (Woo & Kim, 2024). Changes in gut bacteria lead to microbial dysbiosis. Dysbiosis is a dysregulation of the gut flora where the number of pro-inflammatory bacteria increases, while the number of anti-inflammatory bacteria decreases. These changes affect the integrity of the intestinal barrier and exert harmful effects on the body (Zeppa et al., 2019). A state of dysbiosis is characterized by reduced diversity of bacterial species and reduced beneficial bacteria for Health.

With age there are changes in the gut microbiota in the form of decreased diversity and changes in the composition of the microbiota (Lephart and Naftolin, 2022). A significant decrease in Firmicutes and increase in Bacteroidetes occurs from adulthood to old age, suggesting a decrease in the Firmicutes-to-Bacteroidetes (F/B) ratio in old age (Vaiserman et al., 2020). The F/B ratio plays an important role in the formation of short-chain fatty acids (SCFAs), which are an important component in maintaining health beyond the gut (Vaiserman et al., 2020). Age-related gut dysbiosis is believed to accelerate aging, inflammation, and frailty, thus jeopardizing the health and longevity of sufferers (Vaiserman et al., 2020; Woo & Kim, 2024; Ratanapokasatit et al., 2022).

Gut dysbiosis results in a “leaky gut” condition where it causes an increase in intestinal permeability allowing harmful metabolites to enter the stream (Ratanapokasatit et al., 2022). Bacterial antigens, particularly lipopolysaccharides, trigger the release of proinflammatory cytokines such as IL-1 $\beta$ , TNF $\alpha$ , and IL-6. Prolonged exposure to these bacterial antigens which both contribute to persistent low-grade systemic inflammation can lead to cellular senescence and immune system aging (Woo & Kim, 2024). Microbial variation has the potential to influence microbiome function by increasing gut permeability while interfering with nutrient absorption, food metabolism and immune system regulation. Disruption of the gut microflora and the associated consequences may influence the pathology of various diseases, including aging (Ratanapokasatit et al., 2022).

### **Probiotics**

Probiotics are as live microorganisms that are beneficial to health when available in sufficient quantities. Probiotics directly affect the composition of the gut flora through the introduction of healthy bacteria. Probiotics interact with the gut microbiota, affect the immune system and mucosa and improve intestinal barrier function (Peladic et al., 2021 Ren et al., 2023). Probiotics may be beneficial for treating and preventing diseases of several gastrointestinal diseases including IBM (Hor et al., 2019;). Probiotics exert beneficial health effects through several mechanisms, including altering microbiota composition, maintaining epithelial barrier function and modulating mucosal and systemic immune responses (Sharma & Padwad, 2020). Studies have shown that some probiotics can achieve effective therapeutic results by changing the composition of the microbiota to a more balanced structure. Probiotic bacteria also secrete a variety of small bioactive metabolites in the gut that interact with epithelial cells and are absorbed into the circulation through passive and

active mechanisms, allowing cellular modulating effects at sites far from the gut (Tsai et al., 2019). Over the past few years, several studies have reported the effects of probiotic secretory factors on immunomodulation, cell cycle regulation, fighting infection, and antioxidant activity (Matsuki & Pe, 2013). Probiotic secretions are diverse and often include short-chain fatty acids (SCFAs), peptides, lactic acid, vitamins, polyamines and polyphosphates (Sharma & Padwad, 2020). Probiotics can produce metabolites that have anti-inflammatory effects, such as SCFA, L-tryptophan (Trp) metabolites, adenosine, and histamine. These anti-inflammatory metabolites can act locally and systemically and inhibit low-grade chronic inflammation (Ren et al., 2023). SCFAs reduce cytokine production by neutrophils while reducing macrophage NF- $\kappa$ B signaling (Ren et al., 2023).

SCFAs (butyrate, acetate, propionate) work as immunomodulators to maintain anti-inflammatory / pro-inflammatory balance in the body (Reyes-gavil et al., 2019). SCFAs reduce cytokine production by neutrophils while reducing macrophage NF- $\kappa$ B signaling (Ren et al., 2023). A recent meta-analysis showed that probiotic interventions reduce chronic inflammation by lowering IL-6 and C-reactive protein levels in middle-aged and older adults (Ren et al., 2023). Lactobacilli are the most common microorganisms used as probiotics. Studies on the effects of probiotics on aging have also received much attention due to their reported ability to improve health through inhibiting the formation of free radicals and increasing the activity of antioxidant enzymes, thereby reducing damage caused by oxidative stress (Li et al., 2012;). Certain strains of Lactobacillus can produce metabolites that can promote the host's antioxidant system to cope with oxidative stress and can also produce certain antioxidant enzymes in the host body (Ishaq et al., 2021). Probiotic bacteria including the genera Lactobacillus and Bifidobacterium, have been verified to produce diverse therapeutic compounds such as amino acid metabolites, vitamins (folate, vitamins B1, B2, B6, B9, and B12), bacteriocins, diacetyl, hyaluronic acid, exopolysaccharides, fructooligosaccharides (inulin, levan), enzymes (amylase, superoxide dismutase, catalase, sphingomyelinase), immunomodulatory compounds, short-chain fatty acids SCFA (lactic acid, butyric acid, propionic acid, acetic acid), lipoteichoic acid, and peptidoglycan (Lim et al., 2022).

Park et al. (2015) isolated probiotic strains from the feces of elderly Korean residents (over 80 years old) who defecate regularly. The most common strain found was Lactobacillus fermentum, and showed the strongest adhesion to intestinal epithelial cells, had the ability to increase immunity, the greatest anti-inflammatory and anti-oxidation activity, and could withstand gastric acid and bile solution (Park et al., 2015; Zeppa et al., 2023). Previous studies have also shown that feeding a probiotic diet for 6 months to healthy elderly people living in dormitories and private homes showed an increase in fecal Lactobacilli and Bifidobacteria and a decrease in proteobacteria. In addition, SCFA and butyric acid were significantly higher in the probiotic-treated group (Zeppa et al., 2023). Probiotics are live microorganisms (single or mixed) that are present in sufficient quantities in our food, as much as 10<sup>6</sup> to 10<sup>7</sup> colony forming units (CFU) per gram of food (Purwati et al., 2017 Amelia et al., 2021). Recent research provides new hope that probiotics have natural antioxidant abilities and in vitro probiotics have been shown to increase the body's antioxidants. Probiotics can increase SOD and GPX activity and decrease MDA in serum.

### **Probiotics and Aging in the Body**

Probiotics have been recognized to have many beneficial effects on health, including their antioxidant activity, and their ability to prevent and reverse the toxic effects brought about by ROS. The antioxidant activity of probiotics is supported by eight main mechanisms, as proposed by Wang and his collaborators: (1) probiotics, exhibit chelating ability for Fe<sup>2+</sup> or Cu<sup>2+</sup>, thus inhibiting Fenton reaction and ROS production; (2) probiotics possess their own antioxidant enzymes, such as SOD (*L. fermentum*E-3) or CAT (*L. casei* BL23); (3) probiotic Lactobacillus can produce various types of metabolites with antioxidant activity, such as GSH, butyrate, and folate; (4) probiotic Lactobacillus can increase its host's SOD, GPx, and CAT; (5) probiotics can induce the expression of host metabolites with antioxidant activity (GSH, folate); (6) probiotics can modulate signaling pathways, namely Nrf2 activation, a key regulator of antioxidant responses; (7) probiotics inhibit

the activity of ROS-producing enzymes, such as NOX; (8) probiotics can regulate the composition of gut microbiota, by inhibiting the excessive proliferation and virulence of pathological bacteria with potential pro-oxidant activity (Wang et al., 2017; Azzimonti et al., 2023).

However, only recently has literature begun to consider the relationship between aging and microbial dysbiosis. Probiotics can modulate the root causes of aging, particularly inflammation and oxidative stress (Kiouisi et al. 2022). SCFAs and polyamines produced by probiotics are linked to health and aging. SCFA levels decline with age, which can lead to disruption of the intestinal barrier, which may be involved in the pathogenesis of aging and inflammatory disorders (Gao et al., 2009; Reyes-Gavill et al., 2019). SCFAs are important bacterial signals for maintaining various physiological functions. SCFA levels facilitate organ-intestinal interactions, which help control cell-damaging factors such as inflammatory responses. SCFAs can also activate the production of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2). Nrf2 is known as a transcription factor that triggers significant antioxidant pathways in cells (Gupta et al. 2024). Nuclear factor-erythroid-2 related factor 2 (Nrf2) is a transcription factor protein that regulates genes encoding antioxidants and detoxification enzymes (Medoro et al. 2023)

SCFAs and polyamines produced by probiotics have been linked to health and aging. SCFA levels decrease with age which may lead to disruption of the intestinal mucus barrier, which may be involved in the pathogenesis of aging and inflammatory disorders (Gao et al., 2009; Reyes-gavil et al., 2019). SCFAs produced by bacterial fermentation in the gut show evidence of improving inflammation, and aging (Smith et al., 2019). Similarly, polyamines are small molecules that are widely produced by commensal bacteria and play an important role in various cell processes (Sharma & Padwad, 2020). Some studies show the role of probiotics on aging such as the research of Lew LC et al., (2019) showed that, *L.fermentum* DR9, *L.plantarum* DR7, and *Lactobacillus reuteri* 8513d reduced telomere shortening in D-galactose-induced mice. Research by Lin et al., (2018) found that *Lactobacillus plantarum* AR501 greatly increased the expression of the Nrf2 gene and upregulated the expression of several antioxidant genes, such as glutathione reductase and glutathione S-transferase, in the liver of aging mice. Research by Chen Huizhen et al., (2022). *L.fermentum* JX306 can significantly reduce malondialdehyde (MDA) levels and increase glutathione peroxidase (GSH-Px) activity, and total antioxidant capacity (TOC) in serum (Zhang Di, et al 2020) (Zhao et al., 2019). Li, Fang, et al. (2020) found that *L. fermentum* strain KSFY06 increased the activity of (SOD), (GSH-Px), (CAT), (GSH) in serum and liver of aging mice, decreased (MDA), PA analysis showed decreased damage to the liver, spleen, and skin of mice and increased expression of SOD1, SOD2, CAT, eNOS, nNOS, and iNOS in aging mice. *L. fermentum* decreased phosphorylation of PI3K/Akt/mTOR pathway, decreased aging markers p53, p21WAF1, SA- $\beta$ -gal, p38, MAPK, iNOS, COX-2, ROS, NF- $\kappa$ B, and DNA damage response (Kumar Ravi et al., 2019).

Research by Li Fang, et al. (2022) proved that *Lactobacillus fermentum* HFY06 upregulated the expression of Nrf2,  $\gamma$ -GCS SOD1, SOD2, and CAT in liver and brain tissues, increased serum SOD, GSH, CAT, and MDA, and decreased IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and IFN- $\gamma$  in serum. *L. fermentum* HFY06 can prevent aging or reduce oxidative stress. Li Chong et al (2021) proved that *LPlantarum* -HFY01-DR increased glutathione, catalase, SOD, (GSH-Px) and decreased (MDA) in liver, brain, and serum, increased gene expression (Cu/Zn-SOD, SOD1 (Mn-SOD, SOD2), GSH, and GSH-Px in liver, spleen, and kidney of mice with premature aging caused by D-galactose. Ge Qingfeng's et al (2021) found that *L. plantarum* NJAU-01 can increase (T-AOC) (SOD), (GSHPx), (CAT) and decrease (MDA) of serum, heart and liver. *L. plantarum* C29 can reduce NF- $\kappa$ B, AP1, MAPK, decrease the expression of (TNF) $\alpha$ , IL-6 (NF- $\kappa$ B), (AP1), expression of aging markers p16 and p53 in the colon of old mice, and increase the expression of SIRT 1. In view of the many roles of probiotics, there has recently been a development of science in the field of Gerobiotics, to define specific probiotic strains capable of reducing the physiological aging process.

## CONCLUSION

Probiotics have a role in the aging process through their ability to naturally produce certain antioxidant enzymes and produce metabolites such as SCFAs that can increase antioxidants and reduce inflammation in the host body.

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