Review Article

The Role of Probiotics in Parkinson's Disease: A Review Study

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Abstract

An upward trend in the incidence of Parkinson's disease (PD), known as one of the most prominent neurodegenerative maladies, has evoked great concerns among medical community over the past decades. Recently, studies have suggested the initiation of PD in the gastrointestinal tract decades before the advent of manifestations. Accumulating evidence suggests that intracellular deposition of α-synuclein (α-syn) in patients with PD is associated with systemic inflammation leading to the neuroinflammation and neuropsychiatric disorders. The α-syn protein accumulation can be initiated from GI cells and distribute into CNS cells through trans-synaptic cell to cell transmission. Without doubt, gut microbiota affects the enteric nervous system (ENS) known as the "second brain". Patients with PD have a different balance of bacteria in their intestines, as compared to healthy population. Metabolites from gut microbiota affect the enteric wall such as neurodegeneration. Probiotics have a substantial role in the neutralization or inhibition of reactive oxygen species (ROS) and free radicals and thus improve the PD symptoms. The anti-inflammatory role of probiotics also inhibits the neurodegeneration and PD development. Hence, probiotics contribute to the improvement of PD through several mechanisms which need more in-depth verification.

Keywords: Probiotics, Parkinson's disease, Microbiome, inhibitory mechanisms

Introduction

Parkinson's disease (PD) is developed due to the depletion of dopaminergic neurons in the dense region of the substantia nigra in the brainstem (1, 2). The PD signs mostly include the manifestation of symptoms such as tremors, bradykinesia, muscle stiffness, vibration during rest, cognitive and behavioral impairs, autonomic system disorders, and sleep disturbances (3). These changes give rise to functional motor asymmetry, which is commonly measured by the induction of rotation to the same side (ipsilateral) and to the opposite side (contralateral) by direct dopaminergic agonists (apomorphine) and with immediate effect (amphetamine). Regrettably, thus far, there is no therapeutic approach to the disease, and the rate of newly diagnosed cases

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The brain is highly vulnerable to oxidative damage owing to its high metabolic rate. Protection against free radical oxidative damage in the central nervous system (CNS) can be exerted by low molecular weight antioxidants such as vitamins E and C. The fact that vitamin E acts as a free-radical scavenger in brain tissue has led to the convincing idea that several neurological disorders may be prevented by its properties (4).

Dopamine plays a vital role in various functions of the CNS, including emotion, motor behavior, recognition and regulation of endocrine. Additionally, dopamine is a crucial substrate in synaptic plasticity, memory mechanisms, and learning (5). Extrusions related to the dopaminergic neurons of the abdominal ganglion and the substantia nigra are directed to the hippocampus, dentine, and prefrontal cortex (6). Dopamine secreted from this route in the hippocampus affects memory, in particular spatial and learning memories. Thus, the effect of dopamine on memory is induced by synaptogenesis in the hippocampus (7).

Dopamine precursors, analogues, and agonists have been extensively employed for the treatment of PD. However, there is a limitation in the administration of L-DOPA, the precursor of dopamine. Indeed, its chronic administration is associated with long-term motor impairment. Microbiota are divided into pathogenic and beneficial genera (8-16). The beneficial effects of probiotics in human health, through improving the gut microflora and the immune system and prevention or treatment of various diseases has opened up new avenues for further research on their conceivable prophylactic and therapeutic applications via production of various compounds e.g., vitamins, hormones, hydrogen peroxide, diethyl acetaldehyde, lactoperoxidase, short-chain fatty acids, anti-oxidants and bacteriocins (17,18). A healthy human gut is teeming with approximately 100 trillion bacteria, all of which together create the intestinal microbiome. Probiotics also contribute to the intestinal pH reduction, the generation of certain gastrointestinal (GI) enzymes, lowering the LDL cholesterol, preventing bacterial infections, eliminating carcinogenic substances, and improving calcium absorption (19). The differences in the frequency and diversity of mucosal-associated and fecal microbiota between PD patients and healthy subjects has been deciphered. Comparison of 16S ribosomal RNA gene sequences between bacteria isolated from gut of healthy subjects and PD patients has revealed altered abundances in the content of nine genera and 15 species of microorganisms. Such alterations could trigger local inflammation and subsequent aggregation of α-syn, which results in the PD development through deposition of Lewy bodies inside nerve cells (20). The α-syn protein accumulation can be initiated from GI cells and distributed into CNS cells through trans-synaptic cell to cell transmission. Some surveys have also noted an increased population of bacteria belonging to the families *Christensenellaceae* and *Methanobacteriaceae* in PD patients (20). Furthermore, there is ample evidence that exposure to lipopolysaccharide causes neuronal loss through inflammatory circuits and oxidative injury. It has also been shown that fecal short chain fatty acids (SFAs, required for activation of microglial cells) are reduced in PD patients. Interestingly, a shrinking population of SFA-producing bacteria including *Blautia*, *Roseburia*, and *Coprococcus* species has been observed in fecal samples of PD patients (21-23). On the other hand, dysbiosis causes increased epithelial permeability and inflammation of the gut mucus layer, which then triggers the activation of effector T cells, disrupting their balance with immunosuppressive regulatory T cells leading to improper GI function and homeostatic imbalance (24). Apart from that, impact of demographic factors including age, gender, and race has been still the subject of much debate (25).

Searching strategy

In this study, full text published papers found in searching engines including Google Scholar, Web of Science, SCOPUS and PubMed during the period 2009-2020 were selected. The words

"probiotics", "Parkinson's disease", "mechanism", "development" and "inhibition" were adopted for searching. Inclusion criteria included those papers which investigated the role of probiotics in the inhibition of Parkinson's disease. Exclusion criteria included those papers without full text and those publications with therapeutic purposes.

Gut-Brain axis in Parkinson's disease

Neurodegenerative diseases are characterized by loss of neuronal cells. In the PD, the accumulation of Lewy bodies and Lewy neuritis containing misfolded α-synuclein (α-Syn) affect the substantia Nigra and GI nerve cells. The parasympathetic or vagal verves provide the communication between brain and gut. Therefore, the accumulation of α-Syn in the GI cells prior to the CNS cells, initiates the PD symptoms. Recently, mounting evidence has revealed that PD is also associated with other neuronal systems such as enteric neurons. The GI dysfunction in the early stages of the PD is a significant non-motor symptom mostly with constipation in 80% of patients (2, 26). On the other hand, the gut dysbiosis causes absorption and increase in metabolites from GI tract and causes systemic inflammation. The inflammation of enteric nervous system (ENS) and CNS causes neuroinflammation and damage of neuronal cells which develop the PD (27).

Probiotics species and activities

There is voluminous evidence that probiotics ward off many GI maladies through 1) production of inhibitory compounds (28), 2) competitive blocking of microbial binding sites, 3) nutritional competition with pathogens, 4) elimination of toxins receptors, 5) stimulation of immune responses, and 6) amelioration of inflammatory responses in autoimmune and allergic disorders (16, 29). The sum of all the processes by which bacteria control the colonization of other bacterial species in the body through controlled colonization is known as resistance to colonization. *Bifidobacterium* and *Lactobacilli* are major probiotics species (30, 31). Probiotics are theorized to exert these inhibitory effects in several ways. The probiotics employment in preventing diseases and improving the health status has a long history. Probiotics are used not only as a growth stimulant, but also for inducing the immune system and preventing the spread of numerous diseases. These live microorganisms help maintain or increase the growth of livestock and humans in order to replace or strengthen the beneficial microorganisms in the GI tract (32).

Several *in vivo* studies have assessed the beneficial role of probiotic bacteria such as *Lactobacillus casei Shirota* (1× daily for 5 weeks, 6.5 × 10^9 CFU), *Streptococcus salivarius* subsp. *thermophilus*, *Enterococcus faecium*, *Lactobacillus rhamnosus GG, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii, subsp. bulgaricus, and Bifidobacterium* (fermented milk) in PD animal models (33-36). In addition, FMT has been applied (1× daily for 7 days 2 × 10^7 CFU) (37). Among these microorganisms, *L. brevis* is considered to be one of the most prominent members of the probiotic bacterial group (38), firstly isolated from milk and broadly used as an initiator in dairy, meat, vegetable, and cereal industries. Considering the emotional, economic, and psychological effects of PD in community, some desirable features of probiotics, especially low cost and availability, make them as an auspicious agent for the prevention, treatment, and control of numerous diseases. Therefore, unraveling the exact association of probiotics in the improvement or the prevention of PD seems a chief requirement.

Anti-inflammatory effects of probiotics

The colonizing probiotics have crucial role in the control of autoimmune diseases due to regulatory role of immune system via host-bacteria relation (39). The intestinal epithelium encompasses higher number of immune cells compared to the secondary lymphoid tissue. One possible mechanism for lower inflammatory

responses against host microbiota is that they lack stimulating antigens (39). Noticeably, microbiota affects the differentiation of immune cells having a reciprocal relationship. More relevantly, some species of bacteria cause the stability and function of helper T (T-h) and regulatory-T (T-reg) cells in the lamina propria (LP). It was observed that Bacterioides fragilis affects the immune responses (39, 40). It has also been verified that intestinal microbiota effects the arthritis through regulation of Th cells population (41).

Probiotics mechanisms in the PD improvement

There is growing evidence on the link between imbalance of the gut microbiota and certain maladies such as constipation and malnutrition. Fecal microbiota transplantation (FMT) is a procedure that delivers stool from healthy donors to patients with an altered colonic microbiome to restore the normal population of bacteria. While *Clostridium difficile* is the only condition for which FMT is currently used, others such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and PD are also being considered (27, 42, 43).

Oligomerization and accumulation of α-sync play a critical role in the progression of PD and other neurodegenerative diseases (44). Furthermore, α-syn increase owing to GI tract microbiota dysbiosis by genetic or environmental factors gives rise to disruption of ENS, abnormal intestinal permeability, and endotoxemia, highlighting the prohibitory effects of residing microbiota (44, 45). In a study, the treatment of PD patients with probiotics significantly improved the consistency and life quality associated with the constipation outcomes (45). In another study, application of SLAB51 probiotic strain decreased the harmful effects due to the PD *in vitro* and *in vivo* (46).

Since oxidative stress is a potential mechanism contributing to the pathogenesis of PD, numerous studies have investigated the disclosure of the antioxidant effects of various natural products for PD prevention. Among the dietary antioxidants, Vitamins C and E, and carotenoids (β-carotene) exhibit protective effects on cells from oxidative damage. In this respect, there is an inverse association between the intake of vitamin E and the risk of PD development, but no relationship between the intake of vitamin C and β-carotene with the PD has been observed. Probiotics can confer therapeutic effects on PD by production of metabolites and vitamins such as vitamin E (Figure1) (47). Some studies have revealed elevated levels of free iron in basal complexes of patients with PD. Free iron catalyst enhances a reaction for the production of free radicals and is involved in lipid peroxidation and neuro-degeneration. Probiotics also have the potential to neutralize these radicals by producing antioxidant metabolites (48).

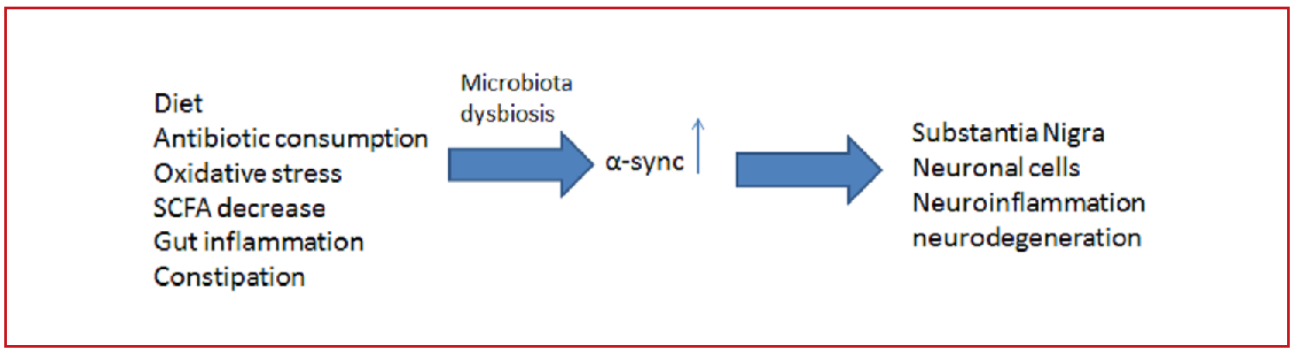

Figure1. The cellular mechanisms of probiotics metabolites on neurodegeneration or neuroinflammation following gut dysbiosis in PD pathogenesis; α-syn aggregation and its transfer through vagal nerve (gut-brain axis) to substansia nigra is the major cause of PD development. This phenomenon occurs because of different factors such as malnutrition, antibiotic consumption, oxidative stress, SCFA decrease, gut inflammation (due to pathogens; increase of neuromodulatory factors), and constipation (49)

In all of the synapses where a neuron terminates in a skeletal muscle, acetylcholine exists, thus PD can be observed as a kind of dopamine imbalance with acetylcholine, and notably recent studies have revealed that probiotics can help its balance in the body (50).

Oxidative stress increased lipid peroxidation, and reduced glutathione levels are common factors influencing the degeneration of dopaminergic neurons. Furthermore, free radicals directly cause cellular damage and affect DNA, proteins and lipids, causing lipid peroxidation and ultimately inducing cellular apoptosis (51). It has been revealed that probiotics contain antioxidant properties by producing antioxidant metabolites, regulating the activity of antioxidants, increasing the antioxidant enzymes through several signaling pathways, and reducing the reactive oxygen species (ROS) levels (52, 53). The antioxidants protect nerve cells through various mechanisms, such as stimulating neuronal regeneration and enhancing the function of remaining neurons. Another study clarified that oxidative stress is substantially effective in the pathogenesis and complications due to the PD and vitamins produced by probiotics have the potential role in the improvement of the PD symptoms through oxidative stress inhibition (54, 55). Therefore, consumption of compounds that can inhibit the effect of oxidants can improve memory, intelligence as well as muscle stiffness in PD and also prevent the destruction of neurons (56). Other studies have revealed that probiotics can act as anti-inflammatory agents which inhibit neuroinflammation (49). In this respect, these effects are conferred through the inhibition of the prostaglandins and leukotrienes production, which in turn, has a positive effect on inflammation decreasing and accordingly, probiotics can reduce the PD through this mechanism (31-33).

Conclusion

The Gut-brain bidirectional relation contributes to PD development. Probiotics are beneficial choices for therapy of GI disorders, though not still considered a panacea owing to data paucity. Accumulating evidence suggests that intracellular deposition of α-syn in patients with PD is associated with intestinal dysbiosis. Undoubtedly, gut microbiota plays a crucial role in fermenting unused energy substrates, influencing the maturation of the immune system, and producing vitamins, hormones and balance of the acetylcholine. Probiotics have a substantial role in the neutralization or inhibition of ROS and free radicals and thus improve the PD symptoms. The anti-inflammatory role of probiotics also inhibits neurodegeneration and PD development. More detailed studies on the signaling of the gut-brain axis should be incorporated. The α-syn protein accumulation can be initiated from GI cells and distributed into CNS cells through the trans-synaptic cell to cell transmission.

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This study was written by the authors.

Conflict of interest

None to declare

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