

The Gut-Brain Axis in Neurodegenerative Disorders: Assessing the Therapeutic Potential of Probiotics and Faecal Microbiota Transplantation

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ABSTRACT

The gut-brain axis (GBA) is a complicated bi-directional communication system connecting the gastrointestinal system and the central nervous system. There is a growing body of experimental and clinical data that gut microbial composition aberrancies are significant contributory factors to the pathogenesis and progression of neurodegenerative conditions such as Alzheimer and Parkinson diseases. This review aims to summarize existing knowledge regarding the role of the gut-brain axis in neurodegeneration and critically assess microbiota-based treatment intervention, i.e. probiotics and faecal microbiota transplantation (FMT). PubMed, Scopus, and Web of Science were used to conduct a thorough literature analysis on preclinical and clinical studies that were published since 2010. Both animal studies as well as human studies were incorporated based on specified qualifying criteria. There is clear evidence that gut microbial dysbiosis also leads to dementia through the following pathways: neuroinflammation, defective protein homeostasis, and compromised blood-brain barrier integrity. Fecal microbial transplantation provides an opportunity to provide greater yet less regulated means by which gut microbial ecosystems can be modified, potentially influencing the development of disease, although probiotic therapies have shown small effects on the cognitive and metabolic outcome. Although with good results, a clinical validation through large-scale, well-conducted clinical studies is required to be shown as effective in therapy and long-term safety guaranteed. In general, our findings indicate that targeting the gut microbiota is a viable method of treatment of neurodegenerative diseases.

Keywords: Gut-Brain Axis, Neurodegeneration, Alzheimer Disease, Parkinson Disease, Probiotics, Fecal Microbiota Transplantation, Dysbiosis, Neuroinflammation, Blood-Brain Barrier

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INTRODUCTION

Neurodegenerative diseases (NDs), such as Alzheimer disease (AD) and Parkinson disease (PD), are a rapidly increasing health burden in the world, and they are expected to surpass infectious and cardiovascular diseases as the commonest ones in the upcoming decades. The characteristics of these disorders are the progressive and irreversible deterioration of neuronal structure and functioning leading to the progressive

movement disability, cognitive impairment and severe deterioration of quality-of-life¹. Simultaneously, the global prevalence of Parkinson's disease has increased more than four fold during the last generation, which demonstrates the urgency of effective disease-modifying treatment options³⁻⁴.

The causes of neurodegenerative disorders are complex and are accompanied by a conjunction of genetic predisposition, environmental exposures, and

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biochemical alterations (accompanied with aging). Although the two have disease-specific differences, comparable pathogenic processes including protein aggregation aberrancies, mitochondrial impairment, oxidative stress, and chronic neuroinflammatory integrate to elicit progressive neuronal demise. Traditional treatment forms still are merely symptomatic with few chances of preventing or reversing the development of diseases. This limitation of treatment has led to the growing exploration in the peripheral biological systems which have the potential to affect the disorders that are central to the nervous system⁵⁻⁸. The gutintestinal tract and the brain interact in a complex bidirectional communication system called the gutintestinal gutbrain axis, which consists of a combination of neurological, endocrine, immunological and metabolic communication systems (between the two) (Gurkan et al. 2015). The vagus nerve, hypothalamic-pituitary-adrenal axis, immunological signaling molecules, and microbial-derived metabolites play a role in communication in this axis. The gut microbiome is central to the operation of the gut 0-axis consisting of a diverse ecosystem with billions of bacteria with direct Trophic effects, host immunity, host metabolism, and host neurochemical balance⁹.

Gut microorganisms are also involved in homeostasis of the brain by producing neuroactive compounds that include serotonin, gamma-aminobutyric acid and short-chain fatty acids, which jointly control brain development, response to stress, and cognition functions¹⁰. The dysbiosis of this natural microbial milieu, which has been increasingly reported to disrupt the etiology of myriad neurological diseases¹¹⁻¹³. Given the poor disease-modifying effectiveness of existing pharmacotherapies for AD and PD¹⁴⁻¹⁵, addressing the gut flora suggests a viable alternative option.

In this regard, the paper comprehensively examines the molecular connections between neurodegenerative disease development and gut microbial dysbiosis, specifically, probiotics and fecal microbiota transplantation as an emerging microbiota-based treatment option.

MATERIALS AND METHODS

Literature Search Strategy: A systematic literature search was done to identify articles that examined the gut-brain axis, changes in gut microbiota, neurodegenerative diseases, probiotics, and fecal

microbiota transplantation. The search in PubMed, Scopus, and Web of Science Core Collection was done electronically. The articles that were reviewed were published in the period of January 2010 and May 2024 in order to ensure that only recent and relevant developments were included.

Search Terms

It was used in both, free-text keywords and Medical Subject Headings (MeSH). The search strategy was enhanced with the help of the use of the operators. The primary search term was the following: AND ("neurodegenerative disease" OR "Alzheimer's disease" OR "Parkinson's disease" OR "dementia" AND) AND ("probiotics" OR faecal microbiota transplantation" OR microbial therapy).

To find further research, the reference lists of pertinent reviews were manually filtered.

Inclusion and Exclusion Criteria

Inclusion criteria:

1. Only original clinical or experiment research studies can be included.
2. Systemic analyses and reviews.
3. Articles in English language.
4. Studies on the use of gut microbiota in AD or PD.
5. The evaluation of FMT as a therapeutic treatment, synbiotics, probiotics or prebiotics as a therapeutic treatment.

Exclusion criteria:

1. Non-English-language works
2. Book chapters, conference abstracts, editorials, or commentary
3. Research on neurodegenerative conditions other than AD or PD that lacks comparative significance
4. Manuscripts that are unpublished or incomplete

Data Extraction and Analysis

Relevancy was initially evaluated using titles and abstracts and then those that were found to be relevant were examined in their entirety. The information that has been extracted is the research design, demographics, interventions, outcomes, and key findings. A meta-analysis could not be conducted because research designs were not homogenous. Rather, synthesis of results was done in terms of themes. **In Figure 1 (PRISMA flow diagram)**, the proposed distribution of the study selection process is illustrated.

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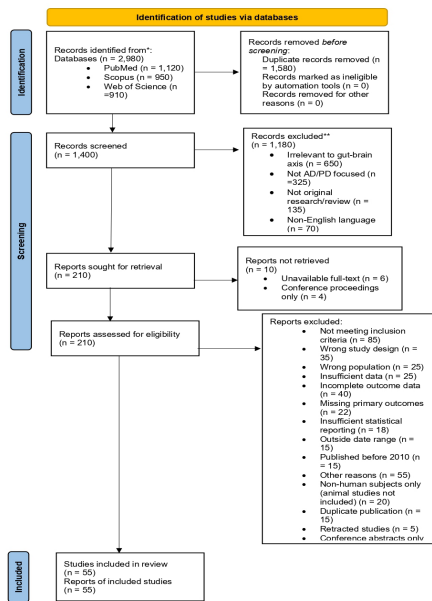


Figure 1: PRISMA flow diagram illustrating the systematic literature search and study selection process.

RESULTS:

Multimodal Communication Pathways of the Gut-Brain Axis

The gut-brain axis has been found to work through numerous interconnected signaling pathways that allow two-way communication at all times between the gastrointestinal and central nervous systems. According to the examined studies, four major pathways have been always involved; namely, neurological, neuroendocrine, immunological and metabolic pathways (Figure 2).

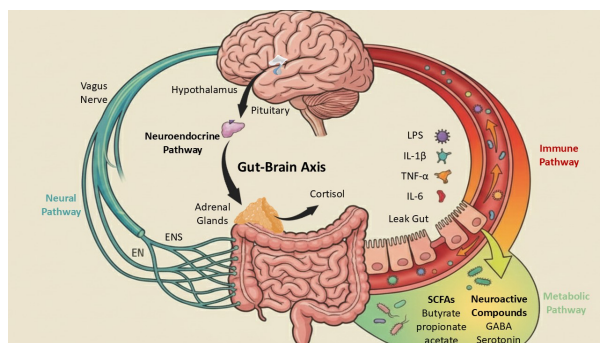


Figure 2: Multimodal Communication within the Gut-Brain Axis

The cerebral pathway, principally mediated by the vagus nerve, represents the most direct route of gut-

brain communication. The vagus nerve conveys sensory information from the enteric nervous system to the brainstem and higher cerebral areas. Experimental data from animal models reveals that vagal signaling is required for microbiota-driven neurophysiological effects. Notably, vagotomy abolishes the neuroprotective and behavioral advantages of some probiotic strains and greatly lowers disease-modifying effects in Parkinson's disease models, underlining the crucial importance of vagal integrity in microbiota-mediated brain regulation¹⁶.

The neuroendocrine pathway involves the hypothalamic-pituitary-adrenal (HPA) axis which is an important regulator of stress responses. The gut microbiota regulates the functioning of this axis, which is done through the effects on the secretion of cortisol. It has been established that dysbiosis creates persistently activated HPA axis response, resulting in increased cortisol levels, which can exacerbate neuroinflammation, become synaptic plasticity impaired, and cause neurodegenerative processes to extend faster¹⁷. Such effects are more eminent in the case of chronic stress conditions whereby neuronal exposure is caused by dysfunctional HPA signaling.

The immunologic pathway shows that there is an underlying mechanistic relationship between intestinal dysbiosis and neurodegeneration. Changes in the composition of gut microbes generally enhance intestinal permeability, which is generally referred to as leak gut. This allows the entry of bacterial components especially lipopolysaccharides (LPS) into the blood. Even though LPS does not traverse an intact blood brain barrier (BBB), it attaches to Toll-like receptor 4 (TLR4) on endothelial cells of the brain. This association encourages the induction of caspase-4/GSDMD-mediated pyroptosis culminating in the degradation of BBB. The compromised barrier allows circulating cytokine, such as interleukin-1 β , tumor necrosis factor- α and interleukin-6 to infiltrate into the brain parenchyma, where they stimulate microglia and ensure continued neuroinflammation that is harmful to neuronal survival¹⁸.

The metabolic route consists of compounds of microbial origin affecting both local and systemic impacts. Short-chain fatty acids (SCFAs) which include acetate,

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propionate, and butyrates are produced in the process of fermenting food fibers by commensal bacteria. Such metabolites have the ability to penetrate the BBB, and have been shown to have anti-inflammatory, neuroprotective and epigenetic control properties. Moreover, the intestinal microbes produce neuroactive molecules such as gamma-aminobutyric acid, serotonin, and dopamine. Even though these neurotransmitters do not access the brain per se, microbial control of tryptophan metabolism and vagal signaling indirectly affects central neurotransmission and synaptic activity^{19–20}.

Comparative Dysbiosis Profiles in Alzheimer’s Disease (AD) and Parkinson’s Disease (PD)

There has been extensive evidence indicating that individuals with either Alzheimer or Parkinson disease possess distinct abnormalities in the composition of gut microbes in comparison with healthy age-matched people. Albeit, exact microbial fingerprints differ between studies due to the variation in location, nutrition and sequencing techniques, some of the trends have now become consistent²¹.

A continuous decrease in total microbial diversity is a characteristic finding in the disease of Alzheimer. Several reports indicate a significant reduction in the beneficial SCFA producing bacteria such as *Faecalibacterium prausnitzii*, *Eubacterium rectale* and the *Lachnospiraceae* family of bacteria². These bacteria play a very essential role in gut barrier preservation and the decrease of inflammatory cues. At the same time, a greater proliferation of pro-inflammatory taxa, including *Escherichia/Shigella* and even some *Bacteroidetes* species, has also been noted, which can trigger a systemic inflammation and exacerbate amyloid pathology²³.

In Parkinson’s illness, dysbiosis is marked by a large drop in *Prevotellaceae*, a bacterial group implicated in mucin formation and immunological regulation. Reduced numbers of these bacteria may damage the intestinal mucus layer and affect host–microbe interactions. In contrast, greater abundance of *Enterobacteriaceae* has been frequently observed and correlates positively with motor symptom severity, notably postural instability and gait disturbances^{24–25}. Elevated levels of *Akkermansia muciniphila*, a mucin-degrading bacteria, have also been identified and may contribute to increased intestinal permeability and

heightened inflammatory signaling^{26–27}. A comparative overview of these microbial alterations and their proposed functional implications is presented in **Table 1**.

Table 1. Alterations in Gut Microbial Taxa Reported in Alzheimer’s and Parkinson’s Diseases

Taxonomic Categorisation	Change in AD	Change in PD	Recommended Functional Impact Sources	References
<i>Firmicutes/Bacteroidetes</i> proportion	Decreased / Variable findings	Decreased	General indicator of gut microbial dysbiosis	28,29
<i>Faecalibacterium prausnitzii</i>	Decreased	Decreased (Commonly observed)	Reduced production of anti-inflammatory SCFA (butyrate)	30,31
<i>Eubacterium rectale</i>	Decreased	--	Decline in SCFA generation	30
<i>Lachnospiraceae</i>	Decreased	--	Reduced SCFA production	30
<i>Prevotellaceae</i>	--	Decreased	Impaired mucin integrity and altered immune modulation	32
<i>Enterobacteriaceae</i>	Increased	Increased	Elevated inflammatory response and lipopolysaccharide (LPS) production	28,32

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<i>Escherichia/higella</i>	Increased	--	Increased inflammation and LPS biosynthesis	28
<i>Akkermansia muciniphila</i>	--	Increased	Greater mucin degradation; potential association with intestinal permeability	32
<i>Bifidobacterium</i>	Decreased (Frequently reported)	Variable findings	Reduction in beneficial commensal bacteria	28
<i>Bacteroides</i>	Increased (Frequently reported)	Variable findings	Context-dependent pro- or anti-inflammatory activity	28

the gut can lead to incorrect folding of α -synuclein in the enteric nervous system. Misfolded α -synuclein can thereafter spread through the vagus nerve to the brain, which facilitates the disease progression of the brain, which is facilitated by prions-like spread (Muller, 2012, p. 306)³⁴.

Modified microbial metabolites also interfere with redox balance and mitochondrial function. Reactive oxygen species levels are raised by decreased SCFA availability and enhanced inflammatory signalling, which causes oxidative stress and gradual neuronal damage. Intestinal and blood-brain barriers are further compromised by dysbiosis, which increases systemic inflammation and speeds up neurodegenerative cascades.⁶. A summary of these interrelated processes may be seen in **Figure 3**.

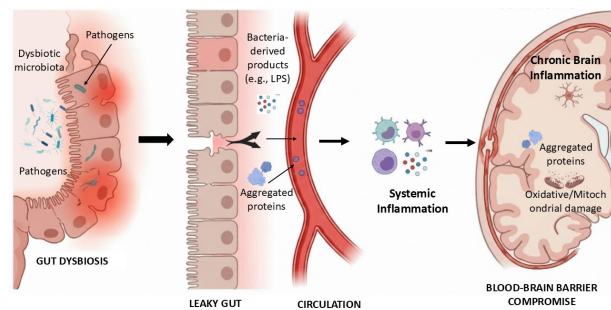


Figure 3: Mechanisms linking gut dysbiosis and neurodegeneration

Mechanisms connecting neurodegeneration and dysbiosis

Dysbiosis of the gut microbiota advances neurodegenerative diseases via a number of interconnected pathways. One of the main pathways is chronic systemic inflammation. Prolonged immunological activation is brought on by increased circulation of pathogen-associated molecular patterns, especially LPS. Endothelial pyroptosis disrupts the blood-brain barrier, allowing inflammatory mediators to enter the brain and induce neuronal injury and chronic microglial activation³³.

Dysbiosis is also associated with pathological aggregations of proteins. Inflammatory signalling supports tau hyperphosphorylation as well as amyloid-2 accumulation in Alzheimer disease and augments kinase activity. Parkinson disease Inflammatory reactions of

Probiotics: preclinical and clinical evidence

Preclinical research employing rodent models of Alzheimer's and Parkinson's illnesses frequently reveal positive benefits of probiotic treatment. In Alzheimer's disease models, multi-strain probiotic formulations comprising *Lactobacillus* and *Bifidobacterium* species enhance learning and memory performance, decrease amyloid plaque burden, and lower neuroinflammatory markers³⁷. In Parkinsonian models, probiotics relieve motor impairment, retain nigrostriatal dopaminergic neurons, and diminish α -synuclein accumulation, typically in combination with enhanced gut barrier integrity³⁸.

Clinical tests to clinicians in humans present conciliating albeit, disparate data. In controlled randomized studies on Alzheimer disease patients, there is an increase in cognitive scores such as the Mini-Mental State Examination, together with a positive

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effect on metabolic and inflammatory markers like reducing C-reactive protein and increasing antioxidant capacity³⁹⁻⁴⁰. Probiotic intervention in Parkinson disease has had insignificant effects on motor symptoms, but has always been beneficial to the gastrointestinal in addition to some non-motor symptoms. Table 2 demonstrates the key characteristics of the clinical trial and its findings:

Table 2. Selected Human Clinical Studies Evaluating Probiotics in Neurodegenerative Disorders

Source	Patient Group	Study Type & Length	Treatment	Primary Results	References
Akbari et al. (2016)	60 patients diagnosed with AD	Randomized control trial, 12 weeks	Four-strain probiotic formulation: <i>Lactobacillus acidophilus</i> , <i>L. casei</i> , <i>Bifidobacterium bifidum</i> , <i>L. fermentum</i> (20 billion CFU per day)	Significant improvement in MMSE scores was reported. Reduction in malondialdehyde (MDA) levels was noted, while increases in glutathione (GSH) and changes in CRP were not statistically significant.	41
Tamajai et al.	60 patients with	Randomized control led	Selenium-fortified probiotic	Improvement in MMSE scores	42
(2019)	AD trial, 12 weeks	containing <i>L. acidophilus</i> , <i>B. lactis</i> , and <i>Saccharomyces cerevisiae</i>	and other cognitive measures were observed. Decreases in insulin resistance and inflammatory biomarkers were also recorded.		
Agahiet al. (2018)	72 patients with PD	Randomized control trial, 12 weeks	Four-strain probiotic mixture: <i>L. acidophilus</i> , <i>L. reuteri</i> , <i>B. bifidum</i> , <i>L. fermentum</i> (20 billion CFU daily)	No significant differences were found in UPDRS scores. However, patients experienced improved bowel movement frequency.	43
Ibrahim et al. (2023)	45 patients with PD	Randomized control trial, 3 months	Three-strain probiotic preparation: <i>Streptococcus thermophilus</i> , <i>L. delbrueckii</i> , <i>B. lactis</i>	Mild improvements in non-motor symptoms such as constipation and overall quality of life were noted. Motor	44

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Fecal microbiota transplantation: evidence in human studies and not just a clever therapy in animals

The concept of fecal microbiota transplantation offers the entire approach to replenish the gut microbial ecology. According to animal studies, transplantation of microbiota of healthy donors into animal models of Alzheimer disease enhances the cognition of animals, reduces the amount of amyloid deposition, and lowers neuroinflammation⁴⁵. On the other hand, unhealthy-donor transplantation enhances cognitive and neuropathology, implying a causal role of the microbiome in the said case⁴⁶.

FMT of healthy donors improves motor movements and prevents dopaminergic neurons, whereas microbiota of Parkinson's disease-afflicted individuals worsen neuroinflammation and alpha-synuclein pathogenesis⁴⁷. There is no definitive human research so far, most of the trials and case reports are short and provide variable results. A few studies indicate positive results with regard to constipation improvement and quality of life, whereas others report a small effect or temporary increase in symptoms worsening⁴⁸⁻⁴⁹. These differences make it necessary to use standardized methods, finding the best donor selection, and the safety of the long run

DISCUSSION

This comprehensive review of the literature demonstrates that the interference of the gut microbiota significantly contributes to the development of the Parkinson and Alzheimer diseases. The therapeutic efficiency of microbiome-specific treatment including faecal microbiota transfer (FMT) and probiotic supplementation is also discussed. The findings accentuate the gut-brain axis as a significant mediator of cognitive impairment both as a direct contributor to significant pathogenic processes and as a secondary effect. Regular trends in the microbial composition of individuals with Parkinson disease (PD) and Alzheimer disease (AD) indicate an increase in pro-inflammatory microbes and a fall in anti-inflammatory microbes that

produce short-chain fatty acids, although these differences are found to vary across researches. These imbalances appear to drive the progression of the disease through the effects of multifaceted interrelated mechanisms, which include abnormal protein aggregation, chronic neuroinflammation, and dysfunctional barrier function as suggested by a mechanistic model (Fig. 3). Although in some of the studies specific dysbiosis patterns are observed in AD, they tend to be weak and not repeatable. On the contrary, the pathology of the microbiome is more evident in PD, so Alzheimer's disease is to be viewed with caution.

A therapeutic justification of the use of probiotics and FMT is the capacity to restore microbial homeostasis and eliminate the adverse biological mechanisms. It is also important to note that probiotics (commonly strains of *Lactobacillus* and *Bifidobacterium*) generally have a series of beneficial effects: they produce neuroactive molecules such as short-chain fatty acids (SCFAs), GABA, serotonin; they enhance the integrity of the intestinal barrier to minimize exposure to systemic toxins; they regulate immune responses to anti-inflammatory effects; and they provide antioxidant protection against free radical damage⁵⁰. It has been demonstrated over and over again in preclinical research that such processes lead to improved cognitive or motor outcomes, decreased neuroinflammation and slower disease progression.

Instead of transplanting particular bacterial strains, FMT transfers a whole healthy microbial community, providing a more thorough approach. The conceptual distinctions are shown in **Figure 4**, where FMT seeks to restore total microbial diversity, supporting vital processes including SCFA synthesis and immune system regulation, while probiotics add specific beneficial microorganisms. While microbiota from sick donors may worsen pathology, evidence from animal studies suggests that microbiota from healthy donors might prevent or cure disease phenotypes⁵¹. These advantages are probably related to the restoration of a healthy and functioning microbial ecosystem⁵² that supports immunological, metabolic, and neuroprotective processes, which may not be entirely accomplished by isolated probiotic administration.

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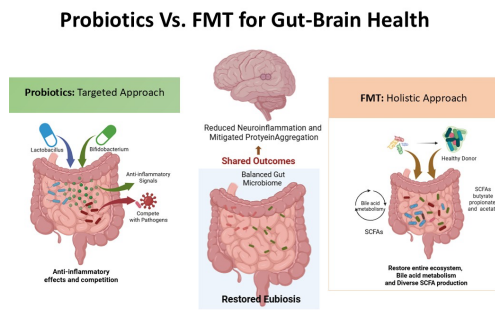


Figure 4: Comparative Framework for Microbiota-Targeted Therapies

Preclinical findings are intriguing, but there are still a number of restrictions. Lack of standardisation makes probiotic treatments difficult; results from one preparation cannot be extrapolated to another, and therapeutic benefits vary with strain⁵³. The best dosage, length of treatment, and microbiological viability during storage are still unknowns. Small, brief, and methodologically diverse, the majority of human studies often prioritise surrogate biological objectives above significant therapeutic advancements.

FMT has more difficulties. There are very little long-term safety data in neurological populations. The danger of spreading diseases persists despite stringent donor screening⁵⁴. In addition to the fact that delivery techniques like colonoscopy, nasojejunal tubes, or oral capsules may have a substantial impact on both effectiveness and patient tolerance, there are no clear standards for choosing the best donors based on microbial makeup, metabolite profiles, or functional characteristics.

Applying sophisticated biological treatments for long-term neurological disorders also raises ethical questions, especially when risk-benefit profiles are unclear. In contrast to controlled animal models, most studies find correlations rather than direct causation, making it intrinsically challenging to establish causal linkages in humans. Interpreting data is made more difficult by variations in subjects, microbiome assessment methods, and outcome measurements.

To apply these findings in clinical practice, the incomplete gaps have to be filled in future studies. There are the necessity of standardised treatments,

clearly defined patient groups, assessment of clinically significant outcomes besides mechanistic biomarkers and long-term, randomised, placebo-controlled trials. More development should be done on the use of advanced live biotherapeutics (e.g., genetically modified bacterial strains capable of synthesizing neuroprotective chemicals or anti-inflammatory cytokines, e.g., brain-derived neurotrophic factor (BDNF) or anti-inflammatory cytokines, respectively). It is also possible to discover bacterial consortia, which replicate important functions of a healthy microbiome⁵⁵.

Gut microbiota is unique to individuals so individual methods are likely to be the most effective. This could be optimised by tailoring therapies on the basis of genetic and dietary and baseline microbial composition. The method involves the microbiome profiling of individual persons, in order to identify dysbiotic patterns and administer targeted interventions to restore the body to a functional state.

CONCLUSION

The growing body of knowledge on the gut-brain axis has significantly increased our knowledge of neurodegenerative diseases. This has led to scientists who are not only focusing their interest in central nervous system alone but are now taking note of the huge contribution that the gut microbes make. Deep analysis reveals that there is a lot of evidence that microbial imbalances of the gastrointestinal tract are commonly linked to Parkinson and Alzheimer diseases that worsen the progression of the disease by causing impaired expression of proteins, oxidative stress at the cell level, impaired protective barriers, and chronic brain inflammation.

The use of therapeutic treatments that alter the interaction between the gut-brain, including microbiome transplantation, probiotic supplements, is a novel and promising strategy to change the course of these disorders. This can result in measures to reduce or even prevent these incapacitating diseases. Preliminary research in using animal models in the laboratory has suggests with a high degree of certainty that restoration of microbial balance could enhance cognitive ability and mobility in addition to reducing the changes associated with these diseases.

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However, this stage of transforming such discoveries into useful applications is still in its infancy. Although some clinical trials depicted some positive results, particularly regarding the positive impact of particular bacteria on their metabolic functions and indicators of inflammation, comprehensive information about their therapeutic effectiveness is still missing. There are also great challenges that must be surmounted such as standardisation problems, patient safety, and the complexity of human research.

Therefore, the prioritization of gut microbes is an important advancement in the potential management of neurodegenerative diseases. In order to confirm these tactics, give standardised procedures, and evaluate their long-term safety profiles, human trials in future should be carefully planned. Lastly, the increasing potential of individually tailored microbiome therapeutics using personalised microbial profiles and clinical histories are bringing in a new age of preventive and therapeutic approaches to neurodegeneration.

ETHICS DECLARATION

Not applicable.

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CLINICAL TRIAL NUMBER

Not applicable

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