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REVIEW

Short-Chain Fatty Acids and Related Postbiotic Mediators in Neurodegenerative Diseases

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ABSTRACT: Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's Disease (PD), and Multiple sclerosis (MS) represent a growing global health burden characterized by progressive neuronal loss, chronic neuroinflammation, immune dysregulation, and metabolic dysfunction. Increasing evidence highlights the gut-brain-immune axis as a critical regulator of disease susceptibility and progression. Microbiota-derived short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, act as key postbiotic mediators that link intestinal microbial activity to the central nervous system. SCFAS modulates neurodegenerative pathways by regulating glial activation, inflammatory signaling, barrier integrity, and epigenetic and metabolic processes. Altered SCFAS production is consistently associated with neuroinflammation, barrier dysfunction, and disease progression. This review aims to synthesize current mechanistic and translational evidence on SCFAs in neurodegeneration by discussing shared and disease-specific pathways and emerging therapeutic and biomarker applications. Preclinical and early clinical studies suggest that restoring SCFAS signaling may influence disease pathways; its disease-modifying effects in humans remain scarce. These findings support further investigation of SCFAs with precision and microbiota-targeted strategies.

KEYWORDS: Neuroinflammation; short-chain fatty acids (SCFAs); gut-brain axis; microbiota dysbiosis; postbiotics

1 Introduction

Neurodegenerative disorders constitute a heterogeneous but interrelated series of chronic progressive disorders, which are marked by selective neuronal loss of structure and function, which eventually lead to cognitive, motor, and behavioral defects. The most common ones in this spectrum include Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple sclerosis (MS), with each having different clinical phenotypic profiles but sharing the characteristic of convergent pathological processes [1]. These disorders have a clinical manifestation as progressive memory and executive dysfunction in AD, motor and non-motor issues in PD, and relapsing and progressive neurological disability in MS [2]. Neurodegenerative diseases collectively impact over 10 million people globally and are represented as a major cause of long-term disability, institutionalization, and death. They are becoming increasingly prevalent both in the developed and the developing areas due to a combination of population aging and improved survival rates of acute neurological and systemic diseases, thereby increasing the disease burden worldwide [3]. At the cellular and molecular level, neurodegeneration is no longer considered a neuron-centered process, but rather recognized as a multicellular process involving chronic dysfunctions of neurons, glial, endothelial, and

immune compartments. Acute microglia and astrocyte activation in AD, PD, and MS contribute to the further increase of a pro-inflammatory central nervous system (CNS) environment, marked by increased cytokine release, reactive oxygen species production, and impaired neuronal metabolic support. This glial dysregulation accelerates impairment of synapses, mitochondrial dysfunction, and axonal injury, thus facilitating progressive neurodegeneration [4]. Although innate immune signaling is initially protective, prolonged activation of pathways, such as Toll-like receptor (TLR) signaling, NF-κB transcriptional programs, and NLRP3 inflammasome assembly, becomes maladaptive and provides support to neuronal injury and facilitates the deposition and dissemination of pathogenic protein aggregates, including amyloid-β (Aβ), tau, and α-synuclein [5]. The resulting self-perpetuating loop of inflammation, proteostatic dysfunction, and cell death contributes to the further development of the disease and explains why the currently used treatments are partially ineffective, as they target downstream pathophysiological features rather than upstream regulatory processes [6].

In this mechanistic framework, there is increasing interest focused on systemic and peripheral pathogenesis of neurodegeneration, contesting the conventional perception of these disorders as distinct CNS diseases. The gut-brain axis is a key regulator of neuroimmune homeostasis, influencing CNS susceptibility through immune, metabolic, and neurovascular signaling pathways [7]. Alteration of microbial composition and activity of the gut has been consistently documented in AD, PD, and MS, and dysbiosis is linked to heightened intestinal permeability, peripheral immune responses, and the discharge of bioactive microbial elements. These signals influence the integrity of the blood-brain barrier (BBB), maturation of the microglia, astrocytic reactivity, and cytokine signaling, thus influencing the CNS inflammatory status and modulatory disease fate [8]. In this regard, microbiota-produced short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, have emerged as significant endogenous modulators of neuroimmune and neurovascular activity [9]. Bacterial fermentation of dietary fibers produces them, and they act on pleiotropic receptors via G-protein-coupled receptors such as free fatty acid receptors 2 and 3 (FFAR2/3), epigenetic regulation through histone deacetylase (HDAC) inhibition, and metabolic signal pathways [10]. In the central nervous system (CNS), SCFAs modulate microglial activation states, enhance astrocyte-mediated metabolic and antioxidant support, stabilize endothelial tight junctions within the BBB, and suppress pro-inflammatory transcriptional programs in a cell-type-specific manner. Through these mechanisms, SCFAs limit excessive neuroimmune activation, preserve homeostasis of the neurons, and constrain secondary neurodegenerative cascades [11]. Conversely, impaired SCFAS production or signaling, reported across AD, PD, and MS, has been linked to heightened neuroinflammation, compromised barrier function, accelerated disease progression, and greater clinical severity [12]. There is emerging evidence that restoring or increasing SCFAS signaling can suppress pathological neuroinflammation, enhance barrier stability, and reduce neurodegenerative disease progression. A decrease in circulating SCFAS ratios is associated with more disability and lesion burden in MS and loss of SCFAS-producing taxa with early pathological alterations and cognitive or motor impairment in AD and PD. These findings support the concept of SCFAs as endogenous counter-regulatory molecules that oppose chronic inflammatory and degenerative events in the CNS [13]. Besides their neurodegeneration functions, SCFAs are also involved in systemic, metabolic, and immune homeostasis, which substantiates their relevance as integrative mediators at the gut microbiota, immunity, and brain health interface [14].

This review will focus on summarizing existing data regarding the importance of the microbiota-derived SCFAs in neurodegenerative diseases, specifically comparing cell-type-specific actions and molecular signaling cascades that mediate neuroinflammation and the pathogenesis of diseases. Although prior reviews have discussed SCFAs, postbiotics, and microbiome alterations in neurodegenerative conditions, most have

focused on individual diseases or have provided descriptive overviews without integrating mechanistic and translational dimensions. The present review addresses this gap by comparatively examining AD, PD, and MS, with particular emphasis on shared and disease-specific neuroimmune mechanisms. Additionally, it highlights cell-type-specific actions of SCFAs across microglial, astrocytic, and endothelial compartments and also evaluates their relevance in the context of therapeutic development, biomarker potential, and clinical translation. By elucidating these mechanisms, this review seeks to contribute to a systems-level perspective of neurodegeneration and highlight microbiome-informed interventions as a promising component of precision medicine approaches for neurodegenerative disorders.

Review Methodology

This narrative review was conducted through a structured literature review by searching electronic databases, including PubMed and Google Scholar. The relevant studies published up to March 2026 were identified using a combination of keywords such as "short-chain fatty acids", "postbiotics", "gut–brain axis", and "neurodegenerative diseases", including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Both experimental (*in vitro* and animal studies) and human studies (observational and interventional) were considered. The priority was given to recent and high-quality studies providing mechanistic understanding or translational relevance. The reference lists of selected articles were also screened to identify additional relevant literature.

2 Gut-Brain-Immune Axis in Neurodegenerative Diseases

2.1 Bidirectional Gut-Immune-CNS Communication

The microbiota-gut-brain axis is a network of communication that involves the intestinal microbiota, the peripheral immune system, and the central nervous system (CNS), with increasing evidence suggesting that microbial imbalance, dysfunction of barriers, and constant inflammation disrupt this axis, which plays a role in the pathogenesis of major neurodegenerative diseases, such as AD, PD, Amyotrophic lateral sclerosis (ALS), and MS [15]. Microbiota-gut-brain axis communication is a result of a complex network of neural, immune, endocrine, and metabolic networks. Intestinal microbes and their products interact with the epithelial cells through interactions with populations of immune cells and enteric neurons and influence mucosal and systemic immune responses and communicate with the CNS via humoral and neural pathways [16]. The enteric nervous system and the vagus nerve constitute the major mediators of the neural signaling that perceives the microbial metabolites and inflammatory mediators and transmits this data to the brainstem and the higher autonomic centers. Vagal afferent activation modulates the microglial activation state and intervention of neuroinflammatory tone, whereas vagal efferent activation triggers the cholinergic anti-inflammatory reflex and inhibits the peripheral synthesis of cytokines and promotes the integrity of gut barriers [17]. The immune-driven communications are based on the cytokines, chemokines, and immune responses on microbial-associated molecular patterns (MAMP) such as lipopolysaccharide (LPS) and peptidoglycans. These signals can cross the BBB or access the CNS at vulnerable interfaces, thereby modulating microglial and astrocytic activity and affecting neuronal viability in neurodegenerative conditions [18,19]. The gut and the brain are also connected by endocrine and metabolic signaling, releasing enteroendocrine hormones and producing bioactive metabolites, including SCFAs, tryptophan derivatives, and BA metabolites. These substances can mediate their actions by stimulating neurogenesis, synaptic activity, and neuroimmune homeostasis via systemic circulation, G-protein-coupled receptors, and epigenetic processes [20]. In the CNS, the microglia and border-related macrophages are some of the major interpreters of peripheral immune signals and gut-derived

signals. These cells can be reprogrammed in response to sustained peripheral inflammation and metabolic changes to a persistent state of neurotoxicity in neurodegenerative diseases [21]. Fig. 1 illustrates the integrated gut-brain-immune axis in neurodegenerative disease, highlighting how gut dysbiosis and barrier dysfunction activate systemic immune and metabolic imbalance to maintain the integrity of the BBB, stimulate glial activation, and perpetuate chronic neuroinflammation and neuronal cell destruction in neurodegenerative diseases.

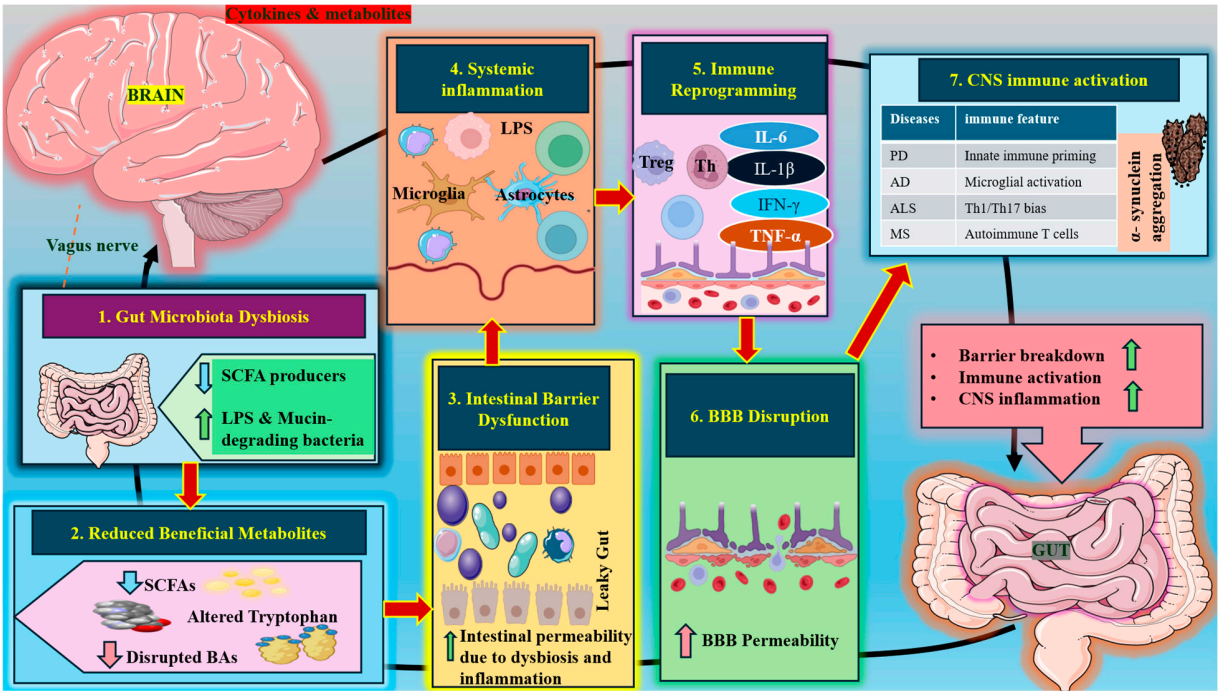

Figure 1: Integrated gut–brain–immune axis in neurodegeneration. This diagram illustrates the integrated gut–brain–immune axis in neurodegenerative diseases. Gut dysbiosis and barrier dysfunction trigger systemic inflammation, immune cell activation, and metabolic imbalance. These signals disrupt blood–brain barrier integrity, promote microglial and astrocytic activation, and drive chronic neuroinflammation, synaptic dysfunction, and progressive neuronal degeneration. Upward arrows indicate increased production of LPS and mucin-degrading bacteria, whereas downward arrows indicate a reduction in short-chain fatty acid (SCFAS)-producing microbiota. This figure is original and was created using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA; version 2019). Abbreviation: AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; BBB, blood–brain barrier; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; CNS, central nervous system; Treg, regulatory T cell; Th, T helper cell.

2.2 Shared and Disease-Specific Dysbiosis Pattern

Despite disease-specific features, neurodegenerative disorders share common alterations in gut microbiota composition. A consistent finding is the depletion of SCFAS-producing commensals, such as *Faecalibacterium* and *Roseburia*, alongside expansion of Gram-negative LPS-producing, pro-inflammatory taxa. This dysbiotic profile promotes systemic inflammation, impairs regulatory T-cell (Treg) function, and promotes microglial overactivation [22]. In PD, reduced abundance of butyrate-producing *Firmicutes* and increased levels of *Enterobacteriaceae* family members, *Akkermansia* spp., and other mucin-degrading species have been repeatedly reported. These alterations correlate with gastrointestinal dysfunction, disease severity, and markers of intestinal inflammation, supporting a link between gut pathology, α-synuclein aggregation,

and nigrostriatal neurodegeneration [23]. AD is similarly characterized by reduced microbial diversity, loss of anti-inflammatory taxa, and enrichment of LPS and amyloid-producing bacteria. Microbial amyloids and endotoxins could precondition the activation of the innate immune system, help the aggregation of Aβ and tau, and maintain the microglial activity in the AD brain [24]. Loss of beneficial SCFAs-producing microbes, such as *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Eubacterium rectale*, and an increase in taxa favoring pro-inflammatory T-cell polarization between T helper type 1/17 cells (Th1/Th17) phenotypes characterize dysbiosis in ALS. These immune changes may worsen motor neuron damage through amplifying oxidative stress, excitotoxicity, and neuroinflammation in spinal motor networks [22]. MS is associated with a unique dysbiosis characterized by decreased production of SCFAs by Clostridia and increased abundance of taxa that stimulate Th17 responses and inhibit Treg differentiation. Such profiles of microbes are associated with disease activity and demyelination in experimental models and MS patients [16]. Overall, these disease-specific patterns converge on impaired SCFAs signaling, heightened endotoxin exposure, and disrupted immune tolerance, suggesting a shared upstream mechanism of gut-driven immune dysregulation across neurodegenerative conditions.

2.3 Gut Permeability, Systemic Inflammation, and BBB Dysfunction

Intestinal epithelial barrier constitutes an important interface between luminal microbes and the host immune system and is sustained through tight junction proteins, mucus, antimicrobial peptides, and secretory IgA, which together ensure maintenance of permeability and restrict microbial translocation [18]. Dysbiosis affects barrier integrity, which lowers the levels of SCFAs, downregulates tight junction proteins, including claudins and occludin, and supports mucosal inflammation, which increases intestinal permeability and translocation of bacteria, LPS, and other pathogen-associated molecular patterns (PAMPs) into the circulation [22]. Chronic exposure to such microbial products induces chronic low-grade inflammation with high levels of TNF-α, IL-1β, and IL-6, which sensitize peripheral and central immune responses. These inflammatory cues, pro-inflammatory cytokines, LPS, and ROS are strongly responsive to the BBB, including endothelial cells, pericytes, and astrocytic endfoot processes, and cause impairment of tight junction integrity, leukocyte infiltration, and astrocytic infiltration of the brain parenchyma [21,25]. Evidence from PD, AD, and MS has shown that high levels of intestinal permeability are often accompanied by BBB dysfunction and ensuing neuroinflammation, and PD studies contributed to linking LRRK2-related defects of epithelial and endothelial barrier regulation [23]. Barrier disruption allows greater immune cell infiltration of peripheral cells, antibodies, and microbial products into the CNS, creating a feed-forward loop where glial activation increases neurodegeneration, amplifying neuroinflammatory signaling. Gut proteins that are misfolded into α-synucleins have the potential to be spread in the CNS, either through prion-like expansion along the vagus nerve, using breached barrier interfaces. In physiological conditions, the SCFAs like butyrate have a barrier-protective and immunoregulatory effect on the intestinal epithelial barrier (IEB) and the BBB; constraints are removed in dysbiosis, permitting progressive peripheral and central inflammation [26]. Together, activated breakdowns in the gut microbial composition, barrier integrity, and systemic immune stimulation have a convergent effect on BBB dysfunction to encourage the activation of microglia, synaptic dysfunction, and neuronal damage, which suggests the therapeutic value of interventions focusing on the restoration of microbial balance and the enhancement of barrier functionality.

3 Postbiotics: Classes and Molecular Signaling Targets

3.1 SCFAs, Indoles, BA Derivatives, Peptides, and Polysaccharides

Postbiotics are functionally diverse microbial-derived metabolites and structural components that mediate host-microbial signaling through distinct but convergent signaling pathways, many of which intersect with neuroimmune mechanisms and neuroinflammatory processes associated with neurodegenerative diseases [27]. The most widely characterized postbiotics with direct mechanistic relevance to CNS homeostasis include SCFAs, indole derivatives, BAs metabolites, microbial peptides, and polysaccharides. However, other emerging microbiota-derived biomarker mediators, including endocannabinoid-like lipids and ALIAmides, are increasingly recognized as contributors to gut-brain signaling, while their roles remain less extensively characterized in neurodegenerative diseases. These lipid mediators, including N-acylethanolamines such as palmitoylethanolamide (PEA), show immunomodulatory and neuroprotective effects through activation of peroxisome proliferator-activated receptor-α (PPAR-α), transient receptor potential vanilloid 1 (TRPV1), and cannabinoid-like signaling pathways. These mechanisms regulate neuroinflammation, mast cell activation, microglial reactivity, and intestinal barrier integrity. The growing evidence suggests that ALIAmides may enhance SCFAs-mediated signaling by modulating neuroimmune responses and redox balance [28]. SCFAs are bacterial fermentation products of dietary fibers that act as key signaling molecules within the gut-brain interface [27,29]. These metabolites also engage G protein-linked receptors, such as FFAR2 (GPR43), FFAR3 (GPR41), and GPR109A, expressed on intestinal epithelial cells, immune cells, vagal afferents, and microglia, thereby regulating peripheral immune tone, BBB integrity, and neuroinflammatory signaling [30]. At the same time, butyrate functions as an antagonist of class I HDACs that trigger epigenetic restructuring of pro-inflammatory gene expression, differentiation of regulatory T-cells, and microglial activation mechanisms, all of which are likely to play a role in the pathogenesis of AD, PD, and MS [31] Microbial tryptophan metabolism generates indole and indole-derived metabolites, such as indole-3-aldehyde and indole-3-propionic acid, which act as endogenous ligands of the aryl hydrocarbon receptor (AhR). Activation of AhR in intestinal immune cells, astrocytes, and microglia promotes IL-22-dependent barrier reinforcement, restricts peripheral immune infiltration, and supports CNS immune surveillance, linking gut microbial metabolism to neuroimmune crosstalk [32,33]. Similarly, conversion of primary to secondary BAs by gut microbiota, such as deoxycholic acid and lithocholic acid, expands postbiotics signaling by activating GPBAR1 (TGR5), farnesoid X receptor (FXR), pregnane X receptor (PXR), and AhR. These BA-receptor axes have a role in systemic metabolism and mitochondrial activity and inflammatory signaling and have increasingly been shown to have a direct effect on microglial energetics and neuroinflammatory tone [34]. Besides small-molecule metabolites, microbial peptides, such as bacteriocins, and cell wall fragments also interact with pattern recognition receptors, including Toll-like receptors and nucleotide-binding oligomerization domain receptors, which indirectly cause CNS inflammation. Microbial polysaccharides such as exopolysaccharides and peptidoglycan derivatives also mediate immune signaling and epithelial barrier integrity through the receptor-mediated pathways [35]. These classes of postbiotics form a networked signaling system, integrating host immune, epigenetic, and metabolic signals with microbial metabolism, which may provide their emerging functions as modulators of neuroinflammation and neurodegenerative diseases. The major classes of postbiotics and their convergent molecular targets in neuroinflammation are summarized in Table 1. These classes converge on a limited number of core-signaling pathways, which are further elaborated in the following sections.

Table 1: Postbiotics classes and their molecular targets involved in neuroimmune and neuroinflammatory regulation.

S. No	Postbiotics Class	Representative Molecules	Primary Receptors/Molecular Targets	Key Downstream Signaling Pathways	Neuroimmune/CNS Effects	Relevance to Neurodegenerative Diseases	References
1.	**SCFAs**	Acetate, propionate, butyrate	FFAR2 (GPR43), FFAR3 (GPR41), GPR109A; HDACs (class I/IIa); AMPK	GPCR–AMPK, ERK1/2, p38 MAPK; HDAC inhibition; NF-κB suppression	Enhances BBB integrity; suppresses microglial activation; promotes Treg differentiation; epigenetic reinforcement of anti-inflammatory genes	AD, PD, MS—reduced neuroinflammation, improved synaptic plasticity, and cognition	[11]
2.	**Indole and tryptophan metabolites**	Indole-3-aldehyde, indole-3-propionic acid	AhR	AhR–STAT1/NF-κB antagonism; SOCS2 induction; Nrf2 activation	Reinforces intestinal and BBB barriers; limits peripheral immune infiltration; promotes astrocyte and microglial immune tolerance	AD, MS—attenuation of chronic neuroimmune activation	[36]
3.	**Secondary BA derivatives**	DCA, LCA	FXR, TGR5 (GPBAR1), PXR, AhR	FXR–NF-κB repression; TGR5–cAMP–PKA–CREB; mitochondrial biogenesis	Regulates microglial energetics; reduces pro-inflammatory cytokine production; improves redox balance	AD, PD—modulation of microglial metabolism and inflammatory tone	[34,37]
4.	**Microbial peptides**	Bacteriocins, cell wall fragments	TLR2, TLR4, NOD1/2	MyD88-dependent signaling; NF-κB and MAPK modulation	Shapes innate immune priming; supports controlled immune surveillance without excessive inflammation	AD, PD—balanced clearance of pathological protein aggregates	[38]
5.	**Microbial polysaccharides**	Exopolysaccharides, peptidoglycan derivatives	TLRs, C-type lectin receptors	Tolerogenic TLR signaling; epithelial barrier signaling	Maintains epithelial and BBB integrity; modulates systemic immune tone	MS, AD—reduced peripheral immune infiltration into the CNS	[39,40]
6.	**Integrated postbiotics signaling networks**	SCFAs, indoles, BAs (combined)	GPCRs, AhR, FXR, TGR5, TLRs	AMPK–NF-κB–AhR–Nrf2 crosstalk; epigenetic and metabolic reprogramming	Long-term neuroimmune resilience; controlled inflammasome priming; enhanced phagocytic capacity	AD, PD, MS—system-level regulation of chronic neuroinflammation	[15]

Note: SCFAs, short-chain fatty acids; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; GPR, G protein-coupled receptor; HDACs, histone deacetylases; AMPK, AMP-activated protein kinase; GPCR, G protein-coupled receptor; ERK1/2, extracellular signal-regulated kinase 1/2; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; BBB, blood–brain barrier; Treg, regulatory T cell; AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; AhR, aryl hydrocarbon receptor; STAT1, signal transducer and activator of transcription 1; SOCS2, suppressor of cytokine signaling 2; Nrf2, nuclear factor erythroid 2–related factor 2; BA, bile acid; DCA, deoxycholic acid; LCA, lithocholic acid; FXR, farnesoid X receptor; TGR5, Takeda G protein-coupled receptor 5; GPBAR1, G protein-coupled bile acid receptor 1; PXR, pregnane X receptor; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP response element-binding protein; TLR, Toll-like receptor; NOD, nucleotide-binding oligomerization domain.

3.2 Receptor-Mediated Signalling

Receptor-mediated signaling constitutes a highly coordinated molecular network through which postbiotic metabolites are translated into integrated immune, metabolic, and neuroprotective responses along the gut-brain axis. In addition to their function as discrete molecular sensors, G protein-coupled receptors (GPCRs), TLRs, AhR, and BA receptors, namely FXR and Takeda G protein-coupled receptor 5 (TGR5), are also involved in large-scale, coordinated signaling networks. These pathways all intersect at common transcriptional regulators and metabolic checkpoints that, together, set the neuroinflammatory tone and cell resilience [20]. However, it is important to note that several of these interactions are derived from integrative reviews and preclinical studies, and direct mechanistic validation in humans remains limited. SCFAS is a major initiator of this network, which occurs when they act via GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A. The activation of these receptors inhibits adenylate cyclase activity and regulates the intracellular Ca^{2+} fluxes, which cause downstream signaling of AMP-activated protein kinase (AMPK), ERK1/2, and p38 MAPK signaling cascades [41]. The GPCR-mediated AMPK stimulation overlaps with FXR and TGR5-regulated pathways in the regulation of cellular energy perception, mitochondrial biogenesis, and redox homeostasis. This immune and glial reprogramming of metabolism prevents the activation of NF-κB and functionally interacts with tolerogenic TLR signals to curb excessive cytokine production [42]. Furthermore, TLRs are central to innate immune recognition of microbial structural components due to the focus of TLR4 on sensing LPS and peptidoglycan-derived motifs. TLR4 activates MyD88-dependent signaling, which can be functionally restrained to limit canonical NF-κB and MAPK networks activation and, consequently, pro-inflammatory gene transcription. This inhibited TLR stimulation worked cooperatively with GPCR-mediated NF-κB inhibition to maintain AhR sensitivity through conserving redox homeostasis [43]. This synchronized communication among the microglia lowers inflammasome-priming through maintenance of phagocytic capacity, a balance that is very important in the removal of pathological protein aggregates without worsening neuroinflammation [44]. AhR is a central transcriptional integrator of microbial tryptophan metabolism with immune and glial homeostasis. The microbial products derived from indole induce AhR, which triggers nuclear translocation and transcriptional programs involved in antioxidant defence, epithelial barrier integrity, and immune tolerance. AhR counterbalances inflammatory responses mediated by STAT1 and NF-κB and triggers SOCS2 expression, thus enhancing the anti-inflammatory response through GPCR signaling and tolerogenic TLR signaling [45]. The overlapping co-regulators of transcriptional regulation of AhR and FXR further allow the coordination of inflammatory gene expression with lipid metabolism. Also, BA products, synthesized by microbes, enter the signal network by FXR and TGR5. FXR activation inhibits the pro-inflammatory transcription and consists of co-repressors recruiting promoters of the NF-κB. This inhibition is also enhanced by concomitant GPCR-AMPK crosstalk. Simultaneously, TGR5 stimulated intracellular cAMP, which activates PKA-CREB signatures that enhance mitochondrial oxidative potential and induce anti-inflammatory macrophages and microglia [46,47]. Particularly, cAMP signaling mediated by TGR5 also enhances AhR-controlled transcription, highlighting the two-way interaction between postbiotic-responsive receptors. Together, this receptor-based combination offers a mechanistic framework of the system-level effectiveness of postbiotics in regulating chronic neuroinflammation in neurodegenerative disease without impairing physiological immune surveillance.

3.3 Epigenetic, Metabolic, and Redox Regulation

The modulatory effects of postbiotics on neurodegenerative signaling, in addition to the receptor-proximal signaling, involve the regulation of epigenetic architecture, cell metabolism, and redox homeostasis.

These downstream regulatory programs are molecular memory systems, which encode transient microbiota-derived cues into long-term changes in gene transcription, bioenergetics, and oxidative resistance of immune and neural cells [48]. Butyrate and propionate are endogenous inhibitors of the class I and class IIa HDACs at the epigenetic level. The inhibition increases the histone H3 and H4 acetylation of promoters and enhancers of anti-inflammatory and neuroprotective genes, such as IL-10, FOXP3, and BDNF. The HDAC-inhibitory effect of butyrate alters chromatin accessibility to homeostatic mediators of tumour necrosis factor-α (TNF-α), IL1β, and NOS2 in microglia [49]. Animal models of AD and PD indicate that the dietary or exogenous SCFAS supplementation recovers synaptic plasticity and cognitive performance by epigenetically reinforced neurotropic signaling [13]. These findings are primarily based on experimental models, and the direct translation to human neurodegenerative conditions remains to be fully addressed. Experimental autoimmune encephalomyelitis (EAE) demonstrates that propionate-driven histone acetylation stabilizes regulatory T cell identity and inhibits pathogenic Th17 polarization, thereby limiting neuroinflammatory pathology [50]. Additionally, postbiotics have a significantly strong impact on cellular metabolism, specifically, mitochondrial activity and immunometabolic programming. SCFAs are transported into cells via monocarboxylate transporters and used in an anaplerotic reaction with the tricarboxylic acid cycle, thereby increasing oxidative phosphorylation and ATP generation. This metabolic shift overcomes the glycolytic bias of the microglia and macrophages in a neurodegenerative state [51]. The experiments performed in germ-free and antibiotic-treated mice also prove the fact that the recovery of microbial metabolites results in the normalization of microglial mitochondrial morphology, respiratory capacity, and NAD+/NADH redox status, which points to a direct mechanism between postbiotics availability and CNS energy homeostasis [52]. The indole derivatives and secondary BAs were found to stimulate endogenous antioxidant defense systems by stabilization of nuclear factor erythroid 2-related factor 2 (Nrf2) and phase II detoxifying enzymes, such as heme oxygenase-1, glutathione S-transferases, and NADPH quinone oxidoreductase 1. Postbiotics are also able to prevent oxidative damage to lipids, proteins, and mitochondrial DNA by inhibiting the overproduction of reactive oxygen and nitrogen species in AD, PD, and MS [15]. Epigenetic reprogramming, metabolic optimization, and redox regulation are all mutually reinforcing regulatory loops that ensure that postbiotics result in long-term system-wide regulation of neurodegenerative pathways [20]. These convergent processes are molecularly based on the benefits observed in preclinical and early clinical trials and provide opportunities for therapeutic stratification and biomarker development. Collectively, these mechanisms represent established and well-characterized downstream regulatory pathways of postbiotics, which provide the mechanistic foundation for their immunomodulatory effects described in subsequent sections.

4 Core Neuroinflammatory Mechanisms Modulated by Postbiotics

4.1 Microglial Immunometabolic Reprogramming by Microbiota-Derived Postbiotics

Microbiota-derived postbiotics exert a decisive influence on microglial functional states through the coordinated integration of receptor-mediated signaling, epigenetic regulation, and immunometabolic remodeling as introduced in Section 3. These convergent mechanisms cause postbiotics to modify the chronic primed phenotype of microglia to reparative and immune-regulatory ones, which play a vital role in defining neurodegenerative processes [20]. SCFAs exemplify these mechanisms by suppressing NF-κB activation and attenuating inflammasome priming. These SCFAs have been shown in experimental models to reduce the expression of TNF-α, IL-1β, and IL-6, while inducing arginase-1, YM1, and IGF-1, thereby promoting phagocytic clearance of pathological protein aggregates without exacerbating cytokine-mediated neurotoxicity in experimental models of AD and PD [49]. Consistent with this regulatory role, germ-free

mice have a phenotype that is normalized upon reconstitution with SCFAS-producing microbial consortia, restoring microglial surveillance, homeostatic gene expression, and responsiveness to systemic immune cues. These findings indicate that postbiotic insufficiency enforces a maladaptive microglial set point characterized by exaggerated inflammatory reactivity [53].

Beyond SCFAS, indole and indole-derived metabolites generated through microbial tryptophan metabolism activate the AhR in microglia and astrocytes, leading to suppression of NF-κB signaling and inhibition of NLRP3 inflammasome activation. AhR engagement reduces secretion of IL-1β, IL-18, and TNF-α and downregulates antigen-presenting and co-stimulatory molecules such as MHC-II and CD86, while preserving phagocytic capacity and synaptic support within an environment of amyloid deposition and focal ischemic injury [54]. Simultaneously, AhR-mediated expression of suppressor of cytokine signaling proteins and antioxidant response pathways breaks self-reinforcing loops of cytokine-ROS interactions that support the occurrence of neuroinflammation [55]. Such effects interact with metabolic reprogramming by SCFAS, characterized by a shift from glycolysis towards oxidative phosphorylation, and stabilizing a less inflammatory and more robust microglial phenotype. At the same time, postbiotics derived by BA, such as taurosodeoxycholic acid (TUDCA) and BA receptor agonists TGR5, stimulate cAMP-PKA signaling in microglia, leading to the suppression of NF-κB and NLRP3 pathways. Activation of TGR5 inhibits enzymes of glycolysis like PKM2, stimulates M2-like tissue-repair phenotypes, and neuronal survival in models of acute neuroinflammation and PD [56]. Notably, TGR5 signaling in peripheral macrophages mediates M1 to M2 polarization and efferocytosis, implying that BA postbiotics have the potential to synchronize microglial and monocyte-based immune responses in neurodegenerative lesions [57,58]. Together, these results create a clear mechanistic model in which microbiota-derived postbiotics mediate microglial phenotype switching by an integrated metabolic, epigenetic, and receptor-mediated signaling. This shows that microglial immunometabolic plasticity is a reason and therapeutic axis in neurodegenerative diseases. The signaling pathways by which postbiotics control the activation of microglia, cytokine signaling, cytokine priming of inflammasomes, and the integrity of the BBB are summarized in Fig. 2. It is important to note that the majority of these mechanistic insights are derived from *in vitro*, germ-free models and experimental disease studies. While these approaches provide strong biological plausibility, they may not fully capture the complexity of human neurodegenerative disease. The current human evidence remains largely associative, and direct interventional data targeting postbiotics-mediated microglial modulation are still limited, which requires further clinical validation and causal confirmation in human studies. In addition to microglial modulation, postbiotics also influence other glial populations, mainly astrocytes, which play a complementary role in neuroinflammation and synaptic homeostasis.

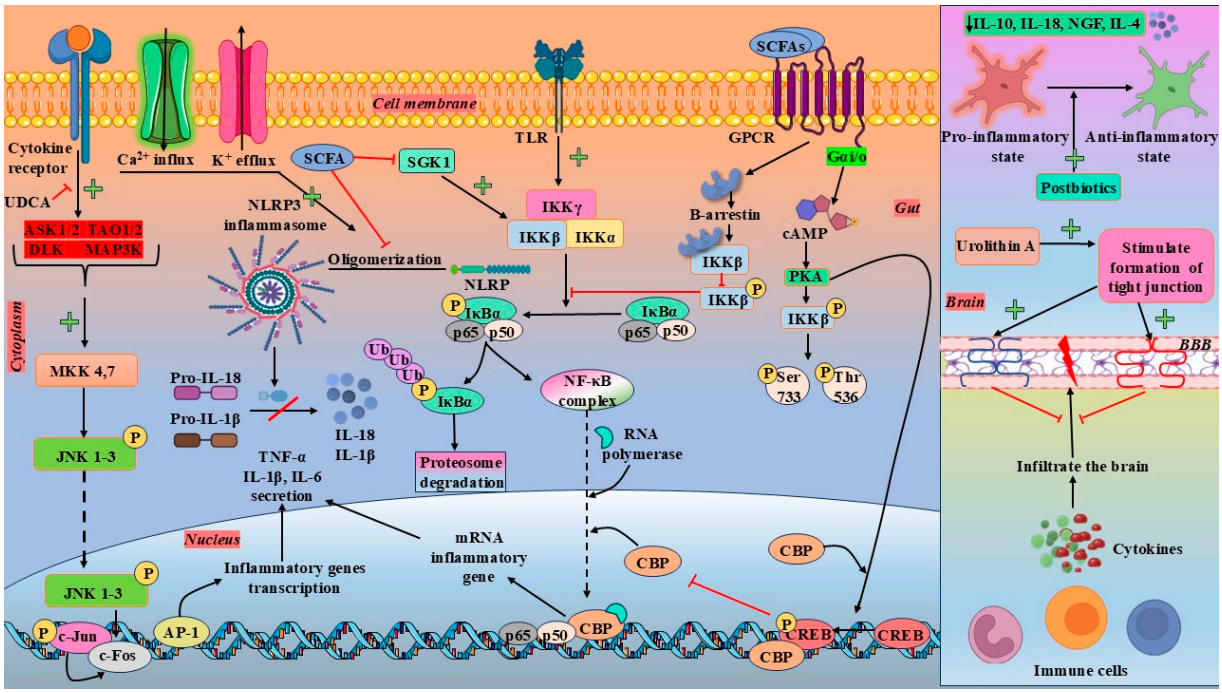

Figure 2: Postbiotics regulation of neuroinflammatory pathways. Integrated molecular mechanisms by which microbiota-derived postbiotics modulate neuroinflammatory signaling across the gut–brain axis. The SCFAs, products of bile acids, and indole metabolic products regulate NF-κB, TLR, and GPCR signaling in order to inhibit NF-κB activation, NLRP3 inflammasome priming, and pro-inflammatory cytokine secretion. GPCR signaling through Gi/o proteins by SCFAS stimulates cAMP/PKA cascades and suppresses phosphorylation of IKK2-dependent phosphorylation of IκBα, which impedes nuclear translocation of the p65/p50 NF-κB complex and inflammatory gene expression. Postbiotics also suppress MAPK-JNK-AP-1 signaling, reduce oligomerization and caspase-1-dependent IL-1β and IL-18 processing, and induce anti-inflammatory microglial phenotype switching. Simultaneously, bile acid signaling via TGR5 represses inflammatory pathways associated with glycolysis and results in the promotion of reparative immune conditions. Postbiotics enhance blood-brain barrier integrity at the neurovascular interface by promoting tight junction formation, cutting off peripheral cytokine entry, and immune cell trafficking into the brain. The green "+" symbol indicates a positive or enhancing effect. This figure is original and was created using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA; version 2019). Abbreviations: SCFAs; short-chain fatty acids, GPCR; G-protein-coupled receptor, TLR; Toll-like receptor, TGR5; Takeda G-protein receptor 5, Gi/o; inhibitory G-protein, cAMP; cyclic adenosine monophosphate, PKA; protein kinase A, IKK; IκB kinase, IKKα/β/γ; IκB kinase alpha/beta/gamma, IκBα; inhibitor of κB alpha, NF-κB; nuclear factor kappa-light-chain-enhancer of activated B cells, NLRP3; NOD-like receptor family pyrin domain containing 3, MAPK; mitogen-activated protein kinase, JNK; c-Jun N-terminal kinase, AP-1; activator protein-1, CBP; CREB-binding protein, CREB; cAMP response element-binding protein, IL; interleukin, TNF-α; tumor necrosis factor alpha, BBB; blood–brain barrier, UDCA; ursodeoxycholic acid, SGK1; serum- and glucocorticoid-regulated kinase 1, MKK; MAPK kinase.

4.2 Postbiotics Modulation of Astrocyte Reactivity and Synaptic Homeostasis

Astrocyte reactivity represents a central neuroinflammatory process in neurodegenerative diseases, wherein chronic activation disrupts synaptic homeostasis and neuronal network synchronization, and metabolic coupling between glial cells and neurons. Building upon these shared signaling pathways, astrocyte-specific responses exhibit distinct functional consequences in synaptic regulation. New evidence incriminates gut microbiota-derived postbiotics as regulators of astrocyte phenotypes by gut-brain axis communication [59].

Glial fibrillary acidic protein (GFAP) and S100β are highly expressed by reactive astrocytes around Ab plaques, and glutamate transporters, especially GLT-1/EAAT2, are reduced in their expression and functional availability. The effect of this impairment encourages extracellular glutamate buildup, excitotoxic stress, and progressive synaptic degeneration [60]. In PD, astrocytic uptake of α-synuclein aggregates induces lysosomal dysfunction, mitochondrial fragmentation, and Ca^{2+} signaling disturbances, collectively disrupting gliotransmitter release and long-term potentiation in dopaminergic circuits [61]. Microbiota-derived postbiotics have been shown to mitigate astrocyte reactivity via convergent receptor-mediated, epigenetic, and immunometabolic mechanisms. SCFAS supplementation in MPTP-induced PD models attenuates astrogliosis, restores Kir4.1-mediated potassium buffering, and maintains synaptic cholesterol homeostasis through enhanced astrocytic apolipoprotein E secretion [61,62]. Mechanistically, SCFAs modulate astrocytic NF-κB signaling and HDAC activity, thereby reprogramming transcriptional responses toward anti-inflammatory and neurotrophic profiles. Complementary evidence from AD cellular models and iPSC-derived astrocyte systems suggests that indole derivatives BA metabolites may act through the FXR and TGR5 signaling to suppress Aβ-induced Ca^{2+} dyshomeostasis, restore EAAT2 expression, and limit tau propagation. These effects are accompanied by attenuation of IL-1β and TNF-α-mediated signaling cascades and a phenotypic shift from neurotoxic A1 astrocytes toward neuroprotective A2 states [60]. At the cellular level, human-induced pluripotent stem cell-derived astrocytes exposed to postbiotics exhibit restored expression of synaptic supporting proteins, including PSD-95 and synaptophysin, along with reduced oxidative stress markers. Consistently, *in vivo* studies in AD and PD models show that transplantation of postbiotics-enriched fecal microbiota increases systemic and CNS SCFAS availability and is associated with reduced astrocyte-mediated synaptic dysfunction and improved behavioral outcomes [63,64]. These findings are predominantly derived from *in vitro* studies, organoid models, and animal studies, whereas human evidence remains limited and largely indirect. Regardless of these promising mechanistic insights, the problem of translational limitations is still important. Reduced CNS bioavailability of some postbiotic metabolites, interpersonal variation in the composition and production of microbiota, and lack of sufficiently powered randomized controlled trials constrain clinical extrapolation. These obstacles will necessitate an accuracy-crafted postbiotics formulation that will have greater BBB penetration, disease-specific stratification depending on astrocytic molecular markers, and standard dose positioning. These approaches are critical to substantiate the astrocyte-targeted postbiotics modulation as an effective therapeutic axis in neurodegenerative disease to the full. Moreover, postbiotics not only regulate glial functions but also modulate intracellular inflammatory and metabolic feedback loops that further amplify neurodegenerative processes.

4.3 Postbiotics Regulation of the Cytokine-Mitochondrial ROS Axis in Neurodegeneration

While these pathways overlap with the above-described sections, their convergence at the cytokine-mitochondrial ROS axis represents a distinct amplification mechanism in neurodegeneration. Cytokine signalling, oxidative stress, and mitochondrial dysfunction are closely overlapping neuroinflammatory centres in neurodegenerative diseases and develop into self-perpetuating feedback loops, which are further augmented by dysbiosis of the gut and are increasingly becoming subjects of postbiotic regulation. Consistent with earlier sections, NF-κB and JAK/STAT are activated by pro-inflammatory cytokines, such as IL-1α, TNF-α, and IL-6, to incite transcription of inducible nitric oxide synthase (iNOS) expression and encourage excessive reactive oxygen and nitrogen (ROS/RNS) production in microglia and astrocytes [11,48]. The aggregation of these inflammatory mediators on mitochondrial electron transport chain (ETC) complexes I and II inhibits oxidative phosphorylation, increases electron leakage, and continues with

the production of ROS, which reinforces the expression of inflammatory genes. Aβ oligomers in AD trigger IL-1β release by astrocytes, which facilitates the formation of peroxynitrite and mitochondrial DNA damage, as well as disturbance in mitochondrial dynamics [15]. α-Synuclein aggregates cause TNF-α-mediated inhibition of complex I activity in susceptible dopaminergic cells in the substantia nigra, thus impairing ATP synthesis and enhancing oxidative damage in PD [20]. These mitochondrial pathologies, in turn, promote redox-sensitive transcription factors like NF-κB and maintain a pathogenic cytokine-ROS-mitochondrial axis. Postbiotics derived from microbiota, and especially SCFAs, have been shown to suppress this axis by inhibition of pro-inflammatory transcriptional programs and activation of antioxidant and mitochondrial defence pathways. NF-κB signaling inhibited by SCFAs, Nrf2-dependent antioxidant responses, such as activation of superoxide dismutase-2 (SOD2) and hemeoxygenase-1 (HO-1), are triggered by SCFAs [41]. Experiments carried out *in vitro* show that the pre-treatment of BV2 microglia with butyrate suppresses the release of IL-6 and TNF-α in response to LPS and oxidative bursts, and maintains mitochondrial membrane potential by activating PGC-1a-mediated mitochondrial biogenesis. These observations provide mechanistic insight but are primarily limited to controlled experimental conditions. Simultaneously, microbial tryptophan metabolites that induce the AhR inhibit NLRP3 inflammasome formation and caspase 1 activation in neuronal cultures with oligomeric α-synuclein. These receptor-interactive processes come to a common path of decreased production of mitochondrial ROS and recovery of redox homeostasis [65]. The preclinical models also support these interactions at the mechanistic level. SCFAS-enriched postbiotics in APP/PS1 mice lower the levels of IL-1β in the hippocampus, replenish glutathione redox homeostasis, and normalize mitochondrial dynamics by returning to the Drp1-Mfn2 balance that controls fission-fusion homeostasis [66]. Propionate supplementation in MPTP-induced PD models inhibits TNF-α-induced oxidative cascades in the substantia nigra, restores functional complex IV, and maintains populations of dopaminergic neurons with tyrosine hydroxylase [67]. Similarly, faecal microbiota transplantation from healthy donors, thereby enriching postbiotic precursors, attenuates cytokine amplification and oligodendroglial oxidative injury in experimental autoimmune encephalomyelitis models [68]. In human observational studies, there are negative associations between peripheral inflammatory and oxidative stress biomarkers, such as IL-6 and 8-oxodG, and faecal SCFAS concentration in AD and PD populations. There is early supplementation data with proof of decreased systemic oxidative stress indices, but disease-specific causality and CNS-targeted effects have yet to be definitively determined [69]. Heterogeneity in patterns of dysbiosis among patient populations, inconsistency in metabolite production, and CNS bioavailability of some postbiotics are major challenges in translational research. To overcome these obstacles, it will be necessary to use randomized controlled trials using BBB-permeable formulations and disease-stratified biomarker systems, and combined multi-omics. Further mechanistic validation using human organoids, metabolomics, and lipidomics will be essential to refine therapeutic targeting of the cytokine-mitochondrial ROS axis in neurodegenerative disease. Moreover, preclinical evidence is substantial, but clinical translation remains in an early phase with limited causal data. Although mechanistic evidence is substantial, the causal role of these pathways in human neurodegenerative disease remains largely unclear, with limited causal evidence in humans, and therefore requires further validation.

4.4 BBB Dysfunction and Immune Cell Trafficking in Neuroinflammation

The BBB, composed of brain microvascular endothelial cells, pericytes, astrocytic end-feet, and the basement membrane, tightly regulates molecular and cellular trafficking between the systemic circulation and the CNS under physiological conditions. In this homeostatic state, immune surveillance is limited to a small population of patrolling T cells and monocytes that monitor CNS integrity without triggering overt

inflammation [70]. During neuroinflammatory states, pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, disrupt BBB integrity by downregulating tight junction proteins such as claudin-5, occludin, and zonula occludens-1 (ZO-1) and activating intracellular signalling cascades including NF-κB and JAK–STAT pathways within endothelial cells. Such alterations in molecules change the organization of cell skeletons and weaken intercellular junctional complexes. At the same time, the ROS production and the activity of matrix metalloproteinases (MMP-2 and MMP-9) break down the basement membrane components and continue the breakdown of the junctional barrier structure, which leads to an increase in paracellular permeability [71,72]. When BBB permeability is elevated, adhesion molecules are upregulated by endothelial cells, such as adhesion molecule-intercellular adhesion molecule-1 (ICAM-1), adhesion molecule-vascular cell adhesion molecule-1 (VCAM-1), and selectins. These molecules mediate serial leukocyte rolling, firm adhesion, and trans endothelial migration. Simultaneously, activated endothelial cells, astrocytes, and microglial cells release chemokines, such as CCL2 and CXCL10, that produce chemotactic gradients attracting the peripheral immune cells to the perivascular space and brain parenchyma [73]. Th1 and Th17 lymphocytes, monocytes, and neutrophils are some of the infiltrating immune populations that are predominant in neuroinflammatory cascades. It is important to note that Th17 cells produce IL-17 that directly disrupts the tight junctions in the endothelium and increases BBB permeability further, which strengthens the recruitment of immune cells into the CNS [74]. In MS, the movement of T cells and monocytes, which are autoreactive, across the BBB to trigger and spread the demyelinating lesions is prominent, and this validates the importance of the immune cell movement in the disease pathogenesis. In MS, α4-intergrin-mediated leukocyte migration is a key pathogenic mechanism, which is therapeutically targeted by adhesion-blocking medications like natalizumab. More BBB leakage and peripheral immune infiltration mechanisms have also been reported in AD, PD, and ALS, where they are associated with increased neuroinflammation and further disease progression [75]. Barrier disruption also allows plasma proteins to enter, which further enhances the inflammatory signaling. Deposition of Fibrinogen in the CNS stimulates receptors, such as CD11β/CD18 integrins, which facilitate oxidative damage and axonal destruction. At the same time, the incorporation of albumin into astrocytes changes intracellular signals and leads to astrocytic responsiveness and hyperexcitability of neuronal networks [76]. Taken together, the BBB dysfunction is an important interface between peripheral and central immune responses. Prolonged permeability allows persistent entry of cytokines, antibodies, and immune cells into the CNS, creating a pathogenic feedback mechanism where glial activation, oxidative and mitochondrial stress, as well as progressive barrier disruption, combine with each other to cause neurodegeneration [77].

5 Disease-Specific Pathological Nodes Targeted by Postbiotics

5.1 Cellular Mechanisms Linking Aβ/Tau Pathology with Neuroimmune Modulation in AD

The cellular-level interactions among microglia, astrocytes, and neuronal signaling pathways play a central role in the pathogenesis of amyloid- and tau-associated neurodegenerative processes. The aggregation of Aβ and tau hyperphosphorylation in AD leads to interlinked pathological nodes, which in turn actively contribute to neuro-immune dysregulation, synaptic failure, and neuronal vulnerability in the hippocampal and cortical circuits. Instead of acting as inert end-stage lesions, Aβ plaques and tau assemblies are constantly interacting with microglia and astrocytes, which causes oxidative stress, cytokine release, and prolonged inflammatory signaling that increases neurodegenerative disease development [78]. Genetic and experimental evidence identify microglia and astrocytes as key cellular mediators between Aβ and tau aggregation and chronic neuroinflammation and progressive neurodegeneration. The evidence is now mounting that the gut microbiota-brain axis participates in the initiation of these pathological

cascades, and that the amplification of these cascades by microbial metabolites and cell-free products, such as postbiotics, is emerging as a regulator of oxidative stress, cytokine signaling, and glial activation that converge on Aβ- and tau-related disease nodes [25]. Postbiotics, in this regard, can be characterized as non-viable microbial products or metabolic by-products, including SCFAs, bacteriocins, vitamins, and cell-wall components that provide health benefits to the host when used in appropriate concentrations and may mediate CNS homeostasis [79]. These metabolites modulate glial activation and inflammatory signaling relevant to Aβ/tau pathology. Direct evidence that lactic acid bacteria (LAB)-derived postbiotics can suppress the major molecular events associated with AD pathology is provided by experimental work with Aβ-challenged microglial cells. These findings are derived from *in vitro* microglial models and provide mechanistic insights under controlled experimental conditions. In Aβ1-42-exposed BV-2 microglia, bacterial-conditioned media (BCM) of *Levilactobacillus brevis* CRL 2013, *Lactobacillus delbrueckii* subsp. *Lactis* CRL 581, or *Enterococcus mundtii* CRL 35, restored antioxidant capacity (ABTS and CUPRAC assays), lowered Aβ-induced overexpression of IL-1β, and had a greater effect on reducing IL-6 and TNF-α levels, thereby attenuating Aβ-triggered oxidative and pro-inflammatory responses in microglia. These postbiotic preparations also suppressed the expression of iNOS in specific circumstances, which further restricted the nitrosative stress, which is known to enhance Aβ toxicity and glial activation [80]. In addition to Aβ-mediated reactions, microglia and astrocytes are involved in tau pathology and in the chronic inflammatory response condition, promoting tau phosphorylation and aggregation. Theories of gut microbiome-targeted treatment in AD suggest that postbiotics may indirectly regulate tau-associated pathology through restructuring of systemic and central immune signaling, decreasing peripheral cytokines, and re-establishing less permissive microglial homeostatic phenotypes to tau propagation [80]. Moreover, LAB-derived BCM has been reported to partially inhibit the acetylcholinesterase activity in erythrocytes and brain tissue, implying the ability of low molecular weight bacterial metabolites to modulate cholinergic neurotransmission, which is tightly coupled with Aβ/tau-mediated synapse malfunctioning in AD [81]. SCFAS is one of the large categories of postbiotic metabolites that have a dual impact on the pathology of AD. On the one hand, germ-free or antibiotic-treated AD models of the mouse immune system portray immature or functionally incapacitated microglia, which might be functionally restored through microbiota reconstitution or SCFAS supplementation, underscoring the critical role of SCFAs in microglial maturation and responsiveness. Contrarily, APPS1 mouse work has shown that systemic SCFAS supplementation enhances Aβ plaque burden and a microglial activation transcriptional program, including ApoE upregulation, that facilitates the deposition of the plaque by modulating plaque-associated microglia. These data suggest that SCFAs are potent immune-metabolic regulators of microglia at the Aβ deposition node, and their overall effects on AD probably rely on the context, concentration, and profile of individual SCFAs [53]. However, these observations are primarily based on animal models, and their relevance to human disease remains to be fully established.

The available evidence is largely derived from preclinical systems, with limited direct validation in human interventional studies. Altogether, recent preclinical and translational evidence suggests that postbiotics act on a variety of AD pathological nodes: (i) Aβ increases oxidative stress and cytokine cascades in microglia, (ii) microglial and astroglial activation states that condition Aβ and tau pathology, (iii) neurotransmitter systems, including cholinergic signals that become secondarily damaged by Aβ/tau aggregates. Through these overlaps between protein aggregation and neuroimmune modulation, postbiotics are becoming mechanistically based adjunctive disease-modifying approaches in AD. These effects collectively highlight microglial inflammatory signaling, astrocyte activation states, and immune-metabolic pathways as key cellular targets influenced by postbiotic metabolites. Fig. 3 illustrates

gut-brain axis-mediated mechanisms linking postbiotics to disease-specific neurodegenerative pathology, showing how gut-derived immune and inflammatory signals contribute to Aβ and tau pathology in AD, α-synuclein aggregation in PD, and Th17-driven demyelination in MS, while postbiotics counteract these processes by restoring immune and glial homeostasis.

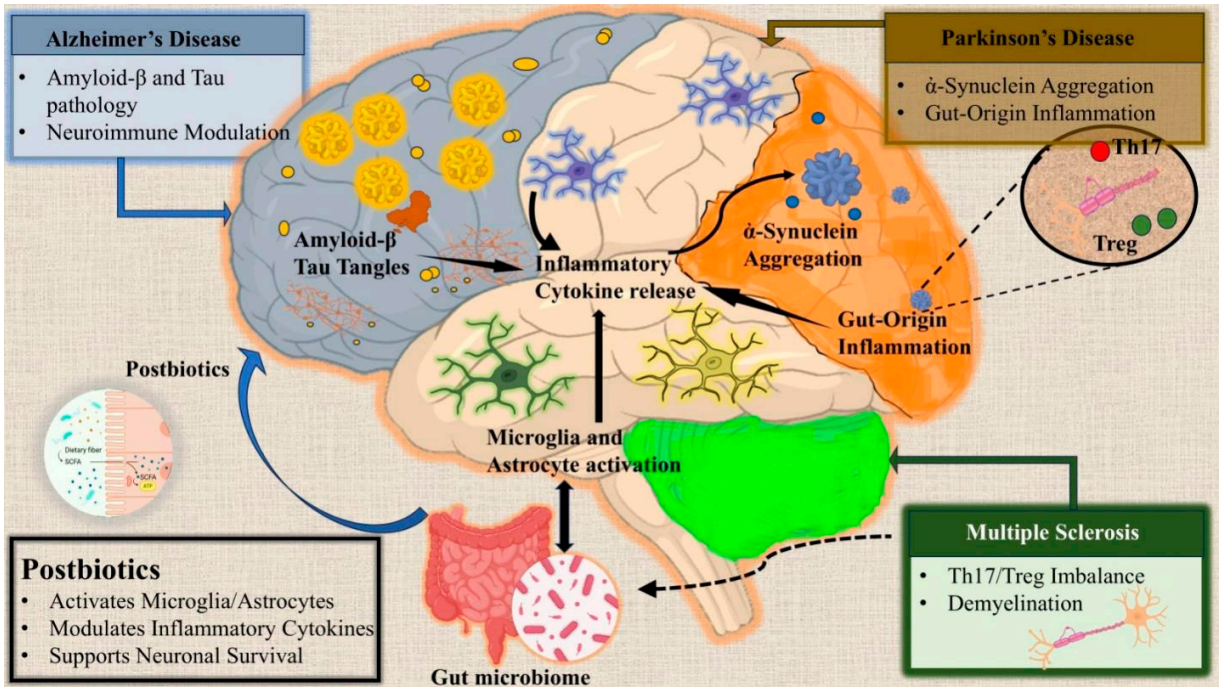

Figure 3: Gut–brain axis–mediated mechanisms linking postbiotics to neurodegenerative disorders. The schematic illustrates how the gut microbiome influences CNS pathology through immune, inflammatory, and neuroglial pathways, and how postbiotics may modulate these processes. Microbial signals originating in the gut translocate via systemic circulation and neuroimmune routes to the brain, where they regulate microglial and astrocytic activation and downstream inflammatory cytokine release. In AD, dysregulated gut–brain signaling promotes Aβ deposition and tau hyperphosphorylation, leading to neuroinflammation and synaptic dysfunction. In PD, gut-origin inflammation contributes to α-synuclein aggregation, which may propagate from the enteric nervous system to the brain, accompanied by an altered Th17/Treg balance. In MS, immune dysregulation driven by microbial factors exacerbates Th17-mediated inflammation, resulting in demyelination. Postbiotics counteract these pathogenic cascades by attenuating pro-inflammatory cytokine production, restoring immune homeostasis, supporting neuronal survival, and modulating glial responses. This figure is original and was created using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA; version 2019). Abbreviations: AD; Alzheimer's disease, PD; Parkinson's disease, MS; Multiple sclerosis, CNS; central nervous system, Aβ; amyloid-β, Th17; T helper 17 cells, Treg; regulatory T cells.

5.2 Cellular Pathways Linking α-Synuclein Aggregation with Gut-Derived Inflammation in PD

α-synuclein misfolding and aggregation are among the most prominent proteinopathies through which neurodegenerative vulnerability is manifested in PD, although there is growing evidence that they are conditioned by peripheral immune and metabolic factors instead of developing in the CNS itself [82]. The deposition of α-synuclein in Lewy bodies and Lewy neurites is linked closely with the selective degeneration of nigrostriatal dopaminergic neurons and extranigral circuit dysfunction that is regulated by inflammatory signaling, oxidative stress, and glial reactivity [83]. Interestingly, gastrointestinal complications, such as constipation and slow colonic movement, also precede motor symptoms and correlate with α-synuclein

pathology and immune response in the enteric nervous system, suggesting early peripheral disease in a subgroup of PD patients. Consistent with this peripheral contribution, changes in gut microbial composition have been suggested to be upstream modulators of PD-relevant pathology [84]. PD-associated dysbiosis can be marked by the diminished abundance of SCFAS, genera, and enrichment of pro-inflammatory microbial communities, alterations associated with diminished epithelial barrier health, increased mucosal immune activation, and increased circulating cytokines [85]. These alterations influence epithelial barrier signaling, immune-cell activation, and downstream inflammatory pathways that can modulate neuronal vulnerability and α-synuclein aggregation. The evidence of experimental studies using the exposure of rotenone and the overexpression of α-synuclein proves that the disruption of microbiota and barrier dysfunction activates inflammatory proteolytic pathways, such as C/EBPb-asparagine endopeptidase signaling, thus promoting enteric and central α-synuclein aggregation and worsening dopaminergic neuron loss and motor impairment. These findings are based on experimental models and may not fully reflect the heterogeneity of human PD. The observations denote gut-derived inflammatory signaling as a disease-relevant node that overlaps α-synuclein pathology in PD [86].

In this framework, postbiotic interventions have been suggested as a method of regulating gut-origin inflammatory and immunometabolic contributions without requiring the administration of live microbes. SCFAs primarily influence PD pathology through modulation of gut-derived inflammatory signaling and barrier dysfunction, which are closely linked to α-synuclein aggregation [87]. The clinical evidence that has supported the translational relevance is that the combination of propionic and butyric acid supplementation with a prebiotic enhances motor function, permits levodopa reduction, and changes immune, barrier-related gene expression in *ex vivo* gut models, indicating that specific postbiotic manipulation can modify PD-related clinical and biological outcomes [88]. However, these observations are taken from limited clinical and *ex vivo* data, and larger controlled studies are required to confirm therapeutic efficacy. These effects extend to central inflammatory pathways linked to α-synuclein toxicity. Experimental and review-based studies show that such interventions have the ability to regulate the responsiveness of microglia, inflammasomes, and oxidative stress, which are known to mediate α-synuclein toxicity, seeding efficiency, and intercellular propagation. Inhibition of these pathways can thus lower the laxity of the CNS to α-synuclein-based injury and curb the dissemination of disease within susceptible systems of neurons [89].

Taken together, the existing data provide the groundwork for a model in which the aggregation of α-synuclein and the dysfunction of the gut barrier and immune activation are pathological nodes that are interconnected in PD. Mechanistically, these mechanisms include epithelial barrier signaling, immune-cell activation pathways, and microglial inflammatory responses, which control α-synuclein toxicity and neuronal degeneration. Postbiotics provide an adjunctive intervention, which is biologically plausible and acts on peripheral inflammatory drivers and neuroimmune modulators related to α-synuclein pathology and changes disease-relevant processes and mechanisms along the microbiota-gut-brain axis.

5.3 Postbiotics Modulation of Th17/Treg Immune Balance in MS

MS is an autoimmune demyelinating encephalopathy where the inflammatory lesions in the CNS are mainly caused by the Th1 and Th17 lymphocytes, which are auto-reactive in nature, and other complementary roles played by the B cells, monocytic, and other myeloid lineage cells. One of the primary immunopathological characteristics of MS is the imbalance of the pro-inflammatory cells, such as Th17 and Tregs, which perpetuate autoimmune inflammation, support the destruction of oligodendrocytes, and speed up the demyelination process [90]. It is becoming more and more evident that the microbiota of the gut and its metabolites are important in the regulation of this Th17/Treg axis. Of these metabolites,

SCFAs, and in particular propionate and butyrate, can serve as key postbiotic mediators, which promote Treg differentiation and suppress Th17 polarization [91]. In MS patients, clinical trials indicate that oral propionate supplementation reduces the rate of relapses per year and disease progression, as well as increases the proportion of peripheral Tregs and reduces that of Th17 cells. Importantly, 1 g of propionate daily during 14 days induced a significant change in the T-cell phenotype, turning to a regulatory one, which demonstrates a causal relationship between SCFAS signaling and immune balancing [92,93]. The available clinical studies are limited in scale and duration and require validation in larger cohorts. Both propionate and butyrate have a significant beneficial effect in controlling the severity of the disease in experimental autoimmune encephalomyelitis (EAE), the animal model of MS, by increasing Treg populations, decreasing the differentiation of Th17 cells, and modulating microglial and oligodendrocyte maturation, potentially via epigenetic control of genes involved in myelin synthesis and repair [94]. These observations are derived from preclinical models and may not fully demonstrate disease complexity in humans. SCFAS has a mechanistic impact on T-cell responses by activating G-protein-coupled receptors such as GPR43 and inhibiting HDACs in order to increase Foxp3 expression and reduce the production of pro-inflammatory cytokines by effector T cells, such as IL-17 and GM-CSF. Other than affecting adaptive immunity, postbiotics also regulate innate and glial inflammatory processes. In MS, SCFAs mainly act by restoring Th17/Treg balance and modulating immune-driven demyelination [95]. Taken together, these results also suggest that microbiota-derived postbiotics can affect various pathogenic pathways in MS, such as an imbalance in Th17/Treg, glial activity, inflammatory demyelination, and BBB dysfunction. By simultaneously modulating systemic immune response and CNS inflammatory signaling, SCFAs emerge as promising adjunctive therapeutic strategies that may complement existing immunomodulatory treatments for MS [96]. Moreover, both preclinical and early clinical findings are encouraging; further large-scale randomized controlled trials are necessary to establish long-term efficacy and safety. Postbiotics target disease-specific pathways across AD, PD, and MS through distinct but partially overlapping mechanisms. Table 2 summarizes the structured comparison across neurodegenerative disorders, key SCFAS or postbiotics alterations, mechanisms, and translational evidence.

Table 2: Cross-disease comparison of SCFAS/postbiotics mechanisms and evidence in AD, PD, and MS.

S. No.	Disease	SCFAS/Postbiotics Alteration	Dominant Mechanisms/Pathways	Strongest Preclinical Evidence	Key Human Findings	Translational Challenges	References
1.	Alzheimer's disease (AD)	Altered SCFAS levels; context-dependent effects (protective vs. plaque-promoting)	Microglial activation, oxidative stress, Aβ deposition, tau phosphorylation, HDAC inhibition, BBB integrity	SCFAs regulate microglial maturation; butyrate improves neuroinflammation and mitochondrial function; it may also enhance plaque deposition in some models	Altered SCFAS profiles associated with cognitive decline and neuroinflammation	Dual role of SCFAs; lack of robust clinical trials; inter-individual microbiome variability	[25,53,78–81]
2.	Parkinson's disease (PD)	Reduced SCFAS-producing bacteria and decreased SCFAS levels	Gut barrier dysfunction, α-synuclein aggregation, neuroinflammation, immune activation	SCFAs improve motor deficits and reduce neuroinflammation in toxin-induced and genetic models	SCFAS + prebiotic supplementation improves motor outcomes and may reduce levodopa requirement	Limited large-scale clinical trials; variability in disease stage and microbiota composition	[85–89]
3.	Multiple sclerosis (MS)	Reduced SCFAs (especially propionate); altered metabolite profile	Th17/Treg imbalance, immune dysregulation, BBB dysfunction, HDAC inhibition, epigenetic modulation	SCFAs promote Treg differentiation and suppress Th17 responses, and reduce disease severity in EAE models	Propionate supplementation increases Tregs and reduces relapse rates	Need for long-term trials; dose standardization; integration with existing immunotherapies	[92–96]

Note: SCFAs, short-chain fatty acids; AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; Aβ, amyloid-β; BBB, blood–brain barrier; HDAC, histone deacetylase; Th17, T helper 17 cells; Treg, regulatory T cells; EAE, experimental autoimmune encephalomyelitis.

6 Translational and Comparative Evidence across Diseases

6.1 In Vitro and Microfluidic Gut–Brain Models

Multiple *in vitro* experiments conducted by different research groups demonstrate that SCFAs exert neuroprotective and immunomodulatory effects across diverse CNS-relevant cell types and experimental models. The primary astrocytes were isolated from the neonatal rat cortex and subjected to oxygen-glucose deprivation (OGD) to mimic hypoxic-ischaemic stress with decreased serum and glucocorticoid-induced kinase 1 (SGK1) level, while overactivation of interleukin-6 (IL-6), NOD-like receptor family pyrin domain-containing 3 (NLRP3), C-C motif chemokine ligand 2 (CCL2), and interferon-γ-induced protein 10 (IP-10) expression. The treatment with SCFAs inhibits astrocyte overactivation primarily through this SGK1/IL-6 signaling pathway. Similarly, oligodendrocyte precursor cells (OPCs) were treated with recombinant IL-6, which increased the levels of cleaved caspase-3 and BCL2-associated X protein (Bax) expression and reduced B-cell lymphoma-2 (Bcl-2) levels, indicating apoptosis. However, the addition of an IL-6 receptor antagonist markedly reduced these apoptotic changes and restored OPC survival, demonstrating that the protective effect of SCFAs observed in this study occurs indirectly, by reducing IL-6 production rather than by acting directly on OPCs [97]. The complementary evidence has been provided using a human microglial clone-3 (HMC3) that was treated with cell-free supernatants (CFSs), derived from *Lactiplantibacillus plantarum*, *Limosilactobacillus reuteri*, and *Lacticaseibacillus rhamnosus*, that contain SCFAS, organic acids, peptides, and other microbial metabolites, either before or after LPS-induced inflammatory stimulation. These postbiotics activated the nuclear factor erythroid 2-related factor 2 (NRF2) pathway in microglia under both basal and inflammatory conditions, leading to enhanced antioxidant gene expression and increased superoxide dismutase (SOD) activity, thereby highlighting an antioxidant and cytoprotective action [98]. The anti-inflammatory role of SCFAS was further supported by murine RAW264.7 macrophages, where SCFAS treatment significantly reduced LPS-induced nitric oxide (NO) production, inducible iNOS activity, and the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. It enhanced IL-10 production at lower concentrations, and acetate and butyrate inhibited NF-κB activation by blocking NF-κB-dependent transcription [99]. Another study revealed that multiple neural inflammation models, including primary rat microglia, mixed neural cocultures, organotypic hippocampal slice cultures, and a transformed murine N9 microglial cell line, were treated with sodium butyrate and related SCFAs that suppressed LPS-induced NO and pro-inflammatory cytokines by inhibiting NF-κB signaling [100]. Beyond immunomodulation, SCFAs have been reported to interact in a direct manner with protein aggregation of interest to neurodegenerative pathologies. Valeric acid, butyric acid, and propionic acid inhibit aggregation of A2-40 and A2-42 peptides, and valeric acid best inhibited A2 aggregation, and propionic acid had lower inhibition at higher concentrations [101]. Such pieces of evidence suggest that SCFAs are highly recommendable postbiotics to control neuroinflammation, oxidative stress, cell survival, and pathological protein aggregation via glial regulation and molecular signaling pathways. However, some of the studies have reported context-dependent effects of SCFAs, including a potential increase in Aβ aggregation under specific experimental conditions, highlighting that their effects may not be uniformly protective. The evidence of the *in vitro* and advanced culture model is provided in Table 3, outlining the postbiotic interventions and the molecular mechanisms. Most of these findings are derived from controlled *in vitro* systems, which may not fully address the complexity of *in vivo* neurodegenerative processes.

Table 3: Gut-derived SCFAs and metabolites attenuate neuroinflammation, Aβ aggregation, and progression in AD, PD, and MS models: preclinical and clinical evidence.

S. No.	References	Experimental Model	Drugs/Interventions	Dose	Frequency	ROA	Study Outcomes
				In vitro studies			
1	[96]	Oxygen–glucose deprivation (OGD) in primary astrocytes and OPCs	SCFAs (acetate:propionate:butyrate = 3:1:1)	40 nmol/L	Single exposure during OGD	Direct media supplementation	↓ SGK1/IL-6; ↓ inflammatory cytokines; ↓ OPC apoptosis (↓ Bax, ↓ caspase-3, ↑ Bcl-2)
2	[97]	Human microglial HMC3 cell line	Cell-free supernatants from *Lactobacillus plantarum*, *L. reuteri*, *L. rhamnosus*	5% (v/v)	Single exposure; 20 h	Direct application	↑ NRF2 nuclear translocation; ↑ HO-1, SOD1/2, GPx, GST, CAT; ↑ SOD activity; ↓ TNF-α; ↑ IL-10
3	[98]	RAW264.7 murine macrophages	Sodium acetate, propionate, butyrate	1–1200 μmol/L	Single exposure	Direct addition	↑ IL-10 (low dose); ↓ TNF-α, IL-1β, IL-6, NO; ↓ iNOS; ↓ NF-κB activation
4	[99]	N9 microglia, rat primary microglia, cocultures, hippocampal slices	SCFAs (butyrate, propionate, valerate, caproate, valproate) ± LPS	Butyrate: 0.6–5 mM; others: 2–3 mM	Pre-/co-treatment with LPS	Direct addition	Butyrate ↑ IL-6, NO, iNOS (with LPS); ↓ NF-κB DNA-binding activity
5	[100]	Aβ1-40 & Aβ1-42 aggregation model	SCFAs (valeric, butyric, propionic, isobutyric, isovaleric, acetic acids)	5 & 20 μM	0–10 days	Direct incubation	Valeric acid blocked Aβ oligomers; butyric acid partially inhibited aggregation; propionic acid had a mild effect; others had no effect
				In vivo studies			
6	[101]	APPswe/PS1 mice; BV2 microglia	*Clostridium butyricum*	NA	4 weeks	Oral	↓ Aβ deposits; ↓ microglial activation; ↓ TNF-α, IL-1β; improved cognition; restored butyrate
7	[102]	APP/PS1 mice	Postbiotics (tyndallized *Bifidobacterium longum*, *Lactobacillus acidophilus*) ± exercise	120 mg/day	20 weeks	Oral	Chelated Cu^{2+}/Zn^{2+}; ↓ Aβ; ↓ APP; ↑ mitochondrial function; ↓ NF-κB; prevented cognitive decline

Table 3: *Cont.*

S. No.	References	Experimental Model	Drugs/Interventions	Dose	Frequency	ROA	Study Outcomes
				In vivo studies			
8	[103]	Rotenone-induced *Drosophila melanogaster* PD model	Sodium butyrate	10 mM	3–7 days	Oral	Improved locomotion; ↓ mortality; ↑ dopamine levels
9	[104]	Rat dopaminergic neurons + rotenone	Propionic acid ± Fasudil	300 μM	48 h	*In vitro* treatment	↑ neuron survival; ↑ TH expression; ↑ STAT3; ↑ neurite outgrowth
10	[105]	EAE mice (CD44KO and wild-type)	CD44 gene deletion	NA	~18 days	Multiple routes	↑ SCFAs; ↑ Treg; ↓ Th1/Th17; attenuated EAE severity
11	[105]	EAE & cuprizone-induced demyelination models	Indole-3-lactate (ILA)	2 mM/10–20 mg/kg	2–4 weeks	Oral/parenteral	↓ Th17-mediated inflammation; ↓ myeloid infiltration; promoted remyelination
				Clinical studies			
12	[106]	HC, aMCI, AD patients	Metabolomic profiling	NA	Single	NA	↓ SCFAs; ↑ IPYA; ↓ LCA; correlated with cognitive decline
13	[107]	38 MS patients vs. controls	Observational	NA	Single	NA	↑ caproic acid; ↓ butyrate; ↓ Treg; ↑ Th1/Th17; ↓ *Roseburia*, *Coprococcus*, *Blautia*; ↑ *Akkermansia*, *Collinsella*
14	[108]	MS patients	Propionic acid	1000 mg/day	14 days–3 years	Oral	↑ Treg; ↓ Th1/Th17; ↓ relapse rate; stabilized EDSS; ↑ gray matter volume; ↑ mitochondrial function

Note: SCFAs, short-chain fatty acids; OGD, oxygen–glucose deprivation; OPCs, oligodendrocyte precursor cells; SGK1, serum- and glucocorticoid-regulated kinase 1; IL, interleukin; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; NRF2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; SOD, superoxide dismutase; GPx, glutathione peroxidase; GST, glutathione S-transferase; CAT, catalase; TNF-α, tumor necrosis factor alpha; NO, nitric oxide; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; Aβ, amyloid beta; APP, amyloid precursor protein; LONP1, Lon peptidase 1; SDHA, succinate dehydrogenase complex flavoprotein subunit A; PD, Parkinson's disease; STAT3, signal transducer and activator of transcription 3; CD44KO, CD44 knockout; $MOG_{35–55}$, myelin oligodendrocyte glycoprotein peptide (residues 35–55); EAE, experimental autoimmune encephalomyelitis; Treg, regulatory T cell; Th, T helper cell; AhR, aryl hydrocarbon receptor; ILA, indole-3-lactate; HC, healthy controls; aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease; MS, multiple sclerosis; IPYA, indole-3-pyruvic acid; LCA, lithocholic acid; PBMC, peripheral blood mononuclear cells; EDSS, expanded disability status scale; ROA, route of administration; NA, not applicable. ↑ indicates an increase, upregulation, or enhancement of the indicated parameter; ↓ indicates a decrease, downregulation, or suppression of the indicated parameter.

6.2 Animal Models of AD, PD, and MS (e.g., EAE for MS)

The experimental autoimmune encephalomyelitis (EAE) mouse model demonstrated that cluster of differentiation 44 (CD44) deficiency altered gut microbiota composition and increased SCFA levels, resulting in reduced disease severity [109]. In animal models of AD, PD, and MS, the mice showed changes in gut microbiota composition and reduced SCFA levels; these alterations were associated with intestinal amyloid deposition and structural abnormalities, suggesting that lower SCFA levels may exacerbate cognitive defects in AD [110]. The variability across animal models and differences in microbiota composition and metabolite availability may influence these outcomes, which limits their generalizability. An *in vivo* amyloid precursor protein with the Swedish mutation (APPswe)/presenilin-1 with exon 9 deletion (PS1dE9) transgenic mouse model was treated with *Clostridium butyricum* (CB) for four weeks, which enhanced cognitive performance, reduced Aβ plaque formation, suppressed microglial activation, and lowered TNF-α and IL-1β, while also restoring gut microbiota balance and increasing butyrate levels. These findings show that the observed protective effects are mediated through the postbiotic metabolite butyrate produced by CB [101]. Another study revealed that postbiotic supplementation, including *Bifidobacterium longum* and *Lactobacillus acidophilus*, in transgenic AD mice reduced amyloid precursor protein (APP) expression, disaggregated Aβ plaques through metal-ion chelation, and enhanced mitochondrial lon peptidase 1 (LONP1) activity, thereby improving cognitive performance and slowing disease progression [102]. The direct administration of acetate, propionate, and butyrate to APP/PS1 transgenic mice enhanced astrocyte glutamine synthetase and glutamate transporter, thereby strengthening the glutamate-glutamine shuttle and improving neuronal antioxidant capacity and mitochondrial energy metabolism, and significant improvements in learning and memory performance [111]. However, dose-dependent and disease-stage-specific effects have been observed, which further suggests that SCFAs supplementation may not exert uniformly beneficial outcomes across all experimental conditions. The rotenone-induced Drosophila PD model treated with sodium butyrate, a postbiotic derivative that preserves motor performance, reduces early mortality, and restores brain dopamine levels [103]. Complementary findings were reported in a rotenone-induced PD model using primary rat mesencephalic dopaminergic neurons, where propionic acid significantly increased the survival of tyrosine hydroxylase (TH)-positive dopaminergic neurons and moderately improved neurite outgrowth [104]. Moreover, the EAE model of MS treated with indole lactate (ILA), a gut microbiome-derived postbiotic, reduces immune activation, CNS immune cell infiltration, and inflammatory disease severity [106]. Overall, while animal models provide strong mechanistic understandings, their translational relevance remains limited due to interspecies differences and simplified disease representations. The key findings from animal models of AD, PD, and MS are consolidated in Table 4, with emphasis on postbiotic treatments and disease-modifying outcomes.

Table 4: Comparative effects of postbiotics/SCFAs across AD, PD, and MS: targeting pathology, inflammation, immunity, and functional outcomes.

S. No.	Functional Axis	AD	PD	MS	Observations	References
2	Key postbiotics studies	SCFAs (acetate, propionate, butyrate)	SCFAs (butyrate, propionate)	Propionic acid and butyrate	SCFAs are common bioactive mediators	[101,105,111]
3	Main cellular targets	Microglia and astrocytes	Dopaminergic neurons and microglia	T lymphocytes and microglia	Postbiotics act divergently by targeting neurons in AD/PD and peripheral immune cells in MS	[102,104,106]
4	Effect on neuroinflammation	Decrease microglial activation and pro-inflammatory cytokines (IL-6, TNF-α)	Decrease microglial and astrocyte inflammation	Decrease peripheral and CNS inflammation via regulatory immune responses	Consistent anti-inflammatory effects across conditions	[88,107,109]
5	Immune modulation	Primarily innate CNS immune modulation	Mild systemic and CNS immune modulation	Strong adaptive immune reprogramming (↑ Tregs, ↓ Th1/Th17)	MS shows dominant adaptive immunomodulation	[104,108]
6	Regulatory T cells (Tregs)	Not assessed in most AD SCFA studies	Not a primary outcome	Increased Treg numbers and IL-10–dependent function with propionic acid	Treg enhancement is central in MS	[109]
7	Neurodegenerative pathway affected	Aβ toxicity and tau hyperphosphorylation	α-synuclein-associated neuronal loss	Immune-mediated secondary neurodegeneration	Disease-specific pathogenic mechanisms	[88,108,109]
8	Functional outcomes	Improved learning and memory	Improved motor performance	Reduced relapse rate, stabilized EDSS, reduced brain atrophy	Disease-specific clinical outcomes	[88,107,112]

Note: AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; Aβ, amyloid beta; SCFAs, short-chain fatty acids; CNS, central nervous system; IL, interleukin; TNF-α, tumor necrosis factor alpha; Tregs, regulatory T cells; Th, T helper cells; EDSS, expanded disability status scale.

6.3 Human Observational Studies and Early-Phase Trials

The human clinical observational model involving healthy controls, individuals with amnestic mild cognitive impairment (aMCI), and patients with AD showed a progressive reduction in SCFAs and a significant disturbance of tryptophan metabolism from aMCI to AD. These metabolic alterations indicate that gut microbial metabolites are closely linked to AD progression and may serve as non-invasive biomarkers and therapeutic targets [107]. However, these associations remain largely correlative and do not establish causality between postbiotic alterations and disease progression. Similar associations have been reported in a cross-sectional observational study in MS patients, showing that decreased serum butyric acid reduces Tregs, increases caproic acid, and Th1/Th17, which disrupts gut microbiota, characterized by depletion of SCFAS-producing bacteria and thus contributing to inflammation [108]. The variability in patient populations and study designs may influence these findings, which requires cautious interpretation. The interventional clinical evidence demonstrates that propionic acid in the serum and stool of an MS patient was reduced. The oral administration of propionic acid for 14 days resulted in a significant reduction in Th1/Th17 cells and an enhancement of Treg suppressive function mediated through IL-10. The long-term intake of propionic acid reduces relapse rates, stabilizes disability, and increases basal ganglia gray matter [109]. Despite these promising findings, the small sample sizes and short-term intervention limit the strength of clinical conclusions. The randomized controlled trial was done on 72 PD patients who received 6 months of propionic and butyric acid with or without the prebiotics and standard therapy. These supplements improved motor symptoms, reduced levodopa dosage, augmented immune reactions and gut barrier functions, and exhibited that SCFAS could alleviate PD symptoms and control intestinal and peripheral immunity [88]. The current clinical evidence remains preliminary, and larger, well-controlled trials are required to establish causality and therapeutic efficacy. The clinical observational and interventional studies are summarized in Table 4, providing an overview of postbiotic interventions, immune and metabolic effects, and clinical outcomes.

6.4 Convergent vs. Divergent Responses across AD, PD, and MS

There are convergent and divergent responses of postbiotics, especially butyrate and propionate, in neurodegenerative and neuroinflammatory diseases, such as AD, PD, and MS. The convergent effects are anti-inflammatory responses, maintenance of gut barrier integrity, gut-brain axis regulation, and oxidative stress, which are uniformly evident in these conditions. These effects may vary depending on disease context, metabolite concentration, and host-specific factors. Conversely, divergent actions are disease-specific and linked to underlying pathophysiology, such as in AD, postbiotics reduce Aβ and tau hyperphosphorylation accumulation [111]; in PD, postbiotics enhance the survival of dopaminergic neurons and motor activity [103,104], and in MS, postbiotics balance the immune system by promoting Tregs and suppressing Th17 cells [109]. These results demonstrate the wide-ranging neuroprotective ability of postbiotics and emphasize the significance of the disease-specific mechanisms in interventions [112]. The heterogeneity of responses across diseases highlights that postbiotics' effects are not universally consistent and require disease-specific evaluation. While data findings are promising, the current evidence should be interpreted with caution, as contradictory findings and context-dependent effects remain insufficiently resolved.

7 Therapeutic Outlook and Future Directions

Postbiotics, such as polyamines, microbial peptides, and SCFAs, have been proposed as promising treatment options for neurodegenerative diseases, as they directly utilize bioactive metabolites to

achieve therapeutic effects; however, there are no specific regulatory measures for postbiotics in dietary supplements [113]. In Europe, certain postbiotics may be classified as biological medicinal products depending on their composition, mechanism of action, and intended use, particularly when the active substance is of biological origin and requires detailed characterization. The Food and Drug Administration (FDA) does not currently provide specific guidelines for postbiotics, whereas Japan has a more organized system with Food for Specified Health Uses (FOSHU), Foods with Nutrient Function Claims (FNFC), and Foods with Function Claims (FFC) frameworks. The significant limitations of postbiotics are the uniform dosage, since the most effective dosage is based on the type of postbiotics, the safety of the product, personal factors, and the duration of the supplement. Regulatory guidelines in the future have to focus on the minimum effective concentrations (MEC) to identify the lowest doses that result in any biological effect, such as immunomodulation, regulation of metabolic functions, or antioxidant effects [114]. Postbiotics can also promote the expression of claudin-5 and occludins to sustain BBB integrity, which is necessary to protect the CNS against peripheral inflammation. The brain endothelial cells have free fatty acid receptors (FFARs) responsible for the SCFAS-mediated BBB structure control [95]. SCFAs have direct brain endothelial cell effects through transporters like monocarboxylate transporter 1 (MCT1), sodium-coupled monocarboxylate transporter 1 (SMCT1), and fatty acid translocase/cluster of differentiation 36 (FAT/CD36), or binding to G-protein-coupled receptors (GPR41, GPR43, GPR109A) or inhibiting HDACs and regulating NF-κB and Nrf2 pathways to reduce oxidative stress and inflammation. The restoration through probiotics, fecal microbiota transplantation, or direct SCFAs supplementation improves tight junction protein expression and barrier function [115]. Postbiotics, with current disease-modifying treatment approaches, probiotics, dietary therapies, or lifestyle changes such as exercise, show synergistic benefits in preclinical models of AD [102]. Another investigation evaluated the occurrence of gut microbiota-derived metabolites within the brain and demonstrated that specific bacterial strains, including *Lactococcus lactis* subsp. *lactis* CRL 58, a lactic acid-producing bacterial strain, can modulate central cholinergic homeostasis. The detection of bioactive metabolites in the CNS further supports the ability of postbiotics to traverse the BBB, suggesting a potential mechanistic role for these metabolites in the therapeutic modulation of AD [80,116]. Several postbiotic preparations are commercially available, but are mostly sold as dietary supplements, medical foods, or functional food substances rather than as licensed pharmaceutical therapies. They contain heat-inactivated bacterial preparations that have been added to beverages and immunomodulatory and gut-brain axis-supportive supplements. Besides that, fermentation metabolites, such as lactic acid bacterial metabolites, are commonly used in gastrointestinal health and dysbiosis treatment. There are also commercially available synthetic SCFAS, especially microencapsulated sodium butyrate and propionate preparations, which are mainly aimed at intestinal barrier functionality and immunoregulation [20]. Although postbiotics offer significant functional and formulation advantages, their application is limited by insufficient knowledge of their precise chemical structure and active components [117]. Their unique weakness lies in failure to adapt or survive in the GIT, and therefore causes temporary biological effects that are reduced upon withdrawal. This is a temporary effect, which highlights concerns regarding the necessity of sophisticated delivery plans to extend bioavailability, maintain therapeutic effect, and reduce the dosing frequency [118,119]. Interindividual variations in the microbiome composition of the gut, food consumption, and epigenetic control, as well as patient compliance variability due to compliance, cost, and palatability, present major challenges to be addressed in a more integrative and in-depth research methodology [120,121]. While the majority of studies report beneficial effects of postbiotics, conflicting findings and variability in outcomes should be considered when interpreting results.

Despite the growing mechanistic and early clinical evidence, several limitations currently contradict the translational application of SCFA- and postbiotics-based strategies. Their biological effects are often transient and dependent on continuous administration, raising concerns regarding long-term sustainability. The challenges related to delivery and bioavailability in achieving consistent systemic and CNS exposure remain unresolved. In addition, substantial interindividual variability in gut microbiome composition, dietary patterns, and hist metabolism may influence therapeutic responsiveness and limit generalizability across populations. The practical considerations, including patient compliance, cost, and palatability of postbiotics or SCFA-based interventions, may further affect real-world implementation. Addressing these challenges will be essential for translating current mechanistic understandings into reliable and scalable clinical strategies. These observations indicate that postbiotic effects are influenced by multiple factors, including disease-dependent factors, host physiology, and microbial composition, necessitating cautious interpretation and further validation. Therefore, current evidence should be interpreted as mechanistically promising but not yet definitive, particularly in the absence of large-scale, well-controlled clinical studies. A structured overview of key knowledge gaps and future research priorities is summarized in Table 5.

Table 5: Knowledge gaps and future research priorities in SCFA/postbiotic-based strategies.

S. No.	Domain	Current Gap	Why It Matters	Future Priority	References
1	Causality	Predominantly associative and preclinical evidence; limited causal human data	Limits confidence in therapeutic targeting	Longitudinal and interventional human studies	[20,21,57]
2	CNS bioavailability	Unclear extent of SCFA penetration and activity in CNS	Uncertain direct vs. indirect mechanisms	Pharmacokinetic and brain-penetration studies	[51,115]
3	Formulation & delivery	Lack of standardized dosing and delivery systems	Leads to inconsistent outcomes	Targeted delivery systems (encapsulation, prodrugs)	[26,116,117]
4	Disease-stage specificity	Effects may differ across early vs. advanced disease	Risk of mistimed interventions	Stage-specific trials with biomarkers	[22,81]
5	Interindividual variability	Microbiome, diet, and host factors vary widely	Variable therapeutic response	Patient stratification and precision medicine	[19,56,61]
6	Duration & sustainability	Effects may be transient; require continuous exposure	Challenges long-term feasibility	Long-term intervention studies	[89,109]
7	Clinical evidence	Limited large-scale RCTs in AD, PD, and MS	Restricts clinical translation	Well-powered randomized controlled trials	[90,93,111]
8	Safety & tolerability	Long-term safety, adherence, and palatability are unclear	Affects real-world implementation	Safety profiling and patient-centered design	[115,118]

8 Conclusion

SCFAs have emerged as crucial metabolic signaling mediators linking gut microbial ecology to neurodegeneration, positioning the gut-brain-immune axis as a central regulatory framework in AD, PD, and MS. In addition to their function as byproducts of microbial fermentation, they contribute to the coordination of neuroimmune homeostasis, mitochondrial activity, epigenetic control, and BBB integrity through an integrated signaling network. This network becomes pro-inflammatory and physiologically impaired due

to changes in SCFAs synthesis brought on by aging and disease, which exacerbates neuroinflammation, synaptic dysfunction, protein aggregation, and neuronal susceptibility. These convergent findings support a view of neurodegenerative disorders as conditions influenced by systemic immunometabolic dysfunction rather than exclusively brain-restricted pathologies. The integrative biology of SCFAs provides a promising basis for exploring dynamic, mechanism-mediated biomarker signatures that define the transformation of healthy aging to prodromal and overt neurodegeneration. SCFAs have been shown in experimental studies to modulate mitochondrial resilience, restore T-cell function, strengthen epithelial and endothelial barrier integrity, and influence microglial and astrocytic phenotypes, targeting key pathogenic markers across neurodegenerative disorders. Notably, their actions may support immune competence and limit chronic inflammation, which separates SCFAS-based strategies from broadly immunosuppressive therapeutic approaches. Translating these insights into clinical impact will require a new generation of longitudinal, multi-omic, and interventional studies with the capacity to reflect temporal fluctuation in SCFAS signaling in relation to cognitive decline, disease progression, and therapeutic responses. Most of the present evidence is derived from preclinical and early-phase human studies, and definitive clinical efficacy remains to be established. These efforts should include sex, genetic risk factors, diet, and microbiome composition to enable precision-guided interventions. Integrating SCFAS biology into models of neurodegeneration provides an overall framework to understand how peripheral metabolic stress converges with central neuroinflammatory pathways. This framework may help guide future efforts toward improved disease understanding and therapeutic development, although its role in prevention and disease modification requires further clinical validation.

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Abbreviations

AD	Alzheimer's disease
PD	Parkinson's disease
MS	Multiple sclerosis
ALS	Amyotrophic lateral sclerosis
CNS	Central nervous system
BBB	Blood-brain barrier
IEB	Intestinal epithelial barrier
LPS	Lipopolysaccharide
Aβ	Amyloid-β
MAMPs	Microbial-associated molecular patterns
Treg	Regulatory T-cell

EAE	Experimental autoimmune encephalomyelitis
FFAR2	Free fatty acid receptor 2 (GPR43)
FFAR3	Free fatty acid receptor 3 (GPR41)
GPR109A	G protein-coupled receptor 109A
HDACs	Histone deacetylases
AMPK	AMP-activated protein kinase
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
AhR	Aryl hydrocarbon receptor
STAT1	Signal transducer and activator of transcription 1
SOCS2	Suppressor of cytokine signaling 2
Nrf2	Nuclear factor erythroid 2-related factor 2
BA	Bile acid
DCA	Deoxycholic acid
LCA	Lithocholic acid
FXR	Farnesoid X receptor
TGR5	Takeda G protein-coupled receptor 5 (GPBAR1)
PXR	Pregnane X receptor
TLR	Toll-like receptor
NOD	Nucleotide-binding oligomerization domain
GPCR	G protein-coupled receptor
ERK1/2	Extracellular signal-regulated kinases 1/2
PKA	Protein kinase A
CREB	cAMP response element-binding protein
IL	Interleukin
TNF-α	Tumor necrosis factor-α
ROS	Reactive oxygen species
GFAP	Glial fibrillary acidic protein
SOD	Superoxide dismutase
iNOS	Inducible nitric oxide synthase
JAK	Janus kinase
MMP	Matrix metalloproteinase
ICAM-1	Intercellular adhesion molecule 1
VCAM-1	Vascular cell adhesion molecule 1
CCL2	C-C motif chemokine ligand 2
CXCL10	C-X-C motif chemokine ligand 10
Th1	T helper 1 cell
Th17	T helper 17 cell
ApoE	Apolipoprotein E
BDNF	Brain-derived neurotrophic factor
FOXP3	Forkhead box P3
TCA	Tricarboxylic acid cycle
ATP	Adenosine triphosphate
NAD+	Nicotinamide adenine dinucleotide
LRRK2	Leucine-rich repeat kinase 2
IgA	Immunoglobulin A
GLT-1/EAAT2	Glutamate transporter 1/Excitatory amino acid transporter 2
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PSD-95	Postsynaptic density protein 95
Drp1	Dynamin-related protein 1
Mfn2	Mitofusin 2
MOG	Myelin oligodendrocyte glycoprotein
PBMC	Peripheral blood mononuclear cell
EDSS	Expanded Disability Status Scale
aMCI	Amnestic mild cognitive impairment

FOSHU	Food for Specified Health Uses
FNFC	Foods with Nutrient Function Claims
FFC	Foods with Function Claims
FDA	Food and Drug Administration
MEC	Minimum effective concentration
MCT1	Monocarboxylate transporter 1
SMCT1	Sodium-coupled monocarboxylate transporter 1
FAT/CD36	Fatty acid translocase/Cluster of differentiation 36
GIT	Gastrointestinal tract

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