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Unraveling the Nexus: Parkinson's Disease, Alpha-synuclein, *Desulfovibrio*, and the Gut Microbiome

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Abstract

Parkinson's disease (PD) is now recognized as a chronic condition which is once considered a highly intricate disorder involving the central, autonomic, and enteric nervous systems. The prevailing perspective attributes the disease by the formation of Lewy bodies, primarily triggered by the misfolding of α-Synuclein, leading to the demise of dopaminergic neurons in the substantia nigra. Constipation, one of the most common non-motor symptoms in PD patients, is believed to be influenced by the composition of gut bacteria. The gastrointestinal tract acts as a significant point of entry through the vagus nerve for potentially harmful microorganisms that can initiate the pathological process of PD. The vagus nerve is proposed to play a role in transmitting signals leading to the over-expression and accumulation of α-Synuclein in the brain. In a study, it was noted that individuals with PD displayed an elevated occurrence of bacteria belonging to the Desulfovibrionaceae family. Desulfovibrio (DSV) are sulfate-reducing bacteria (SRB) that are established as commensal bacteria in the human gastrointestinal tract. Desulfovibrio releases certain metabolites that trigger the aggregation of alpha-synuclein leading to play a role in the pathogenesis of PD. The presence of DSV can lead to a decline in bacterial metabolites, which plays a crucial role in gut health and contributes to the effects observed in individuals with PD. This review consolidates current knowledge on the connection between DSV and PD, emphasizing the role of the gut environment. We address the possibilities that could be considered for reducing the α-Synuclein aggregation in this study by emphasizing Desulfovibrio.

Keywords: Parkinson's disease, neurodegenerative disease, *Desulfovibrio*, α-synuclein, cellular toxicity

INTRODUCTION

Parkinson's disease (PD) is a progressive, incurable, chronic neurodegenerative condition. It is characterized by the production of Lewy bodies, primarily caused by misfolded α-synuclein and death of dopaminergic neurons in the substantia nigra. Globally, over six million people are diagnosed with PD [1]. α-Synuclein, a tiny protein produced in the brain that affects presynaptic signaling, membrane transport, and the stability of neuronal membranes, has been shown to be the main component of Lewy bodies [2]. Constipation is a commonly noted feature in prodromal PD and is apparent as early as 20 years before the diagnosis of motor PD. Therefore, constipation may predict PD occurrence [3].

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According to earlier research, an intestinal infection that passes through intestinal neurons and then enters the central nervous system (CNS) through the vagus nerve may be the origin of PD [4]. The gut is a key point of entry for potentially dangerous bacteria, which may initiate the degenerative process of PD [5]. In both animal and human studies, gut dysbiosis, indicated by differences in the diversity and frequency of the microbial community that make up the gut flora, has

been linked to immune dysregulation, aberrant brain protein aggregation, and inflammation [6]. Dysbiosis of the gut microbiota also causes systemic exposure to bacterial endotoxins, which in turn triggers the over-expression of α-syn and facilitates its misfolding to generate LBs (Lewy Bodies). The substantia nigra will eventually be damaged by intestinal LBs from the ENS (Enteric Nervous System) that have entered the CNS, resulting in the onset of PD symptoms [7]. One method that gut microorganisms may influence their hosts by the creation of various metabolites, including hormones, cytokines, SCFAs, and precursors of neurotransmitters [8]. Dysbiosis affects a wide range of neurotransmitters and microbial metabolites such as trimethylamine N-oxide, derivatives of aromatic amino acids, and SCFAs [9].

Numerous microorganisms in the gut play a crucial role in the development of PD. Among them, the *Desulfovibrionaceae* family of bacteria, particularly the *Disulfovibrio (DSV)* genus, has been identified as potentially influencing PD [10]. *DSV* utilizes hydrogen (H_2) or organic molecules to reduce sulfate or oxidized sulfur compounds, leading to the production of hydrogen sulfide (H_2S). H_2S has both positive and negative effects on the environment. Numerous gut microorganisms play crucial roles in the development of PD [10]. Overproduction of H_2S by gut microorganisms has been proposed as a potential trigger for PD in humans [11].

The uniqueness of the different *DSV* strains suggests that specific strains may possess pathogenic properties that contribute to the development of Parkinson's. Further research is required to fully understand how these strain-specific traits influence illness progression.

ROLE OF ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE

Parkinson’s disease is one of the most common neurodegenerative disorders, with an estimated prevalence of 0.3% in all age groups and 2% in those over 70 years of age [12]. Lewy body formation (due to the aggregation of alpha-synuclein), Lewy neurites, and dopaminergic neuron loss in the substantia nigra are the primary hallmarks of PD [5]. Although non-motor symptoms such as insomnia, constipation, and hyposmia, as well as motor symptoms such as slowness of movement, bradykinesia, hypokinesia, akinesia, hypomimia, hypophonia rigidity, and postural instability, are the main symptoms, gastrointestinal (GI) dysfunction is well known to be the first symptom to appear in patients [13–15]. This problem is attributed in part to an extended transit time in the intestines, which affects both the colon and the small intestine [16]. We discuss various causes of Parkinson's disease in Figure 1.

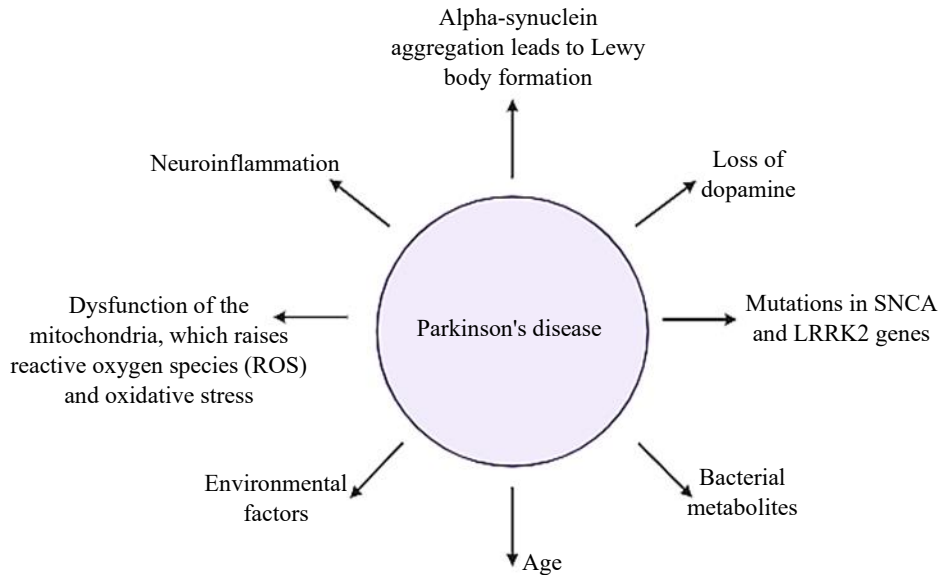

Figure 1. Illustrates the factors that contribute to the increased incidence of Parkinson's disease in patients.

α-Synuclein (α-Syn) is known to be the main constituent of Lewy bodies when harmful point mutations in the α-synuclein (SNCA) gene are found to be linked to familial PD. [17]. Within Lewy bodies, immunoreactive aggregates and misfolded forms of α-syn are observable, and these intraneuronal inclusions located in the substantia nigra may also contain other neurofilament proteins [15, 18]. α-Syn, a 14 kDa intracellular acidic presynaptic protein expressed in the central nervous system, comprises three regions: an acidic C-terminal area, a hydrophobic middle region, and an amphipathic N-terminal domain interacting with phospholipid membranes [14, 19]. α-syn has also been discovered in the stomach, esophagus, and salivary glands [20]. Normal forms of α-Syn can be found unfolded or contained in α-helical membrane-bound forms within the presynaptic areas of neurons [17], but when they aggregate, they become the primary cause of PD. The LB is an ongoing debate in the scientific community. Some studies have proposed that LBs may serve as a cellular defense mechanism against the accumulation of intracellular protein aggregates, while others have argued that LBs have a detrimental role in PD. Consequently, the role of LBs remains controversial and debatable [15].

The presynaptic terminal is the location of α-syn and interacts with synaptic vesicles [21]. Current research suggests that pathogenic forms of α-Syn propagate through the nervous system by inducing recipient cells to aggregate α-Syn, resembling prion-like propagation, which then spreads from one neuron to another [22]. Further exploration is required to gain a deeper understanding of these internal interactions [23].

Mitochondria play a critical role in cellular energy metabolism, mitochondrial dysfunction, and disruption of the electron transport chain (ETC) due to aggregation of α-syn, resulting in increased reactive oxygen species (ROS) and oxidative stress [7, 24]. The significance of mitochondria in PD progression is underscored by their loss of function in terms of ATP production, calcium buffering capability, and their role as mediators of innate immune activation [25]. The destabilization of autophagy is a key factor in the abnormal aggregation of α-synuclein and the exacerbation of PD. Recent research indicates that microglial autophagy is involved in the CNS's ability to regulate inflammation, and its dysregulation may impact phagocytosis and inflammation, which are both integral to neuroinflammatory diseases [26].

The transportation of α-Syn to the gastrointestinal wall and its uptake into vagal nerve terminals or indirectly into enteric neurons and their terminals are essential steps, as highlighted [27]. α-Syn enters the plasma membrane through the endoplasmic Golgi secretion pathway and is released via exocytosis, with specific proteins facilitated by exosomes. Upon uptake by a neuron, it is absorbed by lysosomes, undergoes re-aggregation, forms the Lewy pathology structure, and travels via microtubule axons to distal synaptic terminals, completing the transmission pathway of α-Syn [23].

The vagus nerves, composed primarily of parasympathetic fibers, serve as two mixed cranial nerves supplying both motor and sensory innervation. They play a crucial role in the gastrointestinal tract, regulate the neuromotor functions of smooth muscles, and aid the release of hormones essential for digestion. It also forms a vital connection between the gut and brain, as emphasized [22]. Evidence suggests that the vagus nerve can sense microbial signals in the form of bacterial metabolites, although it does not appear to interact directly with the gut microbiota. For instance, the production of short-chain fatty acids (SCFA) by gut bacteria influences the physiological processes in the intestine, including secretion, motility, and inflammation [28].

The dual hit theory of PD postulates that the vagus nerve and Meissner's plexus allow contributing elements to enter and travel through the substantia nigra due to the increased permeability of the gut or nasal epithelial cell lining [9]. It was discovered that the vagus nerve actively receives all types of α-syn (monomers, oligomers, and fibrils) that are actively carried from the colon [27]. These different conformations of alpha-syn, which have precise roles in the formation of the fibril form, remain unclear [19]. The transition of α-syn from monomeric or dimeric forms to prefibrillar forms and its subsequent assembly into larger aggregates leads to cellular toxicity, with fibrillary α-syn being a significant component of Lewy bodies [21, 29].

Compelling evidence substantiates the hypothesis that the neurodegenerative progression of PD is instigated and propelled by soluble oligomeric (o-α-syn) and phosphorylated (p-α-syn) forms. Several αsyn species have been suggested as biomarkers of PD [30]. To test the theory that α-Syn could travel from the ENS to the CNS via the vagus nerve, researchers isolated three distinct forms of α-syn from the brain lysate of a patient with PD and then directly injected α-syn into the submucosa of the ENS in mice. They noticed that alpha-synuclein was deposited retrogradely from the ENS to the vagus nerve, and ultimately to the brain [22].

In addition to its role in dopamine transportation, α-syn plays a crucial role in regulating vesicle docking, fusion, neurotransmitter release, synaptic activity, and axonal transport [21, 31]. α-syn also appears to be essential for the maturation of dopaminergic neurons. In a study examining the function of α-Syn in neuronal development, it was discovered that the number of dopaminergic neurons in the substantia nigra was greater in wild-type mice than in mice in which the α-syn gene was deleted [22].

In a different experiment, fecal samples from both patients with PD and healthy human donors were administered to mice that received alpha-synuclein enrichment. Mice administered fecal sample injections and supplemented with PD synuclein patients reported decreased motor function and other symptoms of PD, such as substances that cause inflammation in the brain. Animals implanted with the feces of healthy human donors did not show these symptoms [32].

Previous studies have proposed that PD might be triggered by an intestinal pathogen that traverses intestinal neurons, making its way into the CNS through the vagus nerve [17]. This pathogenic process initiates in the dorsal motor nucleus of the vagus nerve in the lower brain stem and gradually ascends through susceptible regions of cerebrospinal fluid (CSF) and other peripheral fluids, such as blood and saliva, including the medulla oblongata, pontine tegmentum, midbrain, and basal forebrain, eventually reaching the cerebral cortex [33]. Impairment of enteric neurons is linked to gastrointestinal (GI) dysfunction and is believed to be triggered by the accumulation of α-syn in the peripheral nervous system (PNS). Individuals with PD, owing to the compromised integrity of the intestinal barrier, are more prone to microbial infections. The heightened accumulation of α-Syn in the intestine, often referred to as "leaky gut," is a common issue observed in individuals with PD [34].

HOW DOES THE GUT AFFECT PARKINSON'S DISEASE AND HOW SIGNIFICANT OF A ROLE DO THE METABOLITES OF GUT BACTERIA PLAY IN THE NARRATIVE?

Various epithelial surfaces throughout the body host distinct microbiota, with the colon harboring the most extensive and diverse population. The gut microbiota, comprising approximately 100 trillion bacteria, possesses approximately 25 times as many genes as the individual human genome [35]. Early symptoms observed in patients with PD, such as constipation, prolonged intestinal transit time, gastroparesis, and dental degradation, are indications of PD and may manifest even before the onset of motor function loss [34].

There is growing interest in understanding the connection between α-syn aggregation and gut microbiota in PD [36]. A significant indication of the influence of the GI tract on PD is the existence of a linkage between the two for signal transmission [9]. The bidirectional communication mechanism enables the brain to affect gut function, and vice versa [33]. The composition of an individual's gut microbiota is influenced by factors, such as genes, environment, age, gender, and diet. To foster healthy gut microbiota capable of modifying the ENS and managing various neurological conditions, a well-balanced diet is crucial [37]. A leaky gut, caused by a pro-inflammatory intestinal environment, promotes the movement of bacteria and bacterial products, such as endotoxins, from the gut to the brain, triggering oxidative stress [34, 38]. Additionally, immunology also plays a pivotal role in regulating communication between the brain, ENS, and gut microbiota, with peptidoglycans (PGNs) and toll-like receptors (TLRs) mediating the immune response to microorganisms [28].

Bacteria entering the bloodstream release immune agonists such as lipopolysaccharides and peptidoglycan, enabling them to breach the blood-brain barrier (BBB). This leads to the release of pro-inflammatory markers and inflammation in the gut due to dysbiosis and increased permeability. These substances can cross the BBB and affect the brain cells, resulting in neuroinflammation and cell death [39]. The production of toxins and metabolites by these bacteria is thought to contribute to the formation of α-syn aggregates [33].

Research has endeavored to investigate the impact of distinct bacterial strains, including Lactobacillus, Saccharomyces, Bacillus, and Escherichia on brain function. The synthesis of bacterial metabolites, including cytokines, hormones, SCFAs, and neurotransmitter precursors, represents a potential mechanism by which gut microbes may impact the host [8]. SCFAs are known to affect the vagus nerve, enteric nervous system, immunological system, and BBB in addition to the gut barrier. A reduction in the quantity and variety of SCFA-producing bacteria, particularly those that produce butyric and propionic acids, is a hallmark of the microbiome in PD. Nevertheless, much remains to be learned about the precise processes and effects of SCFAs in preclinical models of PD [32]. Reduced SCFAs levels have been associated with various illnesses, including cancer, autoimmune diseases, metabolic syndromes, and neurological conditions [40].

Gut bacteria break down dietary fibers to produce gases, organic acids, and three primary SCFAs: butyrate (C4), propionate (C3), and acetate (C2) [35]. Although less abundant, butyrate is the most pharmacologically active SCFA [32]. Butyrate, in particular, has demonstrated immune-modulating properties and effects on the CNS, including reducing BBB permeability and alleviating symptoms of anxiety and depression associated with prodromal PD [41]. The presence of SCFA-producing bacteria such as *Romboutsia* and *Roseburia,* correlates strongly correlated with butyrate levels [42]. *Intestinimonas butyriciproducens, F. prausnitzii,* and *Anaerostipes butyraticus* are examples of butyrate-producing commensals that diminish with a breakdown of the gut mucin layer. This breakdown ultimately leads to an imbalance in the gut microbial composition and increased gut permeability [43]. Butyrate has several advantageous properties, such as lowering inflammation, stopping the advancement of the cell cycle, increasing the expression of proteins that control the integrity of the intestinal barrier, and encouraging the creation of mucus [44].

Since butyrate is the main energy source for the colonic epithelium, reduced levels of butyrate, acetate, and propionate combined with a decrease in the number of bacteria that produce SCFAs could cause the gut microbe Disulfovibrio to overgrow and compromise the integrity of the colonic mucosal barrier. The integrity of this barrier is jeopardized by the proliferation of hydrogen sulfide (H_2S)-producing bacteria, such as *DSV*, because sulfides impede the oxidation of butyrate [41, 45]. Because sodium butyrate (NaB) is associated with the severity of PD, numerous studies have examined the possible advantages of NaB supplementation. NaB therapy improved a few PD-like symptoms and decreased systemic inflammation in animal models of PD. The use of probiotics and prebiotics to improve butyrate synthesis and gut health is also a clever tactic. By preserving healthy gut microbiota and increasing dopamine levels, these therapies may help reduce the symptoms of PD and delay its course [44].

MICROBES AND PARKINSON'S DISEASE

The human intestine harbors a diverse array of approximately 7,000 gut microbiota types, with *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis (TB), being the first pathogen linked to PD [25]. These microbes have the capacity to influence the expression of neurotrophic factors, thereby affecting the growth, maturation, aging, and maintenance of homeostasis in the nervous system [46].

The primary branches of intestinal bacteria, namely *Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia,* and *Cyanobacteria*, constituted the major components [47]. A metagenomic study involving a hundred senior citizens revealed that the core microbiota in the

elderly differs from that in young individuals, with variations in the *Firmicutes* to *Bacteroides* ratio among the participants [43]. Firmicutes, encompassing gram-positive bacteria such as *Lactobacillus, Eubacterium*, and *Clostridium*, and gram-negative Bacteroidetes with prevalent members such as *Bacteroides* and *Prevotella*, constitute a significant portion of the gut microbiota [48]. One of the main bacteria implicated in the synthesis of metabolites that may have harmful consequences for the host is the bacterium Prevotella. Individuals adhering to plant-based, high-fiber diets exhibit elevated levels of the symbiotic *Prevotella*, which is known for fermenting fiber and releasing thiamine and folate. *Prevotella* also contributes to the production of neuroactive SCFAs, supports gut homeostasis, and regulates ENS activity [8, 19, 20]. A decline in *Prevotellaceae* has been associated with increased intestinal permeability and exposure to bacterial endotoxins, which triggers α-syn misfolding [7]. Reduced levels of the gut hormone ghrelin, correlated with decreased *Prevotellaceae* and increased *Lactobacillaceae*, have implications for mitochondrial respiration, ROS production, and preservation of normal dopamine function [20, 49]. Recent research suggests that, as SCFA concentrations decrease, α-synucleinopathies and lower *Prevotella* abundance are observed in patients with PD. This is linked to a potential decrease in mucin synthesis that contributes to increased intestinal permeability [16, 19]. A decline in *Prevotellaceae* has been proposed as a potential biomarker for PD [20].

Several investigations have also revealed the presence of another bacterium, *Akkermansia* in patients with PD [50]. *Akkermansia muciniphila* breaks down the intestinal mucus barrier and increases intestinal permeability when dietary fibers are defective. This major SCFA-producing bacterium may lead to the abnormal aggregation of α-synuclein fibrils. It is expected to occur when increased intestinal permeability exposes the intestinal nervous plexus to toxins such as LPS (Lipopolysaccharides) and pesticides [51]. In PD patients with rapid eye movement sleep behavior disorder (RBD), *A. muciniphila* was found to be significantly more abundant, and this abundance was correlated with non-motor symptoms compared to PD patients without RBD [50].

In a case-control study, it was observed that patients with PD exhibited an increased prevalence of bacteria from the *Desulfovibrionaceae* family, indicating a broader presence of *Desulfovibrio (DSV)* dynamics. *Desulfovibrio* species possess various characteristics that raise questions regarding their potential involvement in the pathophysiology of PD, necessitating further investigation [45]. *Desulfovibrio* releases hydrogen sulfide, which induces the aggregation of alpha-synuclein. As it traverses the vagus nerve from the gut to the brain, this process results in the formation of Lewy bodies (Figure 2). These findings highlight how dysbiosis compromises the integrity of the GI tract and triggers an immunological response that initiates the neurodegenerative cascade associated with PD [52].

DESULFOVIBRIO IMPACT ON PARKINSON'S DISEASE

Another bacterial group under consideration that has recently been linked to Parkinson's is the *Desulfovibrionaceae* family, and there is limited research available on this association [10]. *Desulfovibrio* (*DSV*) species, characterized as rod-shaped, anaerobic, gram-negative, mesophilic, sulfate-reducing bacteria, have been observed to produce significant quantities of α-syn aggregation [9]. *DSV* bacteria are integral components of the ocean sulfur cycle and are prevalent in diverse environments, such as oil fields, marine sediments, and anaerobic wastewater treatment plants. These bacteria primarily inhabit the distal colon of a healthy human host, constituting approximately 66% of all colonic sulfate-reducing bacteria (SRB) [53]. Anaerobic microorganisms known as SRB thrive in oxygen-deprived environments, utilizing sulfate as a terminal electron acceptor to decompose organic compounds and generate sulfide. Sulfate is absorbed as a nutrient and transformed into sulfide, which is subsequently incorporated into amino acids and sulfur-containing enzymes [54]. Among SRB groups, various types of bacteria are present, including mesophilic genera such as *Deltaproteobacteria, Desulfotomaculum* (gram-positive bacteria), *Archaeoglobus*, *Thermodesulfovibrio* (thermophilic gram-negative bacteria), *Desulfovibrio, desulfobacterium, desulfobacter, and desulfobulbus* [55]. They are typically motile and possess flagella, and the physiological characteristics of *DSV* allow them to adapt to their surroundings. *DSV* employs hydrogen (H_2) to yield hydrogen sulfide (H_2S), which has both beneficial and detrimental effects on the environment [53].

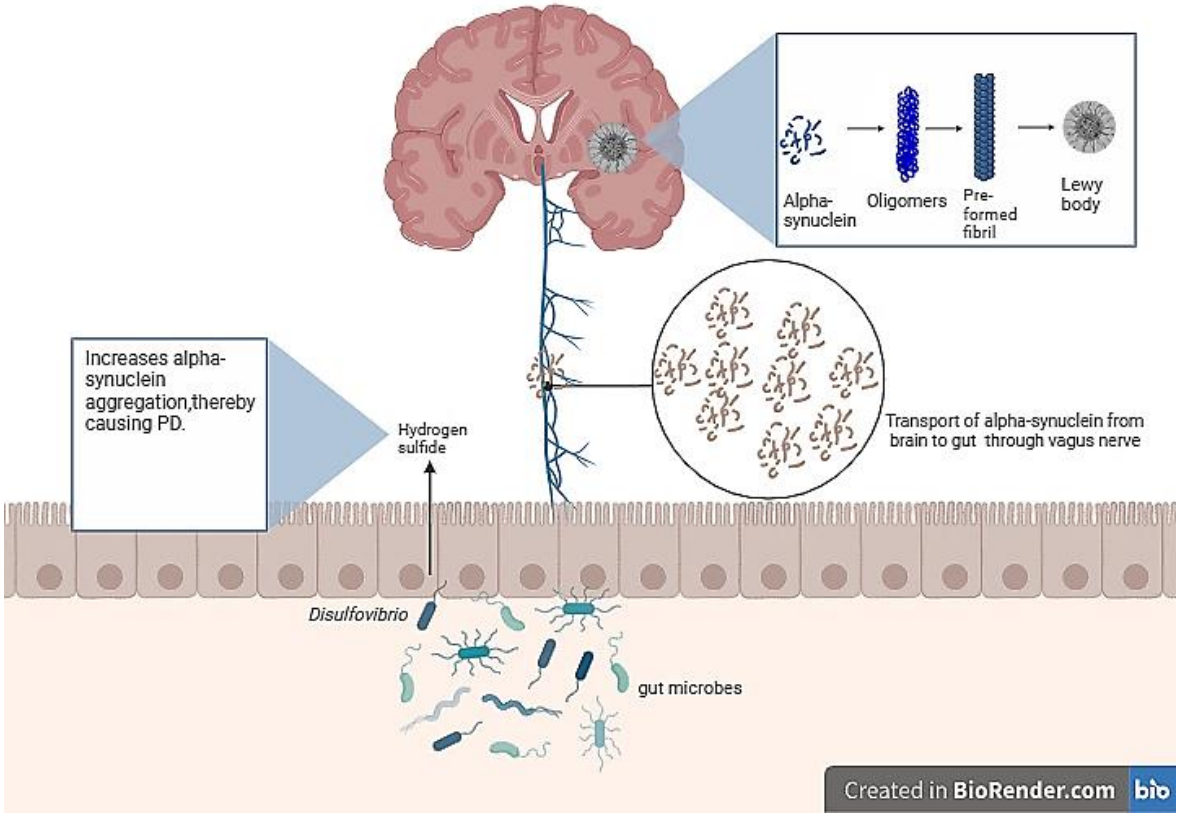

Figure 2. A diagram depicting the microbiota-gut-brain axis illustrates the role of *Disulfovibrio* in the gut microenvironment, contributing to the generation of hydrogen sulfide, ultimately leading to the formation of Lewy bodies.

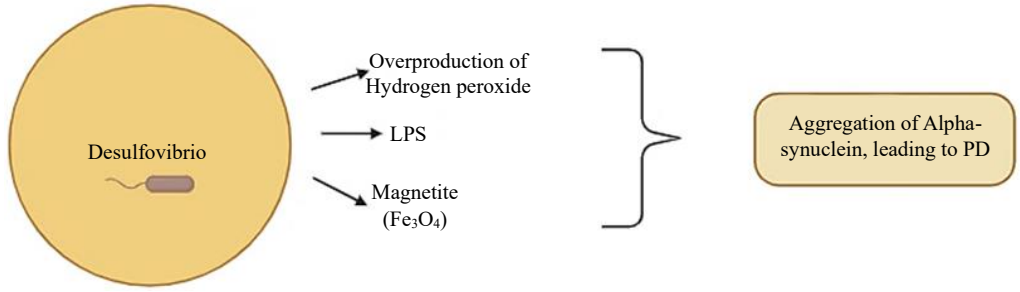

Figure 3. The impact of *Desulfovibrio (DSV)* on PD. *DSV* is known to generate hydrogen sulfide, lipopolysaccharide, and magnetite, factors that are likely contributors to the oligomerization and aggregation of α-Synuclein. Recent research indicates that *DSV* is more prevalent in the fecal samples of individuals with PD compared to those without the condition.

The illustration in Figure 3 outlines the various mechanisms through which *DSV* can impact PD. Overproduction of H_2S by gut microbes has been proposed as a potential causative factor in PD. H_2S, which is more soluble than CO_2 or O_2, can permeate the bloodstream through the gut [45]. Human exposure to low levels of H_2S gas may result in olfactory impairment and ocular discomfort, whereas high concentrations can significantly impair CNS function, potentially leading to severe consequences, including death [33]. Excessive H_2S levels elevate cytosolic ferrous iron levels in gut cells by releasing cytochrome c (Cyt c) from the mitochondria [11]. Cytochrome C interacts with anionic lipids by utilizing α-syn as a substrate to induce peroxidase activity. Consequently, α-syn and cytochrome C oligomerize to form high-molecular-weight aggregates [53].

In a study conducted by Huynh et al. [56], it was found that certain strains of *DSV* bacteria, particularly those sourced from individuals with PD, had a stronger propensity to induce the formation of larger and more frequent α-syn aggregates than E. coli strains producing curli. Additionally, nematodes fed with *DSV* bacteria from PD patients exhibited higher mortality rates, possibly because of the elevated concentration of accumulated α-syn aggregates. Although *DSV* bacteria from healthy individuals also show the ability to induce α-syn aggregation, similar to curli-producing E. coli, it remains uncertain whether *DSV* bacteria alone are fully responsible for inducing α-syn aggregation.

Lipopolysaccharide (LPS) is an endotoxin originating from gram-negative bacteria that is commonly employed in studies exploring the role of inflammation in PD etiology and the development of anti-inflammatory treatments for this condition. This component is found in the cell walls of gram-negative bacteria [57]. Bacterial genes associated with LPS biosynthesis were elevated in the mucosal and fecal samples of patients with PD compared to non-PD individuals. LPS can induce the nitration and polymerization of α-syn, contributing to the progression of PD [19]. *DSV* bacteria are responsible for producing LPS, which is a potential contributor to the oligomerization and aggregation of α-syn [58]. This information may be valuable for targeting LPS as a potential approach for managing or treating PD [53].

Consideration of *DSV* in the production of magnetite (Fe_3O_4) is significant because of its potential impact on α-syn aggregation. *DSV* creates magnetite by reducing ferric iron to ferrous iron through the activity of a periplasmic [FeFe]-hydrogenase enzyme [45]. The interaction between ferrous iron and amorphous ferric hydroxide during the reduction process may have contributed to the formation of magnetite [33]. This process involving Fe_3O_4 can influence α-syn aggregation and promote ROS generation, as observed in previous studies [59]. Magnetite nanoparticles have the potential to enter the intestinal cells and bloodstream through endocytosis. Low-temperature magnetometric tests on skin samples from PD patients revealed the presence of superparamagnetic magnetite particles in the dermal layer, suggesting a gut-borne origin, possibly created by *DSV* [45].

The heightened levels of H_2S, as observed in previous studies, may contribute to a reduction in gastrointestinal motility, potentially influencing constipation [33]. However, it remains uncertain whether *DSV* species actively contribute to constipation in PD or whether constipation is a consequence of their presence [45].

Furthermore, it is plausible that *DSV* plays a role in other neurodegenerative diseases associated with protein aggregation and inclusion bodies, such as Huntington's disease (HD), AD, and amyotrophic lateral sclerosis (ALS) [53].

These findings underscore the distinct characteristics of different *DSV* strains, indicating that those strains with specific pathogenic features may contribute to the pathophysiology of PD. While the importance of these characteristics in the pathophysiology of PD remains unclear [60], maintaining a low concentration of *DSV* or removing these bacteria might be considered as a preventive measure for PD [56]. Future research may involve exploring interventions such as phage therapy, diet modifications, and fecal microbiota transplantation (FMT) to eliminate *DSV* from the human gut [45]. FMT includes reintroducing healthy donor fecal bacteria into the GI tracts of patients with PD in an effort to modify and restore the gut microbiome. FMT has demonstrated its efficacy in treating Clostridium difficile infections, as well as other conditions involving gut dysbiosis, such as irritable bowel syndrome. However, there is still a substantial risk of infection; therefore, further studies are required [38].

Additionally, the isolation of these bacteria and the facilitation of genomic comparisons with ambient and healthy-carrier isolates will help identify potential therapeutic targets unique to PD. A prospective treatment strategy for PD may involve focusing on *DSV* and its metabolites [45].

CONCLUSION

In recent years, *DSV* bacteria have gained prominence as significant pathobionts, being associated not only with intestinal disorders but also with extraintestinal conditions. An example is PD, where the formation of α-syn aggregates, which leads to Lewy body formation, is a characteristic hallmark of the disease and appears to be instigated by *DSV*. Elevated levels of *DSV* were identified in PD samples, signifying a positive correlation between the quantity of *DSV* bacteria in fecal samples and PD severity. However, the precise mechanisms through which *DSV* affects these diseases are not yet fully understood. Therefore, future in vivo and in vitro investigations should focus on elucidating the molecular mechanisms underlying the influence of *DSV* on the host. Among the DSV species that have been identified in connection with PD, it is possible to identify additional varieties. Concentrating on the metabolites of *DSV* may reveal distinctive characteristics that can serve as targets for more in-depth analyses. We can also delve into the genetic dimensions of *DSV*, which entails investigating the influence of particular genes and assessing their association with the α-syn gene SNCA.

REFERENCES

1. Nie S, Wang J, Deng Y, Ye Z, Ge Y. Inflammatory microbes and genes as potential biomarkers of Parkinson's disease. NPJ Biofilms Microbiomes. 2022;8:101. DOI: 10.1038/s41522-022-00367-z. PubMed: 36564391.
2. Yamashita KY, Bhoopatiraju S, Silverglate BD, Grossberg GT. Biomarkers in Parkinson's disease: A state of the art review. Biomark Neuropsychiatry. 2023;9. DOI: 10.1016/j.bionps.2023.100074.
3. Nakahara K, Nakane S, Ishii K, Ikeda T, Ando Y. Gut microbiota of Parkinson's disease in an appendectomy cohort: A preliminary study. Sci Rep. 2023;13:2210. DOI: 10.1038/s41598-023-29219-2. PubMed: 36750613.
4. Ryman S, Vakhtin AA, Richardson SP, Lin HC. Microbiome–gut–brain dysfunction in prodromal and symptomatic Lewy body diseases. J Neurol. 2023;270(2):746-58. doi: 10.1007/s00415-022-11461-9. PubMed: 36355185.
5. Yang X, Qian Y, Xu S, Song Y, Xiao Q. Longitudinal analysis of fecal microbiome and pathologic processes in a rotenone-induced mice model of Parkinson's disease. Front Aging Neurosci. 2017;9:441. DOI: 10.3389/fnagi.2017.00441. PubMed: 29358918.
6. Ullah H, Arbab S, Tian Y, Liu CQ, Chen Y, Qijie L, Khan MIU, Hassan IU, Li K. The gut microbiota–brain axis in neurological disorder. Front Neurosci. 2023;17:1225875. doi: 10.3389/fnins.2023.1225875. PubMed: 37600019.
7. Liu J, Xu F, Nie Z, Shao L. Gut microbiota approach—A new strategy to treat Parkinson's disease. Front Cell Infect Microbiol. 2020;10. DOI: 10.3389/fcimb.2020.570658.
8. Hey G, Nair N, Klann E, Gurrala A, Safarpour D, Mai V, et al. Therapies for Parkinson's disease and the gut microbiome: Evidence for bidirectional connection. Front Aging Neurosci. 2023;15:1151850. DOI: 10.3389/fnagi.2023.1151850. PubMed: 37323145.
9. Rajput C, Sarkar A, Sachan N, Rawat N, Singh MP. Is gut dysbiosis an epicenter of Parkinson's disease? Neurochem Res. 2021;46:425–38. DOI: 10.1007/s11064-020-03187-9. PubMed: 33400024.
10. Nowak JM, Kopczyński M, Friedman A, Koziorowski D, Figura M. Microbiota dysbiosis in Parkinson disease—in search of a biomarker. Biomedicines. 2022;10. DOI: 10.3390/biomedicines10092057. PubMed: 36140158.
11. Murros KE, Murros K. Hydrogen sulfide produced may induce Parkinson's disease. Neurosci.
12. Camerucci E, Stang CD, Hajeb M, Turcano P, Mullan AF, Martin P, et al. Early-onset parkinsonism and early-onset Parkinson's disease: A population-based study (2010–2015). J Parkinson's Dis. 2021;11:1197–207. DOI: 10.3233/JPD-202279.
13. Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's disease. Ageing Res Rev. 2018;45:53–61. DOI: 10.1016/j.arr.2018.04.004.
14. Henderson MX, Trojanowski JQ, Lee VM. α-Synuclein pathology in Parkinson's disease and related α-synucleinopathies. Neurosci Lett. 2019;709:134316. DOI: 10.1016/j.neulet.2019.134316. PubMed: 31170426.

15. Srinivasan E, Chandrasekhar G, Chandrasekar P, Anbarasu K, Vickram AS, Karunakaran R, et al. Alpha-synuclein aggregation in Parkinson's disease. Front Med. 2021;8:736978. DOI: 10.3389/fmed.2021.736978. PubMed: 34733860.
16. Perez-Pardo P, Hartog M, Garssen J, Kraneveld AD. Microbes tickling your tummy: The importance of the gut-brain axis in Parkinson's disease. Curr Behav Neurosci Rep. 2017;4:361–8. DOI: 10.1007/s40473-017-0129-2.
17. Hirayama M, Nishiwaki H, Hamaguchi T, Ohno K. Gastrointestinal disorders in Parkinson's disease and other Lewy body diseases. npj Parkinsons Dis. 2023;9:71. doi: 10.1038/s41531-023-00511-2. PubMed: 37147392.
18. Singh Y, Trautwein C, Romani J, Salker MS, Neckel PH, Fraccaroli I, et al. Overexpression of human alpha-synuclein leads to dysregulated microbiome/metabolites with ageing in a rat model of Parkinson disease. Mol Neurodegener. 2023;18. DOI: 10.1186/s13024-023-00628-1.
19. Huang Y, Liao J, Liu X, Zhong Y, Cai X, Long L. Review: The role of intestinal dysbiosis in Parkinson's disease. Front Cell Infect Microbiol. 2021;11. DOI: 10.3389/fcimb.2021.615075.
20. Shen T, Yue Y, He T, Huang C, Qu B, Lv W, et al. The association between the gut microbiota and Parkinson's disease: A meta-analysis. Front Aging Neurosci. 2021;13:636545. DOI: 10.3389/fnagi.2021.636545. PubMed: 33643026.
21. Savitt D, Jankovic J. Targeting α-synuclein in Parkinson's disease: Progress towards the development of disease-modifying therapeutics. Drugs. 2019;79:797–810. DOI: 10.1007/s40265-019-01104-1. PubMed: 30982161.
22. Fitzgerald E, Murphy S, Martinson HA. Alpha-synuclein pathology and the role of the microbiota in Parkinson's disease. Front Neurosci. 2019;13:369. DOI: 10.3389/fnins.2019.00369. PubMed: 31068777.
23. Chen ZJ, Liang CY, Yang LQ, Ren SM, Xia YM, Cui L, et al. Association of Parkinson's disease with microbes and microbiological therapy. Front Cell Infect Microbiol. 2021;11. DOI: 10.3389/fcimb.2021.619354.
24. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting alpha-synuclein as a therapy for Parkinson's disease. Front Mol Neurosci. 2019;12:299. doi: 10.3389/fnmol.2019.00299. PubMed: 31866823.
25. Munoz-Pinto MF, Empadinhas N, Cardoso SM. The neuromicrobiology of Parkinson's disease: A unifying theory. Ageing Res Rev. 2021;70:101396. DOI: 10.1016/j.arr.2021.101396, PubMed: 34171417.
26. Zhu R, Luo Y, Li S, Wang Z. The role of microglial autophagy in Parkinson's disease. Front Aging Neurosci. 2022;14:1039780. DOI: 10.3389/fnagi.2022.1039780, PubMed: 36389074.
27. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T, et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014;128:805–20. DOI: 10.1007/s00401-014-1343-6, PubMed: 25296989.
28. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain axis: From motility to mood. Gastroenterology. 2021;160:1486–501. DOI: 10.1053/j.gastro.2020.10.066, PubMed: 33493503.
29. Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G, Ghiglieri V. Alpha-synuclein in Parkinson's disease and other synucleinopathies: From overt neurodegeneration back to early synaptic dysfunction. Cell Death Dis. 2023;14:176. DOI: 10.1038/s41419-023-05672-9, PubMed: 36859484.
30. Angius F, Mocci I, Ercoli T, Loy F, Fadda L, Palmas MF, et al. Combined measure of salivary alpha-synuclein species as diagnostic biomarker for Parkinson's disease. J Neurol. 2023;270:5613–21. DOI: 10.1007/s00415-023-11893-x, PubMed: 37552278.
31. Grosso Jasutkar HG, Oh SE, Mouradian MM. Therapeutics in the pipeline targeting α-synuclein for Parkinson's disease. Pharmacol Rev. 2022;74(1):207–37. doi: 10.1124/pharmrev.120.000133. PubMed: 35017177.
32. Kalyanaraman B, Cheng G, Hardy M. Gut microbiome, short-chain fatty acids, alpha-synuclein, neuroinflammation, and ROS/RNS: Relevance to Parkinson's disease and therapeutic implications. Redox Biol. 2024;71:103092. DOI: 10.1016/j.redox.2024.103092, PubMed: 38377788.

33. Knorr D, Sinskey AJ. Biotechnology in food production and processing. Science. 1985;229(4719): 1224-9. doi: 10.1126/science.229.4719.1224. PubMed: 17770800.
34. Ray B, Mahalakshmi AM, Tuladhar S, Bhat A, Srinivasan A, Pellegrino C, et al. "Janus-faced" α-synuclein: Role in Parkinson's disease. Front Cell Dev Biol. 2021;9:673395. DOI: 10.3389/fcell. 2021.673395.
35. Martin-Gallausiaux C, Marinelli L, Blottière HM, Larraufie P, Lapaque N. SCFA: Mechanisms and functional importance in the gut. Proc Nutr Soc. 2021;37–49.
36. Zhu M, Liu X, Ye Y, Yan X, Cheng Y, Zhao L, et al. Gut microbiota: A mechanistic regulator of neurogenesis and therapy in Parkinson's disease. Neural Regen Res. 2023;18:1684–94. DOI: 10.4103/1673-5374.358304, PubMed: 37074718.
37. Baizabal-Carvallo JF, Alonso-Juarez M. The link between gut dysbiosis and neuroinflammation in Parkinson's disease. Neuroscience. 2020;432:160–73. DOI: 10.1016/j.neuroscience.2020.02.030, PubMed: 32112917.
38. Metta V, Leta V, Mrudula KR, Prashanth LK, Goyal V, Borgohain R, et al. Gastrointestinal dysfunction in Parkinson's disease: Molecular pathology and implications of gut microbiome, probiotics, and fecal microbiota transplantation. J Neurol. 2022;269:1154–63. DOI: 10.1007/s00415-021-10567-w, PubMed: 33881598.
39. Bi M, Feng L, He J, Liu C, Wang Y, Jiang H, Liu SJ. Emerging insights between gut microbiome dysbiosis and Parkinson's disease: Pathogenic and clinical relevance. Ageing Res Rev. 2022;82:101759. doi: 10.1016/j.arr.2022.101759. PubMed: 36243356.
40. Jackson A, Forsyth CB, Shaikh M, Voigt RM, Engen PA, Ramirez V, et al. Diet in Parkinson's disease: Critical role for the microbiome. Front Neurol. 2019;10:1245. DOI: 10.3389/fneur.2019.01245, PubMed: 31920905.
41. Xie A, Ensink E, Li P, Gordevičius J, Marshall LL, George S, et al. Bacterial butyrate in Parkinson's disease is linked to epigenetic changes and depressive symptoms. Mov Disord. 2022;37:1644–53. DOI: 10.1002/mds.29128, PubMed: 35723531.
42. Cirstea MS, Yu AC, Golz E, Sundvick K, Kliger D, Radisavljevic N, Foulger LH, Mackenzie M, Huan T, Finlay BB, Appel-Cresswell S. Microbiota composition and metabolism are associated with gut function in Parkinson's disease. Mov Disord. 2020;35(7):1208-17. doi: 10.1002/mds. 28052. PubMed: 32357258.
43. Thangaleela S, Sivamaruthi BS, Kesika P, Bharathi M, Chaiyasut C. Role of the gut–brain axis, gut microbial composition, diet, and probiotic intervention in Parkinson's disease. Microorganisms. 2022;10:1544. DOI: 10.3390/microorganisms10081544, PubMed: 36013962.
44. Elford JD, Becht N, Garssen J, Kraneveld AD, Perez-Pardo P. Buty and the beast: The complex role of butyrate in Parkinson's disease. Front Pharmacol. 2024;15:1388401. DOI: 10.3389/fphar. 2024.1388401, PubMed: 38694925.
45. Murros KE, Huynh VA, Takala TM, Saris PEJ. Desulfovibrio bacteria are associated with Parkinson's disease. Front Cell Infect Microbiol. 2021;11:652617. DOI: 10.3389/fcimb.2021.652617.
46. Sittipo P, Choi J, Lee S, Lee YK. The function of gut microbiota in immune-related neurological disorders: A review. J Neuroinflammation. 2022;19(1):154. doi: 10.1186/s12974-022-02510-1. PubMed: 35706008.
47. Santos SF, De Oliveira HL, Yamada ES, Neves BC, Pereira A Jr. The Gut and Parkinson's Disease-A Bidirectional Pathway. Front Neurol. 2019;10:574. doi: 10.3389/fneur.2019.00574. PubMed: 31214110.
48. Suganya K, Koo BS. Gut–brain axis: Role of gut microbiota on neurological disorders and how probiotics/prebiotics beneficially modulate microbial and immune pathways to improve brain functions. Int J Mol Sci. 2020;21(20):7551. doi: 10.3390/ijms21207551. PubMed: 33066156.
49. Wang Q, Luo Y, Ray Chaudhuri K, Reynolds R, Tan EK, Pettersson S. The role of gut dysbiosis in Parkinson's disease: Mechanistic insights and therapeutic options. Brain. 2021;144:2571–93. DOI: 10.1093/brain/awab156, PubMed: 33856024.
50. Zhang F, Wang D. Potential of Akkermansia muciniphila and its outer membrane proteins as therapeutic targets for neuropsychological diseases. Front Microbiol. 2023;14:1191445. DOI: 10.3389/fmicb.2023.1191445, PubMed: 37440890.

51. Hirayama M, Ohno K. Parkinson's disease and gut microbiota. Ann Nutr Metab. 2021;77(Suppl 2):28–35. DOI: 10.1159/000518147, PubMed: 34500451.
52. Hashish S, Salama M. The role of an altered gut microbiome in Parkinson's disease: A narrative review. Appl Microbiol. 2023;3:429–47. DOI: 10.3390/applmicrobiol3020030.
53. Singh SB, Carroll-Portillo A, Lin HC. Desulfovibrio in the gut: The enemy within? Microorganisms. 2023;11:1772. DOI: 10.3390/microorganisms11071772.
54. Muyzer G, Stams AJM. The ecology and biotechnology of sulphate-reducing bacteria. Nat Rev Microbiol. 2008;6:441–54. DOI: 10.1038/nrmicro1892, PubMed: 18461075.
55. Dordević D, Jančíková S, Vítězová M, Kushkevych I. Hydrogen sulfide toxicity in the gut environment: Meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes. J Adv Res. 2021;27:55–69. DOI: 10.1016/j.jare.2020.03.003, PubMed: 33318866.
56. Huynh VA, Takala TM, Murros KE, Diwedi B, Saris PEJ. Desulfovibrio bacteria enhance alpha-synuclein aggregation in a Caenorhabditis elegans model of Parkinson's disease. Front Cell Infect Microbiol. 2023;13:1181315. DOI: 10.3389/fcimb.2023.1181315, PubMed: 37197200.
57. Bing G, Liu M. Lipopolysaccharide animal models for Parkinson's disease. Parkinson's Dis. 2011.
58. Rose AH. The microbiological production of food and drink. Sci Am. 1981;245(3):126-39. doi: 10.1038/scientificamerican0981-126. PubMed: 6895124.
59. Gorecki AM, Preskey L, Bakeberg MC, Kenna JE, Gildenhuys C, MacDougall G, Dunlop SA, Mastaglia FL, Akkari PA, Koengten F, Anderton RS. Altered gut microbiome in Parkinson's disease and the influence of lipopolysaccharide in a human α-synuclein over-expressing mouse model. Frontiers in neuroscience. 2019 Aug 7;13:839.
60. Gorecki AM, Preskey L, Bakeberg MC, Kenna JE, Gildenhuys C, MacDougall G, Dunlop SA, Mastaglia FL, Akkari PA, Koengten F, Anderton RS. Altered gut microbiome in Parkinson's disease and the influence of lipopolysaccharide in a human α-synuclein over-expressing mouse model. Front Neurosci. 2019;13:839. doi: 10.3389/fnins.2019.00839. PubMed: 31440136.

