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Mini Review

Healthy Aging, Neuroprotection and Decreased Risk of Cardiovascular Death Associated with the Consumption of Probiotic *Bacillus Subtilis*

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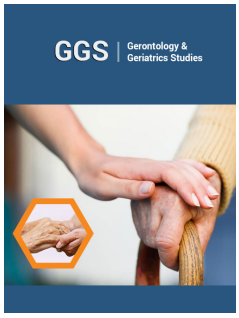

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Aging is a natural process in human beings involving hereditary, environmental, and stochastic factors characterized by a decline in all physiological processes to maintain homeostasis upon life expectancy. This condition is associated with an increased probability to suffer chronic diseases, especially cancer, cardiovascular disorders and neurodegenerative processes. During the next 30 years, people aged 60 or older will increase drastically. By 2050, the world population aged over 60 will increase to two billion. Despite the fact that effective treatments of diseases caused by pathogenic microorganism and cardiovascular conditions increased the mean human lifespan, a number of late-life disabilities are still associated with getting older [1,2].

The intestinal microbiota (the microorganisms that inhabit the gastrointestinal tract of humans) is associated with aging and many studies showed the association between the gut microbiota and the prevention of diverse metabolic diseases like as obesity, type 2 diabetes, cardiovascular and neurodegenerative disorders [1]. The gut microbiota is also associated with the lengthening of the host lifespan. Among the beneficial microorganisms colonizing the human gut, we have the probiotics, defined as live microorganisms intended to have health benefits when consumed to the body in appropriate amounts. However, it is still unknown the mechanisms by which these beneficial microorganisms (i.e., probiotics) would increase host healthy longevity.

Extremely aged individuals (i.e., centenarians and supercentenarians, alive people over 100 and 110 years old, respectively) who survive in good health to the end of the human lifespan are rare. Japan, Switzerland, Singapore, Australia and Spain are the five countries possessing the highest life expectancy with an average life expectancy of 83.16 years [2,3]. Japan shows the highest world longevity (84 years and 81 years, for female and male, respectively) and the highest healthy life expectancy (78 years for both sexes). A natural food consisting of soybean fermented by *B. subtilis* (i.e., natto or vegetable cheese) is the main component of the regular diet among many Japanese people. A recent study related the consumption of several kinds of soy products and mortality due to any natural cause

(i.e., diseases or senility). This analysis was followed nearly 15 years from the beginning of the study and included more than 90,000 participants (50% men and 50% women) aged 45 to 74 years. The results demonstrated no significance association in the decrease in all-cause mortality associated with consumption of soy products but a significantly and inversely association with all-cause mortality in both sexes with the intake of fermented soy products (i.e., natto) nearly 10% [4]. Interestingly, the mortality associated with cardiovascular disease was reduced after the intake of natto food, mainly in men. Given that *B. subtilis* is used for the preparation of natto food [5], we hypothesize that this probiotic bacterium is the main reason to contribute to the long and healthy longevity of Japanese people in a natural form [3].

In one of our recent publications [6] we fed the model organism *Caenorhabditis elegans* on different strains of *B. subtilis*, including *B. subtilis* natto strain RG4365, now renamed *B. subtilis* DG101 [5], to investigate how the biofilm produced by this probiotic affects host longevity. We observed that *B. subtilis* able to produce biofilm colonized the intestine of *C. elegans* and extended its lifespan significantly longer compared to isogenic strains unable to produce a strong biofilm. In fact, *B. subtilis* DG101 extended the host lifespan in more than 53% compared with the control. We have also shown that in addition to the ability to produce biofilm, a small quorum-sensing pentapeptide produced by *B. subtilis*, known as PhrC or CSF and nitric oxide (NO) are the most important properties of *B. subtilis* to exert a healthy longevity over the worm *C. elegans*. An interesting observation was that the ability of *B. subtilis* to produce biofilm correlated very well with the production of higher levels of NO and CSF compared to *B. subtilis* grown under planktonic conditions, reinforcing the main role of the biofilm in increasing host longevity [6].

Highly conserved signaling pathways are responsible for the regulation of lifespan in association with transcription factors sensing stress, environmental cues and energy availability. Among eukaryotic models, including *C. elegans* and humans, the main pathways regulating longevity are Dietary Restriction (DR), the Insulin-Like Signaling (ILS) pathway, germline signaling, stress response and mitochondrial respiration. Two of them (DR and ILS) converge on the positive and negative regulation of the transcription factors DAF-16 (FOXO in humans) and HSF-1, respectively. Our results indicated that DAF-2 (IGF-1 in humans)/DAF-16/HSF-1 are responsible for the increased longevity and healthy aging mediated by *B. subtilis* trough a downregulation of the Insulin-Like Signaling (ILS) pathway [6]. In concordance with our results, many of the genetically analyzed healthy humans aged 100 or more years possess IGF-1 receptor genetic variants associated with a slightly reduced functionality of the insulin signaling [3].

Alzheimer's Disease (AD) is a progressive illness and the most common type of dementia affecting more than 6 million Americans, most of them age 65 or older. It is characterized by a memory loss and other cognitive abilities interfering with daily life. During the early stage of Alzheimer's, toxic changes are taking place in the brain, including abnormal buildups of proteins that form amyloid plaques and tau tangles. Previously healthy neurons stopped functioning, lose connections with other neurons, and die. Currently, no therapy or medicine have been found but intestinal probiotics have emerged as a novel strategy with benefits in mental health. This is the reason why these probiotics are also called psycho biotics. One of the main risk factors associated with the etiology of AD, are aging and neuronal degeneration. In another of our recent publications, we showed an attenuated decline in neuronal degeneration and cognitive impairment when the wild-type *C. elegans* strain N2 was fed on *B. subtilis* compared with N2 worms fed on the control *Escherichia coli* OP50 strain [7]. Interestingly, the transgenic *C. elegans* strain CL2120 expressing the toxic peptides Aβ3-42 in body wall muscle cells, fed on *B. subtilis* showed protection against Aβ-related progressive paralysis. Same results were obtained when a *C. elegans* strain expressing the whole peptide Aβ1-42 was fed on *B. subtilis*. Chemotactic response and a reduction in body bends, two important behavioral deficits were also observed in a *C. elegans* strain expressing the pan-neuronal Aβ1-42 peptide. Notably, *C. elegans* strains expressing Aβ live longer when fed on *B. subtilis*, a restoration of the lifespan level similar to the wild-type strain N2 fed on the control *E. coli* OP50. As abovementioned, CSF peptide and gut biofilm production were also key for *B. subtilis* to exert beneficial properties against AD-related symptoms. Interestingly, we also reported [8] that probiotic *B. subtilis* DG101 protects from neurodegeneration in transgenic *C. elegans* strains (NL5901, VC1024, and BZ555) used as models for studying Parkinson Disease (PD). The probiotic *B. subtilis* strain DG101 (natto strain) not only extended the lifespan expectancy of the transgenic *C. elegans* PD strains but also prevented the PD-related neurodegeneration of dopaminergic neurons and Lewy bodies formation [8,9].

Conclusion

Nearly 10^{14} microorganism, mainly belonging to the bacteria phyla Bacteroides and Firmicutes, form the human intestinal microbiota contributing to the host development, immune system and metabolism [1]. The final composition of the intestinal microbiota is conformed approximately 3 years after birth and is stably maintained depending on the host health and diet. Early in the Twentieth century Metchnikoff proposed that human aging was the result of intestinal microbe dysbiosis (unbalanced gut flora) and that consumption of probiotic Lactic Acid Bacteria (LAB) found in product such as yogurts could delay senility (i.e., enhance healthy longevity) because of the reestablishment of a healthy gut flora [10]. The advantages of *B. subtilis* as a novel probiotic are: (i) as spore-forming bacteria (i.e., highly resistant biological form) refrigeration is not required for maintaining their viability, (ii) *B. subtilis* can be added to a wide range of foods (e.g., dairy products, bred, hot or chilled beverages, rice, cereals, and snack products among others), and (iii) *B. subtilis* protects and enhances the growth of the other type of probiotics (LAB) in the host gut (i.e., *B. subtilis* and LAB show synergic effects) [5]. DR is the only non-genetic intervention extending lifespan in mammals, but given that DR is hard to follow, extending its benefits to human longevity is unlikely. Through these

years of research, we have undoubtedly proven that incorporation of *B. subtilis* natto to the intestinal flora improves neuronal plasticity [7-9] and enhances host longevity [6] without genetic intervention. These findings raise the possibility to feed people with probiotic *B. subtilis* natto (i.e., strain DG101) [5], incorporated in different foods and beverages without affecting organoleptic properties of the food or affecting cultural traditions, to pursue the extension of healthy life expectancy, a pleasant aging, and protection against infections [11-13].

References

1. Khan SS, Singer BD, Vaughan DE (2017) Molecular and physiological manifestations and measurement of aging in humans. Aging Cell 16(4): 624-633.
2. Ayala FR, Bauman C, Cogliati S, Leñini C, Bartolini M, et al. (2017) Microbial flora, probiotics, *Bacillus subtilis* and the search for a long and healthy human longevity. Microb Cell 4(4): 133-136.
3. Kim S, Jazwinski SM (2018) The gut microbiota and healthy aging: A Mini-Review. Gerontology 64(6): 513-520.
4. Katagiri R, Sawada N, Goto A, Yamaji T, Iwasaki M, et al. (2020) Association of soy and fermented soy product intake with total and cause specific mortality: prospective cohort study. BMJ 368: m34.
5. www.kyojin.com.ar
6. Donato V, Ayala FR, Cogliati S, Bauman C, Costa JG, et al. (2017) *Bacillus subtilis* biofilm extends *Caenorhabditis elegans* longevity through downregulation of the insulin-like signalling pathway. Nat Commun 8: 14332.
7. Cogliati S, Clementi V, Francisco M, Crespo C, Argañaraz F, et al. (2020) *Bacillus subtilis* delays neurodegeneration and behavioral impairment in the Alzheimer's disease model *Caenorhabditis elegans*. J Alzheimers Dis 73(3): 1035-1052.
8. Francisco M, Grau R (2018) Probiotic *Bacillus subtilis* prevents alpha-synuclein aggregation and extends the healthy lifespan in Parkinson disease model *Caenorhabditis elegans*. Advances in Alzheimer & Parkinson therapies and AAT-AD / PD Focus Meeting, Italy.
9. Crespo C (2020) Neuroprotective properties of probiotic *Bacillus subtilis* in transgenic *Caenorhabditis elegans* model of Parkinson Disease. Graduate thesis.
10. Metchnikoff E (1908) The prolongation of life: Optimistic studies. In: Mitchell C (Ed.), Putnam's Sons Press, New York, UK.
11. VidyaLaxme B, Rovetto A, Grau R, Agrawal R (2014) Synergistic effects of probiotic *Leuconostoc mesenteroides* and *Bacillus subtilis* in malted ragi (*Eleucine corocana*) food for antagonistic activity against *Vibrio cholerae* and other beneficial properties. J Food Sci Tech 51(11): 3072-3082.
12. Ayala FR, Bauman C, Bartolini M, Sabal E, Salvarrey M, et al. (2017) Transcriptional regulation of adhesive properties of *Bacillus subtilis* to extracellular matrix proteins through the fibronectin-binding protein YloA. Mol Microbiol 104(51): 804-821.
13. Oba M, Rongduo W, Saito A, Okabayashi T, Yokota T, et al. (2021) Natto extract, a Japanese fermented soybean food, directly inhibits viral infections including SARS-CoV-2 in vitro. Bioch & Biophys Res Comm 570: 21-25.