

Review

Harnessing the Gut-Brain Axis for Neuroprotection: Synergistic Role of Natural Bioactive Products and Microbiota

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ABSTRACT

Diseases causing neurodegeneration, including Alzheimer's disease and Parkinson's disease, encompass several pathological processes such as progressive neuronal damage and increased neuronal loss. Currently, there are limited available therapeutic options capable of halting progression of the disease. The Gut microbiota has emerged as a significant pathway in modulating neuroinflammation, oxidative stress, protein aggregation, neurotransmitter disruption and mitochondrial dysfunction.

Simultaneously, natural products including isoflavones, flavonoids, curcumin, alkaloids and turmeric, alongside gut metabolites, have demonstrated great neuroprotective effects through antioxidative and anti-inflammatory mechanisms. This review examines the synergistic interactions between gut microbiota and bioactive compounds in modulating pathways associated with neurodegeneration. Synergy between gut metabolites and bioactives collectively enhances intestinal barrier integrity, regulates immune responses, reduces oxidative damage, and preserves mitochondrial function and influences neurotransmitter synthesis and neuronal signaling. Integrating the gut microbiota with bioactive supplementation of provides a multifaceted intervention for neurodegenerative diseases.

KEYWORDS: Neurodegenerative diseases; Gut microbiota; Bioactive; Neuroprotection.

Overview of Neurodegenerative Diseases

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS), are characterized by the irreversible loss of cholinergic neurons, abnormal protein folding, and synaptic impairment leading to progressive cognitive or memory

loss^{1,2}. Several studies have investigated neurodegenerative diseases at the molecular level; however, the cellular basis underlying disease progression is yet to be fully understood. This has been a major concern in the development of effective therapeutics for these diseases. Neurodegenerative diseases share common threads that underpin their pathophysiology, including protein misfolding and aggregation, chronic neuroinflammation

and mitochondrial dysfunction, indicating common underlying vulnerabilities^{3,4}.

The societal impact of neurodegenerative diseases is staggering and rapidly growing, with an estimated 55 million individuals currently affected, which will almost triple by 2050 due to demographic changes⁵. According to statistics, the average prevalence of Parkinson's disease was projected to be 275 cases per 100 000 individuals in 2050; this suggests a marked increase of 56% to 120% from 2021⁶.

The economic burden is commensurate with this figure, and the cost of dementia exceeds \$1.3 trillion, with a burden predominantly borne by informal carers⁷. This is reflected in the Disability-Adjusted Life Years (DALYs), thus requiring a radical shift that will provide a solution⁸. Management of neurodegenerative diseases poses challenges in the global health and research sectors due to the symptomatic effects of the currently available therapeutic agents rather than the pathogenic effects and adverse effects in the body⁹.

The Gut-Brain Axis

In recent times, neuroscience research has identified the gut-brain axis as a bidirectional communication providing key mechanistic pathways into neurodegenerative diseases¹⁰. It integrates enteric nervous system signaling, vagal signals, immune pathways, and microbial metabolites^{11,12}. Germ-free models underscore the importance of the gut microbiota on brain development and function, revolutionizing understanding of this complex crosstalk. The intriguing aspect is that the convergence of protein misfolding, neuro-inflammation, and oxidative stress in neurodegenerative diseases could be modulated by signals originating within the gastrointestinal tract. This paradigm shift reveals the profound influence of the gut-brain axis on neurological health. Dietary interventions, primarily natural bioactive compounds and their interactions with gut microbiota, promise as an exciting new paradigm for multifaceted neuroprotection¹³.

Major Neural Pathways involved in Gut-Brain Axis

The gut-brain axis orchestrates a complex bidirectional interaction between the gastrointestinal tract and the central nervous system. The intricate dialogue hinges on several major pathways, each contributing to the brain's evaluation of gut

condition¹⁴. This 'information superhighway' conveys information on microbial composition, metabolite concentrations, immune status and mechanical stimuli, and this information acts upon critical regions in the brain responsible for mood, emotion and cognition¹⁵. Vagus nerve stimulation (VNS) exemplifies its mechanism as modulating neuroplasticity and mitigating neuroinflammation¹⁶. The enteric nervous system (ENS) is a vast, semi-autonomous network of neurons embedded within the gut wall that intricately communicates with the brain via the vagus nerve, thereby facilitating bidirectional link and translating microbial signals into neurological impacts¹⁷. This supports the idea that gut dysbiosis can hinder neurodevelopment, thus precipitating neurological disorders¹⁸.

Intestinal Barrier Integrity

Integrity of the intestinal barrier is essential as it separates luminal microbes from the host's internal milieu. An interrupted gut barrier disrupts the gut-brain axis, thereby causing systemic neuroinflammation. The single-layer epithelium of the gut, supported by tight junctions, forms an important barrier of protein complexes (occludin, claudin-1 and ZO-1) close to the paracellular space, which prevents uncontrolled migration of microbial antigens and toxins into circulation^{19,20}. Short-chain fatty acids (SCFAs) like butyrate and valerate play a key role in upholding TJ integrity; depletion of them as a result of dysbiosis precipitates a 'leaky gut'²¹. Gut dysbiosis compromises BBB integrity, facilitating infiltration of peripheral inflammatory mediators and microbial products into the CNS (Beltran-Velasco and Clemente-Suárez). This failure is compounded by activation of HPA axis, especially under stress, creating a vicious cycle between inflammation and barrier failure²². On the other hand, SCFAs, notably butyrate, strengthen BBB integrity by controlling endothelial tight junctions and components of neurovascular units.

The bacteria within the gut release gut metabolites and communicate them to the brain via the vagus nerve to facilitate a bidirectional interaction and translate microbial signals into neurological effects.

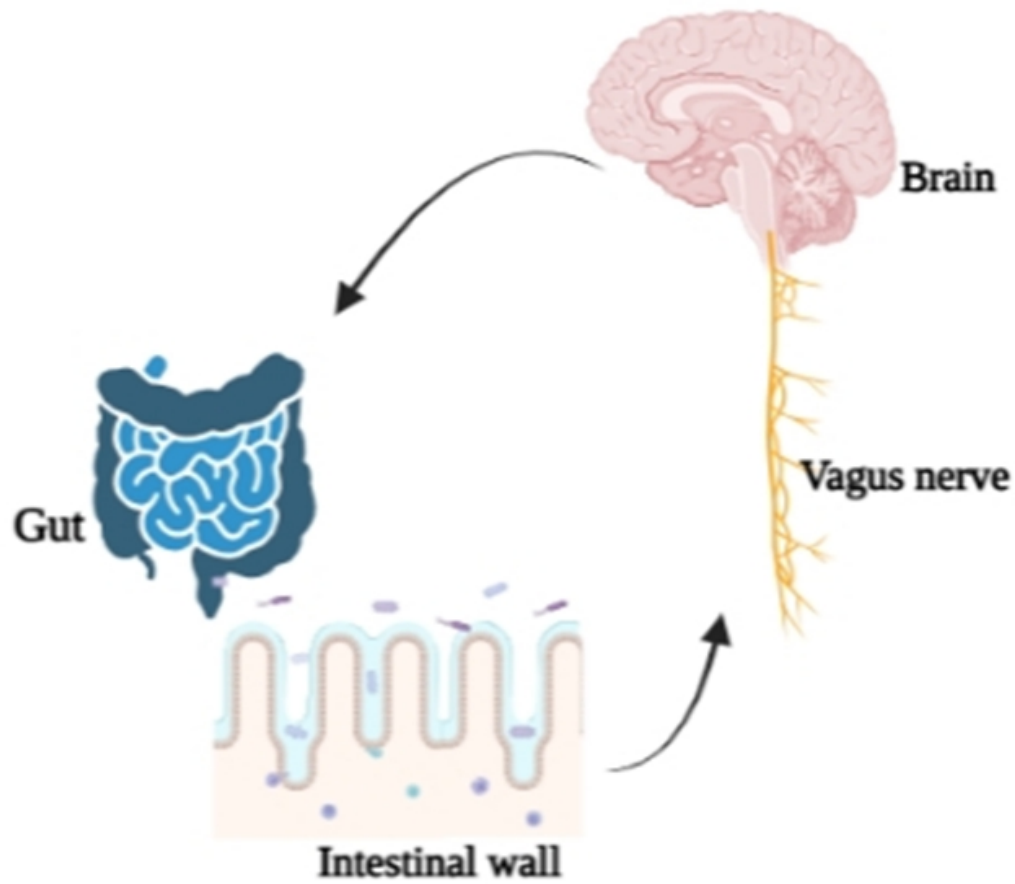


Figure 1: The Gut-Brain Axis

Microbial Metabolites

Metabolic processes of the gut microbiota have profound influence on the host physiology and brain function. Short-chain fatty acids (SCFAs), including butyrate, propionate and acetic acids from bacterial fermentation of dietary fiber, support the integrity of the intestinal barrier. They exert anti-

inflammatory effects, cross the blood-brain barrier (BBB) and help in the development of microglia and neurons¹¹. Enteroendocrine cells, stimulated by microbial presence, release neuroactive molecules like GLP-1, PYY and 5-HT (serotonin); the latter are mostly produced in the gut and impact mood and cognition²³.

Table 1: Major Microbial Metabolites relevant to Bioactive Products

Class of Metabolite	Metabolites	Key Producing Bacteria	Dietary Precursors	Biological Effects
Short-chain fatty acids (SCFAs) ²⁴	Acetate, propionate, butyrate	<i>Faecalibacterium prausnitzii</i> , <i>Roseburia spp.</i> , <i>Eubacterium rectale</i> , <i>Bacteroides spp.</i> , <i>Akkermansia muciniphila</i>	Dietary fiber, resistant starch, non-digestible oligosaccharides	Source of energy for colonocyte (butyrate); HDAC inhibition; GPR41/43 signaling; anti-inflammatory; gut barrier reinforcement; satiety hormone (GLP-1, PYY) induction
Secondary bile acids ²⁵	Deoxycholic acid (DCA), lithocholic acid (LCA)	<i>Clostridium scindens</i> , <i>Eggerthella lenta</i> , <i>Bacteroides spp.</i>	Primary bile acids (cholic acid, chenodeoxycholic acid) from liver	FXR/TGR5 receptor activation; glucose/ lipid metabolism regulation; antimicrobial activity; implicated in colorectal carcinogenesis at high levels
Tryptophan-derived metabolites ²⁶	Indole, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), skatole	<i>Lactobacillus spp.</i> , <i>Clostridium sporogenes</i> , <i>E. coli</i> , <i>Bacteroides spp.</i>	Dietary tryptophan	Aryl hydrocarbon receptor (AhR) agonism; gut barrier integrity; antioxidant activity; neuroprotection (IPA); immune modulation
Trimethylamine (TMA)/TMAO Pathway ²⁶	Trimethylamine (TMA), trimethylamine -N-oxide (TMAO, host-derived)	<i>Clostridium spp.</i> , <i>Anaerococcus spp.</i> , <i>Escherichia spp.</i>	Choline, carnitine, betaine (from red meat, eggs, fish)	TMA oxidized in liver to TMAO; associated with atherosclerosis, cardiovascular risk, platelet hyperreactivity
Polyamines ²⁴	Putrescine, spermidine, spermine	<i>Bacteroides spp.</i> , <i>Fusobacterium spp.</i> , <i>Campylobacter spp.</i>	Arginine, ornithine	Cell proliferation; mucosal growth/repair; autophagy induction (spermidine); longevity-associated pathways
Vitamins (microbial synthesis) ²⁷	Vitamin K2 (menaquinone), B12, folate, biotin	<i>Bacteroides fragilis</i> , <i>E. coli</i> , <i>Lactobacillus spp.</i> , <i>Bifidobacterium spp.</i>	Endogenous synthesis (not diet-dependent)	Coagulation cofactor (K2); one-carbon metabolism; energy metabolism; host micronutrient supplementation

Continued ...

Polyphenol-derived metabolites ²⁸	Urolithins (A, B), equol, enterolactone, enterodiol	<i>Gordonibacter spp.</i> , <i>Eggerthella lenta</i> , <i>Slackia spp.</i>	Ellagitannins (pomegranate, berries), lignans, isoflavones (soy)	Antioxidant; anti-inflammatory; mitophagy induction (urolithin A); estrogen-receptor modulation (equol); cardioprotective
Branched-chain fatty acids (BCFAs) ²⁹	Isobutyrate, isovalerate, 2-methylbutyrate	<i>Bacteroides spp.</i> , <i>Clostridium spp.</i>	Branched-chain amino acids (valine, leucine, isoleucine)	Minor energy source; gut barrier modulation; biomarkers of proteolytic fermentation
Hydrogen sulfide (H ₂ S) ²⁴	H ₂ S	<i>Sulfate-reducing bacteria</i> (<i>Desulfovibrio spp.</i>), <i>Bilophila wadsworthia</i>	Sulfated amino acids (cysteine, taurine), dietary sulfate	Dual role: signaling molecule at low levels (vasodilation, anti-inflammatory); genotoxic/ pro-inflammatory at high levels
Lipopolysaccharide (LPS) ²⁷	Endotoxin	<i>Gram-negative bacteria</i> (<i>Bacteroides</i> , <i>Enterobacteriaceae</i>)	Bacterial cell wall component	TLR4 activation; low-grade metabolic endotoxemia; linked to insulin resistance and systemic inflammation

Role of Microbial Regulation in Activation of Microglia

The gut microbiota influences the CNS immune cells, notably microglia. Germ-free model studies show that microbial signals are vital for microglial development and maintaining their homeostatic protective neural function¹¹. In Alzheimer's disease, gut dysbiosis is implicated in triggering chronic neuroinflammation through microglial dysfunction, thus exacerbating pathology¹⁶. Likewise, in Parkinson's disease, gut-derived inflammatory signals contribute to microglial activation and neuroinflammation that may trigger or accelerate alpha-synuclein pathology³⁰.

Microbiota Alterations across Neurodegenerative Diseases

Gut alterations or dysbiosis have been linked to the progression of Neurodegenerative diseases. These diseases have specific gut dysbiosis signatures. Parkinson's disease consistently showed reduced SCFA-producing *Faecalibacterium* and *Roseburia*, as well as increased *Akkermansia*, *Ruminococcus* and *Lactobacillus*. Alzheimer's disease has been linked to heterogeneous and increased levels of *Erysipelatoclostridiaceae*, *Erysipelotrichales* and *Saccharimonadales*, which are associated with the APOE gene carrier expressed in the disease, thereby causing more deteriorative dementia management³¹.

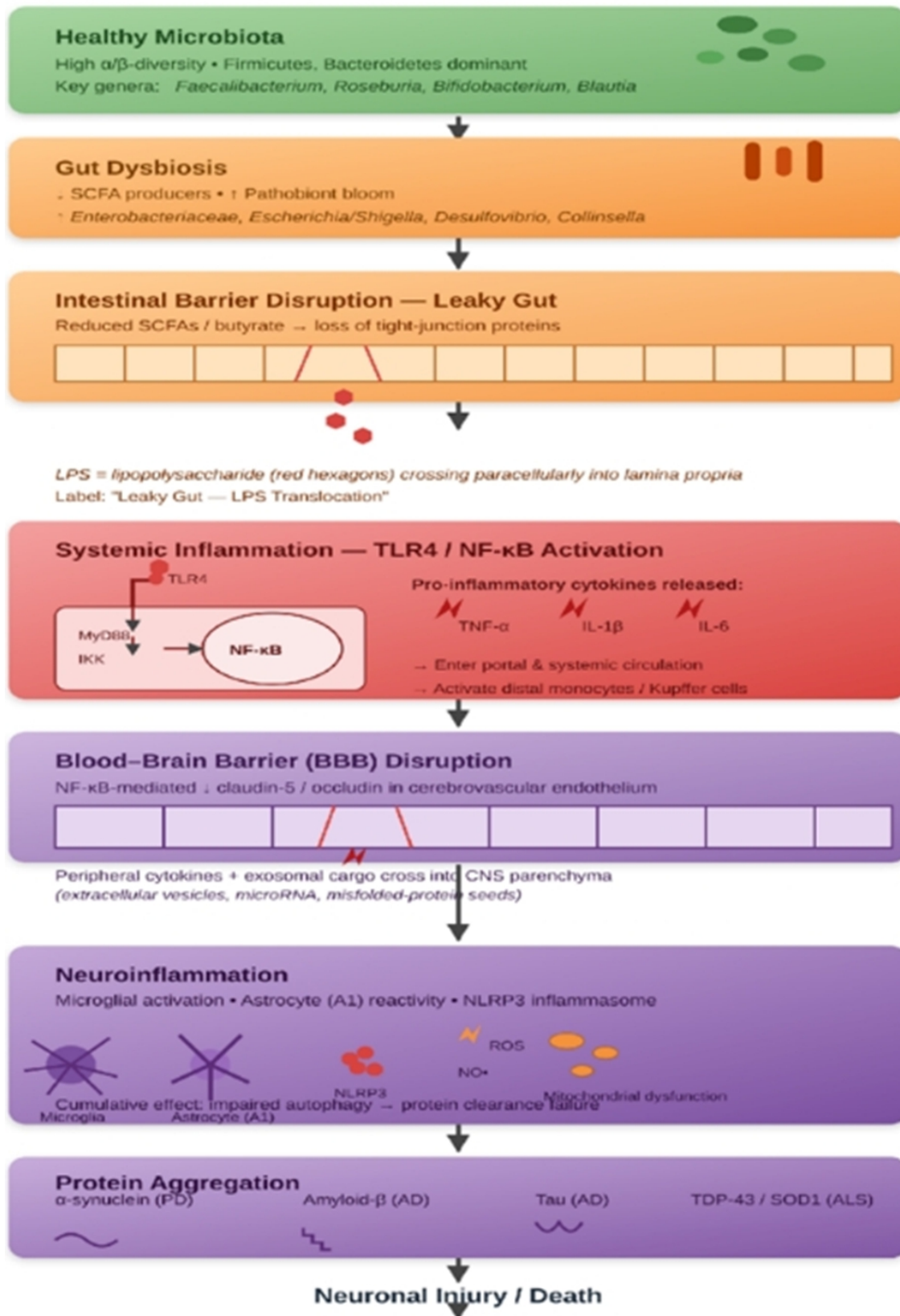


Figure 2: Schematic illustration of Microbiota Alterations in Neurodegenerative Diseases

Natural Bioactive Compounds: Promising Intervention for Neuroprotection

Natural bioactive compounds are emerging in the management of neurodegenerative diseases and are documented for their connections to neuroprotective mechanisms. These act through oxidative stress mitigation, mitochondrial guarding, neurotrophin support, anti-inflammatory tuning, blood-brain barrier reinforcement, and gut microbial biotransformation³². Key representatives include isoflavones from soyabeans and red-clover, polyphenols from grapes, teas and berries, Curcuminoids from turmeric, omega-3s (DHA, EPA) from fatty fish and algae, alkaloids like berberine and piperine, terpenoids such as ginkgolides and ursolic acid, SCFA precursors (inulin, resistant starch) from chicory and oats, carotenoids (astaxanthin, luteins); glucosinolate-derived isothiocyanates from broccoli, and lignans from flaxseed³²⁻³⁴.

Isoflavones

The gut microbiota metabolizes Isoflavones (genistein, daidzein, puerarin) to form bioactive derivatives that can more efficiently cross the BBB than parent compounds. A study demonstrates that an isoflavone-enriched diet ameliorates Parkinson's disease in mice by inhibiting ferroptosis via gut microbiota mediating serotonin production. Daidzein and Puerarin were reported to exhibit neuroprotective effects against MPTP-induced Parkinson's pathology and microglial activation³⁵.

Polyphenols

Bidirectional communication between the gut and microbiota is enhanced by polyphenols; their bioavailability results from bacterial metabolism and concurrently augments important benefits and stifles pathogens. According to reports, polyphenols improved the composition of gut microbes and reduced neuroinflammation across animal models of Alzheimer's, Parkinson's and multiple sclerosis by reducing amyloid deposition and tau hyperphosphorylation in the brain. They exert their effect through antioxidative, anti-inflammatory and MAPK-pathway modulation³⁶.

Flavonoids

Flavonoids such as quercetin, EGCG, kaempferol and naringenin modify the gut-brain axis by promoting SCFA- and GABA-producing bacteria as well as correcting dysbiosis associated with neurodegeneration. Quercetin and kaempferol collectively restored the balance of gut microbiota and attenuated multi-pathogenic mechanisms in Parkinson's disease models. Quercetin particularly reconfigured gut microbiota composition and adjusted brain metabolic profiles to curtail depression-like behavior. Flavonoids act through bitter-taste receptor (TAS2R) activation, thereby linking the gut hormone to reducing Alzheimer's incidence³⁷.

Curcuminoids

Curcumin, and related curcuminoids (demethoxycurcumin, bisdemethoxycurcumin) from turmeric modulate gut microbiota bidirectionally. Bacteria biotransform curcumin into more bioavailable metabolites, while curcumin in turn adjusts microbiota taxa. Curcumin restored short-chain fatty acid profiles in a study of 1-methyl- 4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP) induced Parkinson's mice, mitigated dopaminergic neuron losses, and repaired intestinal barrier dysfunction³⁸. In APP/PS1 Alzheimer's mice, curcumin also altered Bacteroidaceae, Prevotellaceae, and Lactobacillaceae abundance, ameliorated spatial memory and curtailed hippocampal amyloid plaques³⁹.

Alkaloids

Despite the low absorption of alkaloids such as berberine in the gut, they possess significant effects in the GBA. In Parkinson's models, orally ingested berberine improved brain dopa/dopamine levels by modulating gut microbiota⁴⁰. It also inhibited α -synuclein aggregation, thus preventing Lewy body formation. In Alzheimer's models, berberine reduced tau hyperphosphorylation and amyloid- β deposition while restoring gut barrier integrity and microglial M1/M2 polarization balance⁴¹.

Bioavailability Challenges of Natural Products and Gut-Mediated Bioactivation

The bioavailability challenges of natural products are linked to poor solubility, rapid metabolism and excretion, incomplete gut retention and poor stability, thus resulting in limited systemic exposure. The gut microbiota drive reactions such as hydrolysis, reduction, demethylation, and ring fission of parent compounds to form more absorbable bioactive compounds, thus greatly influencing the availability of natural products⁴². These challenges pose significant individual variability depending on initial microbiota composition, diet, medications, and dysbiosis⁴³.

Microbiota-Bioactive Synergy in Neuroprotection

Despite the pharmacological properties of bioactive products, their modulation against neurodegeneration depends strongly on interaction with the gut microbiota. This two-way dialogue orchestrates metabolite generation, barrier function, neuroimmune signaling and microglial behavior, ultimately modulating the trajectory of neurodegenerative and cerebrovascular diseases^{44,45}. Actively sculpting microbial ecosystems favors beneficial microbes such as Bifidobacterium, Lactobacillus, Akkermansia, and Faecalibacterium, while suppressing pro-inflammatory invasion. These bioactives enhance production of SCFAs, reduce lipopolysaccharide (LPS)-producing pathogens, lower

endotoxemia, and dampen gut-brain-inflammatory signaling^{45,46}. SFAs, including acetate, propionate and butyrate that are generated during fermentation of fiber, and polyphenol-rich substrates also function as primary regulators of bioactives and microbiota synergy. They mature microglia, reinforce BBB, and suppress excessive inflammation. Polyphenol consumption amplifies SCFA output, linking dietary patterns to neurological resilience⁴⁷.

Challenges, Future Directions and Therapeutic Opportunities

Persistent problems, including poor bioavailability, short durations, heterogeneity, mismatched endpoints and failure to measure microbiota interaction, pose major challenges to the efficacy of synergy between bioactive products and microbiota^{48,49}. Most research continues to approach bioactives or microbes separately; individual gut microbiota composition represents a major hurdle in the management of Alzheimer's disease. Rather than uniform doses, there is a shift toward precision approaches that see the individual microbiota as a therapeutic variable. Preclinical efforts show that responses to polyphenols vary significantly depending on host genetics, such as APOE status⁵⁰. The bench-to-bed gap still poses challenges to the feasibility of exploring natural products and gut microbes in the management of neurodegenerative diseases. Solving the research-to-translation gap is one of the most persistent research challenges of neuroscience concerning neurodegeneration. Promising compounds with strong preclinical profiles often have disappointing applications in translation research, as translation requires significant precision in dosing, timing, formulation, and patient stratification⁵¹.

Microbiota-Sequencing and Precision Medicine

Advances in multi-omics and deep sequencing allow microbiota profiling in routine clinical practice. Integration of metagenomics, metabolomics, dietary and clinical data provides predictions of a microbiota signature linked to amyloid pathology, microglial activation and SCFA/LPS dynamics. It allows for targeted selection of polyphenols based on an individual's metabolic capacity to generate neuroprotective metabolites⁵²⁻⁵⁴. Also, the exploration of machine learning models is accelerating and considerably reducing the challenges of bioactive-gut interaction. Neural networks have achieved AUCs of 0.89 in predicting cognitive impairment from microbiome patterns, paving the way for early and mechanism-based dosing of bioactives. AI-driven multi-omics integration is moving the science from associations to causation and actionable insights, while standardized analytical pipelines remain required to ensure reproducibility^{53,55,56}.



Gut-brain axis translational intervention for Alzheimer's disease: From Bench to Bed-side

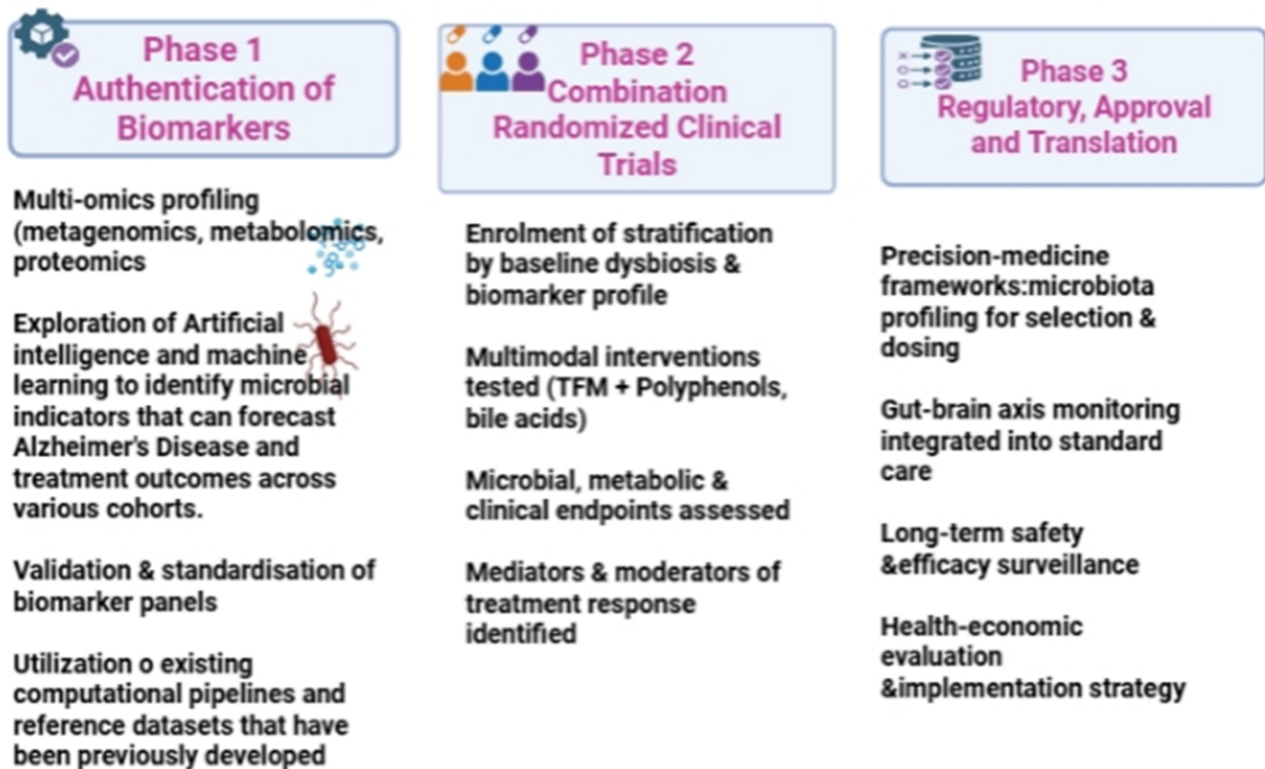


Figure 3: Road-map of Gut-brain Axis to Translational Medicine

CONCLUSION

The microbiota-bioactive axis opens a promising area of research for next-generation neuroprotective therapeutic agents, and future clinical trials must prioritize early-stage, biomarker-stratified trials with advanced formulations, extended durations, and multi-omic biomarkers to close this long-standing gap. Future strategies must consider multi-omics (metagenomics, metabolomics) and address individual microbiota variability to permit personalized approaches.

DECLARATIONS

Funding: None Declared.

Conflict of Interests Disclosure: The author(s) have declared that no competing interests exist.

Declaration of Generative AI and AI-Assisted Technologies: The author(s) declare that no generative AI or AI-assisted technologies were used in the preparation of this manuscript.

ARTICLE INFORMATION

Accepted for Publication: June 13, 2026

Published: June 27, 2026

Peer Review: Externally Peer Reviewed.

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REFERENCES

- Morais LH, Schreiber HL, Mazmanian SK. The gut microbiota–brain axis in behaviour and brain disorders. *Nat Rev Microbiol.* 2021;19(4):241-255. doi:10.1038/s41579-020-00460-0.
- Pathak N, Vimal SK, Tandon I, Agrawal L, Hongyi C, Bhattacharyya S. Neurodegenerative Disorders of Alzheimer, Parkinsonism, Amyotrophic Lateral Sclerosis and Multiple Sclerosis: An Early Diagnostic Approach for Precision Treatment. *Metab Brain Dis.* 2022 Jan;37(1):67-104. doi: 10.1007/s11011-021-00800-w.
- Argueti-Ostrovsky S, Alfahel L, Kahn J, Israelson A. All Roads Lead to Rome: Different Molecular Players Converge to Common Toxic Pathways in Neurodegeneration. *Cells.*2021;10. doi: 10.3390/cells10092438.
- Liddel SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. *Immunity.* 2017;46(6):957-967. doi: 10.1016/j.immuni.2017.06.006.
- World Health Organization. Neurological disorders: public health challenges. 2nd ed. Geneva: World Health Organization; 2023.
- Su D, Cui Y, He C, Yin P, Bai R, Zhu J et al. Projections for prevalence of Parkinson's disease and its driving factors in 195 countries and territories to 2050: Modelling study of Global Burden of Disease Study 2021 *BMJ.* 2025; 388: e080952. doi:10.1136/bmj-2024-080952.
- Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement.* 2017;13(1):1-7. doi: 10.1016/j.jalz.2016.07.150.
- GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(5):459-480. doi:10.1016/S1474-4422(18)30499-X.
- Pooladgar P, Sakhabakhsh M, Taghva A, Soleiman-Meigooni S. Donepezil beyond Alzheimer's disease? A narrative review of therapeutic potentials of donepezil in different diseases. *Iran J Pharm Res.* 2022;21(1): e128408.
- Kim NY, Lee HY, Choi YY, Sung JM, Jeon S, Ha JH, et al. Effect of gut microbiota derived metabolites and extracellular vesicles on neurodegenerative diseases in a gut-brain axis chip. *Nano Convergence.* 2024;11(7). doi: 10.1186/s40580-024-00413-w.
- Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev.* 2019;99(4):1877-2013. doi:10.1152/physrev.00018.2018.
- Yoo BB, Mazmanian SK. The enteric network: interactions between the immune and nervous systems of the gut. *Immunity.* 2017;46(6):910-926. doi: 10.1016/j.immuni.2017.05.011.
- Schneider E, O'Riordan KJ, Clarke G, Cryan JF. Feeding gut microbes to nourish the brain: unravelling the diet-microbiota-gut-brain axis. *Nat Metab.* 2024; 6:1454-1478. doi:10.1038/s42255-024-01108-6.
- Fornai M, Carbone F, Colucci R, Pellegrini C, Antonioli L. Enteric nervous system and its relationship with neurological diseases. *Brain Sci.* 2024;14(9):941. doi:10.3390/brainsci14090941.
- Abavisani M, Khoshrou A, Forouzan S, Sahebkar A, Ebrahimzadeh-Bideskan A. Vagus nerve stimulation and gut microbiota interactions: a novel therapeutic avenue for neuropsychiatric disorders. *Neurosci Biobehav Rev.* 2024; 167:105905. doi: 10.1016/j.neubiorev.2024.105905.
- Jin Z, Dong J, Wang Y, Liu Y. Exploring the potential of vagus nerve stimulation in treating brain diseases: a review of immunologic benefits and neuroprotective efficacy. *Eur J Med Res.* 2023;28(1):444. doi:10.1186/s40001-023-01439-2.
- Wilkins A, Herd MK, Rubin N. The gut microbiota-brain axis in neurological disorders. *MedComm.* 2024;5(7): e656. doi:10.1002/mco2.656.
- Gui Q, Li H, Wang A, Zhong J, Xu X, Shu J, et al. Microbiota-gut-brain axis in neurodegenerative diseases: molecular mechanisms and therapeutic targets. *Mol Biomed.* 2025;6(1):46. doi:10.1186/s43556-025-00307.
- Zheng Y, Bonfili L, Wei T, Eleuteri AM. Understanding the gut-brain axis and its therapeutic implications for neurodegenerative disorders. *Nutrients.* 2023;15(21):4631. doi:10.3390/nu15214631.
- Zhou, Y., Deng, J., Chu, X., Zhao, Y., & Guo, Y. Role of gut microbiota-derived short-chain fatty acids in the gut-brain axis. *Frontiers in Immunology.* 2024;15, 1504443. doi:10.3389/fimmu.2024.1504443.
- Beltran-Velasco AI, Clemente-Suárez VJ. Impact of Peripheral Inflammation on Blood–Brain Barrier Dysfunction and Its Role in Neurodegenerative Diseases. *International Journal of Molecular Sciences.* 2025; 26(6):2440. doi:10.3390/ijms26062440.

22. Zhang, B., Wang, Y., Li, X., & Peng, Y. The microbiota-gut-brain axis and central nervous system diseases: From mechanisms of pathogenesis to therapeutic strategies. *Frontiers in Microbiology*. 2025; 16, 1583562. doi:10.3389/fmicb.2025.1583562.
23. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. 2015;161(2):264-276. doi: 10.1016/j.cell.2015.02.047.
24. Krautkramer KA, Fan J, Bäckhed F. Gut microbial metabolites as multi-kingdom intermediates. *Nat Rev Microbiol*. 2021;19(2):77-94. doi:10.1038/s41579-020-0438-4.
25. Liu JR, Tan YZ, Cheng H, Zhang D, Feng W, Peng C. Functions of gut microbiota metabolites: current status and future perspectives. *Aging Dis*. 2022;13(4):1106-1126. doi:10.14336/AD.2022.0104.
26. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2020;17(4):223-237. doi:10.1038/s41575-019-0258-z.
27. Andreu VP, Augustijn HE, Chen L, Zhernakova A, Fu J, Fischbach MA, et al. GutSMASH predicts specialized primary metabolic pathways from the human gut microbiota. *Nat Biotechnol*. 2023;41(10):1416-1423. doi:10.1038/s41587-023-01675-1.
28. Agus A, Clément K, Sokol H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. *Gut*. 2021;70(6):1174-1182. doi:10.1136/gutjnl-2020-323071.
29. Yoon JH, Velankanni P, Lee CG, Kwon HK. Gut microbial metabolites on host immune responses in health and disease. *Immune Netw*. 2023;23: e6. doi:10.4110/in.2023.23.e6.
30. Lobo C, Fernández-Lázaro D, García I, Monsalve RI. Gut microbiome-brain axis: the crosstalk between the vagus nerve, the ENS and the microbiome in Parkinson's disease. *Neural Regen Res*. 2023;18(12):2611-2614. doi:10.4103/1673-5374.373673.
31. Peters M, Hegelmaier T, Höllerhage M, Yez L, Niesmann C, Schneidereit IV, et al. The role of the gut microbiome in the progression of Parkinson's disease: a systematic review of patient cohorts. *J Neurol*. 2026; 273:8.
32. Caruso G, Torrisi SA, Mogavero MP, Currenti W, Castellano S, Godos J, et al. Polyphenols and neuroprotection: therapeutic implications for cognitive decline. *Pharmacol Ther*. 2022; 232:108013. doi: 10.1016/j.pharmthera.2021.108013.
33. Li M, Li Z, Fan Y. Omega-3 fatty acids: multi-target mechanisms and therapeutic applications in neurodevelopmental disorders and epilepsy. *Front Nutr*. 2025; 12:1598588. doi:10.3389/fnut.2025.1598588.
34. Fahey JW, Liu H, Batt H, Panjwani AA, Tsuji P. Sulforaphane and brain health: from pathways of action to effects on specific disorders. *Nutrients*. 2025;17(8):1353. doi:10.3390/nu17081353.
35. Intharuksa A, Arunotayanun W, Takuathung NM, Chaichit S, Prasansuklab A, Chaikhong K, et al. Daidzein and genistein: natural phytoestrogens with potential applications in hormone replacement therapy. *Int J Mol Sci*. 2025;26(14):6973. doi:10.3390/ijms26146973.
36. Toderescu CD, Parveen M, Trifunski S, Oancea A, Ciubuc GC, Cresneac I, et al. Dietary polyphenols as modulators of Bifidobacterium in the human gut microbiota. *Nutrients*. 2026;18(5):782. doi:10.3390/nu18050782.
37. Wang Y, Tong Q, Zhao ZX, Pan LB, Cong L, Han P, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. *Signal Transduct Target Ther*. 2021; 6:77. doi:10.1038/s41392-020-00456-5.
38. Cai B, Zhong L, Wang Q, Xu W, Li X, Chen T. Curcumin alleviates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice via modulating gut microbiota and short-chain fatty acids. *Front Pharmacol*. 2023; 14:1198335. doi:10.3389/fphar.2023.1198335.
39. Chen J, Wei C, Zhang Y, Chen Q, Li X, Zhang W, et al. Curcumin exerts neuroprotective effects on proliferation of neural stem cells in vitro and APP/PS1 mouse model in vivo. *Sci Rep*. 2025; 15:12937. doi:10.1038/s41598-025-12937-0.
40. Huang J, Yue M, Yang Y, Liu Y, Zeng J. Protopine-Type Alkaloids Alleviate Lipopolysaccharide-Induced Intestinal Inflammation and Modulate the Gut Microbiota in Mice. *Animals*. 2024; 14(15):2273. doi:10.3390/ani14152273.
41. Yang G, Chen Y, Yao L, Lin T. The gut microbiota modulates neuroinflammation in Alzheimer's disease: elucidating crucial factors and mechanistic underpinnings. *CNS Neurosci Ther*. 2024;30(10): e70091. doi:10.1111/cns.70091.
42. Jaber KR, Alamdari-Palangi V, Savardashtaki A, Vatankhah P, Jamialahmadi T, Tajbakhsh A, et al. Modulatory effects of phytochemicals on the gut-brain axis: therapeutic implications. *Curr Dev Nutr*. 2024;8(6):103785. doi: 10.1016/j.cdnut.2024.103785.

43. Mahdi L, Graziani A, Baffy G, Mitten EK, Portincasa P, Khalil M. Unlocking polyphenol efficacy: the role of gut microbiota in modulating bioavailability and health effects. *Nutrients*. 2025;17(17):2793. doi:10.3390/nu17172793.
44. Loh JS, Mak WQ, Tan L, Ng CX, Chan HH, Yeow SH, et al. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. *Signal Transduct Target Ther*. 2024;9(1):82. doi:10.1038/s41392-024-01739-1.
45. Long-Smith C, O'Riordan KJ, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota-gut-brain axis: new therapeutic opportunities. *Annu Rev Pharmacol Toxicol*. 2020; 60:477-502. doi:10.1146/annurev-pharmtox-010919-023628.
46. Li M, Li Z, Fan Y. Omega-3 fatty acids: multi-target mechanisms and therapeutic applications in neurodevelopmental disorders and epilepsy. *Front Nutr*. 2025; 12:1598588. doi:10.3389/fnut.2025.1598588.
47. Lahariya R, Anand G, Kumari B, Priyadarshi K. Postbiotics and the gut-brain axis: a mechanistic review on modulating neuroinflammation and cognitive ageing. *J Neuroimmunol*. 2026; 413:578870. doi:10.1016/j.jneuroim.2025.578870.
48. Kim CK, Lee YR, Ong L, Gold M, Kalali A, Sarkar J. Alzheimer's disease: key insights from two decades of clinical trial failures. *J Alzheimers Dis*. 2022;87(1):83-100.
49. Kingman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Beigi M, et al. Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double-blind, placebo-controlled study. *Alzheimers Res Ther*. 2012;4(5):43. doi:10.1186/alzrt146.
50. Hasan A, Scuderi SA, Capra AP, Giosa D, Bonomo A, Ardizzone A, et al. An updated and comprehensive review exploring the gut-brain axis in neurodegenerative disorders and neurotraumas: implications for therapeutic strategies. *Brain Sci*. 2025;15(6):654. doi:10.3390/brainsci15060654.
51. Kim H, Kim Su, Gil WJ, Yang C. Exploring the therapeutic potential of phytochemicals: challenges and strategies for clinical translation. *Phytomedicine: international journal of phytotherapy and phytopharmacology*. 2025;145: 157090. doi:10.1016/j.phymed.2025.157090.
52. Clemente-Velasco S, de Lucas B, Tabone M, Bressa C, González-Soltero MR, Martínez-López S, et al. Study protocol for design of a personalized dietary supplement based on the gut microbiota of Alzheimer's patients and evaluation of its effects in a pilot randomized controlled trial. *Front. Nutr*. 2025; 12:1653841. doi:10.3389/fnut.2025.1653841.
53. Kumar R, Nagraik R, Lakhanpal S, Abomughaid M, Jha N, Gupta R. Artificial intelligence in gut microbiome research: toward predictive diagnostics for neurodegenerative disorders. *Acta Microbiol Immunol Hung*. 2025; 72:296-312. doi:10.1556/030.2025.02725.
54. Lei W, Cheng Y, Liu X, Gao J, Zhu Z, Ding W, et al. Gut microbiota-driven neuroinflammation in Alzheimer's disease: from mechanisms to therapeutic opportunities. *Front Immunol*. 2025; 16:1582119. doi:10.3389/fimmu.2025.1582119.
55. Franco CD, Sagar RS, Bokhari SFH. From microbes to memories: challenges and future perspectives regarding the gut-brain axis for improved cognitive health in Alzheimer's disease. *Cureus*. 2024;16(1).
56. Thanh Hoa Vo, Nguyen Quoc Khanh Le. Toward trustworthy artificial intelligence in multi-omics: a review of reproducibility, stability, and interpretability. *Briefings in Bioinformatics*. 2026;27(3). doi:10.1093/bib/bbag227.