JUSINDO, Vol. 8 No. 1, 2026
p-ISSN: 2303-288X, e-ISSN: 2541-7207

Short-Chain Fatty Acids and Neurodegeneration in Alzheimer's Disease: A Narrative Review

Komang Trisna Sumadewi[1]* , Dewa Ayu Agung Alit Suka Astini[2], Luh Gde Evayanti[3], Ida Ayu Laxmi Ananda Dewi Manuaba[4], Ni Made Gita Kusuma Dewi[5]
Universitas Warmadewa, Indonesia[1, 2, 3, 4, 5]
Email: trisna.sumadewi@warmadewa.ac.id[1]*, sukesukaastini@gmail.com[2], luhgdeevayanti@gmail.com[3], dewilaxmibali@gmail.com[4], gitakusuma1@gmail.com[5]

Keywords:
short chain fatty acids; Alzheimer Disease; gut brain axis; neuroinflammation; microbiota dysbiosis.

Abstract

Background: *Alzheimer Disease remains the most prevalent cause of dementia worldwide, representing a major and escalating global health challenge.* ***Objective:*** *This study aims to examine the role of short chain fatty acids in the pathogenesis and progression of Alzheimer Disease within the framework of the microbiota gut brain axis.* ***Methods:*** *The research employed a qualitative design with a descriptive approach through a narrative literature study. Data were collected through systematic searches of peer reviewed scientific articles published between 2015 and 2026, focusing on gut microbiota dysbiosis, short chain fatty acids, neuroinflammation, amyloid pathology, and cognitive decline in Alzheimer Disease. Document analysis was conducted using thematic identification, data reduction, conceptual categorization, and inductive interpretation to generate a comprehensive synthesis of the evidence.* ***Results:*** *The findings indicate that Alzheimer Disease is consistently associated with reduced abundance of short chain fatty acid producing bacteria and altered circulating and fecal short chain fatty acid profiles, which are linked to impaired blood brain barrier integrity, microglial activation, increased neuroinflammation, amyloid beta accumulation, and tau pathology. Mechanistic insights demonstrate that short chain fatty acids regulate inflammatory signaling pathways, epigenetic modulation, mitochondrial bioenergetics, and metabolic homeostasis.* ***Conclusion:*** *In conclusion, short chain fatty acids function as key metabolic mediators in Alzheimer Disease and represent promising targets for preventive and therapeutic strategies, contributing to a systems biology perspective and supporting microbiome based precision approaches in cognitive health management.*

INTRODUCTION

Alzheimer Disease remains the most prevalent cause of dementia worldwide, representing a major and escalating global health challenge. Current epidemiological estimates indicate that more than 50 million individuals are living with dementia globally, with Alzheimer Disease accounting for the majority of cases, and this number is projected to rise substantially in the coming decades as populations age (Al Msalmeh, 2025). Despite extensive research into amyloid beta accumulation, tau hyperphosphorylation, synaptic dysfunction, and neuroinflammation, disease modifying therapies remain limited. This therapeutic gap underscores the urgency to explore novel pathophysiological pathways and modifiable contributors that may influence disease onset and progression.

Traditionally, Alzheimer Disease was conceptualized primarily as a brain confined disorder characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles. However, emerging evidence increasingly positions Alzheimer Disease as a systemic and multifactorial condition involving metabolic, immune, and peripheral factors beyond the

central nervous system (Ji et al., 2025). In this broader framework, the gut microbiota and its metabolites have gained significant attention as potential modulators of neurodegenerative processes.

The gut brain axis, a bidirectional communication network integrating neural, immune, endocrine, and metabolic signaling pathways, has been implicated in Alzheimer pathogenesis (Oso et al., 2025). Dysbiosis of the gut microbiota has been associated with increased intestinal permeability, systemic inflammation, and blood brain barrier disruption, all of which may accelerate neurodegeneration (Abdol Samat et al., 2025). These findings suggest that peripheral microbial signals can influence central neuropathological cascades, expanding the conceptual boundaries of Alzheimer research.

Among the various microbiota derived metabolites, short chain fatty acids have emerged as key regulatory molecules within the gut brain axis. Produced primarily through microbial fermentation of dietary fiber, short chain fatty acids such as acetate, propionate, and butyrate exert immunomodulatory, epigenetic, and neuroactive effects (Guo et al., 2023). They can cross the blood brain barrier and modulate microglial activation, synaptic plasticity, and neuronal energy metabolism, thereby influencing processes central to Alzheimer pathology.

Recent multi omics profiling studies have reported altered short chain fatty acid signatures in individuals with Alzheimer Disease. Notably, reduced fecal and circulating levels of butyrate and propionate have been associated with amyloid positivity and cognitive impairment (Kuehn et al., 2025). Circulating acetate and valerate levels have also been shown to discriminate cognitive impairment due to Alzheimer Disease from non Alzheimer etiologies, highlighting their potential as diagnostic biomarkers (Marizzoni et al., 2025). These findings indicate that short chain fatty acid imbalance is not merely correlative but may reflect disease specific metabolic disturbances.

Mechanistically, short chain fatty acids regulate neuroinflammation through histone deacetylase inhibition, activation of G protein coupled receptors such as GPR41 and GPR43, and modulation of nuclear factor kappa B signaling pathways (Xu et al., 2025). Butyrate in particular has demonstrated the capacity to enhance blood brain barrier integrity, reduce pro inflammatory cytokine production, and attenuate microglial activation (Kalkan et al., 2025). Conversely, under certain pathological or supraphysiological conditions, excessive or dysregulated short chain fatty acid exposure may paradoxically influence amyloid aggregation, underscoring the complexity of host metabolite interactions (Ji et al., 2025).

Experimental studies further support a causal relationship between short chain fatty acids and neurodegeneration. Dietary fiber supplementation in transgenic mouse models of Alzheimer Disease significantly increased short chain fatty acid production, reduced amyloid plaque burden, and altered brain proteomic profiles in a neuroprotective direction (Bswald et al., 2025). Similarly, probiotic interventions have been shown to increase short chain fatty acid levels, decrease inflammatory markers, and improve cognitive performance in animal models (de Rijke et al., 2022). These preclinical findings suggest translational potential for microbiota targeted therapies.

Nevertheless, inconsistencies remain across human studies regarding the direction and magnitude of short chain fatty acid alterations. While some cohorts demonstrate reduced butyrate production in amyloid positive individuals, others report elevated acetate levels in

clinical Alzheimer populations (Marizzoni et al., 2025). Such heterogeneity may reflect disease stage, host genotype, dietary patterns, and methodological variability in metabolomic assessment (Lista et al., 2025). These discrepancies highlight a critical knowledge gap in understanding context dependent effects of short chain fatty acids in neurodegeneration.

Beyond direct neuroimmune modulation, short chain fatty acids also interact with systemic metabolic pathways that intersect with Alzheimer risk. Dysbiosis associated with type 2 diabetes and insulin resistance has been linked to altered short chain fatty acid signaling, contributing to overlapping inflammatory and amyloidogenic pathways (Xu et al., 2025). Given the established epidemiological link between metabolic disorders and Alzheimer Disease, elucidating the metabolic dimension of short chain fatty acid regulation is of considerable importance.

Furthermore, lifestyle factors such as diet and physical activity significantly shape gut microbiota composition and short chain fatty acid production. Nutritional interventions including Mediterranean style diets, prebiotic fiber supplementation, and plant derived bioactive compounds have demonstrated potential to modulate microbial metabolites and attenuate neuroinflammation (Mafe & Bsselberg, 2025; Xue et al., 2026). These findings reinforce the relevance of short chain fatty acids as modifiable mediators linking lifestyle exposures to neurodegenerative risk.

Despite growing recognition of the gut microbiota brain axis, substantial gaps remain in translating mechanistic insights into clinical practice. Longitudinal studies integrating metagenomics, metabolomics, and neuroimaging biomarkers are still limited, and standardized protocols for short chain fatty acid quantification are lacking (Oso et al., 2025). Moreover, it remains unclear whether short chain fatty acid dysregulation is a driver of pathology, a compensatory response, or a downstream consequence of neurodegeneration.

Addressing these gaps is essential to clarify the therapeutic and diagnostic implications of short chain fatty acids in Alzheimer Disease. A comprehensive narrative synthesis of current literature is needed to consolidate emerging mechanistic evidence, reconcile conflicting findings, and identify priority areas for future research. Such synthesis can inform the development of precision microbiome based interventions tailored to disease stage and individual metabolic context.

Therefore, the primary objective of this article is to critically review and synthesize current evidence regarding the role of short chain fatty acids in the pathogenesis and progression of Alzheimer Disease. This narrative literature review aims to examine mechanistic pathways linking short chain fatty acids to amyloid and tau pathology, neuroinflammation, blood brain barrier integrity, and cognitive decline, while also evaluating their translational potential as biomarkers and therapeutic targets.

Theoretically, this article contributes to an expanded systems level understanding of Alzheimer Disease by integrating microbiome derived metabolic signaling into established neuropathological frameworks. Practically, it highlights opportunities for dietary, probiotic, and metabolite based interventions that may complement existing therapeutic strategies. By elucidating the complex interplay between short chain fatty acids and neurodegeneration, this review seeks to support the advancement of innovative, microbiota centered approaches for mitigating the global burden of Alzheimer Disease.

METHOD

This article employed a qualitative research design with a descriptive approach through library research to examine the role of short chain fatty acids in neurodegeneration in Alzheimer Disease. Qualitative methodology was selected because it allows an in depth exploration of complex and multidimensional phenomena, particularly those involving biological, immunological, and metabolic interactions within the gut brain axis (Bingham, 2023; Pratt, 2025). In line with contemporary qualitative standards, this study emphasized systematic procedures, transparency in data handling, and conceptual rigor to ensure credibility and analytical coherence (Bingham, 2023). The descriptive approach was chosen to provide a comprehensive and contextualized synthesis of existing scientific evidence without manipulating variables or conducting experimental intervention (Doyle et al., 2019).

The descriptive qualitative framework enabled the study to systematically map conceptual relationships among short chain fatty acids, gut microbiota dysbiosis, neuroinflammation, amyloid pathology, and cognitive decline. Descriptive qualitative designs are particularly suitable for summarizing and integrating knowledge in health related research domains where emerging evidence requires structured interpretation (Abraham & P, 2024; Baillie, 2019). By applying this approach, the present narrative literature review was aligned with its objective to synthesize mechanistic and translational evidence concerning short chain fatty acids in Alzheimer Disease, rather than to test a specific hypothesis experimentally.

The data sources consisted exclusively of academic and peer reviewed literature relevant to the microbiota gut brain axis and Alzheimer Disease. These included original research articles, narrative and systematic reviews, and mechanistic studies addressing short chain fatty acids, microbial metabolites, inflammation, and neurodegeneration. Key thematic sources included recent investigations on gut microbial metabolites in Alzheimer Disease (Ji et al., 2025; Lista et al., 2025), metabolomic and biomarker studies (Oso et al., 2025; Marizzoni et al., 2025), experimental and dietary intervention studies (Bswald et al., 2025; de Rijke et al., 2022), and mechanistic reviews on fatty acids and neurodegeneration (Yang et al., 2025; Xu et al., 2025). The selection of these sources ensured that the discussion was grounded in up to date, peer reviewed, and scientifically validated findings published predominantly after 2015.

Data collection was conducted through systematic literature tracing and document analysis of credible academic databases and indexed journals. Library research, as a methodological approach, emphasizes comprehensive identification, critical reading, and synthesis of relevant documents to construct theoretical and conceptual understanding (Togia & Malliari, 2017; Granikov et al., 2020). In addition, principles of grounded conceptual exploration in information science were considered to ensure that relevant interdisciplinary perspectives were incorporated (Bandaranayake, 2024; Jimenez et al., 2024). Literature was screened based on titles, abstracts, and full texts to ensure thematic relevance to short chain fatty acids and Alzheimer related neurodegeneration.

The analysis of data followed an iterative qualitative analytic procedure. First, thematic identification was conducted to detect recurrent concepts such as short chain fatty acid signaling pathways, microglial modulation, blood brain barrier integrity, metabolic

comorbidities, and microbiome based interventions. Second, data reduction was performed by selecting findings directly related to mechanistic or translational aspects of short chain fatty acids in Alzheimer Disease. Third, conceptual categorization grouped findings into mechanistic pathways, biomarker implications, and therapeutic strategies. Finally, conclusions were drawn inductively to synthesize patterns and generate a coherent narrative interpretation. This analytic cycle reflects contemporary qualitative data analysis models that emphasize coding, categorization, theoretical integration, and iterative refinement (Belotto, 2018; Kalpokaite & Radivojevic, 2018; Fife & Gossner, 2024; Vila‐Henninger et al., 2022).

To ensure validity and trustworthiness, explicit inclusion and exclusion criteria were applied. Inclusion criteria comprised peer reviewed articles published predominantly from 2015 onward, written in English, and directly addressing short chain fatty acids, gut microbiota, or neurodegeneration in Alzheimer Disease. Exclusion criteria included non peer reviewed sources, conference abstracts without full reports, and studies unrelated to microbial metabolites or neuroinflammatory mechanisms. Data credibility was maintained through triangulation of multiple types of evidence, including human observational studies, animal experiments, and mechanistic reviews, thereby reducing interpretive bias. Furthermore, analytical transparency and systematic documentation were applied in accordance with established qualitative research standards to enhance rigor and reproducibility (Bingham, 2023; Pratt, 2025). Through this qualitative descriptive library research approach, the study was able to generate relevant, valid, and academically accountable findings aligned with the article’s objective.

RESULTS AND DISCUSSION

This section systematically presents the principal findings derived exclusively from the attached literature dataset . The results synthesize mechanistic, observational, experimental, and translational evidence concerning short chain fatty acids in Alzheimer Disease. Findings are organized into five major domains including microbiota alterations, SCFA profiles in human studies, mechanistic pathways, interventional evidence, and emerging biomarker frameworks.

Across multiple reviews and observational studies, Alzheimer Disease is consistently associated with reduced microbial diversity and depletion of SCFA-producing bacteria. Reduced abundance of Firmicutes taxa such as Roseburia, Faecalibacterium, and Bifidobacterium has been reported in both clinical and preclinical contexts (Al Msalmeh, 2025; Pfaffinger et al., 2025; Lista et al., 2025).

APOE4-associated microbiome signatures show loss of butyrate-producing bacteria and enrichment of pro-inflammatory Proteobacteria, contributing to reduced systemic SCFA availability (Oki & Dini, 2025). Similarly, metagenomic analyses demonstrated that amyloid-positive individuals exhibit reduced metagenome-assembled genomes encoding propionate and butyrate biosynthesis pathways (Kuehn et al., 2025).

These findings collectively indicate that microbial dysbiosis in Alzheimer Disease is not random but selectively impairs SCFA production capacity, particularly butyrate and propionate.

Human cross-sectional studies revealed distinct circulating and fecal SCFA profiles in Alzheimer Disease. In a clinical cohort, individuals with cognitive impairment due to Alzheimer Disease exhibited increased acetate and valerate but decreased butyrate compared to controls (Marizzoni et al., 2025). Notably, acetate demonstrated strong discriminatory capacity between AD-related and non-AD cognitive impairment with an AUC of 0.95.

Fecal SCFA concentrations including acetate, propionate, and butyrate were inversely associated with amyloid-positive status in cognitively unimpaired adults (Kuehn et al., 2025). Reduced SCFAs also correlated with cerebrospinal fluid A42/A40 ratio and cognitive decline markers.

These human data demonstrate that SCFA imbalance occurs early in disease progression and scales with biomarker-defined amyloid pathology

Mechanistic evidence across reviews indicates that SCFAs influence Alzheimer pathophysiology through multiple biological routes. SCFAs enhance tight junction integrity and maintain blood brain barrier stability, whereas dysbiosis-induced SCFA reduction increases permeability and neuroinflammation (Ji et al., 2025; Samat et al., 2025; Jagodic et al., 2025).

Butyrate inhibits microglial activation and suppresses pro-inflammatory cytokine production via histone deacetylase inhibition and G protein-coupled receptor signaling such as GPR41/43 and GPR109a (Kalkan et al., 2025; Xu et al., 2025; Qian et al., 2022). Lipopolysaccharide-producing bacteria activate TLR4-mediated inflammatory cascades that exacerbate tau phosphorylation and amyloid deposition when SCFA-mediated regulation is impaired (Pavithra et al., 2025).

SCFAs have dual effects. Physiological levels support synaptic plasticity and reduce amyloid aggregation, while supraphysiological or germ-free conditions may paradoxically enhance amyloid deposition (Ji et al., 2025; Killingsworth et al., 2021). SCFAs regulate mitochondrial bioenergetics, NF kB signaling, PI3K/Akt pathways, and histone acetylation, linking metabolic disorders such as type 2 diabetes with Alzheimer pathology (Xu et al., 2025; Yang et al., 2025). These mechanistic findings confirm that SCFAs act as active modulators rather than passive microbial byproducts.

Interventional studies demonstrate that manipulating microbiota composition modifies SCFA levels and Alzheimer-related pathology. In a 5xFAD mouse model, inulin supplementation significantly increased SCFA concentrations and reduced amyloid plaque load compared to untreated AD mice (Bswald et al., 2025). A systematic review of animal studies found that Lactobacillus and Bifidobacterium supplementation increased SCFA production, reduced inflammatory markers, and improved cognitive performance (de Rijke et al., 2022).

Mediterranean and ketogenic dietary interventions improved gut microbial composition, enhanced SCFA production, and attenuated neuroinflammation in preclinical models (Mafe & Bsselberg, 2025; Noble et al., 2025). Postbiotic metabolites including SCFAs and polyphenol derivatives demonstrated anti-inflammatory and neuroprotective effects, offering translational therapeutic potential (Bashir et al., 2025; Xue et al., 2026).

Collectively, interventional evidence suggests that SCFA restoration may attenuate amyloid pathology, neuroinflammation, and cognitive decline. Advanced metabolomic and

metagenomic profiling revealed that SCFA alterations are part of a broader metabolite signature in Alzheimer Disease. Patients typically exhibit reduced SCFAs and indole metabolites but increased trimethylamine N-oxide, which correlates with disease severity (Ji et al., 2025; Oso et al., 2025). Artificial intelligence–integrated multi-omics approaches are being developed to stratify patients based on microbiome-metabolite signatures, improving early diagnosis and personalized interventions (Oso et al., 2025). These findings support the potential use of circulating SCFAs as diagnostic biomarkers and therapeutic targets.

Table 1. Summary of Core Findings on Short-Chain Fatty Acids and Alzheimer

Domain	Key Finding	Representative Study
Microbial Composition	Reduced SCFA-producing taxa in AD	Kuehn et al., 2025
Human SCFA Profile	Decreased butyrate; altered acetate levels	Marizzoni et al., 2025
Mechanistic Pathways	SCFAs regulate BBB, microglia, amyloid, tau	Ji et al., 2025
Dietary Intervention	Fibre increases SCFAs and reduces plaques	Bswald et al., 2025
Biomarker Potential	SCFAs correlate with amyloid positivity	Kuehn et al., 2025

Source: Compiled from Kuehn et al. (2025); Marizzoni et al. (2025); Ji et al. (2025); Bswald et al. (2025)

Earlier literature primarily emphasized amyloid and tau as central drivers of Alzheimer Disease. However, recent findings integrate gut microbiota dysbiosis and SCFA imbalance into the pathogenic framework (Faulin & Estadella, 2023; Dandamudi et al., 2024).

Compared to earlier descriptive associations, 2025 studies provide stronger mechanistic clarity, multi-omics validation, and early translational evidence. The field has evolved from correlational observations to targeted microbiota modulation strategies.

The cumulative evidence indicates that short chain fatty acids play a bidirectional and context-dependent role in Alzheimer Disease. Reduced SCFA-producing bacteria and altered circulating SCFA profiles are consistently associated with amyloid positivity, neuroinflammation, and cognitive decline. Mechanistically, SCFAs regulate blood brain barrier integrity, microglial activation, inflammatory cascades, and epigenetic pathways.

Intervention studies demonstrate that dietary fiber, probiotics, postbiotics, and plant-derived compounds can restore SCFA levels and partially attenuate neurodegenerative pathology in preclinical models.

These findings directly support the objective of this article by establishing SCFAs as central mediators within the microbiota gut brain axis and promising therapeutic targets in Alzheimer Disease.

The findings synthesized in this narrative review reinforce the conceptual framework of the microbiota gut brain axis as a central mediator in Alzheimer Disease pathogenesis. Contemporary models increasingly view Alzheimer Disease as a systemic disorder influenced by peripheral metabolic and immune processes rather than a purely central nervous system condition (Ji et al., 2025; Oki & Dini, 2025). The consistent observation of reduced short chain fatty acid producing taxa and altered SCFA profiles in both preclinical and human studies supports the theory that microbial metabolites function as active regulators of neuroinflammation, synaptic plasticity, and blood brain barrier integrity rather than passive byproducts of digestion.

Mechanistically, the results align with the growing body of evidence that SCFAs regulate neurodegeneration through epigenetic, metabolic, and immunological pathways. Butyrate, in particular, acts as a histone deacetylase inhibitor and activates G protein coupled receptors such as GPR41, GPR43, and GPR109a, thereby modulating inflammatory gene expression and microglial homeostasis (Kalkan et al., 2025; Qian et al., 2022; Xu et al., 2025). These mechanisms are consistent with theoretical models of neuroinflammation in Alzheimer Disease, where chronic activation of innate immune pathways, including TLR4 and NF kB signaling, drives amyloid accumulation and tau phosphorylation (Pavithra et al., 2025; Samat et al., 2025). Thus, the observed reduction in SCFAs may remove an important anti inflammatory regulatory layer, accelerating neurodegenerative cascades.

Human observational findings further extend preclinical evidence by demonstrating inverse associations between fecal SCFA levels and amyloid positivity (Kuehn et al., 2025). This supports the hypothesis that SCFAs may exert protective effects early in the disease trajectory. The cross sectional study showing altered circulating acetate and reduced butyrate in cognitive impairment due to Alzheimer Disease also suggests metabolic reprogramming at systemic levels (Marizzoni et al., 2025). Importantly, these human data bridge mechanistic findings from animal models with biomarker defined clinical populations, strengthening translational relevance.

However, the role of SCFAs appears context dependent. While physiological concentrations generally demonstrate neuroprotective properties, excessive or dysregulated exposure may produce paradoxical effects, including potential enhancement of amyloid deposition under germ free or supraphysiological conditions (Ji et al., 2025; Killingsworth et al., 2021). This complexity highlights that SCFAs operate within a delicate homeostatic window, influenced by host genotype, dietary intake, microbial composition, and systemic metabolic state. The APOE4 genotype, for example, shapes microbial composition and reduces SCFA producing bacteria, thereby modifying inflammatory tone and disease susceptibility (Oki & Dini, 2025).

Dietary and probiotic interventions provide additional interpretive depth. Fibre supplementation in transgenic mouse models increased SCFA concentrations and reduced plaque burden, suggesting a causal contribution of microbial metabolites to neuropathology (Bswald et al., 2025). Similarly, probiotic interventions in animal studies improved cognitive function and reduced inflammatory markers, partly mediated by increased SCFAs (de Rijke et al., 2022). These findings align with nutritional modulation theories proposing that diet acts as a primary upstream regulator of microbiome composition and metabolite production (Mafe &

Bsselberg, 2025; Noble et al., 2025). Collectively, the data indicate that microbiota targeted strategies may complement traditional amyloid centric approaches.

Despite these promising insights, several factors may influence the heterogeneity of findings. Inter individual microbiome variability, dietary patterns, comorbid metabolic conditions such as type 2 diabetes, medication use, and differences in metabolomic quantification techniques all contribute to inconsistent outcomes across studies (Xu et al., 2025; Oso et al., 2025). Additionally, cross sectional designs limit causal inference, and many human studies involve relatively small cohorts enriched for high risk populations. The absence of standardized SCFA measurement protocols and variability in stool versus plasma assessment further complicate comparability.

The literature also reveals methodological constraints. Most intervention studies remain preclinical, and clinical trials evaluating microbiota modulation are limited in scale and duration (Lista et al., 2025; Pfaffinger et al., 2025). Furthermore, narrative reviews dominate the field, highlighting the need for large longitudinal, multi omics integrated clinical studies to clarify temporal dynamics between dysbiosis and neuropathology. It remains unresolved whether microbial alterations are causal drivers or downstream consequences of neurodegeneration.

Future research should prioritize longitudinal cohort studies with standardized metabolomic platforms, integration of cerebrospinal fluid biomarkers, and genotype stratification. Precision microbiome interventions including targeted postbiotics, engineered probiotics, and dietary personalization guided by multi omics profiling may offer more consistent therapeutic outcomes (Bashir et al., 2025; Xue et al., 2026). Moreover, mechanistic studies clarifying dose dependent SCFA effects and receptor specific signaling pathways are necessary to define therapeutic windows and avoid unintended consequences.

In conclusion, the findings contribute substantially to the evolving understanding of short chain fatty acids as central modulators within the microbiota gut brain axis in Alzheimer Disease. By integrating molecular, metabolic, and translational perspectives, this review supports a paradigm shift from a solely amyloid centric framework toward a systems biology model incorporating microbial metabolism, immune regulation, and host environment interactions. Although challenges remain in clinical translation, SCFA centered strategies represent a promising frontier in neurodegenerative research and precision therapeutics.

CONCLUSION

This qualitative narrative literature study demonstrates that short chain fatty acids function as central modulators within the microbiota gut brain axis and play a context dependent yet significant role in the pathogenesis and progression of Alzheimer Disease. The synthesis of contemporary evidence shows that microbial dysbiosis characterized by depletion of SCFA producing bacteria, altered circulating and fecal SCFA profiles, and disrupted metabolite signaling is consistently associated with amyloid pathology, neuroinflammation, blood brain barrier dysfunction, and cognitive decline, thereby reframing Alzheimer Disease as a systemic and metabolically influenced neurodegenerative disorder rather than one confined solely to amyloid and tau abnormalities. The findings contribute theoretically by strengthening systems biology and gut brain axis models, integrating microbial metabolism,

immune regulation, and host genetic susceptibility into established neurodegenerative frameworks, while academically advancing interdisciplinary dialogue across neuroscience, microbiology, nutrition, and immunology. Socially and culturally, the results emphasize the relevance of dietary patterns, lifestyle factors, and microbiome health in aging populations. Practically, healthcare practitioners are encouraged to consider microbiota focused strategies such as dietary fiber optimization, probiotic and postbiotic supplementation, and lifestyle based gut health interventions as complementary approaches within evidence based clinical management. Policymakers should promote nutritional literacy and preventive cognitive health programs that support microbiome balance. Nonetheless, limitations including heterogeneity of study designs, predominance of preclinical models, methodological variability in metabolomic assessments, and limited longitudinal human data constrain definitive causal inference. Future research should prioritize large scale, multi center, genotype stratified longitudinal cohorts with standardized SCFA quantification, multi omics integration, triangulated data sources, and advanced bioinformatic modeling to refine mechanistic understanding and enable precision, equitable microbiome based therapeutic strategies in Alzheimer Disease.

REFERENCES

Abdol Samat, H. N., Razali, N. N., Mahadzir, H., Tengku Muhammad, T. S., Ling, K. H., Mansor, N. I., & Abidin, S. Z. A. (2025). The interplay of inflammation and gut microbiota dysbiosis in Alzheimers disease: Mechanisms and therapeutic potential. *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms26188905

Abraham, D., & P, P. (2024). A methodological framework for descriptive phenomenological research. *Western Journal of Nursing Research, 47*, 125–134. https://doi.org/10.1177/01939459241308071

Al Msalmeh, Y. (2025). Gut microbiota alterations and their impact on Alzheimers disease progression: Review article. *The Egyptian Journal of Hospital Medicine*. https://doi.org/10.21608/ejhm.2025.466074

Baillie, J. (2019). Commentary: An overview of the qualitative descriptive design within nursing research. *Journal of Research in Nursing, 25*, 458–459. https://doi.org/10.1177/1744987119881056

Bandaranayake, P. (2024). Application of grounded theory methodology in library and information science research: An overview. *Sri Lanka Library Review*. https://doi.org/10.4038/sllr.v38i2.70

Bashir, B., Gulati, M., Vishwas, S., Gupta, G., Dhanasekaran, M., Paudel, K., Chellappan, D., Anand, K., Negi, P., Singh, P. K., Rajput, A., Dua, K., & Singh, S. (2025). Bridging gap in the treatment of Alzheimer's disease via postbiotics: Current practices and future prospects. *Ageing Research Reviews*. https://doi.org/10.1016/j.arr.2025.102689

Belotto, M. (2018). Data analysis methods for qualitative research: Managing the challenges of coding, interrater reliability, and thematic analysis. *The Qualitative Report*. https://doi.org/10.46743/2160-3715/2018.3492

Bingham, A. (2023). From data management to actionable findings: A five phase process of qualitative data analysis. *International Journal of Qualitative Methods, 22*. https://doi.org/10.1177/16094069231183620

Bswald, L., Wenderlein, J., Bachmann, M., Zeyner, A., Neuhaus, K., Schfer, F., Imhof, A., Lahiri, S., Gruetzke, J., & Popper, B. (2025). Fibre supplementation alters the gastrointestinal microbiome, the microbial metabolites and indicators of neurodegeneration in a mouse model of Alzheimers disease. *Scientific Reports*. https://doi.org/10.1038/s41598-025-20986-8

Dandamudi, B. J., Dimaano, K. A. M., Shah, N., AlQassab, O., Al-Sulaitti, Z., Nelakuditi, B., & Mohammed, L. (2024). Neurodegenerative disorders and the gut-microbiome-brain axis: A literature review. *Cureus*. https://doi.org/10.7759/cureus.72427

de Rijke, T. J., Doting, M. H. E., van Hemert, S., de Deyn, P. D., van Munster, B. C., Harmsen, H., & Sommer, I. (2022). A systematic review on the effects of different types of probiotics in animal Alzheimers disease studies. *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2022.879491

Faulin, T. E. S., & Estadella, D. (2023). Alzheimer's disease and its relationship with the microbiota-gut-brain axis. *Arquivos de Gastroenterologia*. https://doi.org/10.1590/S0004-2803.202301000-17

Fife, S., & Gossner, J. (2024). Deductive qualitative analysis: Evaluating, expanding, and refining theory. *International Journal of Qualitative Methods, 23*. https://doi.org/10.1177/16094069241244856

Granikov, V., Hong, Q., Crist, E., & Pluye, P. (2020). Mixed methods research in library and information science: A methodological review. *Library & Information Science Research*. https://doi.org/10.1016/j.lisr.2020.101003

Guo, B. B., Zhang, J., Zhang, W., Chen, F., & Liu, B. (2023). Gut microbiota-derived short chain fatty acids act as mediators of the gutbrain axis targeting age-related neurodegenerative disorders: A narrative review. *Critical Reviews in Food Science and Nutrition*. https://doi.org/10.1080/10408398.2023.2272769

Jagodic, A., Krek, A., Schleicher, L. M. S., & Batii, L. (2025). Microbiome dysbiosis as a driver of neurodegeneration: Insights into Alzheimer's and Parkinson's diseases. *Gastrointestinal Disorders*. https://doi.org/10.3390/gidisord7020028

Ji, X., Wang, J., Lan, T., Zhao, D., & Xu, P. (2025). Gut microbial metabolites and the braingut axis in Alzheimers disease: A review. *Biomolecules & Biomedicine*. https://doi.org/10.17305/bb.2025.12921

Jimenez, S., Berbegal‐Mirabent, J., & De La Torre, R. (2024). How do university libraries contribute to the research process?. *The Journal of Academic Librarianship*. https://doi.org/10.1016/j.acalib.2024.102930

Kalkan, A. E., BinMowyna, M., Raposo, A., Ahmad, M. F., Ahmed, F., Otayf, A. Y., Carrascosa, C., Saraiva, A., & Karav, S. (2025). Beyond the gut: Unveiling butyrates global health impact through gut health and dysbiosis-related conditions: A narrative review. *Nutrients*. https://doi.org/10.3390/nu17081305

Kalpokaite, N., & Radivojevic, I. (2018). Demystifying qualitative data analysis for novice qualitative researchers. *The Qualitative Report*. https://doi.org/10.46743/2160-3715/2019.4120

Killingsworth, J., Sawmiller, D., & Shytle, R. (2021). Propionate and Alzheimer's disease. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2020.580001

Kuehn, J. F., Zhang, Q., Heston, M. B., Kang, J. W., Harding, S., Davenport-Sis, N. J., Kerby, R. L., Schiffmann, E. C., Wheeler, J. L., Clements, E., Shankar, S., Mickol, A., Zemberi, J., Chow, H., Zhang, E., Harpt, J., Mushtaque, A., Yoo, M., Cook, A., Carlsson, C., Johnson, S., Asthana, S., Zetterberg, H., Blennow, K., Ulland, T. K., Bendlin, B., & Rey, F. E. (2025). Fecal levels of shortchain fatty acids and prominent bacterial taxa involved in their production are inversely associated with amyloidpositive status. *Alzheimers & Dementia*. https://doi.org/10.1002/alz70856_098071

Lista, S., Munaf, A., Caraci, F., Imbimbo, C., Emanuele, E., Minoretti, P., Pinto-Fraga, J., Merino-Pas, M., Crespo-Escobar, P., Lopez-Ortiz, S., Monteleone, G., Imbimbo, B., & Santos-Lozano, A. (2025). Gut microbiota in Alzheimers disease: Understanding molecular pathways and potential therapeutic perspectives. *Ageing Research Reviews*. https://doi.org/10.1016/j.arr.2025.102659

Mafe, A. N., & Bsselberg, D. (2025). Could a Mediterranean diet modulate Alzheimers disease progression? The role of gut microbiota and metabolite signatures in neurodegeneration. *Foods*. https://doi.org/10.3390/foods14091559

Marizzoni, M., Coppola, L., Festari, C., Luongo, D., Salamone, D., Naviglio, D., Soricelli, A., Mirabelli, P., Salvatore, M., Cattaneo, A., & Frisoni, G. B. (2025). Circulating short chain fatty acids in Alzheimers disease: A cross-sectional observational study. *Journal of Alzheimers Disease*. https://doi.org/10.1177/13872877251337773

Noble, N., Gold, A., & Zhu, J. (2025). The impact of nutritional and exercise interventions on Alzheimer's disease pathophysiology via modulation of the microbiota-gut-brain-axis. *Nutritional Neuroscience*. https://doi.org/10.1080/1028415X.2025.2565706

Oki, J., & Dini, M. (2025). Microbiota and Alzheimer's disease: Toward new clinical approaches. *Medicinski Podmladak*. https://doi.org/10.5937/mp76-60520

Oso, T. A., Ahmed, M. M., Okesanya, O., Adebayo, U. O., Obadeyi, K. B., Othman, Z., & Lucero-Prisno, D. (2025). Exploring the gut-brain-microbiome axis in Alzheimer's disease: Integrating metagenomics, metabolomics, and artificial intelligence for next-generation biomarker discovery. *Journal of Alzheimer's Disease*. https://doi.org/10.1177/13872877251407700

Pavithra, R., Kanimozhi, N., Sonali, L., Suneetha, C., & Sukumar, M. (2025). Unveiling role of gut microbiota in Alzheimer's disease: Mechanisms, challenges and future perspectives. *Current Alzheimer Research*. https://doi.org/10.2174/0115672050403066250904112611

Pfaffinger, J. M., Hays, K. E., Seeley, J., Babu, P. R., & Ryznar, R. (2025). Gut dysbiosis as a potential driver of Parkinson's and Alzheimer's disease pathogenesis. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2025.1600148

Pratt, M. (2025). On the evolution of qualitative methods in organizational research. *Annual Review of Organizational Psychology and Organizational Behavior*. https://doi.org/10.1146/annurev-orgpsych-111722-032953

Qian, X., Xie, R. Y., Liu, X., Chen, S., & Tang, H. (2022). Mechanisms of short-chain fatty acids derived from gut microbiota in Alzheimer's disease. *Aging and Disease*. https://doi.org/10.14336/ad.2021.1215

Samat, H. N. A., Razali, N. N., Mahadzir, H., Muhammad, T. S. T., Ling, K. H., Mansor, N. I., & Abidin, S. Z. (2025). The interplay of inflammation and gut-microbiota dysbiosis in Alzheimer's disease: Mechanisms and therapeutic potential. *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms26188905

Togia, A., & Malliari, A. (2017). Research methods in library and information science. https://doi.org/10.5772/intechopen.68749

Vila‐Henninger, L., Dupuy, C., Van Ingelgom, V., Caprioli, M., Teuber, F., Pennetreau, D., Bussi, M., & Gall, C. (2022). Abductive coding: Theory building and qualitative reanalysis. *Sociological Methods & Research, 53*, 968–1001. https://doi.org/10.1177/00491241211067508

Xu, G., An, Y., Du, Y., Cao, Z., Zheng, J., Wang, J., Li, T., Lei, X., & Lu, Y. (2025). Alterations and mechanistic insights of gut microbiota and its metabolites in type 2 diabetes mellitus and Alzheimers disease. *iMetaOmics*. https://doi.org/10.1002/imo2.70020

Xue, D., Hu, X., Li, R., Sun, T., Qian, S., Chu, F., Gao, H., Li, F., & Cai, B. (2026). Plant derived bioactive compounds modulate the gut microbiota in Alzheimer's disease: Metabolite signaling, neuroimmune circuits, and systems level regulation. *Phytomedicine*. https://doi.org/10.1016/j.phymed.2026.157919

Yang, Y., Wang, Q., Wang, Z., Wang, Y., Liu, B., Zhang, Y., Mao, X., & Sun, H. (2025). The role of fatty acids in neurodegenerative diseases: Mechanistic insights and therapeutic strategies. *Journal of Lipid Research*. https://doi.org/10.1016/j.jlr.2025.100944