Probiotic Lactobacillus in Anti-Ageing

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Probiotics are defined as live microorganisms that confer a health benefit on the host when administered adequately. The most common probiotic strains are associated with the genera Lactobacillus and Bifidobacterium. Recent advancements have witnessed significant achievements in using Lactobacillus during animal studies in ageing models.

Keywords: probiotic ; ageing ; gut microbiota ; oxidative stress ; elderly

1. Introduction

Ageing is a complex process characterized by decline in physiological function caused by continuous deteriorations and changes at cellular and tissue level. It is a predestined physiological phenomenon attributed to the low functional capability of an organ's functioning. Researchers have focused on its possible mechanism. Still, these studies are complex because the process and pace of ageing is greatly varied among individuals [1]. Inside cells, ageing can be evident as the loss of function or unrestrained propagation. Both microscopic and macroscopic changes occur in tissues with indefinite composition and elevated cross linking in the extracellular matrix, which causes stiffness and the loss of mechanical toughness [2]. Constant cell damage is considered as the ultimate reason for tissue failure; hence, ageing is an important risk factor for several diseases. To understand the actual reasons for our mortality, studies have been focused on ageing to sustain the quality of life in the ageing population globally. However, ageing studies are complex because ageing is influenced by genetic and environmental factors throughout life, which also shows great discrepancy among the subjects [3].

The age-related changes in gut microbiota favor the growth of pathogens and gut-associated diseases. Ageing also affects the composition of beneficial microbes in gut, where their abundance and diversity gets lower [4]. There exists a link between dysbiosis and age-associated metabolic disorders during ageing. The elderly has a low diversity of gut microbiota, specifically linked to metabolic disorders (as evident from animal model studies), which further leads to higher inflammation and compromised immune system. Therefore, the maintenance of a stable gut microbiota is crucial for healthier ageing. One of the key reasons for ageing is the decline in metabolism due to continuous exposure to oxidative stress, which further causes mitochondrial dysfunction [5]. So far, most of the previous studies have focused on feeding live probiotic strains to the animals in ageing experiments. However, the use of heat-killed probiotics has several benefits, including safety and long-lasting effects. Heat-killed probiotics confer different biological effects, such as stimulating the intestinal immune responses and anti-inflammatory effects. A recent study showed that the intra-gastric feeding of heat-killed *Lactobacillus paracasei* PS23 to aging mice can improve age-related muscle atrophy. Ghrelin is an essential gut hormone with pleiotropic effects that controls hunger, meal initiation, and nutrient sensing. It can also indirectly improve muscle mass by stimulating the IGF1 pathway in mice with cachexia. The heat-killed PS23 can help maintain the levels of ghrelin in ageing mice; hence, it can improve the muscle function during ageing [6].

Probiotics are defined as live microorganisms that confer a health benefit on the host when administered adequately. The most common probiotic strains are associated with the genera Lactobacillus and Bifidobacterium. Recent advancements have witnessed significant achievements in using Lactobacillus during animal studies in ageing models [7]. Their key benefits on the host health include improving the barrier function, immunomodulation, and the production of neurotransmitters. Additionally, they can positively influence the host gut microbiota and cellular components of gut-brain axis.

2. Brain Ageing and the Role of *Lactobacillus*

Globally, the average lifespan of humans is increasing due to scientific advancements. However, brain disorders, such as neural disorders and neuropsychiatric diseases, still remain a challenge. Anxiety and memory loss are the two most common brain disorders in ageing [8]. Hence, it is necessary to find alternatives that are capable of curing anxiety and memory loss in the aged population. Both inflammation and free radical levels are responsible for increased ageing.

Considering their multiple effects, the provision of some probiotic strains may be a suitable choice for the treatment of some important age-associated declines, such as inflammatory disorders [9], oxidative stress [10], and metabolic disorders [11]. Some studies have reported that effects can be shifted from gut to brain region to increase the levels of certain neural monoamines, like dopamine, serotonin, and brain-derived neurotropic factor [BDNF], which are important for normal performance of the brain, like neuronal plasticity and survival [12]. By maintaining the balanced levels of these monoamines, it is believed that the chances of anxiety and memory loss can be minimized up to certain levels [13]. As the levels of these monoamines decrease during ageing, by maintaining their constant levels, the age-associated mental declines can be treated [14].

Recently studies have demonstrated that probiotics can affect the functioning of the central nervous system and its performance through gut-brain axis. *L. helveticus, B. longum,* and *Bifidobacterium breve* have positive effects during anxiety-like behaviors and can strengthen the memory in murine models [15][16]. These improved behaviors were observed with the reestablishment of neural monoamine levels in major brain regions, like the hippocampus and striatum [17]. In fact, only young and middle-aged animals were studied under such experiments. Therefore, the actual effects of probiotics on the age-associated declines in aged population are still contentious. The ageing-associated experiments are expensive and take longer because the animals to be studied need relatively longer time to reproduce. Therefore, in most cases, prematurely aged animals are being studied for age-related research. Senescence-accelerated mouse prone 8 (SAMP8) is a line developed from senescence-resistant mice (SAMR1). It is distinguished by the early onset of ageing, like hair loss, dull hairs, and short lifespan [18]. The SAMP8 mice are similar to the normal mice (SAMR1) for the first four months, but after six months of age, the SAMP8 mice display prominent emotional and memory weakness. Therefore, these disorders are found to happen earlier in SAMP8 mice than the normal mice (SAMR1) [19]. It was confirmed by Rhea and Banks in 2017 that the SAMP8 mice can be used for age-related studies regarding emotion and memory loss. They also stated that the onset of ageing occurs more rapidly in SAMP8 mice after four months of age [20].

Along with other factors, ageing also affects the brain both at cellular and functional level, which undermines sensory, cognitive, and motor functions of the brain. In an ageing model, the administration of the strain *L. plantarum* DR7 had several positive effects on the brain of ageing rats, such as enhanced memory, higher cognitive function, and lower anxiety. Analysis of hippocampus showed lower levels of pro-inflammatory cytokines, while the apoptosis biomarker gene was also down-regulated. The expression of neurotransmitter biomarker genes in the hippocampus region showed that the effects of DR7 might be due to the mechanism along the serotonin pathways. All these effects were transferred from gut to brain through gut-brain axis [21].

Different *Lactobacillus* strains have shown beneficial effects on the gut-brain axis. During a human trial, the consumption of the strain *L. plantarum* DR7 by stressed adults for 12 weeks decreased the stress symptoms, anxiety, and total psychological scores when they were compared with the placebo group. Subjects treated with the strain were observed with lowered cortisol levels, pro-inflammatory cytokines (interferon-γ and transforming growth factor-α), and higher anti-inflammatory cytokines in plasma. The strain also enhanced cognitive and memory functions, including basic attention, associate learning, and emotional cognition in adults [22]. An important *Lactobacillus* strain (*L. paracasei* LPPS23) can either alone or in combination with other probiotic bacteria offer considerable effects on the brain and overall nervous system [23][24]. *L. paracasei* NTU 101 can enhance the antioxidative and anti-inflammatory responses [25]. Huang et al. (2018) investigated the effects of LPPS23 on age-related cognitive decline in SAMP8 mice. During the study, they reported that the LPPS23 group exhibited less symptoms of ageing (senescence). In addition, the memory weakening and anxiety-like patterns were lower than the control group. The neural monoamines levels were also lesser in the striatum, hippocampus, and serum of the control group. Furthermore, *L. plantarum* PS23 also accelerated the production of anti-oxidative enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx) [26]. Based on the above studies, it can be clearly seen that the great therapeutic potential of using probiotics to treat ageing brain-associated problems. However, more clinical studies are still needed.

3. Skin Ageing and the Role of *Lactobacillus*

Both internal and external factors contribute to skin ageing. Internal factors include genetic alterations monitored by a set of different physiological changes attributed to ageing, including degeneration of epidermal and dermal skin tissue layers and increased dryness [27][28]. External ageing is mostly caused by environmental factors, like UV radiations and toxins like cigarette smoke. The symptoms of external skin ageing are rough wrinkles, decrease in elasticity, epidermal thickness, increased dryness, laxity, coarse appearance, and different pigmentation problems [27]. Most of the age-associated problems appear on the face, neck, forearm, and dorsal regions of hands. As a function of these factors, the ageing process is more evident in these regions. Although both intrinsic and extrinsic skin ageing factors are different, both involve the same molecular mechanism [28][29]. The skin pH is determined by free amino acids, epidermal lactate,

and free fatty acids. Usually, skin health is determined by skin pH, but with ageing, the skin pH rises, leading to abnormal conditions. In a double-blind placebo-controlled trial, the ingestion of *L. plantarum* CJLP55 significantly decreased the skin pH. Although the levels of free fatty acids were affected, the total free fatty acids, such as palmitic acids and stearic acids, were lower in the probiotic-treated group [30]. Studies also suggest that Lactobacillus can enhance the protective mechanism in the skin [31]. The dietary supplementation of *L. Johnsonii* displayed inhibition either alone [32] or in combination with carotenoids [33] against early UV-induced skin by regulating the immune cells as well as inflammatory cytokines.

Further investigations recommend that probiotic supplementations can reduce atopic dermatitis and skin dryness [34][35]. Several experiments by using hairless mice have suggested that along with the control of immune responses in the skin, oral administration of probiotic strains may have anti-ageing effects by suppressing wrinkle formation and increased skin elasticity [36]. As it was reported that *L. plantarum* HY7714 has anti-photoageing properties by reducing the formation of wrinkles and suppressing the epidermal thickness, and after administration of this strain to mice, the skin hydration was increased with the increased level of ceramide by maintaining the serine palmitoyl transferase and the appearance of ceramidase in the skin of mice [37]. In a randomized controlled clinical trial in humans, *Lactobacillus* strain HY7714 increased skin hydration, inhibited the wrinkle formation, and increased the elasticity of skin gloss [38]. Isoflavones are polyphenolic compounds commonly known as phytoestrogens having antioxidant, anti-tumor, and anti-inflammatory effects. Equol is a major isoflavone. A recent study was conducted to investigate the effect of feeding a fermented product that was fermented with equol producing strain *L. paracasei* JS1 on responses of mice. After analysis of gene expression, it was observed that the messenger RNA of seven skin-related proteins was differentially expressed. The skin moisturizing effects of the strain were also confirmed during the study [39].

4. Conclusions

The above-mentioned studies indicate that several age-related physical and physiological aspects of health in laboratory animals and even humans have been improved significantly after the supplementation of *Lactobacillus* strains either alone or in combinations. These aspects include enhancing the ageing-gut microbiota, improvements in host antioxidation system (production of antioxidant enzymes and regulation of gene expression), enhancements of immune system, minimizing the abnormalities related to brain ageing through the gut-brain axis (anxiety and memory loss), and inhibition of both internal and external factors that contribute to skin ageing. Emerging studies at the cellular and molecular level reveal that *Lactobacillus* can increase the resistance of cells, tissues, and organs to ageing and age-related disorders. Although previous studies have shown promising effects regarding the role of *Lactobacillus*, large-scale randomized, placebo-controlled, double-blind clinical trials are still needed to elucidate their substantial role in ageing and age-related problems in humans. The selection of appropriate strain, their optimal dose, method of administration, and duration of treatment period are yet to be confirmed. Progressive research suggests that in the future, probiotic *Lactobacillus* may be used as an alternative treatment to conventional therapy by modulating the gut microbiota and host immune system.

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