EXAMINING THE COMPOUNDS PRODUCED BY THE GUT MICROBIOTA, THEIR ANTI-INFLAMMATORY AND ANTIOXIDANT PROPERTIES, AND THEIR POTENTIAL THERAPEUTIC BENEFITS IN PARKINSON'S DISEASE

Syed Salman Haider[1*], Omar Salloum[2], Hina Kanwal[3], Roshna Devi[4], Ansam Adnan Abedalazeem Alhayek[5], Jamal Ahmad[6], Syed Hassaan Ali[7], Saima Zaheer[8]

ABSTRACT:
Objective: This study seeks to comprehensively examine the role of the intestinal microbiota in the progression of Parkinson's disease through a thorough literature review.
Background: Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra (pars compacta). The disease's incidence varies with age and gender, predominantly affecting men over the age of 60. Despite its prevalence, the primary cause of neuronal death in Parkinson's remains elusive, with potential contributors including mitochondrial dysfunction, α-synuclein aggregation, impaired autophagy, endoplasmic reticulum (ER) stress, deregulation of cell homeostasis, and intracellular calcium.
Microbiota's Impact on Parkinson's Disease: Evidence suggests that compounds produced by the gut mi6crobiota may possess anti-inflammatory and antioxidant properties, potentially offering therapeutic benefits in Parkinson's disease. Moreover, a correlation has been established between the gut microbiota and the production of dopamine, a crucial neurotransmitter significantly reduced in individuals with Parkinson's.
Conclusion: This structured review underscores the significance of the microbiota-gut-brain axis in the context of Parkinson's disease. Understanding the interplay between the intestinal microbiota and the pathological processes associated with Parkinson's may open avenues for novel therapeutic interventions targeting the gut to mitigate the progression of this neurodegenerative disorder..

KEYWORDS: Alpha-Synuclein; Brain-Gut Axis; Gastrointestinal; Intestinal Microbiota, Parkinson's.

[1*]Medical officer, University of Health and Sciences Lahore, Mohtarma Benazir Bhutto Shaheed Medical College Mirpur, Pakistan, Email: syedsalaman512@gmail.com
[2]Department of Medicine, Palestine Polytechnic University, Hebron, West Bank, Palestine, Email: omar.h.h.maree@gmail.com
https://orcid.org/0000-0002-0626-1928,
[3]House officer, Ayub Teaching Hospital, Graduate Ayub Teaching Hospital, Abbottabad, Pakistan, Email: kanwalhina606@gmail.com
[4]Doctor (PG resident) Peoples University of Medical and Health Sciences, Pediatrics, Pakistan, Email: Princessroshni400@gmail.com
[5]Medical Student, Medical Department, Studies at Al Balqaa Applied University, Jordan,
Email: ansamalhayek@gmail.com
[6]Medical Student, Medical Department, Palestine Polytechnic University, Hebron, West Bank, Palestine, Email: jamal.f.ahmad21@gmail.com
[7]Department of Microbiology, Zhejiang University School of Medicine, Karachi, Pakistan,
Email: Syd.HassaanBuisness@gmail.com
[8]Lecturer, Department of Chemistry, The University of Lahore, Sargodha Campus, Sargodha, Pakistan, Email: saima.zaheer@chem.uol.edu.pk

***Corresponding author:** Syed Salman Haider
Medical officer, University of Health and Sciences Lahore, Mohtarma Benazir Bhutto Shaheed Medical College Mirpur, Pakistan, Email: syedsalaman512@gmail.com

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INTRODUCTION:

The incidence rate of Parkinson's disease (PD) varies between 10 and 50 per 100,000 people for incidence and between 100 and 300 per 100,000 inhabitants for prevalence. The incidence and prevalence of Parkinson's disease increase with age, being more common after age 60 and in men. Geographic differences in the frequency of Parkinson's disease are difficult to interpret: prevalence and incidence are slightly lower in Asia than in Western countries, although it is unclear whether this is due to environmental or methodological factors (Markidi, Elford, Berkers, Kraneveld, & Perez-Pardo, 2024)(J. Liu et al., 2024).

These degenerative processes can have many causes, including genetic mutations and environmental toxins. Their origin could be caused by mitochondrial dysfunction, α-synuclein aggregation, impaired autophagy, endoplasmic reticulum (ER) stress, or deregulation of intracellular calcium homeostasis (Wiefels et al., 2024).

The intestinal microbiota is an integral part of the human organism. Some chronic non-communicable diseases are associated with the loss of diversity of the intestinal microbiota and the loss of the ancestral microbial environment (P. Wang et al., 2024).

The interaction between the gut microbiota and the central nervous system is known as the MIC axis. This axis is a complex bidirectional communication network involving biochemical, hormonal, and immunological signals between the gut and the brain. The gut microbiota can produce and release metabolites that influence cognitive function and behaviour and can modulate immune system activity and inflammation in the gut, which may have indirect effects on brain function (Nohesara, Abdolmaleky, Thiagalingam, & Zhou, 2024).

Intestinal dysbiosis, an alteration in the composition and function of the intestinal microbiota, has been found in people suffering from Parkinson's disease. Furthermore, it has been shown that some compounds produced by the intestinal microbiota can have anti-inflammatory and anti-inflammatory properties (Koyanagi, Kassai, & Yoneyama, 2024).

Antioxidants could be helpful in this disease. A relationship has also been found between the gut microbiota and the production of dopamine, a critical neurotransmitter that is decreased in people with Parkinson's. The present study aims to analyze the role of the gut microbiota in the progression of Parkinson's disease, led through a bibliographic review, to provide a new therapeutic and preventive approach to the disease (Nayak et al., 2024).

METHODOLOGY:

This research was based on a bibliographic review of the Pubmed, Scopus, Redalyc, Elsevier and Uptodate databases of articles published in the last 5 years. To search for articles, the keywords were used: Parkinson's, intestinal microbiota, incidence, prevalence and clinical characteristics (Prajjwal et al., 2024; P. Wang et al., 2024)

DEVELOPMENT AND DISCUSSION:

The intestinal microbiota: definition, functions and its relationships with human health. The microbiota is a functional part of the human organism. This contributes to both the microbiome and physiological functions: nutrition, immunity and somatic development(Markidi et al., 2024)

The presence of brain plaques and extracellular deposits of beta-amyloid characterizes Alzheimer's disease. The neural network that controls gastrointestinal functions consists of several systems, including intrinsic and extrinsic nerves, and is organized into four hierarchical levels (Bhat, Chandramohan, & Sabat, 2024; Ebedes & Borlongan, 2024).

Intestinal Dysbiosis In Parkinson's Disease: Alterations In The Composition Of The Microbiota And Its Relationship With The Pathogenesis Of The Disease:

The microbiota plays a fundamental role in homeostasis at the nervous system level through bidirectional communication of the MIC axis. Intestinal dysbiosis can trigger a series of inflammatory pathways characterized by intestinal permeability, metabolites and toxins linked to neurodegenerative diseases, and these diseases a bacterial origin can be attributed (Inchingolo et al., 2024; Jiang et al., 2024).

The presence of the protein α-synuclein is essential in developing Parkinson's disease. According to Braak's hypothesis, this protein originates in the intestine and spreads via the vagus nerve to the central nervous system. Similarly, abnormal expression of α-synuclein has also been found in inflammatory bowel disease (Singh et al., 2024).

A link has also been established between Parkinson's disease and bacterial overgrowth in the small intestine, which can be measured with a breath test. A higher incidence of this overgrowth has been observed in patients with Parkinson's

disease (Han et al., 2024; Hu et al., 2024; Ji, Chen, Zhang, Zhang, & Chen, 2024; X. Liu et al., 2024). Based on a neurotoxicological study, a rotenone-induced neurotoxin model was evaluated for Parkinson's disease, thanks to which it is possible to observe gastrointestinal dysfunction, reproducing it in mice clinically(Lee et al., 2024).

Mechanisms Of Action Of The Intestinal Microbiota In Parkinson's Disease: Inflammation, Microbial Metabolites And Other Possible Pathways Of Interaction:

The alteration of the axis can be related to the appearance of gastrointestinal symptoms, which usually precede the motor ones, but also to the development of the disease itself. This suggests that the pathology extends from the gut to the brain (Murray, Ghomi, Nemani, & O'Connor, 2024).

The protein α-synuclein accumulates in brain neurons and the enteric nervous system (ENS). It has been proposed that the gastrointestinal tract may cause the spread of Parkinson's disease, as α-synuclein inclusions may first appear in the ENS and then be transmitted to the central nervous system via the glossopharyngeal or vagal (Lerner, Benzvi, & Vojdani, 2024).

The microbiota of the human body can influence the onset and progression of Parkinson's disease by influencing the protein α-synuclein. A study by Cirstea found that patients with Parkinson's disease had increased proteolysis activity in the gut microbiota, which allowed them to obtain energy differently than healthy individuals who use carbohydrate fermentation (Ma, Wen, & Xu, 2024)(Bao et al., 2024).

According to Cirstea's study, increased proteolysis in the intestinal microbiota of patients with Parkinson's disease is associated with the production of p-cresol in plasma, a metabolite related to the degradation of mucins by the Akkermansia bacterium, suggesting that patients with the disease Parkinson's patients have increased intestinal permeability (Y. Yang et al., 2024).

There is a possibility that the Helicobacter bacterium was raised. Pylori (H. pylori) may impact the clinical development of Parkinson's disease by activating microglia through the spread of proinflammatory cytokines and leukocytes across the blood-brain barrier. It has also been suggested that H. pylori could produce neurotoxicity substances (Hongyu Zhang, Jiang, Li, & Wang, 2024).

Although the microbiota can influence microglia development, other processes that have not yet been identified may influence Parkinson's disease. Among these is the possible influence of the microbiota on autophagy, a cellular recycling process genetically linked to Parkinson's risk and which, if altered, can lead to insufficient elimination of synuclein. Intestinal bacteria can clear these inclusions, which modulate proteasome function (Mills et al., 2024).

The ability of the microbiota to influence critical cellular functions, such as autophagy and the proteasome, suggests that they could influence not only synucleinopathies but also other amyloid disorders, as Figure 1 summarizes this section (Zou et al., 2024)(Wang, Zeng, Wujin, Ullah, & Su, 2024)(Huang et al., 2024; Seo & Holtzman, 2024). However, it is essential to note that most studies that have examined the relationship between gut microbiota and Parkinson's disease are observational, meaning they cannot demonstrate a causal relationship. Furthermore, many of these studies are small and have methodological limitations that may influence the results. Therefore, although preliminary studies suggest a possible relationship between gut microbiota and Parkinson's disease, further research is needed to confirm these findings. Ultimately, this could lead to new therapeutic approaches (Huang et al., 2024).

Biomarkers Predicting Parkinson's Disease:

Although no definitive biomarker exists for Parkinson's disease, some have been described (Mayer, Horn, Mayer, & Randolph, 2024).

- α-synuclein: This protein is found in large quantities in dopaminergic neurons, and its accumulation in the brain is associated with Parkinson's disease. Several methods are being explored to measure α-synuclein levels in the brain and cerebrospinal fluid for use as a biomarker.
- Tau protein is present in nerve cells, and its accumulation is associated with Parkinson's disease and other neurodegenerative diseases. Its relevance is not fully known, but several methods are being explored to measure tau protein levels in cerebrospinal fluid for use as a biomarker.
- Inflammatory markers: it has been demonstrated that chronic inflammation is involved in the pathogenesis of Parkinson's disease. Some inflammatory markers are Creative proteins and cytosines.

- Brain imaging: magnetic resonance imaging (MRI) and positron emission tomography (PET) detect decreased dopaminergic activity in some brain regions.
- Genetic markers: try to investigate mutations in the LRRK2 and GBA genes.

Role Of Viral Infections And Neurotoxins:.
Future Perspectives: The Intestinal Microbiota As A Therapeutic Target In Parkinson's Disease:

Some studies have shown that brain function can be regulated by consuming probiotics in the diet. Daily consumption of fermented foods, such as yoghurt, can positively affect how the brain responds to environmental stress (Naito, 2024)(Huan Zhang, Mao, & Zhang, 2024; Y.-W. Zhang et al., 2024; Zhou et al., 2024)(Jezkova et al., 2024). Eat regularly products containing S.thermophilus, B. animalis, L. bulgaricus, and Lactococcus lactis have been shown to enhance responses of brain regions responsible for controlling sensations and emotions. In patients with Parkinson's, consuming milk fermented with Lactobacillus casei improved stool consistency and intestinal function. Still, it did not improve the response of brain regions responsible for controlling sensations and emotions. Show improvement in neurological function (Busch et al., 2024).
Prevotella is a commensal microorganism that lives in the colon and is part of one of the enterotypes of the intestinal microbiome. This bacterium can also compose a variety of plant polysaccharides and glycoproteins in the intestinal mucosa and interact with the immune system. This enterotype has been associated with high levels of short-chain fatty acids, which have a health-promoting neuroactive function and a high capacity to produce thiamine and folate. Proposed that the decrease in Prevotella may be related to the decrease in these nutrients in patients with Parkinson's disease and that supplementation with these nutrients and short-chain fatty acids may have therapeutic effects (J. Yang et al., 2024).
Although evidence suggests a connection between the microbiota and the central nervous system, its role in the onset of some of the most common neurological diseases has not yet been determined. The answer to many of these questions will be obtained through clinical studies that will analyze this aspect (He et al., 2024).

DISCUSSION:
The human body is equipped with a microbiota, which performs different functions at various levels: metabolic, focused on diet, structural, protective and neurological, involved in the gut-brain axis. The relationship between the gut microbiota and the gut-brain axis has three mechanisms: increased α-synuclein and decreased short-chain fatty acids due to decreased bacteria and decreased Akkermansia, which increases intestinal permeability, exposing the enteric plexus to toxins (Ye et al., 2024).
Through retrograde flow, α-synuclein reaches the central nervous system via the vagus nerve, where it causes its accumulation and subsequent neuronal damage. Another molecule involved in beta-amyloid accumulation can be used as a biomarker (Lamichhane et al., 2024).

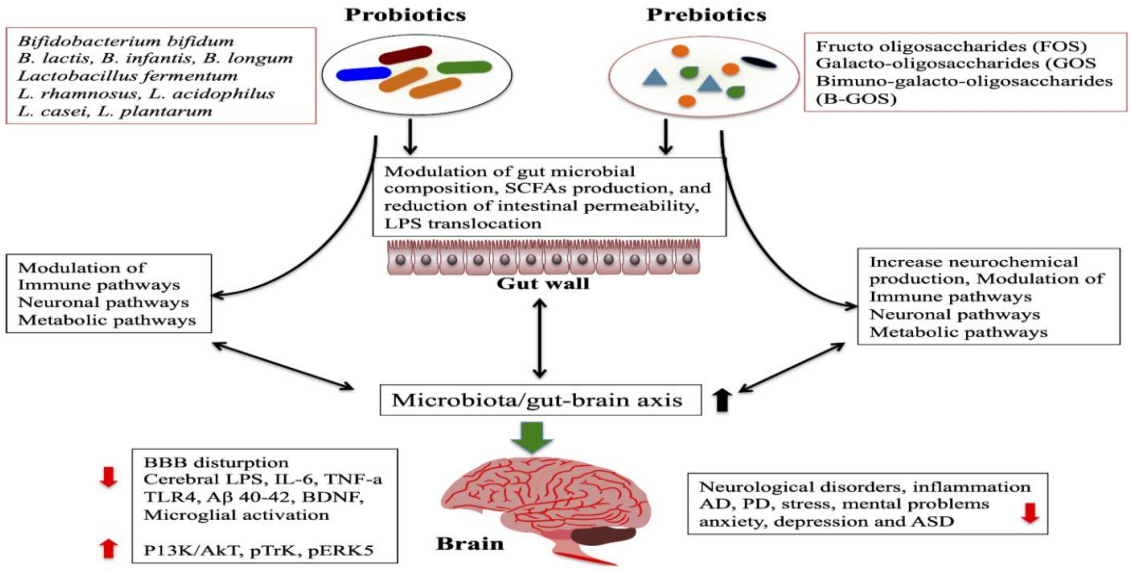

Figure 1. Mechanisms of action of the gut microbiota in Parkinson's disease: inflammation, microbial metabolites and other possible pathways of interaction

Shahnawaz suggests Parkinson's disease is a brain condition that causes the loss of dopamine-producing nerve cells in the black matter. Dopamine is an important neurotransmitter that helps control body movements, and a deficiency in its production can trigger symptoms of Parkinson's disease. Although a possible relationship between specific microorganisms and Parkinson's disease has been identified, this connection is still a preliminary hypothesis that requires further research. Additionally, although there is no cure for Parkinson's disease, treatments are available to relieve symptoms and improve patient's quality of life (Hernandez-Baixauli et al., 2024).

Chesselet and collaborators suggest that the gut microbiota may play an essential role in the motor dysfunction observed in α-synuclein over-expressing mice. The study shows that mice with complex microbiota have significant deficits in fine and gross motor function and intestinal function. Motility, while Germ-free mice show improved performance in motor function tests. These findings are significant as they could open new therapeutic avenues for the treatment of Parkinson's disease, focusing on the modulation of For his part, Xin Fang hypothesizes a possible relationship between the decrease in intestinal bacteria Akkermansia muciniphila and Parkinson's disease (PD), suggested because studies in animal models have shown that supplementation with A. muciniphila can reduce inflammation, protect from neurodegeneration and improve motor function (Tian et al., 2024).

Furthermore, it has been noted that patients with Parkinson's disease have lower levels of A.muciniphila than healthy individuals, and it has also been found that supplementing with prebiotics, which increases the population of A.muciniphila in the gut, can improve symptoms of Parkinson's disease in patients (Zhao et al., 2024).

On the other hand, Gómez-Chavarín proposes that exposure of pregnant rats and their offspring to different doses of rotenone (ROT) for 51 days has significant effects on the number of IR-TH neurons in the substantia nigra and on the motor coordination of the offspring. The number of IR-TH neurons decreased in pregnant rats treated with ROT, and the effects were transmitted to offspring, both in utero and during breastfeeding, being more pronounced in directly exposed offspring (F. Zhang et al., 2024).

Furthermore, offspring exposed to 1 mg/kg of ROT presented more difficulties performing the motor coordination test. The findings suggest that exposure to ROT during pregnancy and breastfeeding may have long-lasting effects on offspring's neural and motor development. However, it is essential to note that this study is conducted on rats, and further research is needed to understand the possible effects of ROT exposure on humans (Ratan et al., 2024).

CONCLUSION:

We can see that gut dysbiosis can have a significant impact on Parkinson's disease. Indeed, a connection has been established between Parkinson's disease and the overgrowth of bacteria in the small intestine, decreased bacteria-producing short-chain fatty acids and increased Akkermansia. Decreased serum LPS-binding protein in Parkinson's disease indicates increased intestinal permeability, possibly exposing the intestinal plexoneural plexus to toxins.

Furthermore, the possibility has been raised that some intestinal bacteria, such as H.pylori, may impact the development of the disease through the activation of microglia and the production of neurotoxic substances. The microbiota's ability to influence critical cellular processes suggests that it could influence not only Parkinson's disease but also other amyloid-related disorders.

Regarding future perspectives, it has been shown that the consumption of probiotics and the presence of certain bacteria in the intestinal microbiome can have positive effects on brain function and the prevention of neurological diseases, but further research is still needed to understand better the connection between the microbiota and the central nervous system and its impact on human health.

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