VILNIUS UNIVERSITY

MEDICAL FACULTY

The Final thesis

The Role of Microbiome in Parkinson's Disease

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2022/05/20

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Abstract:

Environmental aspects of a person's life can define their personalities as well as their microbiomes. In turn, the microbiome can be the key to a person's ongoing health throughout their whole lives. This review seeks to examine the key pathways that connect the microbiome to the central nervous system as well as the microbiological therapies that may aid in treating Parkinson's disease. Detailed examination of the interplay between the connections of human biology and microbiology elucidates that disturbances in the microbiome can not only influence the development of neurodegenerative diseases but outright cause them via retrograde synaptic proliferation of alpha-synuclein aggregates and inflammatory insult bypassing the critical protective barriers of the body. Furthermore, clinical evidence has shown that treatment strategies like Fecal Microbiota Transplant, Immune-modulating antibiotics, and Probiotics are all effective at preventing and treating symptoms related to Parkinson's disease and, with refinement, may become mainstays in clinical treatment.

1.1 – What is Parkinson's Disease?

According to the United States Institute on Aging, "Parkinson's disease is a brain disorder that leads to shaking, stiffness, and difficulty with walking, balance, and coordination (1)." The disease progresses over time, and the severity of these symptoms can lead to great increases in morbidity and mortality. Classified as a neurodegenerative disease, degeneration of primarily dopaminergic neurons in the basal ganglia of the brain is believed to cause the classical symptoms of Parkinson's disease. Though many theories have been put forward, the definitive root cause of the disease, why the neurons in the brain degenerate, is still a mystery.

1.2 – How common is Parkinson's Disease?

Parkinson's disease is the second most common neurodegenerative disease, behind Alzheimer's disease (2). Estimates of Parkinson's disease prevalence span from 6.1 million cases in 2016 (3) to 8.5 million cases in 2019 (4). With a global estimated annual percent change of 0.61%, Parkinson's cases have more than doubled since 1990. As the global medical system revolutionizes and refines healthcare worldwide, diseases like Parkinson's are the beneficiaries, increasing their respective burden directly with Socio-Demographic Index (5). Lengthening the average lifespan and other groundbreaking movements like smoking cessation may increase the overall health of most patients, but inadvertently provide a difficult epidemiologic challenge for the future.

1.3 – Risk Factors

Statistically, the most important risk factors are male sex, age (especially greater than 80 years old), and socio-demographic index (greater than low-middle) (3)(4). Possibly the single most important protective factor, though poorly understood, is a positive history of tobacco smoking (3). Other contributory risk factors to Parkinson's include: pesticide exposure, diet high in saturated fats, heavy metal exposure, low physical activity, obesity, and history of previous head injury (6). Outside of the obvious outlier of head injury, the more acquired risk factors all deal with some sort of metabolic process or exposure to certain substances.

1.4 – Where is Parkinson's common?

Unsurprisingly, the largest proportion of Parkinson's disease cases has occurred in East Asia (4), as the region does contain roughly 22% of the entire world's population and is home to several extremely dense developing to developed-level countries. Considering the pivotal role that the entire region has played in the economic development of the world for the past several decades, paired with some of the highest life expectancies around the globe, it makes solid logical sense that the past 30 years have seen a 256% increase in prevalence of Parkinson's cases, trumping high-income North America's 107%, and second only to Central Latin America at 259%. It is important to note that despite the massive growth in Parkinson's incidence rates of either Latin America or Eastern Asia, 239% and 202% respectively, their age-standardized rates per 100,000, 11.11% and 15.26% respectively, are still well below High-income North America at 25.14% with an annual percentage change of 296%. It will be important to make the considerations that despite their massive increases, these regions have several confounding factors to consider per region - life expectancy, diet composition, cultural factors, etc. - so that moving forward, a clearer understanding of the underlying pathological mechanisms of Parkinson's disease may be elucidated.

1.5 - Diagnosing Parkinson's Disease

Despite a host of classic symptoms and the possibility of very high clinical suspicion, the true gold standard for a proper diagnosis of Parkinson's disease is autopsy (7). Although one can never be completely certain, most physicians can be almost definite on a diagnosis with two main criteria: 1. Presence of typical clinical symptoms (bradykinesia, tremor, rigidity, postural instability) that should respond to levodopa treatment and occur without cause to believe a different diagnosis is more likely, and 2. Pathological formations of alpha-synuclein with dopaminergic neuron loss in the substantia nigra. This standard works for the vast majority of patients (~95%), but is not perfect and potentially misses several key features of Parkinson's disease. Hyposmia can occur in >90% of presenting patients and can occur over 5 years before the onset of any movement disorders (8). Gastrointestinal dysfunction, primarily in the forms of constipation, dysphagia, and impaired gastric emptying, can also predate motor dysfunction by several years (8)(9)(95). These findings raise interesting questions about why the sentinel organs, facing the many antigens of the outside world, are potentially the first to be affected by Parkinson's disease, as well as why their sequential nature of peripheral to central involvement exists.

1.6 – Clinical Outcomes

Typically, Parkinson's disease never fully remits, and the diagnosis is one of eventual progression. A good question to ask is how long does progression take? One of the more natural ways to differentiate patients is by age of onset. Those who present with symptoms at a younger age (<60 years old) typically have a fast onset of symptoms with a protracted course until eventual decompensation (10). Conversely, patients who present at an older age (>70 years old) typically show quick progression into later dementia-stages of the disease. Histologically, those who present early typically present with Alpha-synuclein aggregates (Lewy bodies) in the substantia nigra and slowly show progression into the neocortex, while those presenting at older age present with more widespread Lewy body invasion will express more severe symptoms. Though most common in older ages, Parkinson's may still affect juveniles (<21 years old) and have early onset as well (21-50 years old) (12).

1.7 – Genetic Factors

An estimated 5% of patients with Parkinson's disease are believed to show monogenic inheritance of the disease (11). Roughly 10-15% of patients are estimated to have positive family history, leaving roughly

80% to be sporadic or idiopathic (11)(12). Inherited cases of Parkinson's are important to consider in cases of early-onset (<50 years old), for as clinical outcomes have typically shown, early-onset Parkinson's tends to progress quickly (10). Due to the nature of the genes involved, mutations in alpha-synuclein (PARK1, PARK4) or ubiquitination pathways (PARK2), global involvement is common, whereas acquired cases may be more likely to have a specific nidus that must spread outward (11).

1.8 – Most common interventional techniques

The most common and reliable treatments for most patients are pharmacologic therapies. The most common therapy is treatment with a dopamine precursor like levodopa, generally in combination with peripheral decarboxylase inhibitors like carbidopa (11)(12). Other therapies include MAO-B inhibitors (Selegiline, Rasagiline, safinamide), Ergot Derivative Dopamine agonists (Bromocriptine, Cabergoline, Apomorphine), Non-Ergot Derivative Dopamine agonists (Pramipexole, Ropinirole, Rotigotine), Anticholinergics (Trihexyphenidyl, Benztropine, Procyclidine, Biperiden), NMDA antagonists (Amantadine), catechol-O-methyl transferase inhibitors (Tolcapone, Entacapone, Opicapone), and various other classes of drugs. The unifying factor behind these drugs is that they are all symptomatic treatments and are not expected or intended to slow or modify the course of the disease. Emerging non-pharmacological therapies are on the horizon, though mostly still in experimental phases. Some notable therapies include viral-injected gene replacement/augmentation therapy, dopaminergic neuron transplantation, autophagy inducers, reducers of oxidative stress, and immunomodulatory therapies (11).

1.9 – The importance of the microbiome

Summarizing the points made up until now, Parkinson's disease is a neurodegenerative disease that is typically idiopathically acquired throughout a person's life. External factor exposures are some of the most important risk factors for developing the disease, and often time the disease may present itself in peripheral organs several years prior to classical central symptoms developing. The calling card of the disease is the presence of alpha-synuclein in neural tissue that progresses from peripheral nervous tissue into the substantia nigra. When not due to a primary disorder, alpha-synuclein propagation is a slow and stepwise progression through connecting tissues. When viewed from this perspective, one could make the argument that the primary disorder begins outside of the central nervous system, and probably outside of nervous tissue completely. Considering the massive tract of tissue that is the gateway for macromolecules and toxins alike, the gastrointestinal system seems a likely culprit. Considering trillions of microorganisms colonize this tract, each with the ability to help or hinder the organism, the statistical likelihood that their regulation is not at least associated with almost every facet of the human organism is extremely unlikely. Thus, the rest of the paper will focus on the interplay between the host microbiome and Parkinson's disease expression.

2.1 – Gut-Brain Axis

One of the first to publish a theory on a microbial cause for Parkinson's disease can be found in the 2007 paper by Braak et al: *Parkinson's disease: a dual hit hypothesis* (13). The original proposition was that pathological microbes could enter the brain via two potential passages: directly into the brain through the olfactory system or indirectly via swallowing infected nasal secretions which then penetrate the epithelium of the gut to infect the Vagus nerve which through retrograde transmission end up in the brain. Reasoning behind this theory stemmed from the observation that Parkinson's patients are often hyposmic (8) as well as often present with Lewy inclusion bodies in the gastrointestinal system (8)(9). To prove that the Vagus nerve interacts directly with the substantia nigra and is intimately associated with the gastrointestinal system, neural pathway studies have shown that stimulation of the substantia nigra pars compacta results in an increase to gastric tone and motility by activating dopamine-1 receptors found in

the dorsal vagal complex (14). Not only that, rat models with paraquat-induced Parkinson's showed early compromise of this very pathway. Not only is there a pathway, but Parkinson's disease can propagate through the nerves themselves. Alpha-synuclein aggregates that are found in compromised cell terminals can be released via vesicle-mediated or lysosomal exocytosis and be taken up in a healthy cell where the Alpha-synuclein aggregates can act as a seed to promote more deposition of Lewy bodies (15).

2.2 – Alpha-Synuclein

Alpha-synuclein is a protein spanning 140 amino acids that tends to assume an alpha-helical configuration (11). The amino end is lipophilic and serves to associate with curved membranes (11)(16)(19). The central portion primarily serves structural purposes, allowing the protein to assume its alpha-helical conformation (11)(19). Finally, the c-terminus houses sites for protein-protein interaction, several phosphorylation sites, as well as a handful of glycosylation, oxidation, and nitration sites. The general function of alpha-synuclein consists mostly of maintaining vesicle homeostasis in the terminal axon as well as acting as a chaperone for various proteins involved in endocytosis and exocytosis, primarily of neurotransmitters (16)(19)(20). Studies in triple synuclein deletion (alpha, beta, and gamma synuclein), showed that mice lacking synucleins were hyperactive and released excessive amounts of dopamine not due to increased production but increased usage of tissue dopamine stores (17)(18)(19)(21). Loss of any of the synucleins (alpha, beta, or gamma) can result in impaired synaptic vesicle endocytosis, which can be restored by overexpression of alpha-synuclein (16). Possibly the most important feature of alpha-synuclein is to prevent auto-oxidation from an accumulation of dopamine products. Dopamine metabolism commonly produces reactive oxygen species, and oxidation of dopamine, which is catalyzed by the presence of iron, produces quinone moieties that can covalently bind and damage various cellular macromolecules (22). Alpha-synuclein seems to work almost like a physiological brake for neurons, preventing the excessive release of dopamine as well as reducing overproduction by inhibiting tyrosine hydroxylase, thus preventing possible complications of dopamine autooxidation (16)(19). Ironically, the functions of alpha-synuclein are also probably the cause of its toxicity. Accumulation of alpha-synuclein inside of the cell can bind to dopamine-containing vesicles, and in excess would cause hyper-curving of the membranes inducing pore formation and release of vesicular contents (11). It is hypothesized that the formation of fibrils actually prevents the initial toxicity of excessive alpha-synuclein toxicity, but the accumulation of fibrils eventually causes the same problem. Similar to the under-expression of synucleins, overexpression increases basal firing rates in dopaminergic neurons with a manyfold increase in dopamine efflux from the cell (23)(24). Interestingly, D2-receptor agonism on cells overexpressing alpha-synuclein was seen to return to normal fire rates as D2 agonism hyperpolarized the excessively depolarized neuron (23).

2.3 – Neuroinflammation

Alpha-synuclein is not the only contributing factor to dopaminergic cell death. Levels of reduced glutathione are diminished in the substantia nigra of Parkinson's patients (25). Alpha-synuclein by itself can induce microglial activation and targeting of dopaminergic cells for death (26). NADPH oxidase deficient mice were spared the full brunt of neuronal toxicity, insinuating toxicity is mediated by oxygen radicals and may be a major source of oxidative stress in Parkinson's disease. Building on this, reactive microglia often produce pro-inflammatory cytokines, and they have been shown to be increased in the serum of Parkinson's patients and increase directly with disease severity (27). Microglia don't just react to alpha-synuclein. As Braak had hypothesized before, one of the direct routes to the brain is through the olfactory tract. Cadaveric studies have shown that bacteria, like P. acnes, can be found colonizing the neurons of Parkinson's disease patient's midbrains (28). Direct injection of bacterial lipopolysaccharide into the substantia nigra activates the microglia causing apoptosis with subsequent motor impairment (31). Intranasal doses of lipopolysaccharide induce hypokinesia with the development of alpha-synuclein

aggregates and dopaminergic neuron dysfunction. Peripheral nerves are affected as well. Intraperitoneal injection of lipopolysaccharide induces alpha-synuclein aggregation in enteral neurons, extending into central neurons. Finally, intrarectal injection of lipopolysaccharide increases pro-inflammatory markers and consequently reduces intestinal barrier integrity via reduction of tight junctions.

2.3 – What is a healthy microbiome?

Previous studies estimated the gut microbiota to contain around 500-1000 species, while today the estimate exceeds over 35,000 individual bacterial species (29). Each section of the gastrointestinal tract has different representative species, each adapting to the changes along the tract. The high acidity and relatively high oxygen concentration of the stomach favors the genera Helicobacter, Streptococcus, Prevotella, Veillonella, and Rothia. The lower gastrointestinal tract is less acidic and harbors an anaerobic environment largely dominated by Firmicutes and Bacteroidetes. A good baseline is that most healthy guts will contain >90% of four main phyla: Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria (30)(31). The exact proportions vary significantly from person to person and depend on many individual factors: age, diet, geographic location, antibacterial drug usage, etc. (29). An important trend concerning geographic microbiota is the difference between Eastern and Western countries. Eastern countries tend to have a higher consumption of rice and various vegetables that lead to microbiota high in atypical Bacteroidetes like Prevotella in Korea (32) or Bifidobacterium in Japan (33). Conversely, Western countries tend to be higher in protein consumption and typically see a reduction in microbiota diversity (34), most likely due to a lack of a variety of complex fibers in the diet and bile acids reducing the viability of certain species (35). This notion is further reinforced by immigration studies, where migrants from Eastern countries immigrate to Western countries and develop obesity and atypical, non-levodopa responsive, early-onset Parkinson's at a rate of 4 times baseline (36). Studies on the microbiota of East to West immigrants revealed loss of native gut microbiota with convergence to a Western microbiome (37). Within 9 months, these patients, immigrating from Thailand to the United States, showed displacement of Prevotella with Western-associated Bacteroides as well as loss of overall gut microbiome biodiversity that progressed with every generation present in the US.

2.4 – Changes in the microbiota during Parkinson's disease

Referring back to baselines, 98.4% of bacteria in control patients' microbiota were found to be within 4 phyla: Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria (30). That study found that Parkinson's patients only had 88.1% of their microbiota represented within those 4 phyla. It is difficult to say for sure whether changes found in case-control studies are truly due to Parkinson's alone or involve other factors (38). Some studies try to control for certain potentially confounding factors like the usage of catechol-O-methyl transferase inhibitors (COMT) (39)(40) or levodopa (41).

FIGURE 1 – CHANGES IN PARKINSON'S DISEASE PATIENT MICROBIOMES

HILL-BURNS (39)	Akkermansia ↑, Ruminococceae ↑, Lactobacillus ↑, Bifidobacterium ↑, Lachnospiraeae ↑
NISHIWAKI (40)	Akkermansia ↑, Catabacter ↑, Akkermansiaceae ↑ Roseburia ↓, Faecalibacterium ↓, Lachnospiraceae ↓
WEIS (41)	Faecalibacterium ↓, Fusicatenibacter ↓
KESHAVARZIAN (42)	Faecalibacterium ↑, Ralstonia ↑ Blautia ↓, Coprococcus ↓, Roseburia ↓

GORECKI (31)	Gammaproteobacteria ↑, Verrucomicrobiae ↑ Clostridia ↓
CILIA (43)	Dec Roseburia, Ruminococcaceae, Actinobacteria
SCHEPERJANS (44)	Enterobacteriaceae ↑ Prevotellaceae ↓
SEGUELLA (45)	Ralstonia ↑ Faecalibacterium ↓, Blautia ↓, Coprococcus ↓, Roseburia ↓
PETROV (46)	Chrisensenella ↑, Catabacter ↑, Lactobacillus ↑, Oscillospira ↑, Bifidobacterium ↑ Dorea ↓, Bacteroides ↓, Prevotella ↓, Faecalibacterium ↓, Coprococcus ↓, Ruminococcus ↓
ROMANO (47)	Lactobacillus ↑, Akkermansia ↑, Bifidobacterium ↑ Lachnospiraceae ↓, Faecalibacterium ↓
HOPFNER (48)	Lactobacillaceae ↑, Barnesiellaceae ↑, Enterococcaceae ↑
LI (49)	Escherichia ↑, Shigella ↑, Streptococcus ↑, Proteus ↑, Enterococcus ↑ Blautia ↓, Faecalibacterium ↓, Ruminococcus ↓
QIAN (50)	Clostridium IV ↑, Aquabacterium ↑, Holdemania ↑, Sphingomonoas ↑, Clostridium XVIII ↑, Butyricicoccus ↑, Anaeortruncus ↑
VASCELLARI (51)	Butyrivibrio ↓, Pseudobutyrivibrio ↓, Coprococcus ↓, Blautia ↓
MAO (52)	Bifidobacteriaceae ↑, Disulfovibrio ↑
LIN (53)	Bifidobacteriaceae ↑ Lachnospiraceae ↓
LI C (54)	Akkermansia ↑, Prevotella ↑ Lactobacillus ↓
LI F (55)	Bacteroides ↑, Prevotella ↑ Ruminococcaceae ↓, Verrucomicrobiaceae ↓, Lachnospiraceae ↓, Hydrogenoanaerobacterium ↓, Porphyromondaceae ↓

Explaining why some of these microbiota changes happened is quite difficult. Several of the papers argued that depletion of Blautia, Lachnospiraceae, Prevotella, and Roseburia, especially with a concurrent increase in Akkermansia, is likely to disrupt short-chain fatty acid contents in the gut leading to a pro-inflammatory state (39)(40)(41)(45)(46)(47).

2.5 – Short-chain fatty acids

Short-chain fatty acids (SCFA) are 1-6 carbon length molecules with at least one carboxylic acid group (56). They are most commonly produced via anaerobic fermentation by bacteria in the gut digesting non-digestible dietary fibers, which are carbohydrates. Most of these are produced in the gut by Bacteroidetes (producing acetate and propionate) and Firmicutes (producing mostly butyrate). The main families of Firmicutes producing butyrate are Ruminocecceae (Faecalibacterium parusnitzii) and Lachnospiraceae (Roseburia spp.). Intestinal cells have multiple transporters along with passive diffusion working to absorb SCFAs (MCT1, SMCT1) that once in the cell serve as regulators of metabolism, growth, and maintenance. Butyrate is of critical importance as it serves as the main source of energy for colonic enterocytes. A steady concentration is needed to stabilize Hypoxia Inducible Factor (HIF-1) in colonic enterocytes that have to survive the low oxygen environment of the distal colon as well as to maintain the integrity of the colonic epithelial barrier. Without butyrate, an enterocyte is liable to run low on ATP,

begin autophagy, and weaken the defensive barrier of the gut leading to the eponymous Leaky Gut Syndrome (LGS). Leaks and pores are natural parts of the epithelial barrier, gated by tight junctions, to allow ions and other molecules to pass through the barrier (57). Unrestricted leakiness, as in LGS, occurs when cells undergo apoptosis and is not directly relevant to tight junction functionality. Ulceration of the gut epithelium leading to a lack of a cellular barrier allows bacteria a free path into the mucosa beneath. But this defensive barrier extends to more than just the epithelial lining; the gut is protected at multiple levels: the luminal contents contain acids, proteolytic enzymes, and bile that can kill various bacteria, there is a thick layer of mucous that houses IgA that prevents adhesion of bacteria to luminal walls, and Paneth cells inside of the epithelium secrete various antibiotic products to prevent crypt colonization. Regardless, the important message is that certain bacteria can consume the mucosal barrier, and there are certain bacteria that not only protect the mucosal barrier but increase the entire defensive functionality of the system (56)(57).

2.6 – Akkermansia – phylum Verrucomicrobia. Gram-negative, anaerobic

Considering that several papers have noted the mucin-degrading nature of A. muciniphila, one could expect that this bacterium may be at the center of pathogenicity to nearly every gut-related disease (39)(40). However, A. municiphila is often used as a probiotic and is believed to reduce inflammation (58). Low levels of A. municiphila have been linked to diabetes, Chron's disease, and Ulcerative colitis. One of the easiest ways to increase A. municiphila levels, other than diet, is the anti-diabetic drug metformin. Glucose intolerance is fairly common in Parkinson's patients (~30%), but only ~5% of patients are diagnosed with diabetes (59). Ironically, metformin has been hypothesized to be of use in the treatment of Parkinson's due to potential neuroprotective effects, possibly through mitochondrial protection, on top of glycemic control, but it may also help improve gut health as well (59)(60).

2.7 – Bifidobacterium – phylum Actinomycetota. Gram-positive, anaerobic

One of the most important butyrate producers, low counts of Bifidobacterium are correlated to deterioration of patients to progressive Parkinson's disease (61). In the world, some of the highest concentrations of Bifidobacterium can be found in Japan (62)(63). By genus, Bifidobacterium made up from 13% (62) to nearly 18% of the average Japanese fecal sample (63). Despite the large increases in East Asian Parkinson's disease cases (4), Japan's prevalence numbers are still quite low compared to other countries in its socio-demographic index (64).

2.8 – Prevotella – Phylum Bacteriodota. Gram-negative, anaerobic

Prevotella copri is a bacterium very commonly found in the Eastern microbiota, commonly colonizing the oral cavity and gut (32). Associated with diets rich in a variety of plants, it's interesting to see that Prevotella species are commonly elevated in various inflammatory diseases like arthritis and colitis (65). Possibly due to confounding from diets, Italian (45) and Russian (46) cases showed decreased levels of Prevotella while Chinese (54)(55) cases showed increased levels. Despite these observations, Prevotella has been shown to reduce SCFA concentration with concurrent increases in IL-6 and TNF-alpha and a decrease in IL-18 concentration believed to induce inflammation in Prevotella-colonized mice guts (65). Prevotella species may induce inflammation directly through their antigenicity, as they are one of the highest IgA-coated species (65), with antibodies typically found only in patients developing diseases like Rheumatoid arthritis (66). Prevotella seems to be a species capable of inducing gut dysbiosis, but to what extent and in how many patients is unclear.

2.9 – Helicobacter pylori – Phylum Campylobacterota. Gram-negative, microaerophilic

Along with Prevotella, Helicobacter species are some of the most IgA-coated species (65). Due to its acid-resistant nature, H. pylori is a common stomach commensal along with several other species, Streptococcus, Prevotella, Vellionella, and Rothia, though this diversity is seen to disappear when H. pylori develops pathogenicity (29). Peptic ulcers with increased levels of H. pylori are commonly seen in Parkinson's patients (67)(68). Levodopa on-time was decreased and off-time increased in patients identified with H. pylori infection (68)(69). Eradication of H. pylori significantly increases patient clinical status and may extend the viability period of levodopa treatment.

2.10 – Roseburia and Lachnospiraceae – Phylum Bacillota. Gram-positive, anaerobic.

Frequently mentioned as important SCFA producers potentially involved in various inflammatory bowel diseases, direct connections to disease are mostly speculative (73).

2.11 – Desulfovibrio – Phylum Thermodesulfobacteriota. Gram-negative, microaerophilic

Desulfovibrio species have the capacity to bind mucin and produce Hydrogen Sulfide (70). Hydrogen sulfide can alter cellular signaling, potentially be cytotoxic at higher concentrations, and even induce aggregation of alpha-synuclein. Furthermore, Desulfovibrio often have the capacity to produce magnetite (Fe_3O_4) which can also cause early aggregation of alpha-synuclein (70)(71). Skin samples from Parkinson's patients showed aberrant and possibly increased magnetic activity reminiscent of magnetite (72). While speculative at best, Desulfovibrio provides another interesting contributor to potential inflammatory or alpha-synuclein aggregation events.

2.12 – Iron

Even without magnetic activity in the form of magnetite, iron by itself can produce free radicals via the Fenton reaction (74). Unilateral injection of ferritin into the substantia nigra activates microglia with ~95% reduction in dopamine concentration. Animal studies suggest that iron may enter the brain via a leaky blood-brain barrier (74), and human studies confirm the existence of low integrity blood-brain barriers present in Parkinson's patients (75). It is unknown whether this occurs before the development of Parkinson's disease, possibly due to bacterial-related inflammation, during disease progression, or after Parkinson's disease has already developed. It is also unknown, even if blood-brain barrier deficiency occurs before Parkinson's, if this is a possible primary cause. The blood-brain barrier of the striatum is especially friable in general, and while the theory hints at a potential access point that can fit a general model of microbial-induced iron deposition in the substantia nigra, more research needs to be done to confirm.

3.1 – Rationale of microbial interventions

Concerning the theories posted so far, it is very likely that most cases of Parkinson's disease cannot be immediately treated with any sort of microbiota intervention. However, there is sufficient evidence that certain cases of Parkinson's disease can either be prevented, slowed, or possibly even treated should the root cause be eliminated and homeostasis restored. There have been cases over time where incidental treatments resulted in the amelioration of symptoms (28)(77).

3.2 – Fecal Microbiota Transplant

Arguably the most exciting method for the normalization of dysbiosis in all sorts of patients, ever since 2013, fecal microbiota transplantation (FMT) has been used to great success for patients with Clostridium difficile infections, with results better than antibiotic treatment (78)(79). Unlike antibiotics, FMT offers a solution to dysbiosis that doesn't induce dysbiosis itself and not only serves to remediate commensal

deficits in the gut but potentially offers a bacterial composition the patient may otherwise never have had (79). Various murine studies have shown proof of concept. Rotenone-induced Parkinson's mice were found to have increased levels of Akkermansia and Desuflovibrio, inflammation and destruction of the intestinal and blood-brain barriers, as well as systemic inflammation (80). After FMT, blood-brain barrier irregularity and inflammation of the substantia nigra were ameliorated, gut lipopolysaccharide levels were decreased, and overall Parkinsonian symptoms were decreased. Rotenone-treated mice blood-brain barriers showed dilution of tight junctions with disorganization of related structures and endothelial cells, yet post-FMT rotenone mice showed improved tight junction structure in the barrier. Perhaps most striking, Alpha-synuclein aggregation was significantly increased in rotenone-treated mice but was markedly decreased post-FMT. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's mice were found to have increased levels of Anaerostipes, Bifidobacterium, and Ruminococcus with decreased Blautia (81). In addition to lessening motor dysfunction and relieving gut inflammation, the opposite gut changes were seen in the FMT-treated mice, with an increase in Blautia and decreases in Anaerostipes, Bifidobacterium, and Ruminococcus. Perhaps most strikingly, the activity of Tyrosine Hydroxylase (TH), a key enzyme in dopamine synthesis, was significantly decreased in MPTP-treated mice. While TH activity post-FMT was not completely restored, activity significantly increased. Similarly, inflammatory markers like iNOS and IL-1B were significantly increased in MPTP substantia nigra, which with TH activity, were decreased in FMT-treated mice but not fully restored.

FIGURE 2 HUMAN FMT STUDIES

KUAI (82)	11 Patients	10 patients had significant motor and non-motor symptom improvement 3 months post-FMT
XUE (83)	15 Patients	Nasointestinal FMT was inferior than colonoscopic FMT. All patients had significant motor and non-motor symptom improvement at 1-month follow-up
HUANG (84)	1 Patient	Constipation was treated and tremor abated for 2 months before returning
SEGAL (85)	6 Patients	Improvement in PD motor and non-motor symptoms at 6 months

Kuai et al (82) followed 11 Parkinson's patients suffering from constipation (82). Baseline characteristics were measured including: "BMI, Hoehn-Yahr Grade (H-Y), Unified Parkinson's Disease Rating Scale II Score (UPDRS-II), Non-motor symptom scale for Parkinson's Disease (NMSS), Patient assessment of constipation quality of life questionnaire (PAC-QOL), and Wexner constipation score (WCS)." BMI average increased from 22 to 23 6 weeks post-FMT and from 23 to 24.6 after 12 weeks. Every other scoring metric average improved significantly at 6 weeks and even further at 12 weeks. The study further elaborated on changes in the patients' gut microbiotas. Before FMT, patients' guts showed low alpha-diversity with a domination of Bacteroidetes bacteria. Post FMT, alpha-diversity was increased with Actinobacteria and Firmicutes as the dominant phyla, with notable increases in Faecalibacterium and Blautia genera. Xue et al (83) examined 15 Parkinson's patients, breaking them into two groups by methodology: 10 colonoscopic FMT patients, 5 nasointestinal FMT patients. All 10 colonoscopic FMT patients completed 3-month follow-up with self-satisfaction questionnaire scores of satisfactory for at least 4 months. 2 of 5 nasointestinal FMT patients completed 3-month follow-up with 3 patients dissatisfied after 1 month of treatment and subsequently dropping out. Symptoms were evaluated using:

"Pittsburg sleep quality index (PSQI), Hamilton and Montgomery-Asberg Depression rating scale (HAMD), Hamilton anxiety scale (HAMA), UPDRS-III, and the Non-motor symptoms questionnaire (NMSQ)." Similar to the previous study, average scores improved from baseline at first testing (1 month) and even more so at later testing (3-month) significantly in patients in the colonoscopic FMT group. Patients in the nasointestinal FMT group showed mild improvement in UPDRS-III scores but overall did not show significant improvement. Huang et al (84) followed a 71-year-old male with a 3-year history of constipation unresponsive to laxatives (84). FMT reduced levels of Proteobacteria and Bacteroidetes while increasing Firmicutes, with increases in Lachnoclostridium, Dialister, Alistipes, and Ruminococcaceae at 1 week, and Akkermanisa and Faecalibacterium at 3 months. Improvement in UPDRS-III, UPDRS-II, PAC-QOL, and Wexner scores was greatest 1 week after FMT, with gradual increases towards baseline at 1 and 3 months. Though limb tremor almost disappeared after 1-week, other symptoms like neck and face stiffness were unaffected. Segal et al (85) followed 6 Parkinson's patients with constipation complaints (85). Four weeks after PMT 5 of 6 patients showed improvements in UPDRS-III, NMSS, Wexner, and Bristol Stool Scale scores. FMT appears to have potential in treating constipation as well as motor and non-motor Parkinsonian symptoms.

FIGURE 3 SAFETY OF FMT

KUAI (82)	No adverse events	11 patients
XUE (83)	5 adverse events (2 with diarrhea, 2 with abdominal pain, and 1 with flatulence)	15 patients
HUANG (84)	No adverse events	1 patient
SEGAL (85)	1 adverse event – 8 hours of vasovagal syncope 24 hours post-FMT	6 patients

Adverse events were limited to within one week after the FMT was performed. All of the adverse events were not serious and at worst required hospitalized observation of the patient.

3.2 – Antibiotics

Antibiotics would seem like a natural method to alleviate dysbiosis in the gut. Though incredibly useful in curing primary infections, antibiotics have the potential to induce dysbiosis in the gut, reducing intestinal barrier integrity, causing disbalance in the commensal microbiota (Inc Proteobacteria, Dec Bacteroidetes, Firmicutes), and decreasing the concentration of SCFAs in the gut (86). Paradoxically, dysbiosis can also be protective in certain cases, like a reduction in MPTP neurotoxicity in mice treated with antibiotics (87). Incidental cases of symptom improvement in Parkinson's patients receiving antibiotics have occurred, but rarely (28)(77). In both cases, a patient was prescribed a fluoroquinolone, ciprofloxacin (28), and levofloxacin (77), and in both cases, the authors conjectured about the possibility of the antibiotic's unintentional anti-inflammatory effect causing the suspiciously quick improvement in symptoms.

3.3 – Tetracyclines

In the spirit of repurposing antibiotics for their potentially beneficial side effects, tetracyclines are an interesting candidate. Tetracyclines in general can inhibit neutrophil (PMN) function, capable of inhibiting PMN superoxide production, degranulation, and red blood cell lysis (88). As mentioned previously, using antibiotics at therapeutic levels can cause dysbiosis in the gut, especially with the threat of creating drug-resistant strains. Studies have shown that doxycycline has more effective anti-inflammatory activity at sub-therapeutic doses of 20-40mg/day than at high doses of 100-200mg/day.

Strikingly, doxycycline has also been shown to shunt alpha-synuclein oligomers into producing high-molecular-weight species that form B-sheet structures not conducive to forming alpha-synuclein fibrils (89). Doxycycline directly binds to alpha-synuclein oligomers, and though capable of preventing the formation of indigestible fibrils, there is no effect after fibrillation has reached its exponential phase. Minocycline, another tetracycline, has been shown to prevent damage to nigrostriatal dopaminergic neurons in over-expressing alpha-synuclein mice (90). In addition, minocycline lowered the release of Interleukin-1B, decreased Lewy body production, and injection of minocycline improved motor performance by 15-20%, nearly reaching the performance of control mice.

3.5 – Probiotics

Probiotics are defined as "live microorganisms that when administered in adequate amounts confer a health benefit on the host (91)." This is not to be confused with prebiotics which are non-digestible food components that can selectively stimulate the growth of certain bacteria, and synbiotics which are a combination of pre- and pro-biotics. Cassani et al (92) followed 40 Parkinson's patients over 6 weeks and marked their intestinal function via a patient diary. Fermented milk fortified with Lactobacillus casei strain Shirota showed statistically significant beneficial changes in gastrointestinal function: increased days of normal consistency, decreased bloating, decreased abdominal pain, and decreased sensations of incomplete emptying. Barichella et al (93) followed 120 Parkinson's patients comparing placebo to synbiotic fermented milk, finding a significant increase in complete bowel movements for synbiotic patients. Ghyselinck et al (94) followed 3 Parkinson's patients, testing Symprove, a suspension of Lactobacillus acidophilus, plantarum, and rhamnosus with Enterococcus faecium, versus 3 healthy controls. Compared to controls, before prebiotic treatment, all of the Parkinson's disease patients had a diminished firmicute count with increased Bacteroidetes and Actinobacteria counts. After treatment, all patients showed an increase in Firmicute and Actinobacteria counts. In addition, induced intestinal wounds from donated cell cultures were performed on these patients. Included results (5 of 6 patients), showed significantly improved wound closer with exposure to prebiotic treatment. Georgescu et al (95) followed 40 Parkinson's patients, treating each with either trimebutine (an antimuscarinic prokinetic) or probiotics. Trimebutine effectively reduced all three measured symptoms compared to baseline: incomplete evacuation, bloating, and abdominal pain. Prebiotics were only shown to decrease bloating and abdominal pain significantly, with no difference found in incomplete defecation.

3.6 – Diet

Most people tend to fall within certain dietary trends that determine the basic bacterial composition forming the structure of their gut microbiota, known as an enterotype. Three basic enterotypes are known: Bacteroides-dominant, Prevotella-dominant, and a third type that is mostly Bacteroides-dominant with elevated Ruminococcus (96). The Bacteroides-dominant enterotype typically occurs in people who eat diets filled with proteins and fats, while the Prevotella-dominant enterotype is found in people who eat more carbohydrates and simple sugars, typically found in diets high in various vegetables. Studies on FMTs and probiotics have found quick transitions in the microbiota, but diet cannot produce the same changes. Bacteroides-dominant enterotypes after 10 days of a high-fiber, low-fat diet were resistant to changing to a Prevotella-dominant enterotype. Even the one case that did show changes quickly reverted after discontinuing the diet. Patterns seem to be able to be found in long-term dietary tracking. Patients followed for their dietary patterns from 1986 to 2012 were found to have an inverse relationship between adherence to a Mediterranean-style diet and the development of Parkinson's disease and the severity of the disease (97). Patients adhering to a Mediterranean diet also had lower BMI, were more physically active, and interestingly were less likely to either consume caffeine or smoke cigarettes.

3.7 – Caffeine

Various epidemiological and animal studies purport the potential protective effects of caffeine against various diseases, including Parkinson's (98)(99). Despite claims, a randomized trial on 61 Parkinson's patients showed no improvement in motor symptoms, depression, or quality of life versus placebo, with potential increases in dyskinesia for Parkinson's patients (100). Caffeine also has dose-dependent effects on the microbiota with patients consuming 45-500 ml/day harboring higher levels of Bacteroides/Prevotella, though they were recognized by the same primer sequence (99).

3.8 – Nicotine

Another potentially protective group of substances lauded in epidemiological and animal studies are the thousands of potential chemicals found in cigarette smoke, most notably nicotine (101). Oral and transdermal application has been shown to improve Parkinsonian symptoms in animal models, potentially via nicotinic receptor agonism or through reduction of iron uptake. Injections of subcutaneous nicotine in rotenone-induced Parkinson's mice were found to have significantly improved movement with upregulation of Tyrosine Hydroxylase activity, downregulation of alpha-synuclein, and overall increased retention of dopaminergic neurons (102). Nicotine added to rat chow significantly increases the concentration of Lactobacillus and Lachnospiraceae, while decreasing Bacteroides and Ruminococcaceae (103).

Discussion:

Considering an appreciation of the effects of the microbiome on the gut as a "gut-based" approach would be an injustice. While the microbiome constrains itself to the focus on the microbes inhabiting the gut, the effects of dysbiosis are systemic. Studies on the regulation of short-chain fatty acids show that dysregulations in their quantities, especially alongside dysbiotic inflammation, are critical to the pathology of the protective gut barrier. Damage to this barrier allows for a direct conduit of the typically contained microsphere of the gut to come into contact with the surrounding systems, and whether through circulatory or nervous systems, can disseminate throughout the body. The final line of defense for the brain, the blood-brain barrier, also falls victim to typical Parkinson's pathology. As seen in rotenone and autopsy studies, blood-brain barrier damage is relatively common, and oftentimes is completely bypassed by retrograde dissemination of alpha-synuclein deposits. These patterns of pathology suggest that sources of inflammation external to the brain can potentially be the root causes of non-genetically based Parkinson's disease. Further reinforcement lies in the peculiar cases of sudden amelioration. Cases where antibiotics, Fecal Microbiota Transplant, or other microbiologically based interventions cause rapid improvement in symptoms suggest that an improvement in the homeostasis of the gut is not the underlying mechanism, but more likely suggests that sudden improvement of underlying inflammation in critical regions of the nervous system were the likely culprit. As such, large, sweeping motions such as microbiological eradication are unlikely to produce long-term results, and may potentially exacerbate problems by creating a fresh slate for dysbiosis to blossom once more. Rather than broad strokes, a certain emphasis should be placed on the steady maintenance of a healthy microbiome. The importance of the microbiome is multifold, but the primary emphasis is on providing ample nutrition for the gut enterocytes as well as preventing the development and propagation of pathological strains of commensal or invasive bacteria. As seen with Helicobacter pylori, colonization with the bacteria on its own rarely produces pathology, but conversion to a pathologic strain can quickly result in over-colonization and loss of commensalism. Practices like a healthy, variable, and consistent diet have been shown to induce a stable steady-state in the microbiome that promotes mutualistic benefit for the host while also harboring low-pathogenicity strains of indigenous bacteria. Unfortunately, the advent of antimicrobials has placed

selection pressure on more pathological strains of microbes to proliferate, especially in comparison to prior generations. What is safe and healthy to consume and feed to one's microbiome may not be safe elsewhere, or even within the same locality within a single generational period. Ultimately, luck plays a major part in what antigens will be met in the body at what time, and what reaction those antigens may have to whom. Other than that, general recommendations could be: a wide variety of ingestible carbohydrates (grains, vegetables), passive ingestion of naturally occurring antibiotic compounds (nicotine, polyphenols from plant products – caffeinated beverages, nicotine, rotting forest foliage), sufficient exercise to reduce inflammation from metabolic syndrome, adequate hydration, and most importantly, consistency. The main issue with health advice is that gut health, and by extension the health of the host, is a balancing act. Every compensatory act can lead to overcompensation and catalyze pathological processes rather than slowing them, as well as too little resulting in little to no change. Microbiological interventions like anti-inflammatories or fecal transplants can try to induce homeostasis, but without constant reinforcement and a continuance of habits that caused the issues in the first place, the root causes will inevitably return. Thus, treating the microbiome requires lifestyle modification, because the microbiome is a reflection of lifestyle. Unless the lifestyle can be cured, the life will always be sick.

Conclusion:

Parkinson's disease sits at an interesting crossroads of many potential etiologies converging to create one general symptomatic presentation. Several lines of evidence, from retrograde synucleinopathy to the potential effectiveness of symptomatic treatment via microbiological manipulation, instigate the microbiota as a seeding ground for the disease. Despite potentially being the primary cause of Parkinson's disease in many idiopathic cases, most cases are probably not treatable by microbiological methods. Unless caught in pre-symptomatic stages of the disease, the best-case scenario of treatment of pathological microbiota will probably only be a slowing of progression with a reduction of relevant symptoms. Even in cases where microbiological manipulations like Fecal Microbiota Transplant are helpful, the changes to the microbiota are most likely transitory and will ultimately readapt to the owner's habits. Ultimately, the microbiota of the gut is a reflection of its environment, with the main driver being the various nutrients that pass through. People tend to get sick for specific, but potentially difficult to identify, reasons. Probiotics or oral nicotine consumption may reshape a patient's gut microbiota to mimic that of a "healthy" person's, but without eliminating the root cause, the patients will inevitably wait till they get sick again. Though difficult, the key to a healthy microbiome is consistency. And though medical interventions can kickstart a change for the better, it's up to the patient to carry it through.

Methods:

Research was done through the National Library of Medicine online portal, using the PubMed and PubMed Central databases.

PubMed Central and PubMed Fecal Microbiota Transplant Research Boolean Terms: Results = 644 + 76. 15 papers were selected.

("fmt"[All Fields] AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinson's"[All Fields])) AND ("2017/04/15"[PDat] : "2022/04/13"[PDat])

PubMed Central and PubMed Antibiotics Research Boolean Terms: results = 1,016. 10 papers were selected.

(("anti-bacterial agents"[All Fields] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotics"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR "parkinson's"[All Fields])) NOT ("review"[All Fields] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) AND ("2017/04/16"[PDat] : "2022/04/14"[PDat])

References:

1. Parkinson's disease [Internet]. National Institute on Aging. U.S. Department of Health and Human Services; [cited 2022 Apr 12]. Available from: https://www.nia.nih.gov/health/parkinsons-disease
2. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nat Rev Dis Primers. 2017 Mar 23;3:17013. doi: 10.1038/nrdp.2017.13. PMID: 28332488.
3. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018 Nov;17(11):939-953. doi: 10.1016/S1474-4422(18)30295-3. Epub 2018 Oct 1. Erratum in: Lancet Neurol. 2021 Dec;20(12):e7. PMID: 30287051; PMCID: PMC6191528.
4. Ou Z, Pan J, Tang S, Duan D, Yu D, Nong H, et al. Global trends in the incidence, prevalence, and years lived with disability of parkinson's disease in 204 countries/territories from 1990 to 2019 [Internet]. Frontiers. Frontiers; 1AD [cited 2022 Apr 12]. Available from: https://www.frontiersin.org/articles/10.3389/fpubh.2021.776847/full
5. Dorsey ER, Sherer T, Okun MS, Bloem BR. The Emerging Evidence of the Parkinson Pandemic. J Parkinsons Dis. 2018;8(s1):S3-S8. doi: 10.3233/JPD-181474. PMID: 30584159; PMCID: PMC6311367.
6. Tan LCS. Epidemiology of parkinson's disease - neurology asia [Internet]. [cited 2022 Apr 12]. Available from: https://www.neurology-asia.org/articles/neuroasia-2013-18(3)-231.pdf
7. Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, Goetz CG, Halliday GM, Hardy J, Lang AE, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of Parkinson's disease. Mov Disord. 2014 Apr;29(4):454-62. doi: 10.1002/mds.25844. Epub 2014 Mar 11. PMID: 24619848; PMCID: PMC4204150.
8. Reichmann H. Premotor Diagnosis of Parkinson's Disease. Neurosci Bull. 2017 Oct;33(5):526-534. doi: 10.1007/s12264-017-0159-5. Epub 2017 Aug 3. PMID: 28776303; PMCID: PMC5636732.
9. Jost WH. Gastrointestinal dysfunction in Parkinson's Disease. J Neurol Sci. 2010 Feb 15;289(1-2):69-73. doi: 10.1016/j.jns.2009.08.020. Epub 2009 Aug 29. PMID: 19717168.
10. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Ann N Y Acad Sci. 2010 Jan;1184:188-95. doi: 10.1111/j.1749-6632.2009.05118.x. PMID: 20146698.
11. Inamdar NN, Arulmozhi DK, Tandon A, Bodhankar SL. Parkinson's disease: genetics and beyond. Curr Neuropharmacol. 2007;5(2):99-113. doi: 10.2174/157015907780866893. PMID: 18615181; PMCID: PMC2435348.
12. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ. 2016 Nov 1;188(16):1157-1165. doi: 10.1503/cmaj.151179. Epub 2016 May 24. PMID: 27221269; PMCID: PMC5088077.
13. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobiol. 2007 Dec;33(6):599-614. doi: 10.1111/j.1365-2990.2007.00874.x. Epub 2007 Oct 24. PMID: 17961138; PMCID: PMC7194308.
14. Anselmi L, Toti L, Bove C, Hampton J, Travagli RA. A Nigro-Vagal Pathway Controls Gastric Motility and Is Affected in a Rat Model of Parkinsonism. Gastroenterology. 2017 Dec;153(6):1581-1593. doi: 10.1053/j.gastro.2017.08.069. Epub 2017 Sep 11. PMID: 28912019; PMCID: PMC5705565.
15. Brundin P, Melki R, Kopito R. Prion-like transmission of protein aggregates in neurodegenerative diseases. Nat Rev Mol Cell Biol. 2010 Apr;11(4):301-7. doi: 10.1038/nrm2873. PMID: 20308987; PMCID: PMC2892479.
16. Ryskalin L, Busceti CL, Limanaqi F, Biagioni F, Gambardella S, Fornai F. A Focus on the Beneficial Effects of Alpha Synuclein and a Re-Appraisal of Synucleinopathies. Curr Protein Pept Sci. 2018;19(6):598-611. doi: 10.2174/1389203718666171117110028. PMID: 29150919; PMCID: PMC5925871.
17. Anwar S, Peters O, Millership S, Ninkina N, Doig N, Connor-Robson N, Threlfell S, Kooner G, Deacon RM, Bannerman DM, Bolam JP, Chandra SS, Cragg SJ, Wade-Martins R, Buchman VL. Functional alterations to the nigrostriatal system in mice lacking all three members of the synuclein family. J Neurosci. 2011 May 18;31(20):7264-74. doi: 10.1523/JNEUROSCI.6194-10.2011. PMID: 21593311; PMCID: PMC3154647.
18. Simon C, Soga T, Okano HJ, Parhar I. α-Synuclein-mediated neurodegeneration in Dementia with Lewy bodies: the pathobiology of a paradox. Cell Biosci. 2021 Nov 19;11(1):196. doi: 10.1186/s13578-021-00709-y. PMID: 34798911; PMCID: PMC8605528.
19. Butler B, Sambo D, Khoshbouei H. Alpha-synuclein modulates dopamine neurotransmission. J Chem Neuroanat. 2017 Oct;83-84:41-49. doi: 10.1016/j.jchemneu.2016.06.001. Epub 2016 Jun 19. PMID: 27334403; PMCID: PMC5167661.
20. Burré J, Sharma M, Tsetsenis T, Buchman V, Etherton MR, Südhof TC. Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. Science. 2010 Sep 24;329(5999):1663-7. doi: 10.1126/science.1195227. Epub 2010 Aug 26. PMID: 20798282; PMCID: PMC3235365.
21. Chandra S, Fornai F, Kwon HB, Yazdani U, Atasoy D, Liu X, Hammer RE, Battaglia G, German DC, Castillo PE, Südhof TC. Double-knockout mice for alpha- and beta-synucleins: effect on synaptic functions. Proc Natl Acad Sci U S A. 2004 Oct 12;101(41):14966-71. doi: 10.1073/pnas.0406283101. Epub 2004 Oct 1. PMID: 15465911; PMCID: PMC522043.
22. Stokes AH, Hastings TG, Vrana KE. Cytotoxic and genotoxic potential of dopamine. J Neurosci Res. 1999 Mar 15;55(6):659-65. doi: 10.1002/(SICI)1097-4547(19990315)55:6<659::AID-JNR1>3.0.CO;2-C. PMID: 10220107.
23. Lin M, Mackie PM, Shaerzadeh F, Gamble-George J, Miller DR, Martyniuk CJ, Khoshbouei H. In Parkinson's patient-derived dopamine neurons, the triplication of α-synuclein locus induces distinctive firing pattern by impeding D2 receptor autoinhibition. Acta Neuropathol Commun. 2021 Jun 7;9(1):107. doi: 10.1186/s40478-021-01203-9. PMID: 34099060; PMCID: PMC8185945.

24. Subramaniam M, Althof D, Gispert S, Schwenk J, Auburger G, Kulik A, Fakler B, Roeper J. Mutant α-synuclein enhances firing frequencies in dopamine substantia nigra neurons by oxidative impairment of A-type potassium channels. J Neurosci. 2014 Oct 8;34(41):13586-99. doi: 10.1523/JNEUROSCI.5069-13.2014. PMID: 25297088; PMCID: PMC6608377.

25. Sian J, Dexter DT, Lees AJ, Daniel S, Agid Y, Javoy-Agid F, Jenner P, Marsden CD. Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol. 1994 Sep;36(3):348-55. doi: 10.1002/ana.410360305. PMID: 8080242.

26. McGeer PL. Parkinson's disease symptoms: The ... - wiley online library [Internet]. [cited 2022 Apr 13]. Available from: https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mds.23135

27. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol. 2022 Mar 4:1–17. doi: 10.1038/s41577-022-00684-6. Epub ahead of print. PMID: 35246670; PMCID: PMC8895080.

28. Leheste J. (PDF) parkinson's disease: A case report of motor symptoms resolution ... [Internet]. [cited 2022 Apr 13]. Available from: https://www.researchgate.net/publication/324776315_Parkinson's_Disease_A_Case_Report_of_Motor_Symptoms_Resolution_Following_Antibiotic_Treatment_for_Suspected_Bacterial_Osteomyelitis

29. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World J Gastroenterol. 2015 Aug 7;21(29):8787-803. doi: 10.3748/wjg.v21.i29.8787. PMID: 26269668; PMCID: PMC4528021.

30. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J; MetaHIT Consortium, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010 Mar 4;464(7285):59-65. doi: 10.1038/nature08821. PMID: 20203603; PMCID: PMC3779803.

31. 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 Aug 7;13:839. doi: 10.3389/fnins.2019.00839. PMID: 31440136; PMCID: PMC6693556.

32. Lim MY, Hong S, Chung W-H, Shin J-H, Kim J-H, Nam Y-D. Gut Microbiome Structure and Association with Host Factors in a Korean Population [Internet]. ASM Journals. 2021. Available from: https://journals.asm.org/doi/full/10.1128/mSystems.00179-21

33. Nishijima S, Suda W, Oshima K, Kim SW, Hirose Y, Morita H, Hattori M. The gut microbiome of healthy Japanese and its microbial and functional uniqueness. DNA Res. 2016 Apr;23(2):125-33. doi: 10.1093/dnares/dsw002. Epub 2016 Mar 6. PMID: 26951067; PMCID: PMC4833420.

34. Brooks AW, Priya S, Blekhman R, Bordenstein SR (2018) Gut microbiota diversity across ethnicities in the United States. PLOS Biology 16(12):e2006842. https://doi.org/10.1371/journal.pbio.2006842

35. Ren X, Xu J, Zhang Y, Chen G, Zhang Y, Huang Q, Liu Y. Bacterial Alterations in Post-Cholecystectomy Patients Are Associated With Colorectal Cancer. Front Oncol. 2020 Aug 12;10:1418. doi: 10.3389/fonc.2020.01418. PMID: 32903396; PMCID: PMC7434860.

36. Chaudhuri KR, Hu MT, Brooks DJ. Atypical parkinsonism in Afro-Caribbean and Indian origin immigrants to the UK. Mov Disord. 2000 Jan;15(1):18-23. doi: 10.1002/1531-8257(200001)15:1<18::aid-mds1005>3.0.co;2-z. PMID: 10634237.

37. Vangay P, Johnson AJ, Ward TL, Al-Ghalith GA, Shields-Cutler RR, Hillmann BM, Lucas SK, Beura LK, Thompson EA, Till LM, Batres R, Paw B, Pergament SL, Saenyakul P, Xiong M, Kim AD, Kim G, Masopust D, Martens EC, Angkurawaranon C, McGready R, Kashyap PC, Culhane-Pera KA, Knights D. US Immigration Westernizes the Human Gut Microbiome. Cell. 2018 Nov 1;175(4):962-972.e10. doi: 10.1016/j.cell.2018.10.029. PMID: 30388453; PMCID: PMC6498444.

38. Van Laar T, Boertien JM, Herranz AH. Faecal Transplantation, Pro- and Prebiotics in Parkinson's Disease; Hope or Hype? J Parkinsons Dis. 2019;9(s2):S371-S379. doi: 10.3233/JPD-191802. PMID: 31609702; PMCID: PMC6839600.

39. Hill-Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, Peddada SD, Factor SA, Molho E, Zabetian CP, Knight R, Payami H. Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov Disord. 2017 May;32(5):739-749. doi: 10.1002/mds.26942. Epub 2017 Feb 14. PMID: 28195358; PMCID: PMC5469442.

40. Nishiwaki, H., Ito, M., Ishida, T., Hamaguchi, T., Maeda, T., Kashihara, K., Tsuboi, Y., Ueyama, J., Shimamura, T., Mori, H., Kurokawa, K., Katsuno, M., Hirayama, M. and Ohno, K., 2022. Meta-Analysis of Gut Dysbiosis in Parkinson's Disease. [online] Movement Disorders. Available at: https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.28119

41. Weis, S., Schwiertz, A., Unger, M.M. et al. Effect of Parkinson's disease and related medications on the composition of the fecal bacterial microbiota. npj Parkinsons Dis. 5, 28 (2019). https://doi.org/10.1038/s41531-019-0100-x

42. Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, Mutlu E, Shannon KM. Colonic bacterial composition in Parkinson's disease. Mov Disord. 2015 Sep;30(10):1351-60. doi: 10.1002/mds.26307. Epub 2015 Jul 16. PMID: 26179554.

43. Cilia R, Piatti M, Cereda E, Bolliri C, Caronni S, Ferri V, Cassani E, Bonvegna S, Ferrarese C, Zecchinelli AL, Barichella M, Pezzoli G. Does Gut Microbiota Influence the Course of Parkinson's Disease? A 3-Year Prospective Exploratory Study in de novo Patients. J Parkinsons Dis. 2021;11(1):159-170. doi: 10.3233/JPD-202297. PMID: 33337387.

44. Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M, Kinnunen E, Murros K, Auvinen P. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord. 2015 Mar;30(3):350-8. doi: 10.1002/mds.26069. Epub 2014 Dec 5. PMID: 25476529.

45. Seguella, Luisa; Sarnelli, Giovanni; Esposito, Giuseppe PhD* Leaky gut, dysbiosis, and enteric glia activation, Neural Regeneration Research: June 2020 - Volume 15 - Issue 6 - p 1037-1038 doi: 10.4103/1673-5374.270308

46. Petrov VA, Saltykova IV, Zhukova IA, Alifirova VM, Zhukova NG, Dorofeeva YB, Tyakht AV, Kovarsky BA, Alekseev DG, Kostryukova ES, Mironova YS, Izhboldina OP, Nikitina MA, Perevozchikova TV, Fait EA, Babenko VV, Vakhitova MT, Govorun VM, Sazonov AE. Analysis of Gut Microbiota in Patients with Parkinson's Disease. Bull Exp Biol Med. 2017 Apr;162(6):734-737. doi: 10.1007/s10517-017-3700-7. Epub 2017 Apr 20. PMID: 28429209.

47. Romano, S., Savva, G.M., Bedarf, J.R. et al. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. npj Parkinsons Dis. 7, 27 (2021). https://doi.org/10.1038/s41531-021-00156-z

48. Hopfner F, Künstner A, Müller SH, Künzel S, Zeuner KE, Margraf NG, Deuschl G, Baines JF, Kuhlenbäumer G. Gut microbiota in Parkinson disease in a northern German cohort. Brain Res. 2017 Jul 15;1667:41-45. doi: 10.1016/j.brainres.2017.04.019. Epub 2017 May 12. PMID: 28506555.

49. Li W, Wu X, Hu X, Wang T, Liang S, Duan Y, Jin F, Qin B. Structural changes of gut microbiota in Parkinson's disease and its correlation with clinical features. Sci China Life Sci. 2017 Nov;60(11):1223-1233. doi: 10.1007/s11427-016-9001-4. Epub 2017 May 20. PMID: 28536926.

50. Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, Chen SD, Xiao Q. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. Brain Behav Immun. 2018 May;70:194-202. doi: 10.1016/j.bbi.2018.02.016. Epub 2018 Mar 2. PMID: 29501802.

51. Vascellari S, Palmas V, Melis M, Pisanu S, Cusano R, Uva P, Perra D, Madau V, Sarchioto M, Oppo V, Simola N, Morelli M, Santoru ML, Atzori L, Melis M, Cossu G, Manzin A. Gut Microbiota and Metabolome Alterations Associated with Parkinson's Disease. mSystems. 2020 Sep 15;5(5):e00561-20. doi: 10.1128/mSystems.00561-20. PMID: 32934117; PMCID: PMC7498685.

52. Mao L, Zhang Y, Tian J, Sang M, Zhang G, Zhou Y, Wang P. Cross-Sectional Study on the Gut Microbiome of Parkinson's Disease Patients in Central China. Front Microbiol. 2021 Sep 28;12:728479. doi: 10.3389/fmicb.2021.728479. PMID: 34650532; PMCID: PMC8506127.

53. Lin A, Zheng W, He Y, Tang W, Wei X, He R, Huang W, Su Y, Huang Y, Zhou H, Xie H. Gut microbiota in patients with Parkinson's disease in southern China. Parkinsonism Relat Disord. 2018 Aug;53:82-88. doi: 10.1016/j.parkreldis.2018.05.007. PMID: 29776865.

54. Li C, Cui L, Yang Y, Miao J, Zhao X, Zhang J, Cui G, Zhang Y. Gut Microbiota Differs Between Parkinson's Disease Patients and Healthy Controls in Northeast China. Front Mol Neurosci. 2019 Jul 11;12:171. doi: 10.3389/fnmol.2019.00171. PMID: 31354427; PMCID: PMC6637281.

55. Li F, Wang P, Chen Z, Sui X, Xie X, Zhang J. Alteration of the fecal microbiota in North-Eastern Han Chinese population with sporadic Parkinson's disease. Neurosci Lett. 2019 Aug 10;707:134297. doi: 10.1016/j.neulet.2019.134297. Epub 2019 Jun 11. PMID: 31200089.

56. Parada Venegas D, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for Inflammatory Bowel Diseases. Front Immunol [Internet]. 2019;10:277. Available from: http://dx.doi.org/10.3389/fimmu.2019.00277

57. Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut. 2019 Aug;68(8):1516-1526. doi: 10.1136/gutjnl-2019-318427. Epub 2019 May 10. PMID: 31076401; PMCID: PMC6790068.

58. Ouyang J, Lin J, Isnard S, Fombuena B, Peng X, Marette A, et al. The bacterium Akkermansia muciniphila: A sentinel for gut permeability and its relevance to HIV-related inflammation. Front Immunol [Internet]. 2020;11:645. Available from: http://dx.doi.org/10.3389/fimmu.2020.00645

59. Lu M, Chen H, Nie F, Wei X, Tao Z, Ma J. The potential role of metformin in the treatment of Parkinson's disease. Journal of Bio-X Research [Internet]. 2020 [cited 2022 Apr 14];3(1):27–35. Available from: https://journals.lww.com/jbioxresearch/Fulltext/2020/03000/The_potential_role_of_metformin_in_the_treatment.6.aspx

60. Sportelli C, Urso D, Jenner P, Chaudhuri KR. Metformin as a potential neuroprotective agent in prodromal Parkinson's disease-viewpoint. Front Neurol [Internet]. 2020;11:556. Available from: http://dx.doi.org/10.3389/fneur.2020.00556

61. Minato T, Maeda T, Fujisawa Y, Tsuji H, Nomoto K, Ohno K, Hirayama M. Progression of Parkinson's disease is associated with gut dysbiosis: Two-year follow-up study. PLoS One. 2017 Nov 1;12(11):e0187307. doi: 10.1371/journal.pone.0187307. PMID: 29091972; PMCID: PMC5665539.

62. Nakayama J, Watanabe K, Jiang J, Matsuda K, Chao S-H, Haryono P, et al. Diversity in gut bacterial community of school-age children in Asia. Sci Rep [Internet]. 2015 [cited 2022 Apr 14];5(1):8397. Available from: https://www.nature.com/articles/srep08397

63. Nishijima S, Suda W, Oshima K, Kim SW, Hirose Y, Morita H, Hattori M. The gut microbiome of healthy Japanese and its microbial and functional uniqueness. DNA Res. 2016 Apr;23(2):125-33. doi: 10.1093/dnares/dsw002. Epub 2016 Mar 6. PMID: 26951067; PMCID: PMC4833420.

64. Yamawaki M, Kusumi M, Kowa H, Nakashima K. Changes in prevalence and incidence of Parkinson's disease in Japan during a quarter of a century. Neuroepidemiology. 2009;32(4):263-9. doi: 10.1159/000201565. Epub 2009 Feb 11. PMID: 19209006.

65. Iljazovic, A, Roy, U, Gálvez, E.J.C. et al. Perturbation of the gut microbiome by Prevotella spp. enhances host susceptibility to mucosal inflammation. Mucosal Immunol 14, 113–124 (2021). https://doi.org/10.1038/s41385-020-0296-4

66. Larsen JM. The immune response to Prevotella bacteria in chronic inflammatory disease. Immunology. 2017 Aug;151(4):363-374. doi: 10.1111/imm.12760. Epub 2017 Jun 20. PMID: 28542929; PMCID: PMC5506432.

67. Caputi V, Giron M. Microbiome-gut-brain axis and toll-like receptors in Parkinson's disease. Int J Mol Sci [Internet]. 2018 [cited 2022 Apr 15];19(6):1689. Available from: https://www.mdpi.com/1422-0067/19/6/1689/htm

68. Çamcı G, Oğuz S. Association between Parkinson's Disease and Helicobacter Pylori. J Clin Neurol. 2016 Apr;12(2):147-50. doi: 10.3988/jcn.2016.12.2.147. Epub 2016 Feb 26. PMID: 26932258; PMCID: PMC4828559.

69. Lolekha P, Sriphanom T, Vilaichone R-K. Helicobacter pylori eradication improves motor fluctuations in advanced Parkinson's disease patients: A prospective cohort study (HP-PD trial). PLoS One [Internet]. 2021;16(5):e0251042. Available from: http://dx.doi.org/10.1371/journal.pone.0251042

70. Murros KE, Huynh VA, Takala TM, Saris PEJ. Desulfovibrio Bacteria Are Associated With Parkinson's Disease. Front Cell Infect Microbiol. 2021 May 3;11:652617. doi: 10.3389/fcimb.2021.652617. PMID: 34012926; PMCID: PMC8126658.

71. Joshi N, Basak S, Kundu S, De G, Mukhopadhyay A, Chattopadhyay K. Attenuation of the early events of α-synuclein aggregation: a fluorescence correlation spectroscopy and laser scanning microscopy study in the presence of surface-coated Fe3O4 nanoparticles. Langmuir. 2015 Feb 3;31(4):1469-78. doi: 10.1021/la503749e. Epub 2015 Jan 20. PMID: 25561279.

72. Murros K, Wasiljeff J, Macías-Sánchez E, Faivre D, Soinne L, Valtonen J, Pohja M, Saari P, Pesonen LJ, Salminen JM. Magnetic Nanoparticles in Human Cervical Skin. Front Med (Lausanne). 2019 Jun 4;6:123. doi: 10.3389/fmed.2019.00123. PMID: 31245375; PMCID: PMC6563768.

73. Nie K, Ma K, Luo W, Shen Z, Yang Z, Xiao M, et al. Roseburia intestinalis: A beneficial gut organism from the discoveries in genus and species. Front Cell Infect Microbiol [Internet]. 2021;11:757718. Available from: http://dx.doi.org/10.3389/fcimb.2021.757718

74. Riederer P, Monoranu C, Strobel S, Iordache T, Sian-Hülsmann J. Iron as the concert master in the pathogenic orchestra playing in sporadic Parkinson's disease. J Neural Transm (Vienna). 2021 Oct;128(10):1577-1598. doi: 10.1007/s00702-021-02414-z. Epub 2021 Oct 12. PMID: 34636961; PMCID: PMC8507512.

75. Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. J Cereb Blood Flow Metab [Internet]. 2015;35(5):747–50. Available from: http://dx.doi.org/10.1038/jcbfm.2015.32

76. Researchgate.net. [cited 2022 Apr 15]. Available from: https://www.researchgate.net/publication/324776315_Parkinson%27s_Disease_A_Case_Report_of_Motor_Symptoms_Resolution_Following_Antibiotic_Treatment_for_Suspected_Bacterial_Osteomyelitis

77. El Ayoubi N, Sawaya R, Sawaya R. Does levofloxacin improve parkinsonian features or is the improvement only coincidental? Clin Neuropharmacol [Internet]. 2016 [cited 2022 Apr 15];39(6):335–6. Available from: https://journals.lww.com/clinicalneuropharm/Citation/2016/11000/Does_Levofloxacin_Improve_Parkinsonian_Features_or.16.aspx

78. Baunwall SMD, Terveer EM, Dahlerup JF, Erikstrup C, Arkkila P, Vehreschild MJ, Ianiro G, Gasbarrini A, Sokol H, Kump PK, Satokari R, De Looze D, Vermeire S, Nakov R, Brezina J, Helms M, Kjeldsen J, Rode AA, Kousgaard SJ, Alric L, Trang-Poisson C, Scanzi J, Link A, Stallmach A, Kupcinskas J, Johnsen PH, Garborg K, Rodríguez ES, Serrander L, Brummer RJ, Galpérine KT, Goldenberg SD, Mullish BH, Williams HR, Iqbal TH, Ponsioen C, Kuijper EJ, Cammarota G, Keller JJ, Hvas CL. The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. Lancet Reg Health Eur. 2021 Jul 19;9:100181. doi: 10.1016/j.lanepe.2021.100181. PMID: 34693388; PMCID: PMC8513118.

79. Halaweish HF, Boatman S, Staley C. Encapsulated Fecal Microbiota Transplantation: Development, Efficacy, and Clinical Application. Front Cell Infect Microbiol. 2022 Mar 17;12:826114. doi: 10.3389/fcimb.2022.826114. PMID: 35372103; PMCID: PMC8968856.

80. Zhao Z, Ning J, Bao XQ, Shang M, Ma J, Li G, Zhang D. Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. Microbiome. 2021 Nov 17;9(1):226. doi: 10.1186/s40168-021-01107-9. PMID: 34784980; PMCID: PMC8597301.

81. Zhang T, Wang T, Chen X, Zhao Z, Chen Z. Gut microbiota relieves inflammation in the substantia nigra of chronic Parkinson's disease by protecting the function of dopamine neurons. Exp Ther Med. 2022 Jan;23(1):52. doi: 10.3892/etm.2021.10974. Epub 2021 Nov 16. PMID: 34934429; PMCID: PMC8652398.

82. Kuai XY, Yao XH, Xu LJ, Zhou YQ, Zhang LP, Liu Y, Pei SF, Zhou CL. Evaluation of fecal microbiota transplantation in Parkinson's disease patients with constipation. Microb Cell Fact. 2021 May 13;20(1):98. doi: 10.1186/s12934-021-01589-0. PMID: 33985520; PMCID: PMC8120701.

83. Xue LJ, Yang XZ, Tong Q, Shen P, Ma SJ, Wu SN, Zheng JL, Wang HG. Fecal microbiota transplantation therapy for Parkinson's disease: A preliminary study. Medicine (Baltimore). 2020 Aug 28;99(35):e22035. doi: 10.1097/MD.0000000000022035. PMID: 32871960; PMCID: PMC7458210.

84. Huang H, Xu H, Luo Q, He J, Li M, Chen H, Tang W, Nie Y, Zhou Y. Fecal microbiota transplantation to treat Parkinson's disease with constipation: A case report. Medicine (Baltimore). 2019 Jun;98(26):e16163. doi: 10.1097/MD.0000000000016163. PMID: 31261545; PMCID: PMC6616439.

85. Segal A, Zlotnik Y, Moyal-Atias K, Abuhasira R, Ifergane G. Fecal microbiota transplant as a potential treatment for Parkinson's disease - A case series. Clin Neurol Neurosurg. 2021 Aug;207:106791. doi: 10.1016/j.clineuro.2021.106791. Epub 2021 Jun 30. PMID: 34237681.

86. Feng Y, Huang Y, Wang Y, Wang P, Song H, Wang F. Antibiotics induced intestinal tight junction barrier dysfunction is associated with microbiota dysbiosis, activated NLRP3 inflammasome and autophagy. PLoS One. 2019 Jun 18;14(6):e0218384. doi: 10.1371/journal.pone.0218384. PMID: 31211803; PMCID: PMC6581431.

87. Pu Y, Chang L, Qu Y, Wang S, Zhang K, Hashimoto K. Antibiotic-induced microbiome depletion protects against MPTP-induced dopaminergic neurotoxicity in the brain. Aging (Albany NY). 2019 Sep 3;11(17):6915-6929. doi: 10.18632/aging.102221. Epub 2019 Sep 3. PMID: 31479418; PMCID: PMC6756889.

88. Gabler WL, Smith J, Tsukuda N. Comparison of doxycycline and a chemically modified tetracycline inhibition of leukocyte functions. Res Commun Chem Pathol Pharmacol. 1992 Nov;78(2):151-60. PMID: 1335592.

89. González-Lizárraga, F., Socías, S., Ávila, C. et al. Repurposing doxycycline for synucleinopathies: remodelling of α-synuclein oligomers towards non-toxic parallel beta-sheet structured species. Sci Rep 7, 41755 (2017). https://doi.org/10.1038/srep41755

90. Wang Y, Wang Q, Yu R, Zhang Q, Zhang Z, Li H, Ren C, Yang R, Niu H. Minocycline inhibition of microglial rescues nigrostriatal dopaminergic neurodegeneration caused by mutant alpha-synuclein overexpression. Aging (Albany NY). 2020 Jul 24;12(14):14232-14243. doi: 10.18632/aging.103440. Epub 2020 Jul 24. PMID: 32706757; PMCID: PMC7425448.

91. Gazerani P. Probiotics for Parkinson's Disease. Int J Mol Sci. 2019 Aug 23;20(17):4121. doi: 10.3390/ijms20174121. PMID: 31450864; PMCID: PMC6747430.

92. Cassani E, Privitera G, Pezzoli G, Pusani C, Madio C, Iorio L, Barichella M. Use of probiotics for the treatment of constipation in Parkinson's disease patients. Minerva Gastroenterol Dietol. 2011 Jun;57(2):117-21. PMID: 21587143.

93. Barichella M, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, Pinelli G, Privitera G, Cesari I, Faierman SA, Caccialanza R, Pezzoli G, Cereda E. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. Neurology. 2016 Sep 20;87(12):1274-80. doi: 10.1212/WNL.0000000000003127. Epub 2016 Aug 19. PMID: 27543643.

94. Ghyselinck J, Verstrepen L, Moens F, Van Den Abbeele P, Bruggeman A, Said J, Smith B, Barker LA, Jordan C, Leta V, Chaudhuri KR, Basit AW, Gaisford S. Influence of probiotic bacteria on gut microbiota composition and gut wall function in an in-vitro model in patients with Parkinson's disease. Int J Pharm X. 2021 Jul 2;3:100087. doi: 10.1016/j.ijpx.2021.100087. PMID: 34977556; PMCID: PMC8683682.

95. Georgescu D, Ancusa OE, Georgescu LA, Ionita I, Reisz D. Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope? Clin Interv Aging. 2016 Nov 11;11:1601-1608. doi: 10.2147/CIA.S106284. PMID: 27956826; PMCID: PMC5113937.

96. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105-8. doi: 10.1126/science.1208344. Epub 2011 Sep 1. PMID: 21885731; PMCID: PMC3368382.

97. Molsberry S, Bjornevik K, Hughes KC, Healy B, Schwarzschild M, Ascherio A. Diet pattern and prodromal features of Parkinson disease. Neurology. 2020 Oct 13;95(15):e2095-e2108. doi: 10.1212/WNL.0000000000010523. Epub 2020 Aug 19. PMID: 32817391; PMCID: PMC7713746.

98. Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A, Moscovich M, Filla L, Zanatta D, Rios Romenets S, Altman R, Chuang R, Shah B. Caffeine for treatment of Parkinson disease: a randomized controlled trial. Neurology. 2012 Aug 14;79(7):651-8. doi: 10.1212/WNL.0b013e318263570d. Epub 2012 Aug 1. Erratum in: Neurology. 2012 Oct 16;79(16):1744. PMID: 22855866; PMCID: PMC3414662.

99. Simon DK, Wu C, Tilley BC, Lohmann K, Klein C, Payami H, Wills AM, Aminoff MJ, Bainbridge J, Dewey R, Hauser RA, Schaake S, Schneider JS, Sharma S, Singer C, Tanner CM, Truong D, Wei P, Wong PS, Yang T. Caffeine, creatine, GRIN2A and Parkinson's disease progression. J Neurol Sci. 2017 Apr 15;375:355-359. doi: 10.1016/j.jns.2017.02.032. Epub 2017 Feb 17. PMID: 28320167; PMCID: PMC5386398.

100. González S, Salazar N, Ruiz-Saavedra S, Gómez-Martín M, de Los Reyes-Gavilán CG, Gueimonde M. Long-Term Coffee Consumption is Associated with Fecal Microbial Composition in Humans. Nutrients. 2020 May 1;12(5):1287. doi: 10.3390/nu12051287. PMID: 32369976; PMCID: PMC7282261.

101. Newman MB, Arendash GW, Shytle RD, Bickford PC, Tighe T, Sanberg PR. Nicotine's oxidative and antioxidant properties in CNS. Life Sci. 2002 Nov 1;71(24):2807-20. doi: 10.1016/s0024-3205(02)02135-5. PMID: 12377264.

102. Elgayar SAM, Hussein OA, Mubarak HA, Ismaiel AM, Gomaa AMS. Testing efficacy of the nicotine protection of the substantia nigra pars compacta in a rat Parkinson disease model. Ultrastructure study. Ultrastruct Pathol. 2022 Jan 2;46(1):37-53. doi: 10.1080/01913123.2021.2015499. Epub 2022 Jan 10. PMID: 35001795.

103. Ran Wang, Shiming Li, Lifeng Jin, Wei Zhang, Nan Liu, Hongjiao Wang, Zhong Wang, Pan Wei, Feng Li, Jiaqi Yu, Sheming Lu, Yong Chen, Zhengfeng Li, Chongming Wu. Four-week administration of nicotine moderately impacts blood metabolic profile and gut microbiota in a diet-dependent manner [Internet]. Sciencedirect.com. 2019 [cited 2022 Apr 19]. Available from: https://www.sciencedirect.com/science/article/pii/S0753332219301490