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REVIEW

Ji et al: Gut metabolites and brain–gut axis in AD

Gut microbial metabolites and the brain–gut axis in Alzheimer's disease: A review

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ABSTRACT

Alzheimer's disease (AD) is increasingly recognised as a disorder that extends beyond the brain, with accumulating evidence implicating gut microbiota–derived metabolites in its onset and progression. This narrative review synthesises 92 peer-reviewed animal, human and meta-analytic studies published between 2010 and 2025 that investigated short-chain fatty acids (SCFAs), tryptophan-derived indoles and kynurenines, trimethylamine N-oxide (TMAO) and secondary bile acids in the context of AD. Collectively, the literature shows that SCFAs support blood–brain-barrier integrity, dampen microglial reactivity and enhance synaptic plasticity, yet can paradoxically amplify β-amyloid (Aβ) deposition under germ-free or supraphysiological conditions, highlighting the importance of host status and dosing. Beneficial indole metabolites such as indole-3-propionic acid counter oxidative stress, strengthen intestinal and cerebral barriers and suppress pro-inflammatory cascades, whereas a shift toward neurotoxic kynurenines correlates with cognitive decline. TMAO emerges as a consistently deleterious metabolite that aggravates endothelial dysfunction, neuroinflammation and Aβ aggregation; dietary precursor restriction and microbial enzyme inhibitors are therefore being explored as mitigation strategies. Secondary bile acids and polyphenol derivatives further modulate mitochondrial bioenergetics and NF-κB signalling, broadening the therapeutic landscape. Multi-omics profiling reveals that AD patients typically exhibit reduced SCFAs and indoles but elevated TMAO, changes that scale with Mini-Mental State Examination scores, brain atrophy and cerebrospinal $A\beta_{42}$ levels. Early probiotic and faecal-microbiota-transplant trials have begun to normalise these metabolite profiles and yield modest cognitive benefits, underscoring translational potential. Altogether, gut-derived metabolites are not passive by-products but active modulators of neural, immune and metabolic circuits along the microbiota–gut–brain axis; their targeted manipulation and standardised metabolomic assessment could enable earlier diagnosis and precision microbiome-based interventions for AD, a promise that now warrants validation in large, longitudinal and mechanistically informed clinical studies.

Keywords: Alzheimer's disease, brain–gut axis, gut microbial metabolites, mechanism.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder primarily characterized by cognitive decline, memory impairment, language dysfunction, and deficits in executive function. The global prevalence of AD continues to rise, with the number of patients projected to exceed 150 million by 2050, imposing a substantial burden on public health systems and caregiving resources(1). Although advances have been made in elucidating the roles of genetic predisposition, β-amyloid (Aβ) deposition, and tau hyperphosphorylation, the etiology and pathogenesis of AD remain incompletely understood. In recent years, the gut microbiota has emerged as a potential contributor to the development and progression of AD. As an essential "second genome" of the host, the gut microbiota plays a critical role in nutrient absorption, immune regulation, and metabolic homeostasis. Moreover, it establishes a bidirectional communication network with the central nervous system via the microbiota–gut–brain (MGB) axis (2, 3). Accumulating evidence indicates that individuals with AD exhibit reduced gut microbial diversity, decreased levels of beneficial microbial metabolites such as short-chain fatty acids (SCFAs), and an increased abundance of pro-inflammatory taxa including *Proteobacteria* and *Escherichia–Shigella*, a pattern of dysbiosis closely associated with neuroinflammation and neuronal apoptosis (4, 5).

The gut microbiota can influence brain function through multiple signaling pathways, including: (1) the neural pathway mediated by the vagus nerve; (2) the endocrine pathway regulating the secretion of neurotransmitters such as cortisol and serotonin; (3) the immune pathway activating microglia and pro-inflammatory cytokines; (4) the metabolic pathway involving microbial metabolites that traverse the blood–brain barrier (BBB); and (5) the barrier integrity pathway affecting both the intestinal epithelium and BBB function (5). Preclinical and clinical studies have provided preliminary evidence suggesting that gut dysbiosis may not merely be a consequence of AD, but could serve as a contributing pathogenic factor.In this context, exploring the interplay between the gut microbiota and AD pathogenesis is essential for advancing mechanistic understanding and identifying novel therapeutic targets. Microbiota-based interventions—such as probiotics, prebiotics, and fecal

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microbiota transplantation (FMT)—have demonstrated promising cognitive benefits in AD animal models (1, 6). Thus, elucidating the mechanisms of gut–brain communication, characterizing key metabolic pathways, and pinpointing actionable targets have become pivotal directions in current AD research.

METHODS

To ensure transparency and reproducibility, we conducted a structured literature search across three electronic databases: PubMed, Web of Science, and Scopus. The search covered publications from January 2010 to May 2025 and used combinations of the following keywords and MeSH terms:

"Alzheimer's disease", "gut microbiota", "microbial metabolites", "short-chain fatty acids (SCFAs)", "tryptophan", "trimethylamine-N-oxide (TMAO)", "indole derivatives", "polyphenols", "bile acids", and "brain–gut axis".

The inclusion criteria were as follows: 1.Original research articles (including animal experiments, clinical studies, and meta-analyses) reporting on gut microbial metabolites in the context of Alzheimer's disease; 2.Studies reporting outcomes such as cognitive function, Aβ pathology, neuroinflammation, or gut–brain signaling mechanisms; 3.Articles published in English and in peer-reviewed journals.

Exclusion criteria included: 1.Non-peer-reviewed literature (e.g., conference abstracts, preprints); 2.Editorial opinions or commentaries; 3.Non-systematic narrative reviews, except those providing unique mechanistic insights.

The search initially retrieved 278 records. After screening of titles and abstracts, 122 studies were selected for full-text review. Of these, 92 studies met all inclusion criteria and were included in the final synthesis. Representative studies were selected based on scientific rigor, clarity of metabolite–AD associations, and mechanistic relevance, and are summarized in Table 1.To contextualize the strength of the included evidence, we considered the following hierarchy of study designs: human randomized controlled trials (RCTs) > cohort studies > animal experiments. While several clinical studies and meta-analyses were identified, the majority of included research consisted of heterogeneous designs, varied outcome measures,

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and inconsistent reporting formats, which precluded meaningful quantitative synthesis. Therefore, a formal meta-analysis was not conducted, and the present review remains narrative in nature.

Clinical and neuropathological features of Alzheimer's disease

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder primarily characterized by memory impairment as an initial symptom. Clinically, it evolves from mild cognitive decline to profound loss of daily functioning, eventually leading to global dementia. According to the diagnostic framework proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA), AD can be classified into three stages: preclinical AD, mild cognitive impairment due to AD (MCI), and dementia due to AD (7).In the early stage, patients often experience recent memory loss, attention deficits, mild language impairment, and visuospatial disorientation. As the disease progresses, emotional instability, personality changes, executive dysfunction, and neuropsychiatric symptoms such as delusions, hallucinations, and aggression may emerge. In the terminal stage, patients typically lose the capacity for independent living and become fully dependent on caregivers.Neuropathologically, the hallmark lesions of AD include extracellular deposition of β-amyloid (Aβ) peptides forming senile plaques and intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles (NFTs) (8, 9). Aβ is generated through sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases, with excessive aggregation believed to trigger neurotoxicity, immune activation, synaptic dysfunction, and neuronal loss (9, 10). NFTs, composed of abnormally phosphorylated tau, disrupt microtubule stability and axonal transport, and their spatial distribution correlates strongly with cognitive decline (8, 11). AD pathology also features widespread neuronal loss, reduced synaptic density, microglial activation, and astrogliosis in affected brain regions (8, 12).Neuroimaging studies have confirmed the characteristic progression of structural and functional brain changes in AD. Atrophy is initially localized to the medial temporal lobe, particularly the hippocampus and parahippocampal gyrus, which are critically involved in memory consolidation (13, 14). As AD advances, cortical atrophy

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extends to the parietal, frontal, and posterior cingulate cortices. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have revealed hypometabolism and disrupted functional connectivity in these regions, indicating pathological remodeling at the network level (14, 15). Additionally, PET imaging using Aβ- or tau-specific tracers enables in vivo visualization of AD pathology, contributing to early diagnosis and disease monitoring(16).

Multiple risk factors have been associated with AD, including advanced age, genetic susceptibility such as apolipoprotein E ε4 (ApoE ε4) allele, chronic metabolic conditions (e.g., diabetes, hypertension), adverse lifestyle behaviors (e.g., physical inactivity, unhealthy diet), and psychosocial factors (e.g., depression, social isolation) (17, 18). Familial AD is rare and typically linked to early-onset cases caused by mutations in *PSEN1*, *PSEN2*, or *APP*. In contrast, sporadic AD accounts for the majority of cases and involves a multifactorial etiology encompassing oxidative stress, mitochondrial dysfunction, calcium dyshomeostasis, and chronic neuroinflammation (19).Notably, neuroinflammation has emerged as a central pathological mechanism in AD. Microglia, the primary immune effector cells in the brain, become activated in response to Aβ deposition and release proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), exacerbating neurotoxicity (12, 20).In addition to genetic and lifestyle-related risk factors, increasing attention has been directed toward the gut microbiome as a modifiable element in AD. This has led to growing interest in the microbial metabolites it produces and their potential roles in disease progression, accumulating evidence suggests that gut microbiota dysbiosis may influence central immune and inflammatory responses through the gut–brain axis, potentially contributing to early-stage AD pathology.

Overview of the biosynthesis and functional characteristics of gut microbial metabolites

The human gastrointestinal tract harbors over 10^{14} microorganisms, forming a highly diverse and complex ecological system. Through the fermentation of dietary components, mucin glycoproteins, and host secretions, the gut microbiota generates a wide array of

low-molecular-weight metabolites (21). These metabolites not only maintain local intestinal homeostasis but can also cross the intestinal barrier and influence distant organs—including the central nervous system—via neural, endocrine, and immune mechanisms (22, 23).Representative metabolites include short-chain fatty acids (SCFAs), tryptophan-derived metabolites, secondary bile acids, amine derivatives such as trimethylamine N-oxide (TMAO), and polyphenol-derived compounds. These molecules exert diverse biological functions, including signal transduction, energy regulation, immune modulation, and barrier maintenance.SCFAs, primarily acetate, propionate, and butyrate, are the main fermentation products of indigestible carbohydrates by gut microbes (21). Their production depends on specific bacterial taxa such as *Faecalibacterium prausnitzii*, *Roseburia* spp., and *Akkermansia muciniphila*. SCFAs serve as essential energy sources for colonocytes and regulate host immune responses, inflammatory signaling, and neurotransmitter synthesis by activating G protein-coupled receptors (e.g., GPR41, GPR43) or inhibiting histone deacetylases (HDACs) (21, 24). Among them, butyrate is noted for enhancing intestinal barrier integrity, promoting regulatory T cell differentiation, and suppressing pro-inflammatory cytokines, and has attracted attention for its neuroprotective potential (21). Tryptophan, an essential amino acid, is metabolized by both host and microbial enzymes into a variety of bioactive compounds. Gut bacteria convert tryptophan into indole and its derivatives, such as indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and indolelactic acid (ILA). These metabolites can activate aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR), thereby regulating inflammation, oxidative stress, and intestinal epithelial barrier function (23, 25). Some indole derivatives can cross the blood–brain barrier (BBB) and influence neuronal excitability and glial cell activation, indicating their key role in modulating brain function (23, 26).

TMAO is derived from the microbial metabolism of dietary choline, L-carnitine, and porphyrin compounds. Its precursor, trimethylamine (TMA), is oxidized to TMAO by hepatic flavin-containing monooxygenase 3 (FMO3). Elevated TMAO levels have been positively associated with various chronic diseases, including cardiovascular disease, renal dysfunction,

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and neurodegenerative disorders. These associations are thought to involve endothelial dysfunction, oxidative stress, and activation of pro-inflammatory signaling pathways (27, 28). In the context of AD, increased TMAO levels have been correlated with cognitive decline and Aβ deposition. In addition to these core metabolites, the gut microbiota can transform dietary polyphenols into metabolites with enhanced bioactivity, such as protocatechuic acid and phenylpropanoid derivatives. These compounds participate in free radical scavenging, low-grade inflammation modulation, and neuroprotection (29). Microbial-derived secondary bile acids also contribute to host metabolic and immune regulation via receptors such as farnesoid X receptor (FXR) and Takeda G protein–coupled receptor 5 (TGR5) (23). The biosynthetic profile of these metabolites is influenced by host dietary patterns, microbial composition, and the intestinal metabolic microenvironment. Their biological effects depend on their molecular structure, concentration, receptor-binding capacity, and display regional differences (e.g., between the colon and small intestine) as well as inter-individual variability. Recent advancements in metabolomics and multi-omics have facilitated systematic dissection of these metabolic pathways and laid the theoretical foundation for decoding the microbiota–gut–brain communication network.

The microbiota–gut–brain axis: A bidirectional signaling network linking the gut microbiota to the brain

The microbiota–gut–brain (MGB) axis is a complex bidirectional communication system composed of neural, endocrine, immune, and metabolic networks that maintains homeostatic balance between the gut microbiota and the central nervous system (CNS). This system not only regulates gastrointestinal function but also has profound influences on cognition, mood, stress responses, and neurodegeneration. Accumulating evidence suggests that the gut microbiota affects the CNS via several interconnected pathways, including neural, endocrine, immune, metabolic, and barrier-associated mechanisms.

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Neural pathway

The neural pathway represents the most direct route of gut–brain communication and primarily involves the vagus nerve and the enteric nervous system (ENS). The vagus nerve forms a bidirectional conduit between the gut and brain; its sensory terminals reside within the intestinal epithelium and muscularis and can detect microbial metabolites such as SCFAs and neuroactive compounds, transmitting signals to the nucleus tractus solitarius, hypothalamus, and amygdala (30, 31). The ENS can autonomously sense luminal conditions and regulate gastrointestinal motility and secretion through local reflex arcs. Certain gut bacteria are capable of producing neurotransmitters or their precursors, including γ-aminobutyric acid (GABA), serotonin (5-HT), and dopamine, thereby modulating central neurotransmitter balance (32). Notably, GABA can act via GABA_B receptors at vagal nerve terminals to inhibit excitatory neuronal activity in the CNS, forming a negative feedback loop (31).Certain gut bacteria are capable of producing neurotransmitters or their precursors, including γ-aminobutyric acid (GABA), serotonin (5-HT), and dopamine, thereby modulating central neurotransmitter balance. Notably, GABA can act via GABA_B receptors at vagal nerve terminals to inhibit excitatory neuronal activity in the CNS, forming a negative feedback loop. Although serotonin and dopamine cannot cross the blood–brain barrier, their microbial precursors may influence central nervous function indirectly by activating vagal afferents or modulating precursor supply to the brain.

Endocrine pathway

The gut is one of the largest endocrine organs and houses numerous enteroendocrine cells (EECs), which secrete hormones in response to microbial metabolites. SCFAs can activate GPR41 and GPR43 receptors on EECs, stimulating the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), thereby modulating appetite, glucose metabolism, and neuroprotection (33-35). SCFAs can activate GPR41 and GPR43 receptors on EECs, stimulating the release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), thereby modulating appetite, glucose metabolism, and neuroprotection. These hormones exert their

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effects by interacting with GLP-1 receptors in the pancreas and brain, enhancing insulin secretion, regulating hypothalamic activity, and promoting neuronal survival. Tryptophan-derived metabolites also influence the synthesis of melatonin and serotonin through endocrine routes. Although these hormones do not directly cross the blood–brain barrier, they can influence brain function by acting on peripheral receptors and modulating vagal afferents and hypothalamic pathways(36). In particular, GLP-1 and PYY can affect hypothalamic–pituitary–adrenal (HPA) axis activity by regulating corticotropin-releasing hormone (CRH) expression in the hypothalamus and downstream cortisol secretion, thereby influencing stress responses and neuroinflammation.. The gut microbiota modulates HPA axis responsiveness, thereby affecting stress-related hormones (e.g., cortisol), central inflammation, and synaptic plasticity.

Immune pathway

The gut microbiota plays a pivotal role in the development and function of the host immune system. It regulates the differentiation of dendritic cells, macrophages, and regulatory T cells (Tregs), thereby influencing both local and systemic immune responses. SCFAs—particularly butyrate—promote Treg differentiation, inhibit pro-inflammatory Th17 cell activity, and reduce the production of cytokines such as IL-6, IL-1β, and TNF-α (37, 38). Activated immune cells and circulating cytokines can affect neuroinflammatory states and activate microglia. Specifically, pro-inflammatory mediators such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) can trigger microglial activation via NF-κB signaling, leading to increased Aβ accumulation and neuronal damage. Indole derivatives modulate immune responses and intestinal barrier integrity via the AhR signaling pathway, playing a crucial role in the immuno–neural axis (39). Indole derivatives modulate immune responses and intestinal barrier integrity via the AhR signaling pathway, playing a crucial role in the immuno–neural axis. Upon activation by indole compounds, AhR translocates to the nucleus and regulates the expression of interleukin-22 (IL-22), which promotes mucosal healing and enhances epithelial tight junction protein expression, thereby reinforcing gut barrier function and dampening systemic inflammation(40). Furthermore, dysbiosis-induced translocation of

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microbial endotoxins such as lipopolysaccharide (LPS) may increase systemic inflammation and BBB permeability, exacerbating CNS pathology (2, 41).

Metabolic pathway

Microbial metabolites—including SCFAs, tryptophan-derived compounds, secondary bile acids, TMAO, and polyphenol derivatives—serve as important mediators of host–microbiota interactions. Some small metabolites (e.g., acetate, propionate) can cross the BBB via systemic circulation, directly influencing neuronal excitability and synaptic function (42). SCFAs regulate neurotransmitter synthesis, neurogenesis, and CNS immune states through GPR signaling and HDAC inhibition (43).SCFAs regulate neurotransmitter synthesis, neurogenesis, and CNS immune states through GPR signaling and HDAC inhibition. Activation of GPR41 and GPR43 by SCFAs modulates microglial activity and promotes anti-inflammatory cytokine production, while HDAC inhibition by butyrate enhances brain-derived neurotrophic factor (BDNF) expression and supports neuronal differentiation(44, 45). TMAO, a nitrogenous metabolite, has been associated with cognitive impairment, Aβ deposition, and neuroinflammation, possibly via oxidative stress, endothelial dysfunction, and upregulation of inflammatory mediators (42, 46). Bile acid derivatives and microbial-converted polyphenols can also modulate neuronal energy metabolism and mitochondrial function, contributing to neurodegenerative progression (47).Bile acid derivatives and microbial-converted polyphenols can also modulate neuronal energy metabolism and mitochondrial function, contributing to neurodegenerative progression. For instance, secondary bile acids such as lithocholic acid (LCA) activate TGR5 receptors in neuronal and glial cells, enhancing mitochondrial biogenesis and reducing oxidative stress. Similarly, microbial metabolites of dietary polyphenols like urolithin A improve mitophagy and ATP production in neurons, thereby exerting neuroprotective effects(48, 49).

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Barrier interaction pathway

This pathway underscores the cooperative role of the intestinal epithelial barrier and the BBB in maintaining MGB axis homeostasis. The intact gut barrier, maintained by tight junction proteins such as occludin and claudins, prevents translocation of pro-inflammatory molecules. Microbial dysbiosis can compromise this barrier, facilitating the entry of microbial products and cytokines into circulation, leading to CNS inflammation and microenvironmental disruption. SCFAs enhance tight junction expression, restore barrier architecture, and stabilize intestinal permeability (50). Meanwhile, BBB integrity is also modulated by gut-derived signals. Studies in germ-free (GF) mice have shown increased BBB permeability, which can be partially restored through SCFA supplementation. Microbial metabolites may further influence BBB transport properties and the neuroimmune microenvironment by acting on cerebral endothelial cells, basement membranes, and astrocytic end-feet (51).Recent studies have deepened our understanding of how gut microbiota modulates CNS glial cell function and neuroinflammation in AD. For instance, a comprehensive review by Caradonna E, et al(52). highlighted how gut-derived signals regulate microglia, astrocytes, and oligodendrocytes via SCFA- and cytokine-mediated pathways. Another investigation demonstrated that animal facility conditions (SPF vs SOPF) significantly affect amyloid pathology in 5XFAD mice through microbiota-dependent mechanisms, underscoring environmental influence on gut–brain communication (53).

Role of gut microbial metabolites in the pathogenesis of Alzheimer's disease

Alzheimer's disease (AD) involves multifactorial pathological processes, including β-amyloid (Aβ) deposition, tau protein hyperphosphorylation, neuronal apoptosis, neuroinflammation, and synaptic dysfunction. Emerging evidence suggests that gut microbial metabolites may influence these central nervous system (CNS) pathologies through multiple mechanisms and could be involved in modulating disease progression even in the early stages of AD. Specific metabolites can cross the blood–brain barrier (BBB) to directly affect neurons or indirectly modulate neurodegenerative progression via inflammatory signaling,

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oxidative stress, and synaptic plasticity (54, 55).Short-chain fatty acids (SCFAs), particularly butyrate, exhibit neuroprotective potential in AD models by modulating immune responses and maintaining blood–brain barrier (BBB) integrity(51). Their context-dependent effects on microglial activation and Aβ pathology underscore the importance of host status and treatment timing in therapeutic applications. While numerous studies have demonstrated neuroprotective roles of SCFAs—particularly butyrate—in regulating inflammation, enhancing BBB integrity, and promoting synaptic plasticity, conflicting findings also exist. Notably, Colombo et al. reported that SCFA supplementation in germ-free APPPS1 mice led to increased Aβ plaque deposition and microglial activation, suggesting a context-dependent detrimental effect.These divergent outcomes may be explained by several factors. First, the germ-free status fundamentally alters immune system maturation and brain development, which may exaggerate inflammatory responses to SCFA exposure. Second, dosage and route of administration (e.g., bolus gavage vs gradual dietary intake) can differentially influence metabolic and immune responses. Third, the timing of intervention—especially whether SCFAs are administered during early vs late disease stages—may affect their impact on Aβ pathology.Therefore, SCFAs may exert bidirectional effects in AD models depending on host context, microbiota status, and treatment parameters. This duality underscores the importance of careful experimental design and patient stratification in translational applications. Tryptophan-derived metabolites are also critical molecular mediators of the gut–brain interaction. In AD mouse models, indole-3-propionic acid (IPA) and indole-lactic acid (ILA) activate the aryl hydrocarbon receptor (AhR) signaling pathway, strengthening both intestinal and cerebral barrier functions and suppressing microglial proinflammatory phenotypic transformation. IPA also exhibits antioxidant properties by scavenging reactive oxygen species (ROS) and mitigating oxidative stress-induced neuronal injury (56, 57). Moreover, tryptophan can influence melatonin synthesis via the gut–pineal–CNS axis, affecting circadian rhythm regulation and neuroprotection, disturbances of which may accelerate AD pathology (58). Gut-derived amine metabolites, particularly trimethylamine N-oxide (TMAO), are positively correlated with AD development. TMAO has been shown to promote neuroinflammatory responses, upregulate Aβ precursor protein expression and cleavage, and

enhance Aβ accumulation (59). Additionally, TMAO disrupts the integrity of cerebrovascular endothelial cells, increasing BBB permeability and amplifying inflammatory signaling transmission to the CNS. TMAO levels are inversely associated with cognitive function and may exacerbate neurodegeneration by impairing cholinergic neurotransmission, increasing oxidative stress, and disrupting mitochondrial function (60, 61). Polyphenol derivatives and secondary bile acids also contribute to AD pathogenesis. Polyphenol metabolites inhibit the NF-κB signaling pathway, reduce proinflammatory cytokine expression, and enhance endogenous antioxidant enzyme systems in the brain, thereby reducing oxidative damage (62, 63). Certain secondary bile acids modulate neuronal energy metabolism and lipid homeostasis via TGR5 and FXR pathways, and their dysregulation is closely associated with mitochondrial dysfunction and lipid abnormalities in AD (64).

Multi-omics studies have revealed substantial alterations in the gut microbial composition and metabolic profiles of AD patients. Compared with healthy controls, these individuals show decreased SCFA levels, reduced biosynthesis of indole and polyphenol derivatives, and elevated TMAO levels, suggesting that microbial metabolites may contribute to AD pathogenesis via multiple synergistic mechanisms (65, 66). Integrated metabolomic and transcriptomic analyses further indicate that dysregulated metabolic pathways are significantly associated with inflammatory markers and Aβ-related gene expression in the brain, reinforcing the central regulatory role of microbial metabolites in AD pathophysiology (67). Collectively, these findings underscore that gut microbial metabolites are not merely mediators of microbiota–brain communication but may serve as functional effectors that participate in various pathological processes of AD, including neuroinflammation, oxidative stress, neurotransmitter metabolism, and BBB dysfunction.A schematic overview of these interactions is provided in Figure 1.

Clinical evidence of gut microbial metabolites in Alzheimer's disease

With the advancement of the microbiota–gut–brain axis (MGB axis) theory, increasing clinical translational studies have focused on gut microbial metabolites in Alzheimer's

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disease (AD). Numerous clinical observations, interventional trials, and metabolomic analyses have demonstrated a strong association between these metabolites and cognitive function, inflammatory status, and pathological protein levels in AD patients, providing a theoretical foundation for microbiota-targeted interventions.

Studies have consistently shown that levels of short-chain fatty acids (SCFAs) are significantly reduced in both peripheral blood and fecal samples of AD patients, whereas trimethylamine N-oxide (TMAO) concentrations are elevated, and levels of indole and its derivatives are also decreased (68). These metabolic alterations are significantly associated with Mini-Mental State Examination (MMSE) scores, brain atrophy, and $A\beta_{42}$ levels. For example, A cohort case–cohort analysis of the AgeCoDe study in Germany including 805 older adults without dementia at baseline found that no inflammatory markers discriminated incident dementia; however, certain indole-containing tryptophan metabolites and short-chain fatty acids—including isobutyric acid and 2-methylbutyric acid—were significantly associated with progression to all-cause dementia, whereas SCFAs and TMAO were not independently predictive in adjusted models (69).

Several interventional studies have assessed the functional roles of microbial metabolites in microbiota-based therapies, such as probiotic supplementation and fecal microbiota transplantation (FMT). A double-blind randomized controlled trial from Italy reported that combined probiotic intervention (including *Lactobacillus* and *Bifidobacterium* strains) significantly increased peripheral SCFA concentrations in AD patients, accompanied by improved MMSE scores after 12 weeks (70, 71). Preliminary results from a 2023 Chinese study on FMT further showed that FMT could remodel gut microbial composition, restore SCFA and indole metabolic pathways, reduce inflammatory markers, and yield a trend of cognitive improvement (72). Metabolomic studies integrated with neuroimaging are also progressing. A 2022 study in the United States used ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) to quantify metabolomic profiles and applied PET imaging to assess Aβ burden. The results indicated that higher

plasma levels of indole-3-propionic acid (IPA) were associated with lower Aβ deposition, suggesting a neuroprotective role of this metabolite in regulating Aβ pathology (73).

In addition, multiple translational experiments have attempted to modulate microbial metabolic pathways through nutritional or pharmacological interventions. Supplementation with resistant starch, low-protein diets, and oral sodium butyrate have shown efficacy in improving cognitive function and attenuating neuroinflammation in AD animal models. These approaches also demonstrated increased SCFA levels in healthy elderly individuals, providing preliminary evidence for the clinical feasibility of such interventions (2, 74, 75). Table 1 summarizes representative published studies, outlining changes in key microbial metabolites—such as SCFAs and TMAO—in AD populations, as well as relevant intervention strategies and their potential therapeutic effects.Key studies on gut microbial metabolites in Alzheimer's disease are summarized in Table 1.

Potential therapeutic targets of gut-derived metabolites in Alzheimer's disease

In recent years, modulation of the gut microbiota has emerged as a promising therapeutic strategy for Alzheimer's disease (AD). Targeting microbial metabolites provides a direct intervention approach at the microbe–brain interface. Multiple gut microbiota–derived metabolites have demonstrated regulatory effects on key AD-related pathological processes, including neuroinflammation, oxidative stress, and Aβ metabolism. These metabolites may serve as novel therapeutic targets for personalized interventions. The following section outlines the therapeutic mechanisms and recent advances in several major categories of microbial metabolites.

Short-chain fatty acids (SCFAs)

SCFAs, especially butyrate, have shown therapeutic potential in AD by modulating inflammation, oxidative stress, and blood–brain barrier (BBB) integrity. Butyrate promotes an anti-inflammatory microglial phenotype and supports synaptic plasticity. Interventions such as oral sodium butyrate or probiotics that enhance SCFA production are currently being

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explored for their neuroprotective effects.. Butyrate also induces anti-inflammatory microglial polarization toward the M2 phenotype and inhibits pro-inflammatory M1 microglial activation commonly observed in AD (80). Oral administration of sodium butyrate or butyrate-producing probiotics is currently being investigated as a potential therapeutic strategy (2).

Tryptophan-derived metabolites

Tryptophan metabolism is central to gut–brain communication and proceeds via three major pathways: the kynurenine (KYN) pathway, serotonin synthesis, and microbial indole production. The KYN pathway and its derivatives regulate CNS inflammation and neurotoxicity and are particularly relevant in AD (81). In AD, tryptophan is preferentially metabolized into neurotoxic KYN derivatives, such as 3-hydroxykynurenine, via upregulation of indoleamine 2,3-dioxygenase (IDO), contributing to neuronal damage and microglial activation (82). Meanwhile, levels of neuroprotective metabolites like kynurenic acid (KYNA) are reduced, disrupting metabolic homeostasis (83, 84). Therapeutic strategies aim to shift tryptophan metabolism toward protective pathways while suppressing neurotoxic byproducts.

Indole derivatives

Indole-3-propionic acid (IPA) is a gut microbial metabolite derived from tryptophan, primarily produced by bacterial genera such as Clostridium and Bacteroides. Beyond its role in amyloid regulation, IPA can modulate glial cell activity and suppress neuroinflammatory gene expression in the hippocampus. Notably, IPA can cross the BBB, inhibit Aβ aggregation, and prevent neuronal apoptosis, thus exhibiting strong neuroprotective effects (62).. Strategies to increase indole derivatives—via supplementation of indole-producing bacteria or administration of synthetic metabolites—have demonstrated cognitive benefits and attenuation of pathology in AD models (56).

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TMAO and other amine metabolites

Given its pathogenic role in AD, therapeutic strategies targeting TMAO production have emerged, including dietary restriction of precursors (e.g., choline and L-carnitine) and the use of microbial enzyme inhibitors. These approaches aim to reduce TMAO-induced neuroinflammation and BBB disruption. Therapeutic approaches include dietary restriction of TMA precursors or microbial enzyme inhibitors to reduce TMAO production.A recent review by Oktaviono et al(85). published in Biomolecules and Biomedicine further elaborates the pathophysiological roles of TMAO and discusses potential therapeutic modulation strategies in the context of AD, providing valuable mechanistic insights that complement our discussion.In parallel, recent mechanistic and epidemiological studies have reinforced the pathological role of TMAO in cognitive decline. A meta-analysis including over 80,000 participants confirmed that elevated plasma TMAO is significantly associated with cognitive impairment (OR ≈ 1.39) (60). In vivo studies have shown that TMAO induces neuronal senescence, exacerbates oxidative stress, disrupts mTOR signaling, and worsens neuroinflammation (86). Moreover, comprehensive reviews (2023-2024) have summarized TMAO's negative impact on endothelial and synaptic function, and suggested potential therapeutic strategies targeting dietary precursors and microbial enzymes.(87)

Other gut-derived metabolites

Beyond the aforementioned metabolites, secondary bile acids (e.g., deoxycholic acid, lithocholic acid) also exert regulatory effects in AD by modulating energy metabolism, lipid homeostasis, and neurodevelopment via receptors such as TGR5 and FXR (88, 89). Polyphenol-derived microbial metabolites have demonstrated antioxidant, anti-inflammatory, and neuroprotective properties and may delay AD progression by optimizing metabolic crosstalk (90, 91). Emerging candidates such as γ-aminobutyric acid (GABA), N-acetylneuraminic acid, and short-chain hydroxy fatty acids are also gaining attention (92). While these molecules are endogenously synthesized in the CNS, their peripheral microbial sources and modulatory potential are under increasing investigation. Notably, elevated

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GABA levels have been associated with improved cognition in AD models, although the link between gut-derived GABA and central GABAergic signaling remains to be clarified (92).In summary, gut-derived metabolites are critical effector molecules in the pathogenesis of AD and represent promising targets for precision therapeutic interventions.

Limitations and future directions

Although emerging evidence supports the role of gut microbiota–derived metabolites in the pathogenesis and intervention of Alzheimer's disease (AD), several critical challenges remain to be addressed. First, most current studies rely on animal models or small-sample clinical trials, and their translational applicability and safety in large, diverse human populations have yet to be rigorously validated (93). Second, the brain–gut–microbiota axis represents a complex multilayered communication network involving neural, endocrine, immune, and metabolic pathways. However, mechanistic insights into key signaling molecules and their spatiotemporal dynamics are still limited, particularly regarding differential responses across disease stages and individual variability.Additionally, the levels of microbial metabolites are highly influenced by extrinsic factors such as diet, age, and lifestyle, and there is currently no unified or standardized protocol for their detection, quantification, or clinical interpretation. This lack of standardization hinders the use of gut-derived metabolites as reliable non-invasive biomarkers in clinical settings.

Future research should integrate multi-omics approaches—such as metabolomics, metagenomics, and transcriptomics—to construct multi-pathway synergy models and elucidate the dynamic interplay of metabolites in relation to disease progression. Longitudinal cohort studies are essential for tracking temporal fluctuations in metabolite profiles and identifying disease-specific signatures under different clinical and environmental contexts. Moreover, precision microbiome-based interventions—including targeted prebiotics, microbial modulation, fecal microbiota transplantation (FMT), and synthetic biological therapeutics—should be evaluated in conjunction with individualized assessment frameworks.

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These approaches hold promise for early intervention and long-term management of AD, potentially enabling the development of personalized gut–brain therapeutics.

CONCLUSION

The role of gut microbiota–derived metabolites in Alzheimer's disease (AD) has gradually shifted from associative comorbidity observations to mechanistic investigations, revealing their potential as therapeutic targets. Metabolites such as short-chain fatty acids (SCFAs), tryptophan derivatives, indole compounds, and trimethylamine N-oxide (TMAO) are not only involved in regulating neuroinflammation, blood–brain barrier (BBB) integrity, and neurotransmitter metabolism, but also influence the onset and progression of AD through multiple brain–gut axis signaling pathways.An increasing body of clinical and translational evidence supports the utility of gut-derived metabolites as promising biomarkers and integral components of novel intervention strategies. Although challenges remain—particularly regarding the clarification of underlying mechanisms and the standardization of clinical applications—current findings have opened new avenues for early detection and precision treatment of AD. Furthermore, this line of research provides a robust theoretical and experimental foundation for optimizing future microbiome-based therapeutic approaches.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Summary of selected literature on gut microbial metabolites in Alzheimer's disease research

Researchs	Metabolite / mechanism	Study type	Model / sample	Intervention / analysis	Key findings	Year
Colombo AV et al (74).	SCFAs	Animal experiment	Germ-free (GF) vs SPF APPPS1 mice	Oral SCFA supplementation	SCFAs restored Aβ plaque load and microglial activation in GF mice to SPF levels	2021
Bowerman M et al (76).	SCFAs	Animal experiment	APP/PS1 mice	Oral SCFAs supplementation	Altered gut microbiota diversity, but no significant changes in cognition or Aβ pathology	2022
Wasén C et al (77).	B. fragilis (Bacteroidota phylum)	Animal experiment	APP/PS1-21 and 5xFAD mice	B. fragilis administration or clearance	Increased Aβ deposition, inhibited microglial clearance; antibiotic reversal observed	2024
Gao Q et al (28).	TMAO	Animal experiment	WT and APP/PS1 mice	Systemic TMAO injection	Promoted synaptic loss, Aβ aggregation, and	2022

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					cognitive impairment	
Long C et al (78).	TMAO	Meta-analysis	7 cohort studies	Systematic review and pooled analysis	High TMAO levels significantly associated with cognitive impairment (OR ≈ 1.39)	2024
Zuo Z et al (79).（non-primary source）	SCFAs (mechanistic)	Review article	In vitro and animal studies	Literature synthesis	SCFAs regulate neuroinflammation via HDAC inhibition, GPCRs, immune modulation	2022

Note: 1. Zuo Z et al. (2022) is a review article and does not present primary experimental data. Included for mechanistic reference. 2. Wasén C et al. reported microglial clearance impairment as a key mechanistic link between B. fragilis colonization and Aβ accumulation. **Abbreviations:** GF, germ-free; SPF, specific pathogen-free; APP/PS1, amyloid precursor protein/presenilin 1; SCFAs, short-chain fatty acids; TMAO, trimethylamine-N-oxide.

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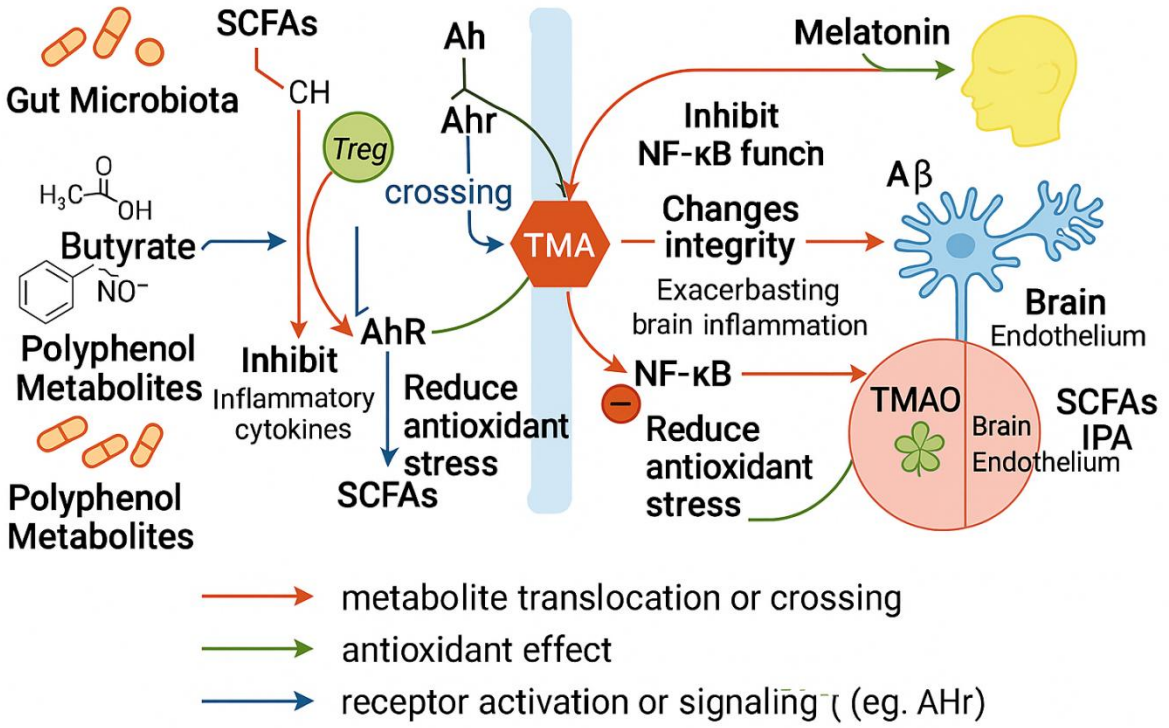

Figure 1. Gut microbial metabolites regulate Alzheimer's disease via immune, oxidative, and barrier-related mechanisms. Gut microbiota-derived metabolites influence Alzheimer's disease (AD) through multiple pathways.Short-chain fatty acids (SCFAs), especially butyrate, promote regulatory T cell (Treg) differentiation, inhibit pro-inflammatory cytokines (e.g., IL-1β, TNF-α), and enhance blood-brain barrier (BBB) integrity. However, SCFAs may also exacerbate Aβ plaque deposition under specific conditions such as germ-free environments, high doses, or inappropriate timing of administration. Tryptophan metabolites such as indole-3-propionic acid (IPA) activate aryl hydrocarbon receptor (AhR) signaling and exert antioxidant and anti-inflammatory effects. Polyphenol metabolites suppress NF-κB activation and reduce oxidative stress.In contrast, trimethylamine (TMA) and its derivative trimethylamine-N-oxide (TMAO) disrupt BBB integrity, promote β-amyloid (Aβ) accumulation, and aggravate neuroinflammation. These metabolites serve as key mediators linking gut dysbiosis to AD pathology via the gut–brain axis.