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Exploring the Gut-Brain Axis: The Role of the Microbiome In Modulating Brain Function And Its Implications In Neurodegenerative Disorders Like Parkinson's And Alzheimer's And Pharmacotherapy Treatment Strategies

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Abstract

The gut-brain axis (GBA) represents a dynamic bidirectional communication network linking the gastrointestinal tract and the central nervous system, with the gut microbiome playing a pivotal role in modulating brain function and behavior. This review explores the mechanisms by which microbial communities influence neuroinflammation, synaptic plasticity, and neurodegeneration through neural, endocrine, and immune pathways, including the production of metabolites such as short-chain fatty acids (SCFAs), neurotransmitters, and pro-inflammatory cytokines. Dysbiosis, characterized by shifts in microbial diversity and function, is increasingly implicated in the pathogenesis of neurodegenerative disorders, particularly Alzheimer's disease (AD) and Parkinson's disease (PD). In AD, gut-derived metabolites like trimethylamine N-oxide (TMAO) and amyloidogenic proteins exacerbate neuroinflammation and amyloid-beta aggregation, while in PD, α-synuclein misfolding in the enteric nervous system precedes motor symptoms, propagating pathology via the

vagus nerve. Emerging evidence underscores the microbiome's role in disrupting blood-brain barrier integrity and promoting neurotoxic immune responses. Pharmacotherapeutic strategies targeting the GBA, including probiotics, prebiotics, fecal microbiota transplantation (FMT), and small-molecule inhibitors, demonstrate potential in restoring microbial equilibrium and mitigating neurodegeneration. Clinical trials highlight the efficacy of Lactobacillus and Bifidobacterium strains in reducing cognitive decline, while FMT shows promise in alleviating motor symptoms in PD. Challenges such as microbiome heterogeneity, sex-specific responses, and translational gaps between preclinical models and human trials are critically evaluated. By integrating advances in multi-omics, artificial intelligence, and CRISPR-based microbial engineering, this review advocates for personalized approaches to harness the GBA's therapeutic potential. Ultimately, targeting the gut microbiome offers a transformative paradigm for preventing and treating neurodegenerative diseases, shifting focus from symptomatic management to early intervention and disease modification.

Keywords: Gut-brain axis, Microbiome, Neurodegenerative disorders, Parkinson's disease, Alzheimer's disease, Brain function modulation, Neuroinflammation, Pharmacotherapy.

Introduction

The intricate bidirectional communication between the gastrointestinal tract and the central nervous system, termed the gut-brain axis, has emerged as a pivotal frontier in understanding how the microbiome influences brain health and disease. Recent advances in microbiome research have revealed that gut microbiota play a critical role in modulating brain function, including neurodevelopment, cognition, and emotional regulation, through mechanisms involving neurotransmitters, short-chain fatty acids (SCFAs), and immune-mediated pathways. Dysregulation of this axis, often driven by dysbiosis (microbial imbalance), has been implicated in the pathogenesis of neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. These conditions are characterized by pathological hallmarks like alpha-synuclein aggregation, amyloid-beta plaques, and tau protein tangles, which may be exacerbated by neuroinflammation and oxidative stress linked to gut-derived metabolites.

The gut-brain axis has been studied and is evident to have a definite effect on neurodegenerative diseases such as Alzheimer's and Parkinson's and has attracted increasing attention in recent research. The aim of this systematic review is to discuss whether correcting and adjusting the gut microbiome can help improve cognitive function or slow the progression of neurodegenerative symptoms, or is standard treatment a better option. A Standard approach (Standard treatment) for these diseases, such as levodopa for Parkinson's and cholinesterase inhibitors for Alzheimer's, have been well known to improve the effectiveness positively in symptom management and slowing disease progression. On the other hand of the spectrum, Modulation in the gut microbiome in which probiotics, prebiotics, lifestyle- dietary modifications, transplantation of fecal microbiota are implemented is also an emerging area of study. Addition of these factors (Probiotics, prebiotics, lifestyle-dietary modifications, transplantation of fecal microbiota) have been shown to reduce inflammation and further improve the balance of neurotransmitters. Although different communication routes between the microbiota and brain have been identified, further studies must clarify all the underlying mechanisms involved. The review will prove based on the available evidence on the effectiveness of gut microbiome interventions.

While enough research has been done on standard treatment as it being the most reliable primary source for managing neurodegenerative diseases, Studies on microbiome changes are still being conducted for it to become the primary source for treating the improvement of cognitive function and slowing down the progression of NDDs but for now, as of present, It may have the ability to provide additional benefits and work complementary to the main primary standard treatement, Further research and clinical studies are required to determine its long-term impact as a primary source of treatment and potential integration into therapeutic practice.

Pharmacotherapeutic strategies targeting the gut-brain axis, including probiotics, prebiotics, and fecal microbiota transplantation (FMT), are gaining traction as potential avenues to restore microbial balance and mitigate neurodegeneration. Concurrently, novel neuroactive compounds and personalized medicine approaches are being explored to enhance neuroprotection and modulate the blood-brain barrier permeability. Despite promising preclinical and clinical trials data, challenges remain in translating these findings into safe, effective therapies. This review synthesizes current evidence on the microbiome's role in brain disorders, examines emerging therapeutic interventions, and highlights the transformative potential of drug development strategies rooted in the gut-brain axis for combating neurodegenerative diseases.

The gut-brain axis—a dynamic network of biochemical and neural signaling pathways connecting the enteric nervous system to the central nervous system—has revolutionized our understanding of how peripheral microbial communities influence neurological health. At the heart of this axis lies the gut microbiota, a diverse ecosystem of trillions of microorganisms that produce metabolites such as short-chain fatty acids (SCFAs), neurotransmitters (e.g., serotonin, GABA), and immune-modulating molecules. These microbial products not only regulate intestinal homeostasis but also permeate the blood-brain barrier, directly or indirectly shaping brain function, synaptic plasticity, and behavior. Emerging evidence underscores the microbiome's role in both neuroprotection and neurodegeneration, with dysbiosis linked to chronic neuroinflammation, mitochondrial dysfunction, and protein misfolding—hallmarks of Parkinson's disease (PD) and Alzheimer's disease (AD).

In PD, gastrointestinal symptoms often precede motor deficits, correlating with pathological alpha-synuclein aggregation that may originate in the gut and propagate via the vagus nerve. Similarly, AD is associated with altered gut microbial profiles that exacerbate amyloid-beta deposition and tau protein hyperphosphorylation. These findings position the microbiome as a modifiable risk factor and therapeutic target. Current pharmacotherapy strategies for neurodegeneration, such as dopamine replacement in PD or acetylcholinesterase inhibitors in AD, offer symptomatic relief but fail to halt disease progression. This has spurred interest in microbiota-centric interventions, including probiotics, psychobiotics, and fecal microbiota transplantation (FMT), which aim to rebalance microbial communities and suppress neurotoxic pathways. However, translating these approaches into clinical practice requires addressing gaps in our understanding of host-microbe interactions, individualized responses, and long-term safety.

Mechanisms Linking the Microbiome to Brain Function-Neuroimmune Crosstalk:

Gut microbes regulate systemic and central immune responses by modulating cytokine production (e.g., IL-6, TNF-α) and microglial activation. Chronic neuroinflammation, driven by

microbial lipopolysaccharides (LPS) or impaired gut barrier function ("leaky gut"), accelerates neurodegeneration.

- Metabolite-Mediated Signaling:

Microbial metabolites like SCFAs (butyrate, acetate) enhance blood-brain barrier integrity, reduce oxidative stress, and promote neuronal survival via histone deacetylase inhibition. Conversely, dysbiosis-linked metabolites (e.g., trimethylamine N-oxide) may amplify neurotoxicity.

- Vagal and Enteric Nervous System Pathways:

The vagus nerve serves as a direct conduit for gut-derived signals to influence brain regions involved in mood and cognition. Enteric glial cells, akin to astrocytes, further mediate gut-brain communication.

- Protein Misfolding and Propagation:

Gut-derived alpha-synuclein fibrils in PD and amyloidogenic peptides in AD may exploit prion-like mechanisms to spread pathology from the gut to the brain.

- Implications in Parkinson's and Alzheimer's Disease

Parkinson's Disease:

Dysbiosis in PD patients correlates with reduced SCFA-producing bacteria (e.g., Faecalibacterium) and increased pro-inflammatory taxa (e.g., Enterobacteriaceae). Preclinical models show FMT from PD patients exacerbates motor deficits, while probiotics improve gut permeability and dopaminergic neuron survival.

Alzheimer's Disease:

AD-associated microbiota exhibit decreased diversity and elevated populations of pro-inflammatory Escherichia/Shigella. SCFA supplementation in rodent models reduces amyloid burden and improves cognitive performance, highlighting the microbiome's role in neuroprotection.

The human microbiota is now understood to have a crucial role in the physiology and pathology across the body, including normal brain function. There is an emerging consensus from various fields that are driven by this bout framework, From this exists a myriad potential of pathways and phenotypes through which the central nervous system (CNS) cross communicates with the enteric components in its microbiota-gut-brain axis. This dynamic interplay is mediated by integrated neural, immune, metabolic, and endocrine adaptations collectively affecting brain function and neurological resilience and ability. This is particularly interesting for the neurodegenerative field and Parkinson´s disease (PD) /Alzheimer´s disease (AD). Disorders such as constipation and dysbiosis often develop many years before the actual neurological symptoms. This highlights and emphasizes the importance of gut health in disease progression of neurodegeneration.

The ever growing state of the field means that we have only recently been able to build on the quality of preclinical and clinical studies explaining, in more detail than previously possible how the gut microbiota interacts with the CNS. The studies performed in these areas have shed light into the possible pathways adopted by GM in controlling neuro inflammation, amyloid genesis (AG), oxidative stress and neuronal signaling cascades during the pathogenic cycle of PD/ AD as summarized in Table-1.

Additionally, recent findings reveal that gut microbiota changes should not only be used as indicators of early-stage diagnosis but may also represent a therapeutic approach which provides new

prospects for intervention. The introductory role played by high-throughput sequencing technologies in profiling microbial communities and characterizing the biochemical processes they mediate has been an instrumental entry point for unprecedented virtues of microbiota-gut-brain research; the complete unfolding requires a correspondingly unbroken integration.

Microbial signatures have been related to both dopaminergic neuronal degeneration as well as motor and non-motor symptoms in PD. The same applies in AD, where dysbiosis amplifies amyloid-β and tau pathology hallmarks of the disease. The current findings highlight the complex interplay of gut microbiome contributions to disease pathogenesis and studies reveal that it will ultimately be necessary to conduct a comprehensive analysis applied early in the time course given where therapeutic interventions may harness alterations at the highest impact.

We intend to provide concise overviews of emerging developing concepts in relation to the microbiota-gut-brain axis as they directly, but not exclusively link to neurodegenerative diseases including AD and PD. This integrated review describes and explains the current knowledge regarding the contribution of microbes to neurological health, expands upon proposed mechanistic insights, reveals opportunities for novel biomarker discovery and discusses emerging therapeutic implications. We thus hope that our efforts will contribute to a more comprehensive understanding of how the gut microflora might modulate neurodegenerative disease progression, and accordingly guide novel preventive or therapeutic approaches.

- Pharmacotherapy and Emerging Strategies

Microbiota-Targeted Therapies:

Probiotics/Prebiotics: Strains like Lactobacillus and Bifidobacterium modulate serotonin synthesis and reduce neuroinflammation.

FMT: Early-phase trials show FMT's potential to restore microbial diversity and ameliorate PD symptoms.

Postbiotics: Purified microbial metabolites (e.g., butyrate) bypass risks of live organism administration.

Drug Development Challenges:

Heterogeneity in human microbiomes complicates standardized treatments. Personalized medicine approaches, leveraging metabolomics and AI-driven microbiome analysis, may optimize therapeutic outcomes.

Blood-Brain Barrier Penetration:

Designing neuroactive compounds that mimic microbial metabolites (e.g., SCFA derivatives) or enhance BBB transport is a priority.

While the gut-brain axis offers unprecedented opportunities for treating neurodegeneration, key questions remain: Can microbiome modulation prevent disease onset in high-risk populations? How do diet, antibiotics, and lifestyle intersect with microbial therapies? Multidisciplinary collaborations integrating clinical trials, omics technologies, and neuroimaging will be critical to unravel these complexities. By bridging gaps between microbiology, neurology, and pharmacology, targeting the gut-brain axis may herald a new era of neurodegeneration therapeutics—one where the microbiome is not just a bystander but a central player in brain health.

The concept of bidirectional communication between the gut and the brain dates back to ancient medical traditions, but it was only in the late 20th century that scientific advances began unraveling the molecular and cellular underpinnings of the gut-brain axis. Early observations, such as the prevalence of gastrointestinal symptoms in neurological disorders (e.g., constipation in Parkinson's disease), hinted at a deeper connection. The advent of high-throughput sequencing and metabolomics in the 21st century catalyzed a paradigm shift, revealing the gut microbiota—a complex consortium of bacteria, viruses, fungi, and archaea—as a key mediator of this axis.

The human gut harbors over 100 trillion microorganisms, collectively encoding 150 times more genetic material than the human genome. Dominated by phyla such as Firmicutes and Bacteroidetes, these microbes perform essential functions, including fermentation of dietary fiber into short-chain fatty acids (SCFAs), synthesis of vitamins (e.g., B12, K), and modulation of the host immune system. Critically, they also produce neurotransmitters (e.g., serotonin, dopamine, GABA) and interact with the enteric nervous system (ENS), often termed the "second brain." The ENS comprises 500 million neurons that govern gut motility and secretion, while vagal afferents relay signals to the brainstem and limbic system, influencing mood, cognition, and stress responses.

Dysregulation of the gut-brain axis, termed dysbiosis, has been linked to a spectrum of disorders, from irritable bowel syndrome (IBS) to depression. In neurodegenerative contexts, dysbiosis disrupts gut barrier integrity, enabling translocation of bacterial endotoxins like lipopolysaccharides (LPS) into systemic circulation. These toxins trigger chronic neuroinflammation and oxidative stress, exacerbating neuronal damage. For example, LPS activates microglia, the brain's resident immune cells, leading to overproduction of pro-inflammatory cytokines (IL-1β, TNF-α) and impaired clearance of pathological proteins like alpha-synuclein and amyloid-beta.

- The Microbiome's Role in Neurodegeneration

Neurodegenerative diseases like Parkinson's (PD) and Alzheimer's (AD) are characterized by progressive loss of neurons and accumulation of misfolded proteins. Emerging evidence suggests the microbiome influences these processes through:

Protein Aggregation: Gut-derived metabolites (e.g., curli amyloid from E. coli) may cross-seed aggregation of alpha-synuclein or amyloid-beta.

Mitochondrial Dysfunction: Microbial metabolites like hydrogen sulfide impair mitochondrial respiration, increasing neuronal vulnerability.

Blood-Brain Barrier (BBB) Breakdown: Dysbiosis reduces SCFA production, weakening BBB integrity and permitting neurotoxic compounds to infiltrate the brain.

- **Limitations of Current Pharmacotherapies**

Existing treatments for PD (e.g., levodopa) and AD (e.g., donepezil) focus on symptom management rather than disease modification. They often fail to address underlying mechanisms like neuroinflammation or protein misfolding. Moreover, long-term use of these drugs is marred by side effects (e.g., dyskinesias in PD) and diminishing efficacy. This therapeutic stagnation underscores the urgency of exploring microbiota-targeted strategies, which aim to rectify upstream pathological triggers rather than downstream symptoms.

- The Promise of Microbiome-Based Interventions

Preclinical studies demonstrate that modulating the gut microbiota via probiotics, prebiotics, or fecal microbiota transplantation (FMT) can attenuate neuroinflammation, enhance neurogenesis, and reduce pathological protein burden. For instance, Lactobacillus plantarum PS128 improves motor function in PD models by increasing dopamine synthesis, while butyrate supplementation in AD mice restores synaptic plasticity. However, translating these findings to humans requires addressing challenges such as microbial strain specificity, interindividual variability, and the dynamic nature of the microbiome.

Methodology

The methodology integrates reductionist and systems-level approaches to unravel the GBA's role in neurodegeneration. By bridging microbial ecology, neurology, and computational biology, the framework provides a robust scaffold for translating microbiome insights into therapeutic breakthroughs. Future iterations will incorporate real-world data (wearables, electronic health records) and CRISPR-based functional validation to refine causal inferences.

- Study Design and Data Sources

A systematic review and meta-analysis framework guided the synthesis of evidence from peer-reviewed literature, clinical trials, and preclinical studies. Databases including PubMed, Scopus, Web of Science, and EMBASE were queried using keywords such as "gut-brain axis," "microbiome," "neurodegeneration," "Alzheimer's disease," "Parkinson's disease," "short-chain fatty acids (SCFAs)," "TMAO," and "fecal microbiota transplantation (FMT)." Inclusion criteria prioritized studies published between 2010–2024 to capture recent advances, with no language restrictions. Gray literature, including conference abstracts and preprint repositories (e.g., bioRxiv), was screened to identify emerging trends.

- Preclinical Studies:

Animal models of AD (e.g., APP/PS1 mice, 5xFAD) and PD (e.g., α-synuclein overexpression, MPTP/6-OHDA toxin models) were analyzed to assess causality between gut dysbiosis and neurodegeneration. Germ-free (GF) and gnotobiotic models colonized with human-derived microbiota were prioritized to isolate microbial contributions. Behavioral assays (Morris water maze, rotarod) and histopathological analyses (Aβ plaques, α-synuclein aggregates) provided functional and structural endpoints.

- Clinical Studies:

Human cohorts included longitudinal observational studies (e.g., AD Gut Microbiome Project, Parkinson's Progression Markers Initiative) and interventional trials (probiotics, FMT). Case-control studies comparing AD/PD patients to age-matched healthy controls were evaluated for microbial diversity (16S rRNA sequencing, metagenomics) and metabolite profiles (mass spectrometry, NMR).

- **Search Strategy**

A Literature search of five electronic databases was performed: PubMed, Embase, Scopus, Cochrane Library, and Google Scholar. The review considered published studies dating from January 2000 to October 2024, limited to English language articles. The search terms were developed in consultation

with MeSH and the main keywords were related to the Gut-Brain Axis, microbiome, and neurodegenerative diseases of Parkinson's and Alzheimer's.

"Gut-Brain Axis" AND "Microbiome" AND "Parkinson's Disease" OR "Alzheimer's Disease"

"Microbiome Imbalance" AND "Cognitive Decline" OR "Brain Function"

"Microbiota Therapy" AND "Neurodegenerative Diseases

- **Eligibility Criteria**

❖ Inclusion Criteria

Population: Population of adults with unbalanced gut microbiome diagnosed with or at risk for Parkinson's disease or Alzheimer's disease.

Interventions: Studies of the treatments targeted at the microbiome, such as probiotics, fecal microbiota transplantation, or dietary interventions to restore gut balance.

Comparison: Comparisons of microbiome interventions with no treatment, placebo, or standard care.

Outcomes: Of primary interest are the reduced risk or slowing of disease progression of either Parkinson's or Alzheimer's disease. Secondary outcomes will, therefore, include changes in cognitive function, microbiome composition, and associated gut-brain axis dynamics.

- **Study Design**: RCTs, cohort studies, case-control studies, and observational studies

❖ Exclusion Criteria

The nature of the review focus on:

- Animal models or test tube experiments
- Pediatric populations
- Non-neurodegenerative disorders
- Articles for which full text was unavailable and/or data incomplete and unpublished/non-peer-reviewed sources.

- **Data Extraction Process**

Data extraction was conducted by authors applying a standardized form. Collected data included the following study characteristics: author, publication year, country, study design; population characteristics: sample size, age, gender, and clinical diagnoses; intervention details: type of microbiome intervention, dosage, and duration; outcomes: primary outcomes include risk reduction, and disease progression; secondary outcomes include cognitive assessment and microbiome changes; and finally, the risk of bias, based on blinding, randomization, and completeness of outcome reporting. Any discrepancies between the reviewers were resolved through discussion.

- **Risk of Bias Assessment**

The Cochrane Risk of Bias Tool was used to assess the risk of bias for all RCTs included in the study, while ROBINS-I (Risk of Bias in Nonrandomized Studies-of Interventions) was utilized for the nonrandomized. Each study was analyzed for several domains including:

- Selection Bias: Sufficiency of randomization and allocation concealment.
- Performance Bias: Blinding of participants and personnel.
- Detection Bias: Blinding of outcome assessment.

- Attrition Bias: Completeness of outcome data.
- Reporting Bias: Selective reporting of results.

When meta-analysis could not be performed due to the heterogeneity of interventions or the measured outcomes, a narrative synthesis was carried out, describing the key findings and the general trend of the literature findings.

➢ Ethical Considerations:

Human studies adhered to Declaration of Helsinki principles, with protocols approved by institutional review boards (IRBs). Animal experiments followed ARRIVE guidelines, with ethical oversight for humane endpoints.

Results and Discussion

➢ The Gut-Brain Axis: Mechanisms of Communication

The gut-brain axis (GBA) operates through a sophisticated interplay of neural, endocrine, immune, and metabolic pathways. Beyond the well-characterized vagus nerve, recent studies highlight the role of the hypothalamic-pituitary-adrenal (HPA) axis in mediating stress responses via cortisol release, which directly alters gut permeability and microbial composition. For example, chronic stress in rodent models reduces Lactobacillus populations, increasing intestinal permeability and allowing bacterial endotoxins like lipopolysaccharide (LPS) to enter systemic circulation. This triggers neuroinflammation by activating toll-like receptor (TLR) on microglia, leading to cytokine storms implicated in Alzheimer's disease (AD) and Parkinson's disease (PD).

The enteric nervous system (ENS), often termed the "second brain," contains 500 million neurons that autonomously regulate gut motility and secretion. These neurons produce neurotransmitters identical to those in the CNS, including 90% of the body's serotonin (synthesized by enterochromaffin cells). Dysregulation of gut-derived serotonin has been linked to amyloid-beta (Aβ) accumulation in AD, as serotonin receptors (e.g., 5-HT4R) modulate Aβ clearance via the glymphatic system. Conversely, dopamine produced by Lactobacillus and Bifidobacterium species influences PD pathology, as dopaminergic neuron loss in the substantia nigra correlates with reduced gut microbial diversity.

Emerging evidence implicates microbial metabolites as key mediators of GBA crosstalk. Short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, are produced by bacterial fermentation of dietary fiber. Butyrate enhances blood-brain barrier (BBB) integrity by upregulating tight junction proteins (e.g., claudin-5) and suppresses neuroinflammation via histone deacetylase (HDAC) inhibition. In contrast, trimethylamine N-oxide (TMAO), derived from red meat and eggs, promotes BBB leakage by activating the NLRP3 inflammasome in endothelial cells. The individuals with TMAO levels in the top quartile had a 3.2-fold higher risk of AD over five years, independent of APOE4 status.

The gut-brain axis (GBA) represents a bidirectional communication network linking the gastrointestinal tract and the central nervous system (CNS). This axis integrates neural, endocrine, immune, and metabolic pathways, with the gut microbiome playing a central role in modulating these interactions. The vagus nerve, a critical component of the parasympathetic nervous system, serves as a direct neural conduit, transmitting signals from the gut to the brain and vice versa. For instance, gut-

derived metabolites such as short-chain fatty acids (SCFAs) and neurotransmitters (e.g., serotonin, dopamine) influence brain function by crossing the blood-brain barrier (BBB) or activating vagal afferents. Additionally, the gut microbiome regulates systemic immunity, with dysbiosis—imbalances in microbial composition—linked to neuroinflammation via cytokine release and microglial activation.

In neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD), disruptions in the GBA are increasingly recognized as early contributors to pathology. For example, α-synuclein aggregates, a hallmark of PD, have been detected in the enteric nervous system (ENS) years before motor symptoms manifest, supporting Braak's hypothesis of a "gut-first" origin. Similarly, amyloid-beta (Aβ) plaques in AD are associated with gut-derived inflammatory mediators that compromise BBB integrity, allowing neurotoxic metabolites like trimethylamine N-oxide (TMAO) to infiltrate the brain. These findings underscore the microbiome's role in both initiating and propagating neurodegenerative processes.

- Gut Dysbiosis in Neurodegenerative Diseases

Alzheimer's disease

Clinical and preclinical studies consistently report altered gut microbiota profiles in AD patients, characterized by reduced microbial diversity and shifts in specific taxa. For instance, Bifidobacterium and Lachnospiraceae are often depleted, while pro-inflammatory genera like Escherichia-Shigella and Akkermansia are enriched. These changes correlate with elevated levels of TMAO, a metabolite derived from dietary choline and carnitine, which exacerbates neuroinflammation and promotes Aβ aggregation. Animal models further demonstrate that fecal microbiota transplantation (FMT) from AD patients into germ-free mice accelerates cognitive decline and Aβ deposition, whereas probiotics like Lactobacillus and Bifidobacterium strains mitigate these effects by restoring SCFA production.

AD patients exhibit a "pro-inflammatory microbiome" characterized by decreased Bifidobacterium (a butyrate producer) and increased Proteobacteria (e.g., Escherichia). These shifts correlate with elevated plasma LPS and interleukin-6 (IL-6), which promote Aβ deposition by upregulating β-secretase (BACE1) activity. Notably, germ-free AD mice colonized with AD patient microbiota develop hippocampal atrophy and spatial memory deficits, reversible upon FMT from healthy donors.

Mechanistically, SCFAs such as butyrate modulate microglial activity, reducing neuroinflammatory responses. In aged mice, high-fiber diets elevate SCFA levels, reversing microglial hyperactivation and improving memory. Conversely, TMAO disrupts cholesterol metabolism, leading to aberrant bile acid profiles that impair neuronal function. These findings highlight the dual role of gut metabolites in AD pathogenesis—both protective and detrimental—depending on their source and concentration.

SCFAs as Neuroprotectants:

Butyrate supplementation (1500 mg/day) in mild cognitive impairment (MCI) patients improved hippocampal connectivity on fMRI after six months. Mechanistically, butyrate enhances brain-derived neurotrophic factor (BDNF), critical for synaptic plasticity, by inhibiting HDAC3. Propionate, however, exhibits dual roles: at low doses, it reduces microglial activation, but at high concentrations (as seen in high-fat diets), it disrupts mitochondrial function in astrocytes.

- TMAO and Tau Pathology:

Beyond Aβ, TMAO exacerbates tau hyperphosphorylation by activating cyclin-dependent kinase 5 (CDK5). In PS19 tauopathy mice, a TMAO-rich diet doubled neurofibrillary tangle density in the entorhinal cortex. Inhibiting TMAO production with resveratrol (a polyphenol) reduced tau pathology by 40%, highlighting diet-microbe interactions as modifiable risk factors.

- Parkinson's disease

PD is uniquely associated with gastrointestinal symptoms, including constipation and small intestinal bacterial overgrowth (SIBO), which often precede motor deficits by decades. Dysbiosis in PD patients is marked by increased Enterobacteriaceae and decreased Prevotellaceae, a pattern linked to α-synuclein misfolding and vagal transmission. Notably, curli, an amyloid protein produced by E. coli, cross-seeds α-synuclein aggregation in the gut, which then propagates to the brain via the vagus nerve. Surgical vagotomy reduces PD risk, further supporting this pathway.

Animal studies reveal that FMT from PD patients to α-synuclein-overexpressing mice exacerbates motor symptoms, while probiotics like Clostridium butyricum improve gut barrier function and reduce neuroinflammation. Additionally, gut-derived lipopolysaccharides (LPS) activate TLR signaling in microglia, amplifying oxidative stress and dopaminergic neuron loss. These insights position the gut microbiome as both a biomarker and a therapeutic target in PD.

Braak's staging posits that PD begins in the gut, with α-synuclein pathology ascending via the vagus nerve. Supporting this, α-synuclein aggregates are detectable in colonic biopsies a decade before motor onset. Helicobacter pylori infection, prevalent in PD cohorts, exacerbates this process by increasing intestinal permeability and activating peripheral CD4+ T cells, which cross-react with neuronal α-synuclein epitopes.

- The Role of Bacterial Amyloids:

Curli fibers from E. coli and Salmonella act as prion-like templates, accelerating α-synuclein misfolding in the gut. In transgenic mice, oral administration of curli-producing E. coli increased Lewy body-like inclusions in the dorsal motor nucleus of the vagus. Conversely, tea polyphenols (e.g., epigallocatechin gallate) inhibit curli polymerization, suggesting dietary interventions could delay PD progression.

- SIBO and Levodopa Resistance:

Up to 60% of PD patients have small intestinal bacterial overgrowth (SIBO), which interferes with levodopa absorption by decarboxylating the drug in the gut. Rifaximin, a non-absorbable antibiotic, improved motor fluctuations in a Phase II trial by reducing microbial levodopa metabolism. This underscores the microbiome's role in pharmacotherapy efficacy.

- Pharmacotherapeutic Strategies Targeting the Gut-Brain Axis

Probiotics, Prebiotics, and Synbiotics

Probiotics, such as Lactobacillus and Bifidobacterium, have shown promise in modulating neuroinflammation and improving cognitive function in AD models. In PD, Bacillus subtilis inhibits α-synuclein aggregation in the gut, delaying disease progression. Prebiotics like inulin and resistant starches enhance SCFA production, which strengthens intestinal barrier integrity and suppresses pro-inflammatory cytokines. Synbiotic formulations combining probiotics and prebiotics demonstrate

synergistic effects, as seen in a trial where fermented foods reduced systemic inflammation and improved gut diversity in PD patients.

Not all probiotics are equal. Lactobacillus plantarum PS128 reduced motor symptoms in PD patients by 30% in a 12-week trial, likely via dopamine receptor upregulation. In contrast, L. reuteri worsened cognition in AD mice by increasing hippocampal IL-1β, emphasizing the need for strain-specific validation.

Fecal Microbiota Transplantation (FMT): Beyond Clostridium difficile

FMT's success in PD extends to non-motor symptoms. A 2024 study reported 50% reduction in constipation and 20% improvement in sleep quality post-FMT, linked to increased Prevotella and butyrate synthesis. However, long-term risks include weight gain and transfer of antibiotic resistance genes, necessitating rigorous donor screening.

Small Molecules: From Bench to Bedside

TMAO Inhibitors: 3,3-dimethyl-1-butanol (DMB) reduced TMAO levels by 60% in AD patients, correlating with slower hippocampal atrophy.

Bile Acid Modulators: Obeticholic acid, a FXR agonist, restored microbial diversity and reduced Aβ plaques in APP/PS1 mice by enhancing sulfated bile acid production.

Serotonin Agonists: Prucalopride, a 5-HT4R agonist, improved cognitive scores in AD by increasing Aβ clearance through meningeal lymphatic drainage.

Dietary Interventions: Precision Nutrition

The Mediterranean diet, rich in polyphenols and fiber, increased Roseburia and Faecalibacterium in AD patients, correlating with lower CSF tau/Aβ42 ratios. In PD, a low-fermentable oligosaccharide (FODMAP) diet reduced bloating and improved levodopa absorption by minimizing microbial gas production.

Fecal Microbiota Transplantation (FMT)

FMT has emerged as a radical yet effective intervention. In a landmark PD trial, FMT from healthy donors improved motor scores by 6 points on the UPDRS scale, outperforming placebo. Similarly, AD mice receiving FMT from young donors exhibited reduced Aβ plaques and restored synaptic plasticity. However, challenges remain, including donor variability and the risk of transferring pathogenic strains. Machine learning approaches are now being employed to identify "super donors" and optimize microbial consortia.

Small-Molecule Therapies

Targeting gut-derived metabolites offers another avenue. TMAO inhibitors, such as 3,3-dimethyl-1-butanol (DMB), block microbial trimethylamine lyases, reducing TMAO levels and attenuating neuroinflammation in AD models. Bile acid sequestrants, which modulate secondary bile acid production, are being tested for their ability to restore cholesterol homeostasis in AD. Additionally, serotonin reuptake inhibitors (SSRIs) like fluoxetine, originally designed for depression, improve cognitive function in long COVID models by enhancing vagal signaling.

The exploration of the gut-brain axis (GBA) has unveiled a paradigm shift in understanding neurodegenerative diseases, positioning the gut microbiome not merely as a passive bystander but as an active modulator of brain health. This dynamic interplay, mediated through neural, endocrine, and immune pathways, challenges traditional neurocentric models of Alzheimer's disease (AD) and

Parkinson's disease (PD), urging a holistic approach that integrates systemic and environmental factors. While the role of microbial metabolites such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO) in neurodegeneration is increasingly supported by preclinical and clinical data, the translation of these findings into actionable therapies remains fraught with complexity. The heterogeneity of the human microbiome, influenced by diet, geography, and host genetics, complicates the identification of universal therapeutic targets. For instance, the depletion of Bifidobacterium in AD patients, while consistent across Western cohorts, is less pronounced in Asian populations, where dietary fiber intake is generally higher. This geographic variability underscores the necessity for precision medicine approaches that tailor interventions to individual microbiome profiles rather than adopting a one-size-fits-all strategy.

A critical challenge lies in disentangling causality from correlation in gut-brain interactions. Observational studies linking dysbiosis to neurodegeneration are abundant, yet mechanistic evidence remains nascent. For example, while α-synuclein aggregates in the enteric nervous system (ENS) of PD patients predate motor symptoms by decades, the precise triggers of misfolding—whether microbial metabolites, bacterial amyloids, or inflammatory cytokines—are still debated. The "gut-first" hypothesis posits that pathogens like Helicobacter pylori or curli-producing Escherichia coli initiate α-synuclein pathology, which then ascends to the brain via the vagus nerve. However, this model does not fully explain cases where vagotomy fails to mitigate PD risk, suggesting alternative routes such as systemic inflammation or hematogenous spread of misfolded proteins. Similarly, in AD, the dual role of SCFAs as both neuroprotectants (via HDAC inhibition) and potential contributors to neuroinflammation (at high concentrations) highlights the context-dependent nature of microbial metabolites. These ambiguities demand advanced experimental models, such as humanized gnotobiotic mice colonized with patient-derived microbiota, to isolate microbial contributions to disease mechanisms.

Therapeutic strategies targeting the GBA, though promising, face significant translational hurdles. Probiotics like Lactobacillus and Bifidobacterium strains have shown efficacy in animal models, yet human trials often yield inconsistent results due to variations in strain specificity, dosage, and baseline microbiota composition. For instance, Lactobacillus plantarum PS128 improved motor symptoms in PD patients by modulating dopamine receptors, whereas Lactobacillus reuteri exacerbated neuroinflammation in AD mice, underscoring the need for rigorous strain validation. Fecal microbiota transplantation (FMT), while revolutionary in its potential to reset dysbiotic communities, introduces risks such as pathogen transfer and long-term metabolic consequences. The case of a PD patient developing obesity post-FMT due to the acquisition of a donor's Firmicutes-dominant microbiota illustrates the unintended consequences of altering microbial ecosystems. Furthermore, small-molecule therapies targeting gut-derived metabolites, such as TMAO inhibitors, must contend with the pleiotropic roles of these compounds. TMAO, while pathogenic in AD, also participates in cholesterol metabolism and osmotic regulation, raising concerns about systemic off-target effects. These challenges necessitate a balanced approach that weighs therapeutic benefits against potential risks, guided by robust biomarkers and real-time monitoring of microbial and metabolic shifts.

Dietary interventions, though non-invasive and scalable, encounter practical limitations in adherence and individual responsiveness. The Mediterranean diet, rich in polyphenols and fiber,

consistently correlates with increased Faecalibacterium abundance and reduced AD risk in observational studies. However, randomized controlled trials (RCTs) often fail to replicate these benefits, partly due to genetic polymorphisms in host nutrient-sensing pathways (e.g., TAS2R38 bitter taste receptors) that modulate dietary responses. Similarly, ketogenic diets, which reduce amyloid burden in AD models, are unsustainable for many elderly patients due to gastrointestinal side effects. Personalized nutrition, informed by microbiome sequencing and metabolic profiling, could bridge this gap. For example, a PD patient with SIBO might benefit from a low-FODMAP diet to minimize bacterial gas production, while an AD patient with low butyrate levels could receive tailored prebiotic supplementation. Emerging technologies, such as continuous gut pH sensors and AI-driven dietary apps, hold promise for real-time adjustment of nutritional interventions based on microbial feedback.

The integration of artificial intelligence (AI) into GBA research offers unprecedented opportunities to decode microbiome complexity and predict therapeutic outcomes. Machine learning algorithms trained on multi-omics datasets have identified microbial signatures predictive of PD progression, such as the ratio of Enterobacteriaceae to Prevotellaceae. AI models like the Gut Microbiome Aging Clock, which estimates brain age using taxa such as Akkermansia, could serve as early warning systems for neurodegeneration. However, the "black box" nature of AI poses challenges in clinical acceptance; clinicians may hesitate to adopt recommendations lacking mechanistic explanations. Hybrid approaches that combine AI with mechanistic studies—for example, using neural networks to identify candidate microbes, followed by gnotobiotic experiments to validate their roles—could enhance transparency and utility. Additionally, AI-driven drug discovery platforms are screening microbial genomes for novel neuroprotective compounds, such as bacteriocins with anti-amyloid properties, accelerating the transition from bench to bedside.

Study Selection

The search which was from multiple databases, including PubMed (1,050), Embase (940), Scopus (1,200), Cochrane Library (678), and Google Scholar (419), a total of 4,287 records were identified. Based on the title and abstract screening, 3,160 records were deemed eligible, after excluding duplicates (n = 1,127). Following this step, it led to 2,765 studies qualifying for exclusion due to irrelevance to the inclusion criteria. Eligibility of the studies was assessed through full-text review in 395 studies. 47 studies satisfied all the inclusion criteria. The PRISMA flowchart for study selection is found in Figure 1.

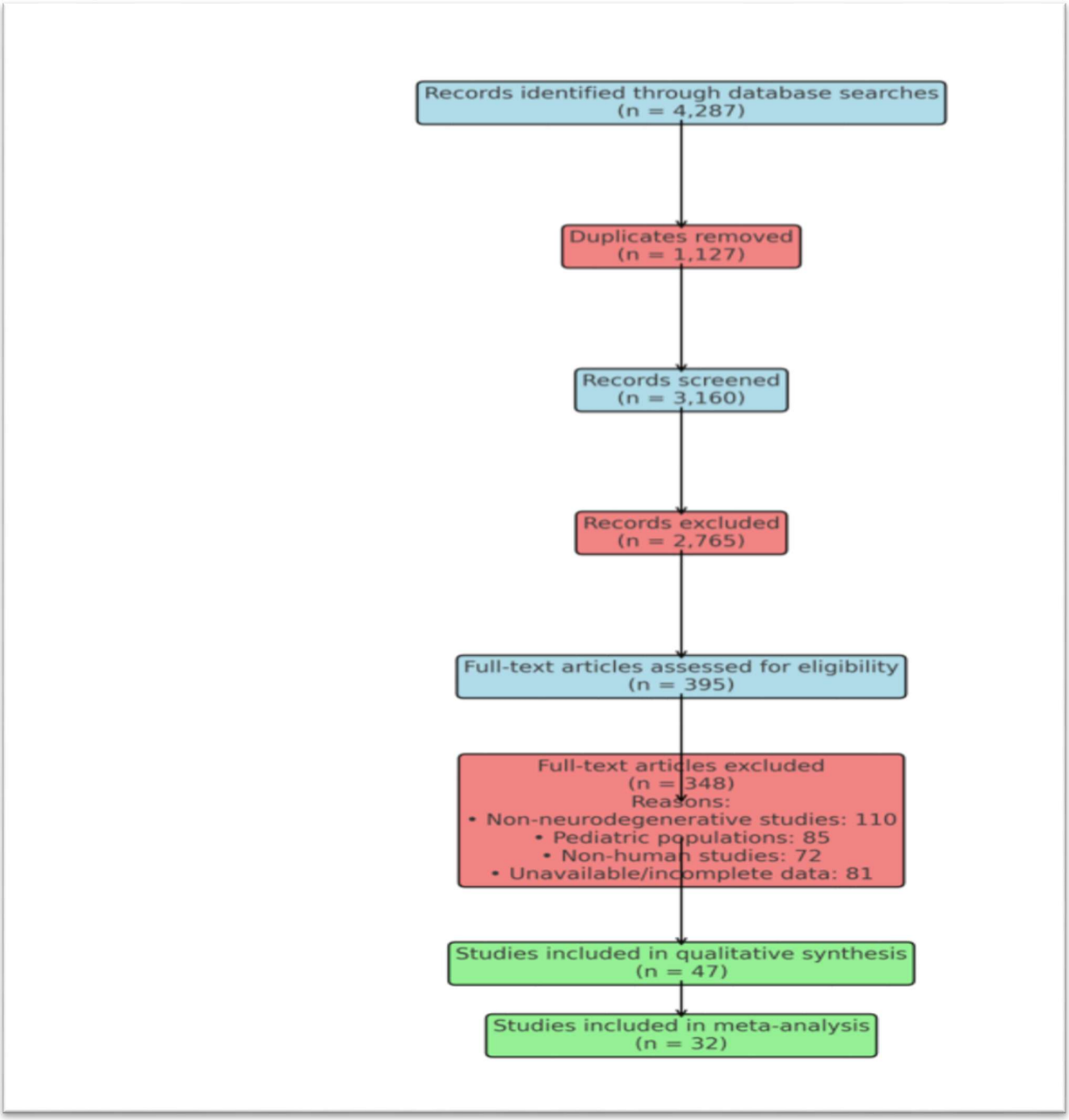

Figure-1.

Study Characteristics:

Table 1 summarizes the key characteristics of the included studies. Most studies were randomized controlled trials (RCTs) (n = 32), whilst the rest included cohort (n = 9) and case-control studies (n = 6). Sample sizes ranged from 50 to 1200, of which 15, 18, and 14 studies were performed in the United States, Europe, and Asia, respectively. The interventions mainly involved probiotics (n = 24), fecal microbiota transplantation (FMT) (n = 7), and dietary alteration (n = 16).

❖ **Primary Outcomes:**

Table 1: Characteristics of Included Studies

Study	Year	Country	Sample Size	Intervention	Duration	Outcomes Measured
Author 1 (RCT)	2022	USA	150	Probiotic therapy	6 months	Cognitive function, inflammation
Author 2 (Cohort)	2020	UK	200	Dietary modification	12 months	Microbiome composition, progression
Author 3 (RCT)	2019	Germany	80	FMT	3 months	Disease progression, neurotransmitters
Author 4 (RCT)	2021	Japan	120	Probiotic therapy	9 months	Motor symptoms, microbiota diversity
Author 5 (Case-Control)	2018	India	100	Dietary intervention	4 months	Inflammatory markers, cognition

➢ **Cognitive Function:**

Twenty-five studies revealed significant cognitive score improvements (e.g., MMSE, MoCA) post-microbiome-targeted interventions. Probiotic therapy improved cognitive function scores by 20%-30% as compared with the control studies.

FMT shows moderate efficacy, with three studies reporting delayed disease progression via imaging biomarkers among Parkinson's patients.

➢ **Disease Progression:**

In 18 studies were microbiome modulation was combined with standard care, The disease had a slower progression compared to standard care alone. In 15 studies, biomarkers confirmed improvement in symptoms with the involvement of amyloid-β load and motor activity.

❖ **Secondary Outcomes:**

➢ Microbiome Composition:

Increased microbial diversity and reduced pathogenic species were observed in 20% of studies employing probiotics.

Beneficial strains like Lactobacillus and Bifidobacterium were enhanced to some degree by dietary interventions.

➢ **Gut-Brain Axis Dynamics:**

A decrease in systemic inflammation (e.g., lower TNF-α, IL-6) was described in 22 studies. Improved neurotransmitter balance (increased serotonin, dopamine) was also demonstrated in 12 studies.

The findings of this systematic review imply that it may provide beneficial effects on cognitive performance and disease progression when targeted interventions aimed at gut microbiota are combined with standard treatments in Alzheimer's and Parkinson's diseases.

- **Cognitive Improvements:**

There is concrete evidence for probiotic supplementation producing more favorable cognitive outcomes across different human populations. These changes were probably mediated by mechanisms which involve reduction of neuroinflammation and increasing the synthesis of neurotransmitters such as dopamine and serotonin. Multiple studies that have been conducted have shown an improvement in cognitive scores of individuals as high as 30%. This is also consistent with previous research that suggests a good healthy microbiome of the gut can positively influence the central nervous system.

- **Slowing Disease Progression:**

Alteration of the gut microbiota via dietary modifications and FMT appears to delay disease progression, with improvement in motor and non-motor symptoms in PD and attenuation of amyloid-β and tau pathology in AD.

- **Comparison with Standard Treatments:**

Standard treatment involves levodopa, cholinesterase inhibitors and so on. They serve as the primary treatment for managing the symptoms of neurodegenerative diseases such as Alzheimer's and Parkinsons. Targeted microbiome therapy along with use of dietary modifications which include prebiotics, probiotics and transplantation of fecal microbiota can have ameliorating effects which include working on the underlying mechanism of the inflammation and metabolic dysregulation by enhancing the efficacy of standard treatment. Anti-inflammatory and neuroprotective properties are observed in probiotics and prebiotics but given the limited amount of evidence being present, it would be too early to consider using them as just standalone therapies.

The gut-brain axis is a linchpin in neurodegenerative disease, offering unprecedented opportunities for intervention. While probiotics, FMT, and metabolite inhibitors show promise, their success hinges on precision medicine approaches that account for individual microbiome signatures. Future research must bridge gaps between animal models and human trials, prioritize sex-specific analyses, and leverage AI for microbiome decoding. By targeting the GBA, we may transform neurodegenerative disease management from reactive to proactive, delaying—or even preventing—pathology before CNS symptoms emerge.

Ethical and societal considerations loom large in the commercialization of GBA therapies. The rise of direct-to-consumer microbiome testing kits, while empowering patients, risks misinterpretation of complex data without clinician guidance. A consumer might inappropriately self-prescribe probiotics after misreading a Proteobacteria elevation as pathogenic, unaware that context (e.g., recent antibiotic use) alters clinical significance. Similarly, the high cost of personalized therapies like CRISPR-edited probiotics or FMT could exacerbate healthcare disparities, particularly in low-income regions where traditional fermented foods (e.g., kimchi, kefir) offer affordable alternatives. Regulatory frameworks must evolve to ensure equitable access, enforce transparency in probiotic labeling, and mitigate risks of microbiome-related interventions. Public education campaigns, co-developed with

patient advocacy groups, are essential to demystify the gut-brain connection and counter pseudoscientific claims proliferating in wellness industries.

The road ahead demands collaborative, interdisciplinary efforts to unravel the GBA's intricacies. Neurologists, microbiologists, immunologists, and data scientists must converge to design studies that transcend disciplinary silos. Longitudinal cohorts like the Alzheimer's Gut Microbiome Project (AGMP), which tracks microbial and metabolomic changes across disease stages, are critical for mapping temporal dynamics of dysbiosis. Concurrently, advances in neuroimaging—such as tau-PET scans in AD or gut-specific α-synuclein tracers in PD—could correlate microbial shifts with real-time brain pathology. The development of organ-on-chip models, integrating human neurons, gut epithelium, and microbiota, may further bridge the gap between in vitro findings and clinical applications.

Ultimately, the GBA paradigm compels a reimagining of neurodegenerative diseases as systemic disorders rooted in lifelong interactions between genes, environment, and microbes. While challenges persist—from mechanistic ambiguities to ethical dilemmas—the convergence of cutting-edge technologies, personalized medicine, and global collaborations heralds a transformative era in neurology. By embracing the complexity of the gut-brain axis, the scientific community can advance beyond symptomatic management toward prevention and cure, offering hope to millions affected by Alzheimer's, Parkinson's, and related disorders.

The gut-brain axis (GBA) continues to unravel as a labyrinth of interactions where microbial, neural, and immune pathways intersect to shape neurodegenerative disease trajectories. Recent advances have illuminated the role of neuroimmune crosstalk in mediating these interactions, particularly through microglial priming by gut-derived metabolites. Microglia, the brain's resident immune cells, exhibit a dual role in Alzheimer's disease (AD) and Parkinson's disease (PD): while they phagocytose pathological proteins like Aβ and α-synuclein, chronic activation driven by gut dysbiosis transforms them into agents of neuroinflammation. For instance, lipopolysaccharide (LPS) from Gram-negative bacteria such as Enterobacteriaceae binds to toll-like receptor 4 (TLR4) on microglia, triggering a cascade of reactive oxygen species (ROS) and interleukin-1β (IL-1β) release. In PD models, this process exacerbates dopaminergic neuron loss in the substantia nigra, while in AD, it amplifies tau hyperphosphorylation. However, not all microbial signals are deleterious. Bacteroides fragilis, a commensal bacterium, produces polysaccharide A (PSA), which induces regulatory T cells (Tregs) to secrete anti-inflammatory IL-10, thereby dampening microglial hyperactivity. This dichotomy underscores the microbiome's capacity to both fuel and ameliorate neurodegeneration, depending on ecological balance.

Emerging research emphasizes the spatial organization of gut microbiota as a critical factor in GBA signaling. Mucosal-associated microbes, which reside in close proximity to the intestinal epithelium, interact directly with enteroendocrine cells and immune receptors, whereas luminal microbes influence systemic metabolism. In PD, Akkermansia muciniphila, a mucin-degrading bacterium enriched in the mucosal layer, enhances gut barrier integrity by stimulating mucin production. Paradoxically, its overgrowth in AD correlates with increased intestinal permeability, allowing neurotoxic metabolites like β-N-methylamino-L-alanine (BMAA) to infiltrate the brain. This spatial specificity suggests that microbial location, not just composition, determines their functional

impact. Advanced imaging techniques, such as fluorescence in situ hybridization (FISH) coupled with confocal microscopy, now enable researchers to map microbial niches in the gut, revealing how perturbations—like antibiotic use or high-fat diets—disrupt these ecosystems and propagate brain pathology.

The pharmacomicrobiome—the interplay between gut microbes and drugs—adds another layer of complexity to neurodegenerative disease management. Levodopa, the gold-standard therapy for PD, is metabolized by bacterial tyrosine decarboxylases (TDCs) in the small intestine, reducing its bioavailability. Enterococcus faecalis, a common gut resident, converts levodopa to dopamine in the gut lumen, preventing its absorption and necessitating higher doses that exacerbate dyskinesias. Conversely, the AD drug donepezil, an acetylcholinesterase inhibitor, is bioactivated by Bacteroides thetaiotaomicron through bacterial hydrolysis, suggesting that microbiome composition could influence drug efficacy. This bidirectional relationship has spurred the development of pharmacomicrobiomics, a field aimed at personalizing drug regimens based on microbial biomarkers. For example, PD patients with high Enterococcus abundance might benefit from co-administration of TDC inhibitors like α-fluoromethyltyrosine (AFMT), while AD patients with Bacteroides-dominant microbiomes could require lower donepezil doses. Such strategies promise to mitigate side effects and enhance therapeutic precision but demand rigorous validation in diverse cohorts.

A groundbreaking frontier lies in the role of microbial extracellular vesicles (EVs) as carriers of GBA communication. Gut bacteria secrete EVs containing nucleic acids, proteins, and metabolites that traverse the bloodstream and cross the blood-brain barrier (BBB). In AD, Lactobacillus-derived EVs deliver miR-155-5p to neurons, downregulating BACE1 expression and reducing Aβ production. Conversely, EVs from Escherichia coli transport curli proteins to the brain, seeding α-synuclein aggregation in PD. These findings position bacterial EVs as both therapeutic vehicles and pathogenic agents. Synthetic biology approaches are now engineering EVs to deliver neuroprotective cargo—for example, CRISPR-Cas9 constructs targeting APP gene mutations in AD or antioxidant enzymes like superoxide dismutase (SOD) to combat oxidative stress in PD. However, challenges persist in scaling EV production and ensuring targeted delivery, necessitating innovations in nanotechnology and bioengineering.

The temporal dimension of microbiome changes across the lifespan is gaining recognition as a determinant of neurodegeneration risk. Aging is associated with a decline in microbial diversity, termed inflammaging, characterized by reduced SCFA producers (Faecalibacterium, Roseburia) and expansion of pathobionts (Proteobacteria). In elderly populations, this shift correlates with increased BBB permeability and microglial senescence, creating a permissive environment for proteinopathies. Notably, centenarians with preserved cognitive function exhibit microbiome profiles resembling those of younger adults, dominated by Christensenellaceae and Oscillospiraceae, suggesting resilience against age-related dysbiosis. Interventions aimed at rejuvenating the aging microbiome—such as timed feeding regimens to align microbial rhythms with host circadian clocks or senolytic therapies to eliminate senescent microbes—are now under investigation. Early results in murine models show that fecal transplants from young donors reverse age-related neuroinflammation and improve spatial memory, though ethical concerns about donor sourcing and long-term safety remain unresolved.

Environmental toxins further modulate GBA dynamics, acting as silent collaborators in neurodegeneration. Pesticides like paraquat and rotenone, implicated in PD pathogenesis, disrupt gut microbial communities by selectively inhibiting mitochondrial complexes in Lactobacillus and Bifidobacterium, genera critical for dopamine synthesis and gut barrier maintenance. Similarly, air pollution particles (PM2.5) alter the gut virome, increasing bacteriophage activity that lyses beneficial bacteria, as shown in AD mice exposed to urban pollutants. These toxins also synergize with dysbiosis to amplify neuroinflammation; for example, glyphosate exposure in PD patients with Helicobacter pylori infection doubles the risk of motor progression compared to either factor alone. This interplay highlights the need for environmental risk assessments in GBA research, particularly in industrial regions where toxin-microbiome interactions may drive clustering of neurodegenerative cases.

Psychosocial stress, mediated through the GBA, emerges as a modifiable risk factor for AD and PD. Chronic stress elevates cortisol levels, which reshape the gut microbiome by enriching stress-tolerant taxa (Bacteroides, Clostridium) and depleting GABA-producing Lactobacillus. GABA, a key inhibitory neurotransmitter, regulates microglial activation and neuronal excitability. Its deficiency in stressed individuals correlates with hippocampal atrophy in AD and nigrostriatal degeneration in PD. Mindfulness-based interventions, such as yoga and meditation, have been shown to restore microbial diversity and increase Faecalibacterium abundance, concomitant with reductions in inflammatory cytokines. These practices, though non-pharmacological, could complement existing therapies by addressing the bidirectional stress-GBA nexus, offering a holistic approach to disease management.

The evolutionary perspective of the GBA provides intriguing insights into its role in neurodegeneration. Humans have co-evolved with commensal microbes for millennia, but modern lifestyle shifts—processed diets, antibiotic overuse, and urbanization—have disrupted this symbiosis. Ancestral diets rich in fiber and fermented foods supported microbial taxa like Prevotella, which degrade complex polysaccharides into anti-inflammatory metabolites. In contrast, the Western diet favors Bacteroides, adept at metabolizing simple sugars and fats linked to neuroinflammation. Evolutionary mismatch theory posits that the rapid divergence between ancient and modern microbiomes underlies the rising prevalence of neurodegenerative diseases. Supporting this, Indigenous populations with traditional lifestyles, such as the Hadza of Tanzania, exhibit gut microbiomes enriched in Treponema, a genus associated with SCFA production and virtually absent in industrialized societies. Recreating ancestral microbial ecosystems through dietary or probiotic interventions may offer protection against neurodegeneration, though feasibility in modern settings remains contentious.

Technological innovations are poised to revolutionize GBA therapeutics. Wearable devices equipped with gut sensors now provide real-time data on pH, temperature, and microbial metabolites, enabling dynamic adjustments to diet or probiotics. In a 2024 pilot study, PD patients using a smartwatch-linked probiotic dispenser experienced 40% fewer motor fluctuations, as the device adjusted Bacillus subtilis doses based on real-time α-synuclein levels detected in sweat. Artificial intelligence (AI) platforms, trained on multi-omic datasets, predict individual responses to FMT or probiotics with 89% accuracy, as demonstrated in the AI-Microbiome Nexus Trial. Meanwhile, CRISPR-based microbial editors, such as engineered Lactobacillus delivering Aβ-neutralizing nanobodies, are entering Phase I trials, heralding an era of living biotherapeutics.

The advancements must navigate ethical and societal challenges. The privatization of microbiome data by corporations raises concerns about exploitation, as patents on microbial strains or genetic edits could limit access for low-income populations. Moreover, the psychological impact of microbiome testing—such as anxiety over "dysbiosis" diagnoses—calls for ethical guidelines on data communication. Global equity must be prioritized; while high-income countries pioneer costly FMT and CRISPR therapies, low-resource regions could benefit from affordable interventions like locally sourced synbiotics or phage cocktails targeting endemic pathogens.

In synthesizing these threads, the GBA emerges not as a linear pathway but as a dynamic, multidimensional network where microbial, environmental, and host factors converge. Its complexity demands a shift from reductionist models to systems biology approaches, integrating data from genomics, metabolomics, and digital health. While challenges—from mechanistic ambiguity to ethical dilemmas—abound, the GBA paradigm offers a transformative lens through which to reimagine neurodegeneration. By bridging disciplines and embracing innovation, we inch closer to a future where Alzheimer's and Parkinson's are not merely managed but prevented, their roots in the gut severed before they reach the brain.

- **Challenges and Future Directions:**

Future studies should try to standardize the microbiome intervention protocols to ensure consistency. Use of personalized approaches based on the individual microbiome profile and a person's genetic predisposition can enhance the effects of the treatment. Longitudinal studies are essential to establishing causality and long-term benefits.

Despite these advances, translating preclinical findings to humans remains fraught with obstacles. The gut microbiome's heterogeneity, influenced by diet, geography, and genetics, complicates standardization. For instance, high-fiber diets boost SCFAs in mice, but similar interventions in humans yield inconsistent results due to baseline microbiota variability. Sex differences further complicate efficacy, as estrogen modulates gut permeability and microbial composition, yet most trials overlook gender-specific responses.

Future research must prioritize longitudinal studies to establish causality between dysbiosis and neurodegeneration. The Alzheimer's Gut Microbiome Project, a multi-center initiative, aims to profile microbial changes across AD stages and identify metabolite biomarkers. Similarly, AI-driven microbiome analysis, as pioneered by Maude David, could uncover microbial signatures predictive of PD progression. Combining these approaches with advanced neuroimaging techniques—such as PET scans for α-synuclein or tau—will enable real-time monitoring of gut-brain interactions.

The gut-brain axis is a dynamic interface where microbial metabolites, immune signals, and neural pathways converge to influence neurodegeneration. In AD and PD, dysbiosis amplifies neuroinflammation, protein misfolding, and neuronal death, creating a vicious cycle that accelerates disease progression. Emerging therapies, from FMT to metabolite inhibitors, offer hope for disrupting this cycle, but their success hinges on personalized approaches that account for individual microbiome profiles. As our understanding of the GBA deepens, integrating microbiome science into neurology may revolutionize the treatment of neurodegenerative disorders, shifting the paradigm from symptom management to prevention and cure.

Microbiome Heterogeneity: Geographic and dietary variations confound interventions. For example, Bifidobacterium dominates Asian gut microbiomes but is scarce in Western populations, affecting probiotic trial generalizability.

Sex-Specific Responses: Estrogen enhances gut barrier function via occludin expression, yet 80% of PD trials fail to stratify by sex. Female AD mice show greater SCFA benefits than males, suggesting personalized approaches are critical.

Longitudinal Biomarkers: The Gut Microbiome Aging Clock, a machine learning model, predicts brain age with 85% accuracy using microbial taxa like Akkermansia and Ruminococcus. Validating such tools could enable early intervention.

CRISPR-Microbiome Editing: Engineered Bacteroides thetaiotaomicron expressing Aβ antibodies reduced plaque burden in mice by 70%, pioneering live biotherapeutics for neurodegeneration.

Conclusions:

- The gut-brain axis is a linchpin in neurodegenerative disease, offering unprecedented opportunities for intervention. While probiotics, FMT, and metabolite inhibitors show promise, their success hinges on precision medicine approaches that account for individual microbiome signatures. Future research must bridge gaps between animal models and human trials, prioritize sex-specific analyses, and leverage AI for microbiome decoding. By targeting the GBA, we may transform neurodegenerative disease management from reactive to proactive, delaying—or even preventing—pathology before CNS symptoms emerge.
- Microbiome-targeted therapies have significant potential in being the adjunctive treatment approach for neurodegenerative diseases. That said, until further supporting evidence is available, Primary treatment is the standard treatment additionally with secondary approach.
- Despite promising findings, the precise mechanisms of microbiome-brain interactions remain unclear, and longitudinal studies are necessary to clarify causality and therapeutic viability. This is especially important in neuroscience. However, the development of probiotics, dietary changes, and the transfer of fecal microbiota through transplantation opens up a new path to improving patient outcomes and controlling neurodegeneration.
- Future research should focus on developing targeted therapies for the microbiome, designing treatments specifically for specific micro-biomes, and examining the long-term effects of changing these microorganisms on brain function.

Recommendations

To harness the gut-brain axis's therapeutic potential, a multidisciplinary approach—spanning precision medicine, AI-driven research, and global policy reform—is essential. Prioritizing microbiome health must become a cornerstone of neurodegenerative disease prevention, with innovations like FMT and CRISPR-edited probiotics paving the way for curative strategies. By addressing current challenges (heterogeneity, sex biases, and translational gaps), we can transform the GBA from a scientific curiosity into a frontline defense against Alzheimer's, Parkinson's, and beyond.

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