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Review

The Gut–Brain Axis Mechanism in Alzheimer's Disease: From Animal Models to Clinical Translation and Emerging Treatment Strategies

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Abstract

Research on gut microbiota in Alzheimer's disease (AD) has progressed from observational correlation studies toward investigation of causal relationships in preclinical models. Human observational studies have reported associations between alterations in gut microbiota and the entire spectrum of AD, from the preclinical stage to dementia, and are associated with Amyloid-beta (Aβ) deposition, phosphorylated Tau (p-tau) positivity, dysregulation of bile acid and short-chain fatty acid (SCFA) metabolism, as well as impaired intestinal barrier function. The strongest causal evidence currently derives from germ-free or antibiotic-treated animal models, fecal microbiota transplantation (FMT) between healthy controls and AD patients, and colonization by specific bacterial strains or metabolites—interventions that have been shown to modulate Aβ load, tau phosphorylation, microglial activation, synaptic pruning, and cognitive behavior in animal models. Mechanistically, the gut–brain axis in AD has been proposed to integrate four interconnected pathways, with the strength of evidence and the extent of human validation varying considerably across them: (1) reduced production of SCFA-producing bacteria accompanied by upregulation of pro-inflammatory pathways; (2) disruption of intestinal epithelial tight junctions, allowing lipopolysaccharide (LPS) and bacterial toxins to enter the systemic circulation; (3) reprogramming of peripheral and central innate immune systems, leading to hyperactivation of microglia and complement-mediated synaptic clearance; and (4) global rearrangement of microbial metabolite networks (including SCFAs, bile acids, tryptophan metabolites, and LPS), has been proposed to collectively regulate Aβ homeostasis, tau pathology, microglial activation, and blood–brain barrier (BBB) integrity. Clinically, the evidence base remains uneven: probiotics have been associated with some improvements in some inflammatory markers and cognitive measures in small randomized controlled trials (RCTs); FMT has been reported in case studies in human AD; modified ketogenic diets have been associated with cerebrospinal fluid (CSF) biomarkers; and molecules such as GV-971 (Sodium Oligomannate) provide proof-of-concept for microbiota-targeted strategies, though independent validation is needed. Overall, gut microbiota research in AD has advanced considerably, with animal and human studies suggesting that dysbiosis may contribute to AD pathology through immune, metabolic, and barrier-related pathways, although clinical intervention evidence remains preliminary and requires further validation.

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1. Introduction

AD has traditionally been viewed as a neurodegenerative disorder of the elderly; however, recent perspectives suggest it may be understood as a complex syndrome involving innate immune dysfunction, metabolic alterations, and environmental-gene interactions [1]. The neuropathological hallmarks of AD include extracellular senile plaques formed by β-amyloid deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated Tau protein aggregates, accompanied by synaptic loss and neuronal death [2]. In recent years, the role of gut microbiota as the human "second genome" has become increasingly prominent. Early studies in the 2000s challenged the view that "the brain is a sterile organ," and large-scale metagenomic association studies after 2016 have explored the potential link between AD and gut–brain axis dysfunction [3,4].

The human gut harbors approximately 10^{13} to 10^{14} microorganisms, with the total number of genes they encode being approximately 150 times that of the human genome [5,6]. These commensal microorganisms continuously engage in bidirectional information exchange with the host's central nervous system through the fermentation of dietary fiber to produce SCFAs, modification of host-synthesized bile acids, metabolism of essential amino acids such as tryptophan and tyrosine, and release of structural molecules including LPS and microbial extracellular vesicles, collectively constituting the core communication network of the "microbiota–gut–brain axis" [7]. 16S rRNA sequencing studies have identified microbial signatures associated with AD, with expansion of pro-inflammatory taxa (such as *Escherichia*/*Shigella*) and depletion of SCFA-producing bacteria (such as *Faecalibacterium prausnitzii*) commonly reported [8]. However, the causal significance of these microbial alterations in neurodegeneration remains an active area of investigation. Germ-free animal models, FMT, and experimental interventions have provided evidence that gut microbiota dysbiosis may influence Aβ pathology, Tau hyperphosphorylation, and cognitive outcomes in recipient animals [9,10].

Substantial challenges remain in clinical translation. The effects observed in animal models, where FMT has been reported to be associated with reduced pathology, have not consistently translated into comparable improvements in human AD clinical trials [11]. This translational gap may stem from fundamental differences between species in terms of gut ecological colonization resistance, immune system developmental status, and brain structural complexity. Moreover, current reviews have largely failed to delve into the roles of microbiota-derived non-coding RNA trans-kingdom regulation and epigenetic reprogramming in AD, emerging areas that, while speculative, may provide novel insights into the translational deadlock.

This review aims to summarize the current evidence for the gut–brain axis in AD, outline four core signaling pathways from the intestinal lumen to the synapse, compare preclinical and human studies, and discuss the emerging concept of a "microbiota-neuro-immune-epigenetic axis" as a theoretical framework for future investigation [12]. We hypothesize that (1) gut microbiota dysbiosis may function as an upstream contributor to AD pathogenesis through the four interconnected signaling pathways; (2) the magnitude and nature of microbiota-mediated effects may differ substantially between preclinical models and human patients, partly due to differences in gut ecological colonization resistance, immune developmental status, and brain structural complexity; and (3) early-stage microbiota-targeted interventions may have greater potential to modify disease trajectory than late-stage interventions.

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2. Materials and Methods

2.1. Review Type and Rationale

This is a narrative review rather than a systematic review or meta-analysis. A narrative approach was selected because the field of gut–brain axis research in AD spans multiple disciplines and is characterized by substantial methodological heterogeneity across studies, which would preclude a meaningful quantitative synthesis. The narrative format allows for the integration of mechanistic hypotheses from preclinical models with observational and interventional human data, which is the primary objective of this review.

2.2. Search Strategy

We searched PubMed and Web of Science databases through December 2025. The search terms included combinations of the following keywords: "Alzheimer's disease" or "AD" and "gut microbiota" or "gut microbiome" or "gut–brain axis" or "microbiota–gut–brain axis" and "short-chain fatty acids" or "SCFAs" or "bile acids" or "tryptophan" or "kynurenine" or "lipopolysaccharide" or "fecal microbiota transplantation" or "probiotics" or "gut barrier." Reference lists of retrieved articles were manually screened for additional relevant studies.

2.3. Inclusion and Exclusion Criteria

Inclusion criteria: (1) original research articles, systematic reviews, and narrative reviews with comprehensive literature coverage published in peer-reviewed journals; (2) studies investigating the relationship between gut microbiota and AD pathology, cognitive function, or gut–brain axis mechanisms; (3) human studies and animal studies where human data were limited.

Exclusion criteria: (1) conference abstracts, editorials, and non-peer-reviewed literature; (2) studies not reporting original data or systematic synthesis; (3) studies focused exclusively on non-AD neurodegenerative diseases without relevance to AD mechanisms.

3. From Correlation to Causation: Core Evidence for Gut Microbiota in the AD Continuum

3.1. Microbiota Signatures in the Human AD Continuum

In the preclinical stage of AD and mild cognitive impairment (MCI), gut microbiota perturbations have been reported to often precede significant brain atrophy and dementia symptoms (Figure 1) [5]. Cross-sectional studies have shown that the microbial composition in cognitively normal individuals with positive Aβ positron emission tomography (PET) already differs from those who are Aβ-negative, and reductions in microbial diversity have been correlated with the extent of Aβ deposition [13]. Among apolipoprotein E (APOE) ε4 allele carriers, dysbiosis has been reported to occur earlier and to be more severe, suggesting that host genetic background and the microbiome interact at the very initiation stage of AD [14]. APOE ε4 may modulate the gut microbiome through effects on lipid metabolism, bile acid homeostasis, and innate immune responses, potentially creating a permissive environment for pro-inflammatory taxa expansion; conversely, microbial metabolites may influence APOE expression and function, suggesting a bidirectional relationship that warrants further investigation. APOE genotype shapes gut microbial diversity, taxonomic composition, short-chain fatty acid production, bile acid metabolism, and inflammatory responses; compared with APOE2 and APOE3, APOE4 is consistently associated with gut dysbiosis, reduced beneficial microbial taxa, and increased lipopolysaccharide sensitivity [15].

At the metabolomic level, reduced fecal SCFA concentrations, particularly butyrate, have been reported in some AD patient cohorts, while levels of secondary bile acids such

as deoxycholic acid (DCA) have been reported to be elevated [16]. Plasma LPS-binding protein (LBP), an indirect marker of microbial translocation and gut barrier impairment, has been reported to be elevated and associated with a 30% increased risk of AD over 12 years, independently of IL-6 levels [17].

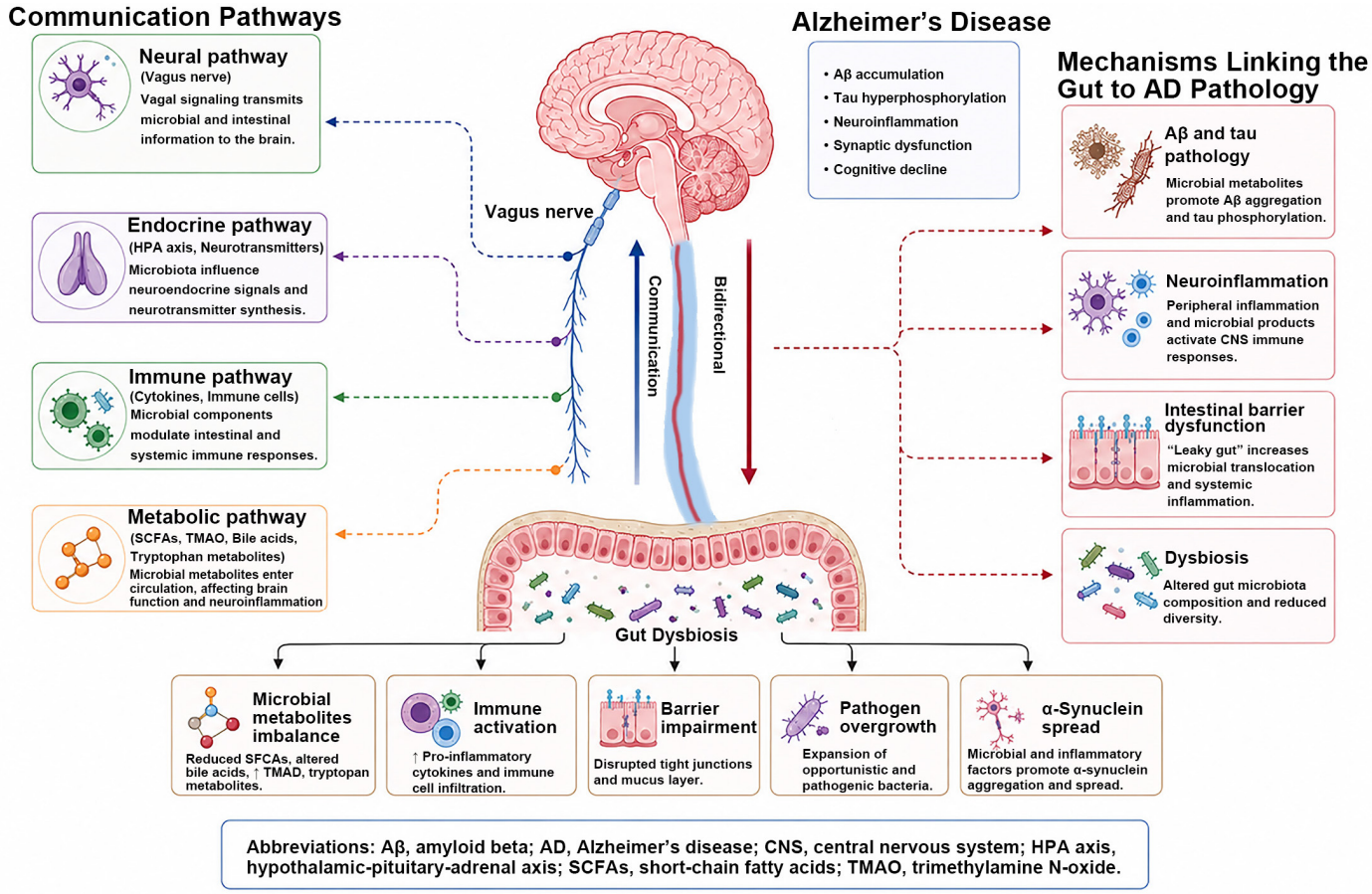


Figure 1. Gut–Brain Axis Dynamics in the AD Continuum. This figure illustrates how gut microbiota dysbiosis contributes to the pathogenesis of AD through neural, immune, endocrine, and metabolic pathways**.** The vagus nerve originates from the brainstem (medulla oblongata) and provides bidirectional communication between the CNS and the gastrointestinal tract, with approximately 80% of fibers being afferent (sensory) and ~20% efferent (motor) [18]. Altered microbial metabolites, gut barrier dysfunction, systemic inflammation, and vagal nerve signaling collectively lead to microglial activation, amyloid-β accumulation, tau pathology, and neurodegeneration. The figure highlights the bidirectional communication mechanisms between the gut and the brain, which represent the core pathological basis of AD progression.

At the population level, available evidence suggests that the most critical information regarding AD-associated microbial changes may not be "whether a particular genus is elevated," but rather that changes tend to occur early, show functional biases, and are associated with AD pathology rather than with aging alone, although the cross-sectional nature of most studies precludes causal inference and the specific taxa identified are not entirely consistent across cohorts. Ferreiro et al. [19], in a cohort of 164 cognitively normal elderly individuals, reported that the 49 participants with positive preclinical AD biomarkers already exhibited gut microbial composition different from those without preclinical AD, and this difference was associated with Aβ and tau pathology but not with neurodegeneration markers; Jia et al. [20], conducting five-stage fecal shotgun metagenomic analysis in 476 Chinese subjects, reported that over 10% of species and gene

families changed along the AD course, with cross-validation area under the curve (AUC) of 0.80 and external validation performance of 0.75.

Earlier Chinese cohort studies also provide mutually supporting directional evidence. Liu et al. [3] reported that microbiota could distinguish among AD, amnestic MCI, and healthy populations; Li et al. [21] further suggested that gut microbial alterations in MCI are continuous with those in AD; Guo et al. [22], in a newly diagnosed, minimally intervened population, reported a decrease in potentially protective bacteria such as *Bacteroides*; Khedr et al. [23] also reported a significant association between AD and gut microbiota dysbiosis. Although the specific bacterial taxa identified are not entirely consistent across studies, it is possible that these changes are not generalizable across populations but instead reflect host-specific factors including genetics, diet, medication use, and geography. Moreover, the cross-sectional design of most studies precludes causal inference, and the observed correlations may be non-causative rather than causal. Therefore, these microbial alterations should be interpreted as host-related and correlative, and their causal role in AD pathogenesis remains to be established. They collectively suggest an ecological shift characterized by (1) reduced fermentative capacity and (2) a shift in the inflammatory balance, encompassing both diminished anti-inflammatory signaling and enhanced pro-inflammatory signaling—two related but distinct aspects of immune dysregulation [23].

Verhaar et al. [13] reported associations between microbial differences and CSF pathology. In a cohort of 170 memory clinic patients, microbial composition was associated with amyloid and p-tau positivity with modest AUCs of 0.64 and 0.63, respectively. Lower abundances of *Lachnospiraceae* and *Roseburia hominis* were associated with a higher risk of amyloid/p-tau positivity, suggesting SCFA deficiency as a relatively consistent signal across studies [24].

3.2. Causal Validation: From Animal Models to Human Colonization

The strongest evidence for a causal role in this field comes from FMT experiments. Transplantation of fecal microbiota from AD patients into germ-free mice or antibiotic-treated young wild-type mice has been reported to induce intestinal barrier impairment, reduced hippocampal neurogenesis, Aβ oligomer deposition, and cognitive deficits in recipient mice [25]. Reverse validation has also been reported: transplantation of fecal microbiota from healthy young donors into aged mice or AD model mice (e.g., amyloid precursor protein/presenilin 1 (APP/PS1)) has been reported to improve some pathological features by restoring SCFA-producing bacteria and modulating the microglial complement pathway [10].

Furthermore, colonization studies with specific pathogenic bacteria provide additional evidence at the single-strain level. For example, *Porphyromonas gingivalis*, primarily a pathogen of periodontitis, has been reported to colonize the gut after swallowing. Its secreted gingipains have been reported to hydrolyze intestinal epithelial tight junctions and may cross the BBB, with detection reported in brain tissues of AD patients in some studies [26]. More elegantly, curli amyloid fibers produced by laboratory-engineered *Escherichia coli*, although not directly entering the brain, have been reported to induce intestinal plasma cells to secrete interleukin-17 (IL-17) via activation of toll-like receptor 1/2 (TLR2/TLR1) receptors, which eventually cross the BBB and trigger microglia-mediated neuroinflammation [27].

Studies by Harach et al. [28] with germ-free APP/PS1 mice, Sun and Kim et al. [9,10] with healthy microbiota transplantation, and Elangovan et al. [29] with short-course FMT in 5xFAD mice demonstrate "plaque-busting" effects; all suggest that Aβ burden, tau phosphorylation, neuroinflammation, and behavior may be modified by gut manipulation. Of particular importance is the humanization study by Grabrucker et al. [25]: AD

patient donor microbiota was associated with cognitive deficits in recipients that depended on adult hippocampal neurogenesis, significantly shortening the distance between "population correlation" and "animal causality" (Figure 1).

4. Four Core Pathways of Gut–Brain Axis-Driven Neurodegeneration

The AD gut–brain axis is not mediated by a single agent but rather by four highly interconnected signal cascade pathways that together constitute the full chain from gut ecological imbalance to synaptic demise (Figure 1), potentially amplifying the initial signal of gut dysbiosis into central nervous system (CNS) damage [5,7]. These four pathways are not independent but rather interconnected, collectively contributing to the amplification of gut-derived signals into central nervous system pathology. A schematic summary of these four core pathways, including their key mediators, affected cell types, and evidence sources (Figure 2).

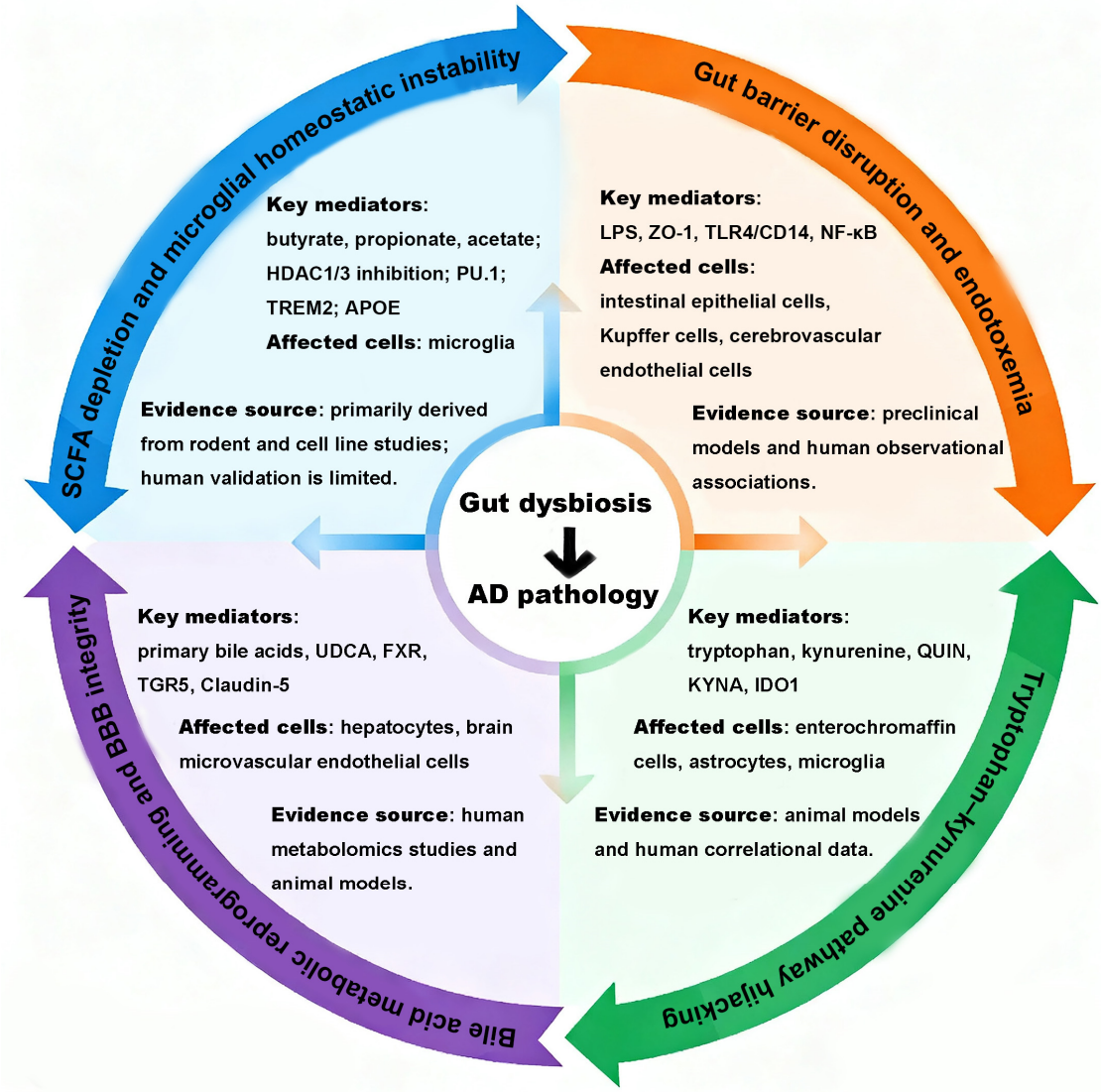


Figure 2. Circular summary of the four core pathways of gut–brain axis-driven neurodegeneration in AD. The figure is a circular diagram divided into four segments, each representing one core pathway. Sector 1 (top, blue): SCFA depletion and microglial homeostatic instability. Key mediators: butyrate, propionate, acetate; HDAC1/3 inhibition; PU.1; triggering receptor expressed on myeloid cells 2 (TREM2); APOE. Affected cells: microglia. Evidence source: primarily derived from rodent and cell line studies; human validation is limited. Sector 2 (right, orange): Gut barrier disruption

and endotoxemia. Key mediators: LPS, zonula occludens-1 (ZO-1), TLR4/CD14, NF-κB. Affected cells: intestinal epithelial cells, Kupffer cells, cerebrovascular endothelial cells. Evidence source: preclinical models and human observational associations. Sector 3 (bottom, green): Tryptophan–kynurenine pathway hijacking. Key mediators: tryptophan, kynurenine, QUIN, KYNA, IDO1. Affected cells: enterochromaffin cells, astrocytes, microglia. Evidence source: animal models and human correlational data. Sector 4 (left, purple): Bile acid metabolic reprogramming and BBB integrity. Key mediators: primary bile acids, UDCA, FXR, TGR5, Claudin-5. Affected cells: hepatocytes, brain microvascular endothelial cells. Evidence source: human metabolomics studies and animal models. At the center: Gut dysbiosis → AD pathology. Arrows indicate crosstalk between adjacent pathways.

4.1. Pathway One: SCFA Depletion and Microglial "Homeostatic Instability"

SCFAs—primarily acetate (C2), propionate (C3), and butyrate (C4)—are the major end products of anaerobic fermentation of indigestible carbohydrates by gut bacteria. They also function as histone deacetylase (HDAC) inhibitors. In AD patients, the abundance of SCFA-producing genera has been reported to be reduced. Multiple cohort studies have reported that butyrate-producing bacteria—especially *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, *Eubacterium rectale*, and *Anaerostipes hadrus*—are reduced in relative abundance in feces of AD and MCI patients compared to cognitively normal controls [4,21]. Concurrently, absolute fecal SCFA concentrations have been reported to be decreased: in a single cohort, Wu et al. [30] reported a progressive decline in fecal butyrate and SCFAs from healthy controls to amnestic mild cognitive impairment (aMCI) and AD. This profound SCFA depletion may constitute one of the initiating factors of downstream neuroinflammation in the AD gut–brain axis.

Under physiological conditions, butyrate crosses the BBB via monocarboxylate transporters and accumulates in microglial nuclei [31]. It has been reported to inhibit HDAC1/3, maintaining histone acetylation and thus preserving the expression of transcription factors such as PU.1, which have been associated with microglial homeostatic phenotype [32]. When butyrate-producing gut bacteria continuously decrease due to AD-associated dysbiosis, fecal butyrate concentrations may decline progressively [30], potentially leading to HDAC hyperactivation, chromatin accessibility rearrangement in microglia toward a pro-inflammatory state resembling "disease-associated microglia" [33], with overexpression of TREM2 [34] and APOE, loss of normal synaptic pruning discrimination, and aberrant phagocytosis of functional synapses [35,36]. These mechanisms have been demonstrated primarily in rodent and cell line studies, whereas direct human validation of these intermediate steps is largely absent. Furthermore, propionate has been reported to regulate intestinal epithelial immune barrier function via G protein-coupled receptor (GPR)s 41/43, and its deficiency may exacerbate intestinal permeability [37].

Collectively, SCFA depletion may drive microglial homeostatic instability, which in turn can promote tau hyperphosphorylation via impaired synaptic pruning and aberrant phagocytosis [30,38].

4.2. Pathway Two: Gut Barrier Disruption and Endotoxemia

The mechanical barrier of the intestinal epithelium is maintained by the tight junction protein complex. AD-associated pro-inflammatory taxa (such as *Bacteroides vulgatus* and, under certain conditions, *Akkermansia muciniphila*) have been reported to produce metabolites that may activate the nuclear factor-kappa B (NF-κB) pathway in intestinal epithelial cells, leading to redistribution and degradation of ZO-1 [39].

Enriched microbial taxa in the AD gut disrupt the tight junction barrier through multiple mechanisms. In the initial phase of gut barrier disruption, LPS entering the liver via the portal vein is recognized and cleared by Kupffer cells (liver-resident macrophages)

within the hepatic sinusoids. In preclinical models, Kupffer cells have been reported to possess high endotoxin clearance capacity, normally eliminating approximately 90% of portal vein LPS within minutes; this quantitative estimate is derived from a limited number of animal studies and may not directly translate to human physiology [40]. However, under sustained high-concentration LPS stimulation, Kupffer cells may develop endotoxin tolerance; although this tolerance may prevent acute liver injury, it may allow LPS to enter the systemic circulation, potentially exposing the peripheral immune system to low-dose endotoxin [40]. Circulating LPS may bind to TLR4/CD14 complexes on cerebrovascular endothelial cells, causing BBB leakage, and may be transported across the BBB into the brain parenchyma via adsorptive transcytosis [41]. Once in the brain, LPS has been reported to exert synergistic toxicity with Aβ fibers, directly forming complexes with Aβ oligomers and reducing Aβ clearance by microglia [34,41].

LPS-induced microglial activation may exacerbate tau pathology through inflammatory signaling cascades, linking gut dysfunction to AD neurodegeneration [41].

4.3. Pathway Three: Hijacking of the Tryptophan–Kynurenine Metabolic Pathway

Gut microbiota participate in and regulate tryptophan metabolism. Under normal conditions, approximately 95% of tryptophan is metabolized via the kynurenine pathway (KP), with only 1–3% metabolized via tryptophan hydroxylase 1/2 (TPH1/TPH2) to generate 5-hydroxytryptamine (5-HT/serotonin) and melatonin [42]. Under chronic low-grade inflammation, interferon-γ released by enterochromaffin cells and local immune cells has been reported to activate indoleamine 2,3-dioxygenase 1 (IDO1), redirecting tryptophan metabolism away from 5-HT and melatonin production toward generation of neurotoxic quinolinic acid (QUIN) and 3-hydroxykynurenine [42].

Peripheral kynurenine can be actively transported across the BBB. Once in the brain, QUIN has been reported to act as an N-methyl-D-aspartate (NMDA) receptor agonist, causing calcium influx-mediated excitotoxicity; simultaneously, it stimulates astrocytes to release more glutamate, forming a vicious cycle. Corresponding to Aβ pathology, these metabolites are also potent drivers of Tau hyperphosphorylation. Animal experiments suggest that blocking IDO1 activity may restore gut microbial diversity and reduce hippocampal Tau phosphorylation [42]. Pioneering work by Zelante et al. [43] reported that indole-3-aldehyde (IAld) produced by *Lactobacillus* species activates the AhR receptor on intestinal type 3 innate lymphoid cells (ILC3), promoting interleukin-22 (IL-22) transcription and secretion, which in turn enhances intestinal epithelial barrier function and suppresses local inflammation, indirectly reducing IFN-γ-dependent induction of IDO1. Sun et al. [38], in a single study using APP/PS1 AD mouse models, further reported that oral supplementation with indole-producing *Lactobacillus* strains (*L. reuteri* and *L. plantarum*) or direct supplementation with indole-3-propionic acid (IPA) was associated with increased plasma and brain kynurenic acid (KYNA) concentrations, decreased QUIN levels, and inhibition of microglial activation and reduction in hippocampal Aβ plaque burden, as well as significantly shortened escape latency in the Morris water maze. This finding is derived from a single rodent study and requires independent replication.

Conversely, butyrate produced by *Clostridium* species has been reported to inhibit HDAC activity in intestinal epithelial cells, thereby downregulating IFN-γ-stimulated signal transducer and activator of transcription 1 (STAT1) phosphorylation and IDO1 transcription, reducing overall KP flux at the source [44]. This may form a negative feedback regulatory loop of "butyrate-producing bacteria-IDO1 inhibition-reduced KP flux."

QUIN-mediated excitotoxicity and microglial activation may synergistically promote tau hyperphosphorylation, providing a mechanistic link between tryptophan metabolism and AD pathology [42].

4.4. Pathway Four: Bile Acid Metabolic Reprogramming and BBB Integrity

Primary bile acids (BAs) synthesized in the liver undergo 7α-dehydroxylation by gut microbiota to generate secondary bile acids (e.g., DCA, lithocholic acid (LCA)). In the AD spectrum, *Lactobacillus* and *Bifidobacterium* species possessing bile salt hydrolase activity have been reported to be reduced, while anaerobic secondary bile acid-producing bacteria have been reported to be increased [45]. BAs are not merely digestive aids but also signaling molecules that have been reported to regulate host metabolism, energy homeostasis, immune responses, and neurological functions through activation of various nuclear and membrane receptors [46].

BA receptors include the nuclear receptor farnesoid X receptor (FXR/NR1H4) and the membrane receptor G protein-coupled bile acid receptor 1 (GPBAR1/TGR5), both of which are expressed in peripheral tissues (liver, intestine, brown adipose tissue) and the central nervous system (neurons, astrocytes, microglia, cerebrovascular endothelial cells) [47]. Multiple independent large-scale metabolomic studies consistently show that BA profiles in serum and CSF of AD and MCI patients exhibit significant and reproducible quantitative alterations, and these changes are closely associated with core AD biomarkers and neuroimaging indicators [16,45]. Specific gut bacteria capable of 7α-dehydroxylation convert primary bile acids into DCA. In animal models of AD, dysbiosis has been reported to promote the overproduction of this secondary bile acid. Excess DCA has been reported to disrupt intestinal epithelial mitochondrial and plasma membranes, potentially resulting in the loss of barrier integrity and exacerbation of intestinal leakage [48]. Meanwhile, after entering the cerebral circulation, DCA has been reported to inhibit oxidative phosphorylation in brain microvascular endothelial cells, reduce expression of the tight junction protein Claudin-5, and directly impair BBB integrity [49,50]. Conversely, certain primary bile acids such as ursodeoxycholic acid (UDCA) possess mitochondrial protective effects, and UDCA content in feces of AD patients is significantly lower than in healthy individuals. Current research suggests that characteristic BA profile changes in AD patients are "decreased primary BAs, increased secondary BAs, and elevated DCA/cholic acid (CA) ratio," and these changes are independently associated with Aβ and Tau biomarkers and neuroimaging atrophy indicators [16,45]. BA profiling, being relatively standardized (targeted LC-MS/MS quantification), holds promise as an auxiliary metabolic biomarker for early AD screening and progression monitoring.

DCA-induced BBB impairment and microglial activation may facilitate tau propagation and neurodegeneration, connecting bile acid dysmetabolism to AD progression [49,50].

5. Systematic Comparison Between Animal Models and Human Clinical Studies: Bridging the Translational Gap

Directly extrapolating findings from rodent models to human AD remains a significant challenge in this field. Current human AD FMT evidence is limited to individual case reports. Hazan reported one case of an 82-year-old AD patient who, after receiving FMT from a healthy young donor, showed an improvement in the Montreal Cognitive Assessment (MoCA) score from 18 to 20 within one month; however, this report lacked imaging assessment of brain Aβ or Tau and had no placebo control [11]. Ongoing Phase I/II clinical trials of FMT for AD (e.g., NCT04842552) have primary endpoints of safety and tolerability, with cognitive score improvement serving only as a secondary exploratory endpoint. This attenuation of effect size, from substantial plaque reduction reported in animal models to modest cognitive changes in human reports, may illustrate the translational gap in this field.

In recent years, observational and interventional studies conducted in AD patients and cognitively normal control populations have covered gut microbiota composition, markers of intestinal barrier integrity (e.g., zonulin), microbial metabolites (e.g., SCFAs, bile acids, KP metabolites), and the impact of probiotic interventions on cognitive function and inflammatory markers, with study design limitations also listed (Table 1).

Table 1. Major evidence and limitations of human clinical studies on the gut–brain axis in AD.

Study	Subjects and Sample	Primary Methods	Key Findings	Major Limitations
Ferreiro [19] 2023	164 cognitively normal elderly, 49 with preclinical AD	Fecal microbial taxonomic/functional analysis	Preclinical AD already shows distinct gut microbial composition; changes correlate with Aβ and tau, not neurodegeneration markers; adding microbial features improves classifier performance	Cross-sectional; cannot prove causation
Verhaar [13] 2022	170 memory clinic patients (33 AD, 21 MCI, 116 subjective cognitive decline (SCD))	16S rRNA + CSF/magnetic resonance imaging (MRI) biomarkers + machine learning	Amyloid/p-tau prediction AUC ~0.64/0.63; lower SCFA producers associated with amyloid/p-tau positivity	Modest predictive performance; single-center
Jia [20] 2025	476 Chinese subjects, covering 5-stage AD pathology	Shotgun metagenomics	>10% species/gene families change along disease course; cross-validation AUC 0.80, external validation AUC 0.75; functional modules outperform taxonomy alone	Fecal-based primarily; requires multi-center replication
Liu [3] 2019	Chinese cohort: AD, aMCI, healthy controls	16S rRNA	AD and aMCI distinguishable by microbial signatures; supports disease continuum	Regional cohort; limited functional-level information
Li [21] 2019	MCI vs. AD comparative study	16S rRNA	MCI already exhibits gut microbial abnormalities similar to AD, supporting early window existence	Cross-sectional; confounded by diet and medications
Guo [22] 2021	Newly diagnosed AD/MCI Chinese patients	Fecal microbiome	Dysbiosis present in newly diagnosed patients; potential protective bacteria such as *Bacteroides* decreased	Limited sample size; insufficient functional validation
Mahmoudian-Dehkordi [16] 2019	1464 ADNI-related subjects	Plasma bile acid metabolomics	Primary/secondary bile acid ratio imbalance, associated with cognitive impairment and MCI-to-AD progression	Cannot distinguish microbial vs. hepatic metabolic contributions
Gao [51] 2023	MCI vs. normal controls	Fecal SCFA quantification	Fecal SCFAs decreased in MCI and correlated with Aβ deposition/inflammation	Still early-stage validation; requires combined CSF/plasma measurements
Leblhuber [52] 2018	20 AD outpatients	Multi-strain probiotic, 4-week intervention	*F. prausnitzii* increased, fecal zonulin decreased, Kyn/Trp altered	No placebo; small sample
Akbari [53] 2016	60 AD patients	12-week randomized double-blind probiotic beverage	Reported mini-mental state examination (MMSE) and metabolic parameter improvements	small sample sizes, short intervention durations, and heterogeneous outcome measures

Tamtaji [54] 2019	79 AD patients	Probiotic + selenium RCT	Cognitive and some metabolic/inflammatory markers improved	Combined intervention makes it difficult to isolate microbial effects
Loffredo [55] 2025	40 mild AD patients	Randomized double-blind placebo-controlled; *Escherichia coli* Nissle 1917 (ECN) 6 weeks	Zonulin, LPS, tumor necrosis factor-alpha (TNF-α), sNOX2-dp decreased; mini-mental state examination (MMSE) improved	Single-center, small sample, short treatment duration

This disparity has led to a typical "translational paradox": in some germ-free or antibiotic-treated AD mouse models, FMT has been reported to reduce Aβ plaques, whereas preliminary human FMT case reports only show modest stabilization of clinical dementia rating-sum of boxes (CDR-SB) scores or improvement in intestinal function, without significant plaque regression on imaging [11]. It is important to note that amyloid burden is only weakly associated with cross-sectional cognitive performance in humans, whereas tau pathology is a stronger and more consistent correlate of cognitive decline [56,57]. Furthermore, anti-amyloid monoclonal antibodies achieve greater amyloid clearance in humans than the plaque reduction reported for FMT in animal models, yet a recent review concluded that amyloid-lowering therapies produced little to no difference in cognitive decline compared with placebo [58]. Human FMT evidence remains limited to a case report showing symptomatic cognitive improvement without direct assessment of amyloid plaque burden [11]. This comparison substantially tempers the plausibility that a more indirect, pleiotropic microbiome intervention could achieve clinically meaningful cognitive benefit in humans. The modest MMSE/MoCA changes reported in Table 1, derived from open-label, small-sample, short-duration studies, should therefore be assessed against established minimal clinically important difference (MCID) thresholds for cognitive scales in AD [59]. Published MCIDs for the CDR-SB are approximately 0.64–0.98 points per year in MCI and 1.08–1.63 points per year in mild dementia [59]. The treatment effect observed with lecanemab in the CLARITY-AD trial (0.45 points on CDR-SB over 18 months) falls below these thresholds [60], and a Cochrane review of 17 RCTs (n = 20,342) rated the cognitive effects of amyloid-targeting drugs as "trivial" [61]. By analogy, the even more modest cognitive changes reported in probiotic and FMT trials in Table 1 likely also fall below MCID thresholds, underscoring the need for larger, methodologically rigorous trials with MCID-anchored endpoints.

This may reflect multiple factors, including inter-individual variability in gut ecological niche competition and metabolic network adaptability. Animal experiments employ standardized same-strain donor–recipient pairing with highly consistent genetic background and housing conditions, which may yield more consistent colonization outcomes; whereas human FMT may face fundamental differences in baseline microbial structure and immune status [62].

The mismatch in disease stage between animals and humans may also be relevant: animal experiments typically administer FMT at early AD pathology stages when the central immune microenvironment still exhibits high plasticity; human AD patients are mostly enrolled at MCI or dementia stages, by which time chronic inflammatory signals may have already influenced phenotype [63].

The dimensional mismatch in assessment metrics is another consideration: animal core efficacy endpoints are histopathological measures (Aβ plaque area, Tau phosphorylation levels, etc.), whereas human primary endpoints are cognitive function scales, and the two are nonlinearly mapped.

Taken together, this translational gap may be an inevitable consequence of the superposition of host-microbiota interaction complexity, central pathology irreversibility, and interspecies systems biology differences [64]. This suggests that once human AD crosses the clinical threshold, microbial interventions may function more through modulation of systemic metabolism to provide neurovascular protection rather than directly clearing already formed dense plaques [62]; future efforts should focus on advancing the intervention window to the preclinical stage, establishing individualized FMT screening systems based on donor–recipient functional matching, and using neuroinflammatory and metabolic markers as early efficacy assessment indicators instead of plaque burden.

6. Current and Emerging Therapeutic Strategies: From Probiotics to Precision Microbiome Engineering

Based on the mechanisms discussed above, intervention strategies targeting the gut–brain axis are evolving from "probiotic supplementation" toward "modulation of microbial network" (Figure 3) [5]. The evidence from preclinical and clinical studies for current major strategies is summarized (Table 2). Among these strategies, dietary pattern modulation serves as the foundational, sustaining driver of microbiome structure, whereas the remaining nine strategies function as corrective or adjunctive measures whose durability depends on concurrent dietary support.

Table 2. Evidence hierarchy of gut–brain axis-based intervention strategies for AD.

Intervention Strategy	Representative Modalities/Agents	Core Mechanisms	Preclinical Evidence	Human Evidence	Translational Status and Challenges
Dietary Pattern Modulation	Modified ketogenic diet, Mediterranean–DASH intervention for neurodegenerative delay (MIND) diet	Ketone body provision, reduced oxidative stress; increase polyphenol intake	Restores synaptic plasticity and improves cognition in APP/PS1 mice [65]	CSF Aβ42 improvement observed in small trials; cognitive benefits heterogeneous	Foundational driver; efficacy varies with compliance and APOE genotype
Targeted Metabolites	Sodium butyrate, propionate, UDCA, GV-971	HDAC inhibition, BBB repair, GPR109A activation, microbiota modulation	Reduces Tau and Aβ pathology in APP/PS1 and 5xFAD models [66]	GV-971 approved in China (Phase III); butyrate/UDCA limited to small exploratory studies	Adjunctive; GV-971 requires more international validation; butyrate limited by odor and short half-life
Probiotics/Synbiotics	*Lactobacillus plantarum*, *Bifidobacterium breve*	SCFA production, competitive pathogen exclusion, neurotransmitter modulation	Improves cognition and reduces neuroinflammation in AD mouse models [63]	Modest MMSE and inflammatory markers improvement in RCTs; some studies under Expression of Concern [53]	Adjunctive; Strain-specific effects; currently adjunctive only
FMT	Healthy donor capsules; colonoscopy	Overall microbial ecosystem reset	Reduces Aβ plaques and reverses cognitive deficits in multiple AD mouse models [10,29]	Limited to case reports and Phase I safety trials	Adjunctive; barriers: donor screening, standardization, long-term safety
Phage Therapy	Lytic phages targeting *E. coli*	Precision elimination of virulence factor-bearing bacteria	Lytic phages targeting E. coli have been shown to reduce	None	Adjunctive; Highly pathogen-specific; requires pre-treatment strain identification

			neuroinflammation and improve cognition in experimental models [67]		
Postbiotics	Inactivated bacterial cells, exopolysaccharides, bacterial components	Immune modulation, TLR antagonism	Anti-inflammatory effects in vitro and in some animal models [68]	No AD-specific clinical trial data available	Adjunctive; Superior safety profile; suitable for immunocompromised; AD-specific data needed

Key emerging therapeutic strategies (Figure 3): First, the small-molecule drug GV-971 (generic name: Sodium Oligomannate), a linear acidic oligosaccharide mixture (molecular weight range 1–3 kDa) extracted from the brown alga (Ecklonia kurome), is a novel AD drug independently developed and approved for marketing in China. Its proposed mechanism of action involves remodeling gut microbiota balance, reducing abnormal accumulation of peripheral branched-chain amino acids, thereby inhibiting amino acid-induced infiltration of Th1 immune cells into the brain and microglia-mediated neuroinflammation [48]. However, its Phase III trial reported a high placebo effect differential in the Chinese population, and independent validation remains a focus of attention [69]. GV-971 has generated substantial controversy. The drug was granted conditional approval in China in 2019 based on a Phase III trial [69]. But the drug's mechanism of action has been revised multiple times, and the Phase III trial showed an unusual placebo decline. In 2024, GV-971 was pulled from production after the manufacturer failed to submit required confirmatory clinical trial data to Chinese regulators. The drug's conditional approval was not renewed in August 2025, and Fosun Pharmaceutical subsequently acquired a controlling stake in Green Valley with plans to conduct post-marketing confirmatory trials. These events underscore the need for independent, international validation of microbiota-targeted therapies before they can be considered evidence-based treatments for AD.

Regarding FMT: in the field of the AD gut–brain axis, FMT holds promise for significantly alleviating cognitive deficits, Aβ accumulation, synaptic dysfunction, and neuroinflammation. However, a prevailing limitation at the current stage is that this therapeutic strategy has thus far been validated predominantly in murine models, which precludes its direct translation to human disease paradigms [10,29]. Strict regulatory and safety barriers currently restrict FMT primarily to early-phase safety trials. Documented transmission of multidrug-resistant organisms (MDRO) through FMT has raised significant safety concerns, leading regulatory agencies to implement stringent donor screening protocols. These barriers, combined with the batch-to-batch heterogeneity of donor microbiota and long-term risks of pathogen transmission, underscore the need for standardized, well-characterized donor screening systems. Washed microbiota transplantation (WMT) may remove potential parasites and food residues, improving safety. Moving from "whole-microbiota FMT" toward "minimal microbial consortia" is a recognized direction in the field. FMT has inherent limitations. Batch-to-batch heterogeneity of donor microbiota is difficult to standardize, long-term risks of potential pathogen transmission cannot be completely excluded, and the metabolic effects of full-spectrum FMT may produce unpredictable consequences depending on donor characteristics [70]. Bioinformatic screening of a defined number of specific SCFA-producing strains to constitute a minimal effective microbial consortium has been proposed as a potential strategy to circumvent the metabolic risks of full-spectrum FMT (Figure 3) [71]. However, no consensus currently exists regarding the optimal number or composition of such a consortium. A rational design pipeline could integrate constraint-based metabolic models to predict community-level butyrate

production and cross-feeding interactions, together with ecological network analysis to evaluate colonization resistance and community stability. Such a framework would require iterative validation in animal models and, eventually, in human trials. This strategy should therefore be regarded as a hypothesis-generating direction for future research rather than an evidence-based recommendation at this stage.

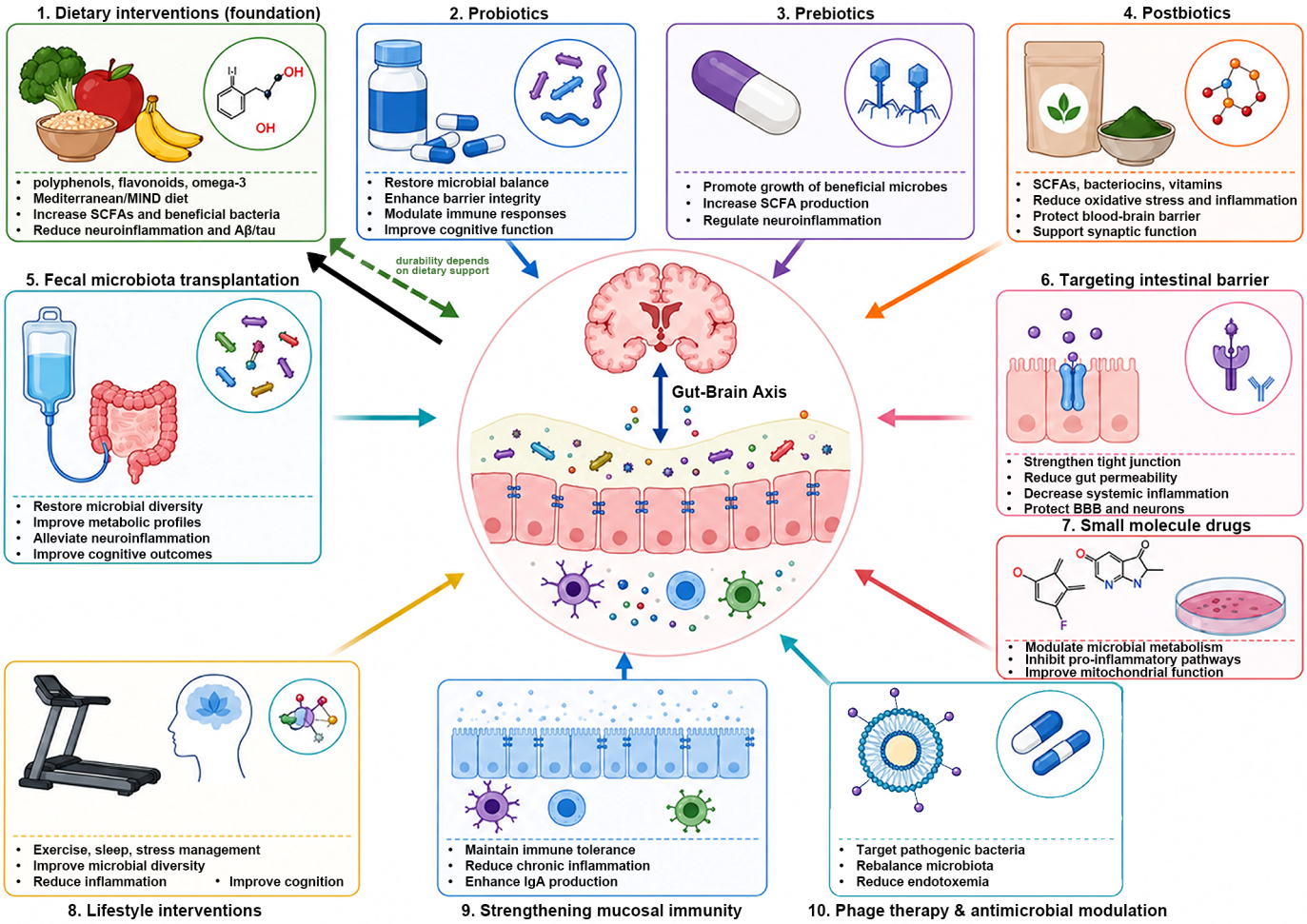


Figure 3. Comprehensive Landscape of Current and Emerging Therapeutic Strategies Targeting the Gut–Brain Axis in AD. This figure illustrates current and emerging microbiota-targeted therapeutic strategies aimed at modulating gut–brain axis function in AD. Dietary pattern modulation (including Mediterranean diet and MIND diet) is positioned as the foundational, sustaining/preventive driver of microbiome structure. The remaining nine strategies—probiotics, prebiotics, postbiotics, FMT, targeting the intestinal barrier, small molecule drugs, lifestyle interventions, strengthening mucosal immunity, and phage therapy/antimicrobial modulation—are presented as corrective or adjunctive measures whose durability depends on concurrent dietary support. These strategies collectively target microbial dysbiosis, chronic neuroinflammation, amyloid-β accumulation, tau pathology, and cognitive dysfunction through synergistic modulation of the gut–brain axis.

7. Innovative Perspectives: Broadening the Theoretical Extensions of the AD Gut–Brain Axis

7.1. Microbiota-Neuroimmune-Epigenetic Axis: A Potential Paradigm of Trans-Kingdom Regulation

Beyond traditional metabolite and pattern recognition receptor pathways, extracellular vesicles released by gut microbiota, particularly the microRNAs they contain, represent an emerging area of investigation in gut–brain communication. Preclinical studies

have suggested that microRNA-like fragments secreted by gut bacteria may be packaged within extracellular vesicles from gastrointestinal epithelial cells, resist RNase degradation, and potentially cross the BBB to enter neurons; however, direct evidence for this pathway in the context of AD remains limited [7]. Bacterial extracellular vesicles have been reported to regulate brain gene expression and induce pathology during multiple stages of neuroinflammation and neurodegeneration, suggesting they may play a causal role in diseases such as Alzheimer's [72].

Certain bacterial miRNA sequences (e.g., specific miRNAs derived from *Fusobacterium nucleatum*) complementary to human 3′-untranslated regions have been proposed to achieve trans-kingdom regulation. It has been hypothesized that bacterial miRNAs might mimic the seed sequence of host miRNA-146a and target a Tau-directed deubiquitinase gene (such as USP6), thereby inhibiting its expression and potentially contributing to impaired ubiquitination and abnormal Tau aggregation. However, although miRNA-146a dysregulation has been implicated in AD-related Tau phosphorylation and neuroinflammation, whether bacterial miRNAs can mimic its seed sequence to target USP6 remains speculative and awaits experimental validation in AD [73].Cross-kingdom miRNA interactions have been documented between host miRNAs and gut bacteria, where these miRNAs can enter bacteria and specifically regulate bacterial gene transcripts [74]; however, the reverse direction—bacterial miRNAs regulating host genes—remains far less characterized. It has been speculated that these exogenous microRNAs might enter microglia and induce expression of DNA methyltransferases, potentially leading to demethylation of CpG islands in the promoter region of the complement C1q gene; however, while CpG methylation at the C1q locus has been associated with microglial activation states in mouse models, the specific link to bacterial miRNA-induced DNA methyltransferase expression and C1q demethylation remains to be established in the context of AD. In App NL-G-F AD model mice, amyloid area has been significantly associated with hypomethylation of a CpG site that in turn is associated with upregulation of C1qc, suggesting that DNA methylation may play a role in regulation of plaque-induced genes including C1q [75]. These findings suggest a potential mechanism of "epigenetic memory", which remains an emerging hypothesis: even if gut pathogens are cleared later, the epigenetic reprogramming of microglia may persist long-term, explaining potentially explaining why FMT has limited efficacy in late-stage AD—the "aggressiveness" of microglia has been locked in at the chromatin level [76].

7.2. Chronobiology of the Gut–Brain Axis: Circadian Rhythm Disruption as an Upstream Driver

Sleep fragmentation and circadian rhythm disturbances (sundowning syndrome) in AD patients often precede cognitive symptoms by decades. A novel perspective posits that gut microbiota may function as "peripheral oscillators" of circadian rhythms. The composition and function of gut microbiota exhibit diurnal fluctuations. In preclinical models, mice with knockout of *Bmal1* have been reported to lose circadian rhythmicity in gut microbial composition and have been reported to show accelerated Aβ plaque deposition [77,78]. These findings are primarily derived from rodent studies, and human validation is limited. Targeted restoration of microbial circadian rhythms, such as time-restricted feeding at specific times or administration of sustained-release butyrate formulations within specific time windows (e.g., before bedtime), may confer higher neuroprotective efficiency than round-the-clock unguided interventions by restoring circadian rhythmic signals of microbial metabolites (Figure 3).

8. Limitations

This review has several limitations. First, as a narrative review, it is subject to selection bias and may not comprehensively capture all relevant literature. Second, most

human studies in this field are cross-sectional, precluding causal inference. Third, the translational gap between animal models and human patients remains substantial, and most mechanistic detail described herein remains unvalidated in humans. Fourth, the specific microbial taxa identified across studies are heterogeneous, and findings may not be generalizable across populations. Fifth, standardized outcome measures for microbiota-targeted interventions are lacking, limiting comparability across trials. Finally, the field is rapidly evolving, and conclusions may require revision as new evidence emerges.

9. Conclusions and Future Perspectives

Research on the AD gut–brain axis suggests that gut microbiota dysbiosis may contribute to AD pathogenesis rather than being merely an epiphenomenon of cerebral Aβ and Tau pathology, potentially influencing disease progression. However, it should be explicitly stated that most mechanistic detail described in this review—particularly the molecular intermediates linking gut dysbiosis to Aβ accumulation, tau phosphorylation, microglial activation, and BBB disruption—remains unvalidated in humans. The four signaling pathways we have described are based predominantly on preclinical evidence, and direct human validation of these intermediate steps is largely absent. This review has summarized four interconnected signaling pathways-SCFA metabolic changes, endotoxin leakage, tryptophan pathway alterations, and bile acid rearrangement-and provided a comparison of the differences between animal models and human clinical studies. Dietary pattern modulation should be regarded as the foundational, sustaining driver of microbiome structure, with other interventions functioning as corrective or adjunctive measures that require concurrent dietary support for durability. The complexity of the human gut–brain axis suggests that moving beyond simplistic approaches such as fecal transplantation or probiotic supplementation toward precision metabolomics-guided optimization may be warranted. Early targeted microbiome remodeling may potentially prevent or delay the transition from preclinical AD to dementia; however, once microglial epigenetic changes are established, simple microbial interventions may have limited ability to reverse synaptic loss.

Therefore, future research could focus on three aspects: first, developing cross-species translational biomarkers, identifying gut metabolite profiles conserved across mice and humans that respond consistently to microbial interventions, for screening patient subgroups responsive to FMT or probiotics. Second, combination therapy of postbiotics with epigenetic drugs, combining oral butyrate formulations targeting HDAC with robustly colonizing engineered probiotics, may—if the epigenetic memory hypothesis is validated—help to clear the current inflammatory milieu and potentially attenuate microglial pathological memory. Third, chronobiology-guided microbiota-targeted therapy, based on the diurnal fluctuations of gut microbiota, involves administering postbiotics or prebiotics within specific time windows to maximize neuroprotective effects.

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Abbreviations

5-HT	5-Hydroxytryptamine (Serotonin)
Aβ	Amyloid-beta
AD	Alzheimer's Disease
AhR	Aryl Hydrocarbon Receptor
aMCI	Amnestic Mild Cognitive Impairment
APOE	Apolipoprotein E
APP/PS1	Amyloid Precursor Protein/Presenilin 1
AUC	Area Under the Curve
BA	Bile Acid
BAs	Bile Acids
BBB	Blood–Brain Barrier
CA	Cholic Acid
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DCA	Deoxycholic Acid
ECN	Escherichia coli Nissle 1917
FMT	Fecal Microbiota Transplantation
FXR/NR1H4	Farnesoid X Receptor
GPBAR1/TGR5	G Protein-coupled Bile Acid Receptor 1
GPR	G Protein-coupled Receptor
GV-971	Sodium Oligomannate
HDAC	Histone Deacetylase
IAld	Indole-3-aldehyde
IDO1	Indoleamine 2,3-dioxygenase 1
IL	Interleukin
IL-17	Interleukin-17
IL-22	Interleukin-22
ILC3	Type 3 Innate Lymphoid Cells
IPA	Indole-3-propionic Acid
KP	Kynurenine Pathway
KYNA	Kynurenic Acid
LCA	Lithocholic Acid
LPS	Lipopolysaccharide
MCID	Minimal Clinically Important Difference
MCI	Mild Cognitive Impairment
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MDRO	Multidrug-resistant Organism
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
NF-κB	Nuclear Factor-kappa B
NMDA	N-methyl-D-aspartate

PET	Positron Emission Tomography
p-tau	phosphorylated Tau
QUIN	Quinolinic Acid
RCT	Randomized Controlled Trial
SCD	Subjective Cognitive Decline
SCFA	Short-Chain Fatty Acid
STAT1	Signal Transducer And Activator Of Transcription 1
TLR	Toll-like Receptor
TMAO	Trimethylamine N-oxide
TNF-α	Tumor Necrosis Factor-alpha
TPH	Tryptophan Hydroxylase
TREM2	Triggering Receptor Expressed On Myeloid Cells 2
UDCA	Ursodeoxycholic Acid
WMT	Washed Microbiota Transplantation
ZO-1	Zonula Occludens-1

References

1. Heneka, M.T.; Carson, M.J.; El Khoury, J.; Landreth, G.E.; Brosseron, F.; Feinstein, D.L.; Jacobs, A.H.; Wyss-Coray, T.; Vitorica, J.; Ransohoff, R.M.; et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* **2015**, *14*, 388–405. https://doi.org/10.1016/s1474-4422(15)70016-5.
2. Scheltens, P.; De Strooper, B.; Kivipelto, M.; Holstege, H.; Chételat, G.; Teunissen, C.E.; Cummings, J.; van der Flier, W.M. Alzheimer's disease. *Lancet* **2021**, *397*, 1577–1590. https://doi.org/10.1016/s0140-6736(20)32205-4.
3. Liu, P.; Wu, L.; Peng, G.; Han, Y.; Tang, R.; Ge, J.; Zhang, L.; Jia, L.; Yue, S.; Zhou, K.; et al. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. *Brain Behav. Immun.* **2019**, *80*, 633–643. https://doi.org/10.1016/j.bbi.2019.05.008.
4. Vogt, N.M.; Kerby, R.L.; Dill-McFarland, K.A.; Harding, S.J.; Merluzzi, A.P.; Johnson, S.C.; Carlsson, C.M.; Asthana, S.; Zetterberg, H.; Blennow, K.; et al. Gut microbiome alterations in Alzheimer's disease. *Sci. Rep.* **2017**, *7*, 13537. https://doi.org/10.1038/s41598-017-13601-y.
5. Dou, J.; Wang, J.; Chen, S.; Hsueh, E.B.; Scott, I.L.; Xue, F. Mediterranean Diet and Neurodegenerative Diseases: Recent Advances from the Gut–Immune–Brain Axis to Multi-Omics-Guided Precision Nutrition. *Cells* **2026**, *15*, 1287. https://doi.org/10.3390/cells15141287.
6. Qin, J.; Li, R.; Raes, J.; Arumugam, M.; Burgdorf, K.S.; Manichanh, C.; Nielsen, T.; Pons, N.; Levenez, F.; Yamada, T.; et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* **2010**, *464*, 59–65. https://doi.org/10.1038/nature08821.
7. Cryan, J.F.; O'Riordan, K.J.; Cowan, C.S.M.; Sandhu, K.V.; Bastiaanssen, T.F.S.; Boehme, M.; Codagnone, M.G.; Cussotto, S.; Fulling, C.; Golubeva, A.V.; et al. The Microbiota-Gut-Brain Axis. *Physiol. Rev.* **2019**, *99*, 1877–2013. https://doi.org/10.1152/physrev.00018.2018.
8. Cattaneo, A.; Cattane, N.; Galluzzi, S.; Provasi, S.; Lopizzo, N.; Festari, C.; Ferrari, C.; Guerra, U.P.; Paghera, B.; Muscio, C.; et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol. Aging* **2017**, *49*, 60–68. https://doi.org/10.1016/j.neurobiolaging.2016.08.019.
9. Kim, M.S.; Kim, Y.; Choi, H.; Kim, W.; Park, S.; Lee, D.; Kim, D.K.; Kim, H.J.; Choi, H.; Hyun, D.W.; et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut* **2020**, *69*, 283–294. https://doi.org/10.1136/gutjnl-2018-317431.
10. Sun, J.; Xu, J.; Ling, Y.; Wang, F.; Gong, T.; Yang, C.; Ye, S.; Ye, K.; Wei, D.; Song, Z.; et al. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. *Transl. Psychiatry* **2019**, *9*, 189. https://doi.org/10.1038/s41398-019-0525-3.
11. Hazan, S. Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: A case report. *J. Int. Med. Res.* **2020**, *48*, 030006052092593. https://doi.org/10.1177/0300060520925930.
12. Wang, X.; Rong, Z.; Xue, F. Multi-Dimensional Transcriptomics Reveals the Prominent Role of Neuroinflammation in Alzheimer's Disease. *Int. J. Mol. Sci.* **2026**, *27*, 5020. https://doi.org/10.3390/ijms27115020.
13. Verhaar, B.J.H.; Hendriksen, H.M.A.; de Leeuw, F.A.; Doorduijn, A.S.; van Leeuwenstijn, M.; Teunissen, C.E.; Barkhof, F.; Scheltens, P.; Kraaij, R.; van Duijn, C.M.; et al. Gut Microbiota Composition Is Related to AD Pathology. *Front. Immunol.* **2022**, *12*, 794519. https://doi.org/10.3389/fimmu.2021.794519.

14. Tam, T.; Corsini, S.; Kellingray, L.; Hegarty, C.; Le Gall, G.; Narbad, A.; Müller, M.; Tejera, N.; O'Toole, P.; Minihane, A.-M.; et al. APOE genotype influences the gut microbiome structure and function in humans and mice: Relevance for Alzheimer's disease pathophysiology. *FASEB J.* **2019**, *33*, fj.201900071R. https://doi.org/10.1096/fj.201900071R.
15. Brinati, L.L.; Santos, E.A.; Alvarez-Leite, J.I. APOE and Gut-Atherosclerosis Crosstalk. In *Apolipoprotein E: From Biochemistry and Biology to Translational Medicine*; Oriá, R., Ashford, J.W., Smith, C.J., Eds.; Springer Nature: Cham, Switzerland, 2026; pp. 567–591.
16. MahmoudianDehkordi, S.; Arnold, M.; Nho, K.; Ahmad, S.; Jia, W.; Xie, G.; Louie, G.; Kueider-Paisley, A.; Moseley, M.A.; Thompson, J.W.; et al. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease—An emerging role for gut microbiome. *Alzheimers Dement.* **2019**, *15*, 76–92. https://doi.org/10.1016/j.jalz.2018.07.217.
17. André, P.; Samieri, C.; Buisson, C.; Dartigues, J.F.; Helmer, C.; Laugerette, F.; Féart, C. Lipopolysaccharide-Binding Protein, Soluble CD14, and the Long-Term Risk of Alzheimer's Disease: A Nested Case-Control Pilot Study of Older Community Dwellers from the Three-City Cohort. *J. Alzheimers Dis.* **2019**, *71*, 751–761. https://doi.org/10.3233/jad-190295.
18. Bonaz, B.; Bazin, T.; Pellissier, S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* **2018**, *12*, 49. https://doi.org/10.3389/fnins.2018.00049.
19. Ferreiro, A.L.; Choi, J.; Ryou, J.; Newcomer, E.P.; Thompson, R.; Bollinger, R.M.; Hall-Moore, C.; Ndao, I.M.; Sax, L.; Benzinger, T.L.S.; et al. Gut microbiome composition may be an indicator of preclinical Alzheimer's disease. *Sci. Transl. Med.* **2023**, *15*, eabo2984. https://doi.org/10.1126/scitranslmed.abo2984.
20. Jia, L.; Ke, Y.; Zhao, S.; Liu, J.; Luo, X.; Cao, J.; Liu, Y.; Guo, Q.; Chen, W.H.; Chen, F.; et al. Metagenomic analysis characterizes stage-specific gut microbiota in Alzheimer's disease. *Mol. Psychiatry* **2025**, *30*, 3951–3962. https://doi.org/10.1038/s41380-025-02973-7.
21. Li, B.; He, Y.; Ma, J.; Huang, P.; Du, J.; Cao, L.; Wang, Y.; Xiao, Q.; Tang, H.; Chen, S. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimers Dement.* **2019**, *15*, 1357–1366. https://doi.org/10.1016/j.jalz.2019.07.002.
22. Guo, M.; Peng, J.; Huang, X.; Xiao, L.; Huang, F.; Zuo, Z. Gut Microbiome Features of Chinese Patients Newly Diagnosed with Alzheimer's Disease or Mild Cognitive Impairment. *J. Alzheimers Dis.* **2021**, *80*, 299–310. https://doi.org/10.3233/JAD-201040.
23. Khedr, E.; Omeran, N.; Ramadan, H.; Ahmed, G.; Abdelwarith, A. Alteration of Gut Microbiota in Alzheimer's Disease and Their Relation to the Cognitive Impairment. *J. Alzheimers Dis.* **2022**, *88*, 1103–1114. https://doi.org/10.3233/JAD-220176.
24. Ling, Z.; Huang, S.; Cheng, Y.; Liu, X.; Xu, X.; Chen, Y.; Hu, P.; Wu, L.; Cai, G. Short-chain fatty acid-producing commensals: Key modulators of AD neuroinflammation via the microbiota-gut-brain axis. *Curr. Res. Microb. Sci.* **2026**, *11*, 100660. https://doi.org/10.1016/j.crmicr.2026.100660.
25. Grabrucker, S.; Marizzoni, M.; Silajdžić, E.; Lopizzo, N.; Mombelli, E.; Nicolas, S.; Dohm-Hansen, S.; Scassellati, C.; Moretti, D.V.; Rosa, M.; et al. Microbiota from Alzheimer's patients induce deficits in cognition and hippocampal neurogenesis. *Brain* **2023**, *146*, 4916–4934. https://doi.org/10.1093/brain/awad303.
26. Dominy, S.S.; Lynch, C.; Ermini, F.; Benedyk, M.; Marczyk, A.; Konradi, A.; Nguyen, M.; Haditsch, U.; Raha, D.; Griffin, C.; et al. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci. Adv.* **2019**, *5*, eaau3333. https://doi.org/10.1126/sciadv.aau3333.
27. Chen, S.G.; Stribinskis, V.; Rane, M.J.; Demuth, D.R.; Gozal, E.; Roberts, A.M.; Jagadapillai, R.; Liu, R.; Choe, K.; Shivakumar, B.; et al. Exposure to the Functional Bacterial Amyloid Protein Curli Enhances Alpha-Synuclein Aggregation in Aged Fischer 344 Rats and Caenorhabditis elegans. *Sci. Rep.* **2016**, *6*, 34477. https://doi.org/10.1038/srep34477.
28. Harach, T.; Marungruang, N.; Duthilleul, N.; Cheatham, V.; Mc Coy, K.D.; Frisoni, G.; Neher, J.J.; Fåk, F.; Jucker, M.; Lasser, T.; et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. *Sci. Rep.* **2017**, *7*, 41802. https://doi.org/10.1038/srep41802.
29. Elangovan, S.; Borody, T.; Holsinger, R.M.D. Fecal Microbiota Transplantation Reduces Pathology and Improves Cognition in a Mouse Model of Alzheimer's Disease. *Cells* **2022**, *12*, 119. https://doi.org/10.3390/cells12010119.
30. Wu, L.; Han, Y.; Zheng, Z.; Peng, G.; Liu, P.; Yue, S.; Zhu, S.; Chen, J.; Lv, H.; Shao, L.; et al. Altered Gut Microbial Metabolites in Amnestic Mild Cognitive Impairment and Alzheimer's Disease: Signals in Host–Microbe Interplay. *Nutrients* **2021**, *13*, 228. https://doi.org/10.3390/nu13010228.
31. Vijay, N.; Morris, M. Role of Monocarboxylate Transporters in Drug Delivery to the Brain. *Curr. Pharm. Des.* **2013**, *20*, 1487–1498. https://doi.org/10.2174/13816128113199990462.
32. Wenzel, T.J.; Gates, E.J.; Ranger, A.L.; Klegeris, A. Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. *Mol. Cell. Neurosci.* **2020**, *105*, 103493. https://doi.org/10.1016/j.mcn.2020.103493.

33. Zhou, Y.; Huang, Y.; Fan, Y.; Xue, F. Co-regulation of microglial subgroups in Alzheimer's amyloid pathology: Implications for diagnosis and drug development. *PLoS ONE* **2025**, *20*, e0337741. https://doi.org/10.1371/journal.pone.0337741.
34. Xue, F.; Du, H. TREM2 Mediates Microglial Anti-Inflammatory Activations in Alzheimer's Disease: Lessons Learned from Transcriptomics. *Cells* **2021**, *10*, 321.
35. Erny, D.; Hrabě de Angelis, A.L.; Jaitin, D.; Wieghofer, P.; Staszewski, O.; David, E.; Keren-Shaul, H.; Mahlakoiv, T.; Jakobshagen, K.; Buch, T.; et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat. Neurosci.* **2015**, *18*, 965–977. https://doi.org/10.1038/nn.4030.
36. Joglekar, P.; Ding, H.; Canales-Herrerias, P.; Pasricha, P.J.; Sonnenburg, J.L.; Peterson, D.A. Intestinal IgA Regulates Expression of a Fructan Polysaccharide Utilization Locus in Colonizing Gut Commensal Bacteroides thetaiotaomicron. *mBio* **2019**, *10*, e02324-19. https://doi.org/10.1128/mBio.02324-19.
37. Bilotta, A.J.; Ma, C.; Yang, W.; Yu, Y.; Yu, Y.; Zhao, X.; Zhou, Z.; Yao, S.; Dann, S.M.; Cong, Y. Propionate Enhances Cell Speed and Persistence to Promote Intestinal Epithelial Turnover and Repair. *Cell. Mol. Gastroenterol. Hepatol.* **2021**, *11*, 1023–1044. https://doi.org/10.1016/j.jcmgh.2020.11.011.
38. Sun, J.; Zhang, Y.-h.; Kong, Y.; Ye, T.; Yu, Q.; Satyanarayanan, S.K.; Su, K.-P.; Liu, J. Microbiota-derived metabolite Indoles induced aryl hydrocarbon receptor activation and inhibited neuroinflammation in APP/PS1 mice. *Brain Behav. Immun.* **2022**, *106*, 76–78. https://doi.org/10.1016/j.bbi.2022.08.003.
39. Ghosh, S.S.; Wang, J.; Yannie, P.J.; Ghosh, S. Intestinal Barrier Dysfunction, LPS Translocation, and Disease Development. *J. Endocr. Soc.* **2020**, *4*, bvz039. https://doi.org/10.1210/jendso/bvz039.
40. Araujo David, B.; Andreata, F.; Blériot, C.; Ginhoux, F.; Kubes, P.; Iannacone, M. Kupffer cells in liver homeostasis and disease: From immune sentinels to metabolic gatekeepers. *Nat. Rev. Immunol.* **2026**, *26*, 538–554. https://doi.org/10.1038/s41577-026-01288-0.
41. Zhan, X.; Stamova, B.; Sharp, F. Lipopolysaccharide Associates with Amyloid Plaques, Neurons and Oligodendrocytes in Alzheimer's Disease Brain: A Review. *Front. Aging Neurosci.* **2018**, *10*, 42. https://doi.org/10.3389/fnagi.2018.00042.
42. Platten, M.; Nollen, E.A.A.; Röhrig, U.F.; Fallarino, F.; Opitz, C.A. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. *Nat. Rev. Drug Discov.* **2019**, *18*, 379–401. https://doi.org/10.1038/s41573-019-0016-5.
43. Zelante, T.; Iannitti, R.G.; Cunha, C.; De Luca, A.; Giovannini, G.; Pieraccini, G.; Zecchi, R.; D'Angelo, C.; Massi-Benedetti, C.; Fallarino, F.; et al. Tryptophan Catabolites from Microbiota Engage Aryl Hydrocarbon Receptor and Balance Mucosal Reactivity via Interleukin-22. *Immunity* **2013**, *39*, 372–385. https://doi.org/10.1016/j.immuni.2013.08.003.
44. Martin-Gallausiaux, C.; Marinelli, L.; Blottière, H.M.; Larraufie, P.; Lapaque, N. SCFA: Mechanisms and functional importance in the gut. *Proc. Nutr. Soc.* **2021**, *80*, 37–49. https://doi.org/10.1017/S0029665120006916.
45. Nho, K.; Kueider-Paisley, A.; MahmoudianDehkordi, S.; Arnold, M.; Risacher, S.L.; Louie, G.; Blach, C.; Baillie, R.; Han, X.; Kastenmüller, G.; et al. Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: Relationship to neuroimaging and CSF biomarkers. *Alzheimers Dement.* **2019**, *15*, 232–244. https://doi.org/10.1016/j.jalz.2018.08.012.
46. Chiang, J.Y.L.; Ferrell, J.M. Bile acid receptors FXR and TGR5 signaling in fatty liver diseases and therapy. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2020**, *318*, G554–G573. https://doi.org/10.1152/ajpgi.00223.2019.
47. McMillin, M.; DeMorrow, S. Effects of bile acids on neurological function and disease. *FASEB J.* **2016**, *30*, 3658–3668. https://doi.org/10.1096/fj.201600275R.
48. Wang, X.; Sun, G.; Feng, T.; Zhang, J.; Huang, X.; Wang, T.; Xie, Z.; Chu, X.; Yang, J.; Wang, H.; et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res.* **2019**, *29*, 787–803. https://doi.org/10.1038/s41422-019-0216-x.
49. Quinn, M.; McMillin, M.; Galindo, C.; Frampton, G.; Pae, H.; Demorrow, S. Bile acids permeabilize the blood brain barrier after bile duct ligation in rats via Rac1-dependent mechanisms. *Dig. Liver Dis.* **2014**, *46*, 527–534. https://doi.org/10.1016/j.dld.2014.01.159.
50. Li, C.; Wang, L.; Xie, W.; Chen, E.; Chen, Y.; Li, H.; Can, D.; Lei, A.; Wang, Y.; Zhang, J. TGR5 deficiency in excitatory neurons ameliorates Alzheimer's pathology by regulating APP processing. *Sci. Adv.* **2024**, *10*, eado1855. https://doi.org/10.1126/sciadv.ado1855.
51. Gao, C.; Li, B.; He, Y.; Huang, P.; Du, J.; He, G.; Zhang, P.; Tang, H.; Chen, S. Early changes of fecal short-chain fatty acid levels in patients with mild cognitive impairments. *CNS Neurosci. Ther.* **2023**, *29*, 3657–3666. https://doi.org/10.1111/cns.14252.
52. Leblhuber, F.; Steiner, K.; Schuetz, B.; Fuchs, D.; Gostner, J.M. Probiotic Supplementation in Patients with Alzheimer's Dementia -An Explorative Intervention Study. *Curr. Alzheimer Res.* **2018**, *15*, 1106–1113. https://doi.org/10.2174/1389200219666180813144834.

53. Akbari, E.; Asemi, Z.; Daneshvar Kakhaki, R.; Bahmani, F.; Kouchaki, E.; Tamtaji, O.R.; Hamidi, G.A.; Salami, M. Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front. Aging Neurosci.* **2016**, *8*, 256. https://doi.org/10.3389/fnagi.2016.00256.
54. Tamtaji, O.R.; Heidari-soureshjani, R.; Mirhosseini, N.; Kouchaki, E.; Bahmani, F.; Aghadavod, E.; Tajabadi-Ebrahimi, M.; Asemi, Z. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: A randomized, double-blind, controlled trial. *Clin. Nutr.* **2019**, *38*, 2569–2575. https://doi.org/10.1016/j.clnu.2018.11.034.
55. Loffredo, L.; Alfano, A.R.; Ettorre, E.; Desideri, G.; Carnevale, R.; Forte, M.; Maglione, V.; Bartimoccia, S.; Castellani, V.; Totè, C.M.; et al. Effect of the probiotic *Escherichia coli* Nissle 1917 on serum levels of NADPH oxidase-2 and lipopolysaccharide in patients with Alzheimer's disease. *J. Alzheimers Dis.* **2025**, *106*, 774–782. https://doi.org/10.1177/13872877251345157.
56. Ossenkoppele, R.; Schonhaut, D.R.; Schöll, M.; Lockhart, S.N.; Ayakta, N.; Baker, S.L.; O'Neil, J.P.; Janabi, M.; Lazaris, A.; Cantwell, A.; et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain* **2016**, *139*, 1551–1567. https://doi.org/10.1093/brain/aww027.
57. Brier, M.R.; Gordon, B.; Friedrichsen, K.; McCarthy, J.; Stern, A.; Christensen, J.; Owen, C.; Aldea, P.; Su, Y.; Hassenstab, J.; et al. Tau and Aβ imaging, CSF measures, and cognition in Alzheimer's disease. *Sci. Transl. Med.* **2016**, *8*, 338ra366. https://doi.org/10.1126/scitranslmed.aaf2362.
58. Santos, D.H.; da Silva, A.M.P. Amyloid-beta-targeting monoclonal antibodies in early Alzheimer's disease: A cochrane review summary and appraisal for the neurological community. *Neurol. Sci.* **2026**, *47*, 794. https://doi.org/10.1007/s10072-026-09401-w.
59. Andrews, J.S.; Desai, U.; Kirson, N.Y.; Zichlin, M.L.; Ball, D.E.; Matthews, B.R. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement.* **2019**, *5*, 354–363. https://doi.org/10.1016/j.trci.2019.06.005.
60. van Dyck Christopher, H.; Swanson Chad, J.; Aisen, P.; Bateman Randall, J.; Chen, C.; Gee, M.; Kanekiyo, M.; Li, D.; Reyderman, L.; Cohen, S.; et al. Lecanemab in Early Alzheimer's Disease. *N. Engl. J. Med.* **2023**, *388*, 9–21. https://doi.org/10.1056/NEJMoa2212948.
61. Nonino, F.; Minozzi, S.; Sambati, L.; Del Giovane, C.; Baldin, E.; Bassi, M.C.; De Santis, C.; Gonzalez-Lorenzo, M.; Vignatelli, L.; Filippini, G.; et al. Amyloid-beta-targeting monoclonal antibodies for people with mild cognitive impairment or mild dementia due to Alzheimer's disease. *Cochrane Database Syst. Rev.* **2026**, *4*, CD016297. https://doi.org/10.1002/14651858.CD016297.
62. Ren, J.; Wang, Q.; Hong, H.; Tang, C. Fecal Microbiota Transplantation in Alzheimer's Disease: Mechanistic Insights Through the Microbiota–Gut–Brain Axis and Therapeutic Prospects. *Microorganisms* **2025**, *13*, 1956.
63. Bonfili, L.; Cecarini, V.; Cuccioloni, M.; Angeletti, M.; Berardi, S.; Scarpona, S.; Rossi, G.; Eleuteri, A.M. SLAB51 Probiotic Formulation Activates SIRT1 Pathway Promoting Antioxidant and Neuroprotective Effects in an AD Mouse Model. *Mol. Neurobiol.* **2018**, *55*, 7987–8000. https://doi.org/10.1007/s12035-018-0973-4.
64. Roy, S.; Chattopadhyay, D.; Choudhury, L.; Ghosh, S.; Mahajan, A.A. Harnessing the power of faecal microbiota transplantation: Optimizing neuroimmune function for improved treatment of Parkinson's, Alzheimer's, and multiple sclerosis. *Discov. Neurosci.* **2025**, *20*, 21. https://doi.org/10.1186/s13064-025-00221-w.
65. Di Lucente, J.; Persico, G.; Zhou, Z.; Jin, L.-W.; Ramsey, J.J.; Rutkowsky, J.M.; Montgomery, C.M.; Tomilov, A.; Kim, K.; Giorgio, M.; et al. Ketogenic diet and BHB rescue the fall of long-term potentiation in an Alzheimer's mouse model and stimulates synaptic plasticity pathway enzymes. *Commun. Biol.* **2024**, *7*, 195. https://doi.org/10.1038/s42003-024-05860-z.
66. Govindarajan, N.; Agís-Balboa, R.; Walter, J.; Sananbenesi, F.; Fischer, A. Sodium Butyrate Improves Memory Function in an Alzheimer's Disease Mouse Model When Administered at an Advanced Stage of Disease Progression. *J. Alzheimers Dis.* **2011**, *26*, 187–197. https://doi.org/10.3233/JAD-2011-110080.
67. Salman, B.; Haidar, R.; Faour, V.; Ali, W.A.; Aridi, L.; Harb, F.; Azar, S.; Khattar, Z.A.; Ghadieh, H.E. Microbiota gut-brain axis dysfunction in Alzheimer's Disease: From pathogenesis to potential treatments—A review. *Health Sci. Rev.* **2026**, *18*, 100251. https://doi.org/10.1016/j.hsr.2025.100251.
68. Elmas, S.; Cîrțînă, D.; Dîrnu, R.; Plută, I.D.; Varut, R.M.; Vladulescu, C.; Kamal, A.M.; Pura, G.; Popa, R.; Sakizlian, D.D.; et al. Postbiotics in Functional Foods: Preparation-Based Characterization, Gut-Brain Axis Interactions, and Translational Perspectives. *Foods* **2026**, *15*, 2457. https://doi.org/10.3390/foods15142457.
69. Xiao, S.; Chan, P.; Wang, T.; Hong, Z.; Wang, S.; Kuang, W.; He, J.; Pan, X.; Zhou, Y.; Ji, Y.; et al. A 36-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial of sodium oligomannate for mild-to-moderate Alzheimer's dementia. *Alzheimers Res. Ther.* **2021**, *13*, 62. https://doi.org/10.1186/s13195-021-00795-7.
70. Defilipp, Z.; Bloom, P.P.; Soto, M.T.; Mansour, M.K.; Hohmann, E.L. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. *N. Engl. J. Med.* **2019**, *381*, 2043–2050. https://doi.org/10.1056/NEJMoa1910437.

71. Magnúsdóttir, S.; Heinken, A.; Kutt, L.; Ravcheev, D.A.; Bauer, E.; Noronha, A.; Greenhalgh, K.; Jäger, C.; Baginska, J.; Wilmes, P.; et al. Generation of genome-scale metabolic reconstructions for 773 members of the human gut microbiota. *Nat. Biotechnol.* **2017**, *35*, 81–89. https://doi.org/10.1038/nbt.3703.
72. Pirolli, N.; Bentley, W.; Jay, S. Bacterial Extracellular Vesicles and the Gut-Microbiota Brain Axis: Emerging Roles in Communication and Potential as Therapeutics. *Adv. Biol.* **2021**, *5*, e2000540. https://doi.org/10.1002/adbi.202000540.
73. Long, Y.; Liu, J.; Wang, Y.; Guo, H.; Cui, G. The complex effects of miR-146a in the pathogenesis of Alzheimer's disease. *Neural. Regen. Res.* **2025**, *20*, 1309–1323. https://doi.org/10.4103/nrr.Nrr-d-23-01566.
74. Pös, O.; Styk, J.; Buglyó, G.; Zeman, M.; Lukyova, L.; Bernatova, K.; Hrckova Turnova, E.; Rendek, T.; Csók, Á.; Repiska, V.; et al. Cross-Kingdom Interaction of miRNAs and Gut Microbiota with Non-Invasive Diagnostic and Therapeutic Implications in Colorectal Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 10520. https://doi.org/10.3390/ijms241310520.
75. Krunic, A.; Bellio, T.A.; Cohen, B.Z.; Labadorf, A.; Stein, T.D.; Lin, H.; Mellott, T.J.; Blusztajn, J.K. Brain DNA Methylation Atlas of App(NL-G-F) Alzheimer's Disease Model Mice Across Age and Region Reveals Choline-Induced Resilience. *Aging Cell* **2025**, *24*, e70241. https://doi.org/10.1111/acel.70241.
76. Abdelaziz, A.M.; Eladawy, R.M. Immunopharmacological reprogramming of innate immune memory in Alzheimer's disease: From microglial priming to therapeutic resilience. *Biochem. Pharmacol.* **2026**, *254*, 118381. https://doi.org/10.1016/j.bcp.2026.118381.
77. Liang, X.; Bushman, F.D.; FitzGerald, G.A. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 10479–10484. https://doi.org/10.1073/pnas.1501305112.
78. Kress, G.J.; Liao, F.; Dimitry, J.; Cedeno, M.R.; FitzGerald, G.A.; Holtzman, D.M.; Musiek, E.S. Regulation of amyloid-β dynamics and pathology by the circadian clock. *J. Exp. Med.* **2018**, *215*, 1059–1068. https://doi.org/10.1084/jem.20172347.

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