

Research Progress on the Gut–Brain Axis in the Pathogenesis and Progression of Alzheimer’s Disease

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Abstract. Memory impairment and broader cognitive decline emerge gradually in Alzheimer’s disease (AD), although amyloid- β deposition, tau abnormalities, and neuroinflammatory changes often develop well before the clinical picture is fully established. Drug therapy can lessen selected symptoms, but it does not prevent continuing neuronal loss, and its long-term value is further limited by adverse effects and inadequate delivery across the blood–brain barrier. These shortcomings have increased interest in the microbiota–gut–brain axis (MGBA) as a framework for studying how intestinal biology may influence the brain. In this framework, microbial products and host responses are transmitted through vagal, endocrine, immune, and metabolic routes, while central nervous system activity can in turn alter intestinal conditions. This review evaluates those reciprocal pathways and discusses the roles of the hypothalamic–pituitary–adrenal axis, inflammatory signaling, short-chain fatty acids, tryptophan-derived metabolites, and trimethylamine N-oxide. It then examines microbial diversity and composition in AD and considers evidence for probiotics, fecal microbiota transplantation, and lifestyle-based intervention. Reports of dysbiosis before overt cognitive decline suggest that microbial change may participate in early disease development rather than simply accompany advanced pathology. That possibility remains unproven because most mechanistic evidence comes from animal models and much of the human literature is cross-sectional. Differences in cohort selection, sampling, and control of confounding variables further weaken causal interpretation. Longitudinal cohorts, integrated multi-omics analysis, and clinically meaningful patient stratification will therefore be essential for determining whether the MGBA can be used in AD prevention or treatment.

Keywords: Alzheimer’s disease, microbiota–gut–brain axis, gut microbiota, neuroinflammation, microbial metabolites, short-chain fatty acids, fecal microbiota transplantation.

1. Clinical and Pathological Features of AD

Alzheimer’s disease (AD) is a prevalent neurodegenerative disorder of older age [1]. Its clinical course usually begins with disruption of neural systems involved in memory and then extends to language, reasoning, and other cognitive functions [2]. The underlying pathology includes amyloid- β (A β) deposition, tau aggregation, neuritic plaques, and neurofibrillary tangles [3-5]. Despite extensive research, treatment remains centered on symptom control. Donepezil and memantine can provide temporary benefit, but neither reverses neuronal degeneration [6], and adverse reactions such as nausea, vomiting, and bradycardia may limit use. Short systemic persistence and restricted penetration of the blood–brain barrier also reduce sustained efficacy. Non-pharmacological measures may complement medication, although their benefits are often modest and depend heavily on continued patient participation.

1.1. Development of the Gut–Brain Axis Concept

The concept now described as the gut–brain axis (GBA) was assembled from observations made over several centuries. Hippocratic medicine linked mental states with bodily function [7], and Robert Whytt’s 1765 idea of “nervous sympathy” gave this relationship a neural interpretation [7]. William Beaumont later demonstrated that emotional changes could alter gastric activity [7]. Recognition of the enteric nervous system (ENS) as a distinct part of the autonomic nervous system then supplied an anatomical basis for communication in both directions between the intestine and brain [7]. Metagenomic analysis subsequently revealed that intestinal microorganisms are also active

participants, leading to the broader concept of the microbiota–gut–brain axis (MGBA) [8]. Within the expanded MGBA model, microbial metabolites together with neuroendocrine and immune signals can influence brain development and function, while neurotransmitter release under central control can reshape intestinal conditions [9]. AD research has adopted this reciprocal framework to determine whether MGBA disruption contributes to pathology and whether the same pathways could support intervention before clinical decline becomes established [10].

1.2. Objective and Structure of This Review

Studies of the gut–brain axis in AD now span neural signaling, immunity, endocrine regulation, microbial metabolism, and therapeutic intervention. The evidence, however, is distributed across separate research traditions, so findings that describe mechanism are not always evaluated alongside those that claim clinical relevance. This separation makes it difficult to judge which observations are reproducible, how the proposed pathways interact, and where the strongest gaps remain. The present review therefore organizes the literature around the biological sequence linking intestinal change to AD-related pathology. It integrates domestic and international findings, compares the principal mechanistic pathways, and assesses the extent to which current evidence supports prevention or treatment based on the gut–brain axis.

2. Overview of the Gut Microbiota

The adult intestinal ecosystem is populated mainly by members of Bacteroidetes and Firmicutes. Within Bacteroidetes, Bacteroides and Prevotella are frequently reported, whereas the Firmicutes fraction includes genera such as Clostridium, Enterococcus, Lactobacillus, and Faecalibacterium [11]. The relevance of these organisms extends beyond their abundance because their metabolic activity changes the chemical environment of the gut [12] and supports epithelial integrity and immune development [13]. When community balance is lost, several processes connected with AD may change together. Impaired barrier function can increase exposure to inflammatory stimuli [14, 15]; altered metabolism can modify the supply of short-chain fatty acids and tryptophan-derived molecules [16, 17]; and persistent microglial activation can promote A β accumulation and tau phosphorylation [18]. Dysbiosis therefore links the intestine with AD through the combined effects of barrier failure, metabolic disruption, and immune activation.

2.1. Neural Pathway: The Vagus Nerve and Enteric Nervous System

Communication through the vagus nerve includes both sensory input from the gastrointestinal tract and efferent control of peripheral inflammation. As a major neural connection within the gut–brain axis, the vagus conveys intestinal information to the central nervous system [19]. Mechanoreceptors and chemoreceptors in the stomach, esophagus, and gastric mucosa convert local mechanical and chemical changes into neural signals [19], which pass through the nucleus tractus solitarius to regions involved in feeding, emotion, and visceral reflexes [19]. Because some of these functions change early in AD, altered afferent signaling could affect neural networks that support cognition. The efferent arm is also relevant: acetylcholine released from vagal pathways acts on $\alpha 7$ nicotinic acetylcholine receptors expressed by macrophages and microglia, reducing pro-inflammatory signaling and mediator release [20, 21]. In animal models, activation of this cholinergic anti-inflammatory pathway has additionally been associated with greater microglial clearance of A β and protection of synapses from neurotoxic injury [22].

2.2. Endocrine Pathway: The Hypothalamic–Pituitary–Adrenal Axis and Gut Hormones

The hypothalamic–pituitary–adrenal (HPA) axis regulates the endocrine response to stress. In AD, defective negative feedback may prolong cortisol elevation [23], exposing the hippocampus to sustained glucocorticoid signaling. Corticosterone has been shown to increase p21 expression in the dentate gyrus, promote reactive oxygen species accumulation, and reduce hippocampal neurogenesis

[24]; together, these changes may contribute to early memory impairment. Glucagon-like peptide-1 (GLP-1) receptor agonists have attracted attention because they can restore cyclin expression, counter p21-dependent cell-cycle arrest, and protect hippocampal neural stem cells from glucocorticoid injury [25]. The receptor also activates the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway and modulates nuclear factor κ B (NF- κ B), which can reduce microglial activation, pro-inflammatory cytokine expression, and oxidative stress [25]. The convergence of these effects provides the main rationale for investigating GLP-1 receptor agonists in AD.

2.3. Immune Pathway: Bridging Intestinal Immunity and Neuroinflammation

During aging, intestinal barrier integrity gradually deteriorates, and patients with AD frequently exhibit additional marked dysbiosis. Together, these conditions lead to abnormally increased intestinal permeability, commonly referred to as a “leaky gut” state [15]. Lipopolysaccharide (LPS) and related bacterial products can consequently enter the circulation [26], amplify peripheral inflammatory signals, and stimulate microglia in the brain. These products subsequently activate microglia, the principal active immune cells of the central nervous system, promote their transition toward an M1-like pro-inflammatory phenotype, and stimulate the release of multiple pro-inflammatory factors, thereby aggravating neuroinflammation [18]. In addition, in carriers of the APOE ϵ 4 allele, exposure of microglia to fibrillar A β can induce ACSL1 expression, promote triglyceride synthesis and lipid-droplet accumulation, and consequently cause tau phosphorylation and neurotoxicity, further exacerbating neuronal injury [27, 28].

2.4. Microbial Metabolite Pathways

Gut microorganisms produce multiple biologically active small-molecule metabolites. Among them, short-chain fatty acids (SCFAs) and tryptophan metabolites are the two most extensively studied groups. These metabolites can directly or indirectly reach and affect the central nervous system and play key regulatory roles in AD pathological progression [16, 17]. SCFAs mainly include acetate, propionate, and butyrate. Experimental evidence indicates that they can alleviate enhanced stress responses and stress-induced increases in intestinal permeability [29]. Their levels are also markedly reduced in patients with AD, which is closely associated with reductions in SCFA-producing clostridial bacteria and members of the phylum Firmicutes [17]. Tryptophan metabolism links microbial activity with neuroimmune regulation through a separate pathway. Compounds produced from dietary tryptophan (Trp) can activate the aryl hydrocarbon receptor (AhR) and thereby modify microglial behavior and inflammatory mediator release in the central nervous system [30]. In AD, the normal division of tryptophan metabolism between host and microbiota appears to be disturbed, with altered production of indole derivatives and serotonin. This metabolic shift connects dysbiosis with abnormal central immune signaling and may contribute to disease progression [17].

3. Changes in Microbial Diversity and Composition

Compared with cognitively healthy controls, AD cohorts generally show a less diverse and differently organized intestinal community, reflected in lower α -diversity and altered β -diversity [26, 31]. Firmicutes are often reduced and Proteobacteria increased [31], although findings for individual genera and families are less uniform. The functional consequence may be a loss of butyrate production together with expansion of Gammaproteobacteria, Enterobacterales, and Enterobacteriaceae, a combination that can favor intestinal and systemic inflammation [32]. Because A β deposition begins long before cognitive symptoms, prospective evidence has drawn attention to whether microbiome alterations can also be detected during this preclinical interval [33]. The observations remain associative, but they place the microbiome among the biological features that may be modifiable early in the AD course.

3.1. Associations Between Specific Microbial Taxa and AD Pathology

The significance of microbial diversity in AD depends less on the total number of taxa than on the functions of the organisms that are lost or expanded. *Lachnospiraceae*, *Faecalibacterium prausnitzii*, and *Roseburia* are important butyrate producers, and their depletion has been associated with cognitive decline and greater A β deposition [32]. Reduced *Lachnospiraceae* abundance has also been reported at multiple stages of AD pathology [34]. In contrast, higher *Desulfovibrio* abundance is associated with lower Mini-Mental State Examination (MMSE) scores [35], while *Lactobacillaceae* and *Christensenellaceae* have also been linked to cognitive impairment [34]. Mendelian randomization (MR) studies suggest that *Desulfovibrionaceae* and methanogenic microorganisms may increase susceptibility to AD, whereas the *Lachnospiraceae* NK4A136 group may be protective [36, 37]. The resulting pattern is therefore functional as well as taxonomic: butyrate-producing communities decline while organisms with greater inflammatory potential become more prominent.

3.2. Dynamic Trajectories and Causal Relationships of Microbial Changes

The microbiome changes continuously over the long course of AD. A community profile measured before symptoms may therefore differ substantially from one observed during mild cognitive impairment (MCI) or dementia. Ageing, lifestyle, medication, and other exposures continue to act on the intestinal ecosystem throughout this period, producing microbial patterns that vary by disease stage [38]. An increased abundance of the class Actinobacteria may indicate AD risk, whereas enrichment of *Faecalibacterium* may exert a protective effect [39]. However, observational studies cannot readily determine the temporal sequence of these associations. In recent years, numerous studies have therefore adopted bidirectional MR approaches. Their findings suggest that the microbiota may act as a mediating variable and support a “bidirectional vicious cycle” hypothesis. On the one hand, dysbiosis activates pro-inflammatory pathways through the gut–brain axis, induces neuroinflammation, and affects brain function. On the other hand, central pathological changes and stress-hormone release act in the reverse direction on the enteric nervous system, reshaping the intestinal environment and microbial structure [39, 40]. This bidirectional interaction highlights the potentially important driving role of the intestinal microecosystem in AD progression.

4. Dual Roles of Short-Chain Fatty Acids

As core metabolites of the gut microbiota, short-chain fatty acids play a “double-edged sword” role in AD progression. When their relative concentrations remain balanced, SCFAs support several protective processes in the nervous system. They increase tight-junction protein expression and reinforce the blood–brain barrier, thereby limiting the entry of circulating toxins [41, 42]. SCFAs can also reduce excessive microglial activation and pro-inflammatory cytokine production [39], while butyrate may enhance brain-derived neurotrophic factor synthesis through vagal signaling and support cognition [42]. These effects are not uniform under all conditions. Patients with AD have been reported to show relatively high acetate and valerate but low butyrate [17], a profile that may favor neuroinflammation. The inflammatory effect produced by intracerebroventricular propionate further shows that biological outcome depends on both exposure site and dose [42].

4.1. Tryptophan Metabolites: Indoles versus Kynurenine

Tryptophan can be processed through microbial and host pathways that generate metabolites with markedly different effects on neural tissue. *Clostridium sporogenes* produces indole-3-propionic acid (IPA) from tryptophan [43]. After entering the circulation, IPA can cross the blood–brain barrier and act as an antioxidant and anti-inflammatory molecule [43, 44]. Experimental work indicates that IPA reduces free-radical damage, limits A β aggregation and microglial activation, and supports barrier integrity through neuronal pregnane X receptor (PXR) signaling [43–45]. During chronic inflammation, however, higher indoleamine 2,3-dioxygenase (IDO) activity diverts tryptophan toward kynurenine metabolism. Excessive accumulation of kynurenine and its downstream toxic

product quinolinic acid causes oxidative stress and further aggravates symptoms in patients with AD [45]. Studies have shown that patients with AD commonly exhibit a metabolic imbalance characterized by reduced IPA and elevated kynurenine, which is closely associated with an abnormal cerebrospinal-fluid A β and tau biomarker profile [45]. These findings further suggest that restoring tryptophan metabolic homeostasis is an important target for AD intervention [17].

4.2. TMAO: Pro-Aggregation and Pro-Inflammatory Signaling

Trimethylamine N-oxide (TMAO) is an important gut microbiota-derived metabolite. Dietary choline or L-carnitine is enzymatically converted by the gut microbiota into trimethylamine (TMA), which is subsequently oxidized by hepatic FMO1/3 to generate TMAO [46]. Clinical studies have shown that plasma and cerebrospinal-fluid TMAO levels are significantly elevated in patients with AD and are positively correlated with AD pathological biomarkers and the degree of neurodegeneration [46, 47]. Two processes may account for its pathogenic influence. At the protein level, TMAO changes the hydration environment, favors compact tau structures, and accelerates oligomer formation by A β and tau [48]. At the cellular level, it has been reported to promote neuronal senescence and disturb redox balance [46]. If blood–brain barrier integrity is already reduced, the associated systemic inflammatory state can more easily affect the central nervous system, increase glial activation and cytokine release, and aggravate cognitive impairment [49].

4.3. Other Metabolites, Including Secondary Bile Acids

AD-related signaling may also be influenced by microbial metabolites outside the major pathways described above. Lithocholic acid and other secondary bile acids can activate G protein-coupled bile acid receptor 1, also known as TGR5, in neurons and glial cells, thereby supporting mitochondrial biogenesis and reducing oxidative stress [50]. Polyphenol metabolites appear to act differently by inhibiting NF- κ B signaling, decreasing pro-inflammatory factor expression, and strengthening antioxidant enzyme activity [50]. In addition, neuroactive substances such as histamine and γ -aminobutyric acid (GABA) affect AD progression by regulating microglial chemotaxis, migration, autophagy, and other functions [51]. These metabolites play important roles in energy metabolism, inflammatory regulation, and the immune microenvironment and therefore provide potential targets for AD intervention.

5. Evidence from Animal Models

Animal models are essential tools for elucidating causal relationships between the gut microbiota and AD. Evidence indicates that, compared with specific pathogen-free (SPF) mice, germ-free AD mice show significantly reduced cerebral A β and phosphorylated tau, while their microglia exhibit anti-inflammatory and highly phagocytic phenotypes. Recolonization of germ-free mice with microbiota from conventional mice markedly increases cerebral A β pathology, suggesting that central neuroinflammation and protein aggregation are substantially suppressed in the absence of gut microorganisms [52]. However, results differ among studies [53]. Microbiota transplantation and probiotic interventions have provided further evidence. Transplanting the gut microbiota of patients with AD into 3 $\times$ Tg mice significantly aggravates AD-like pathological changes and cognitive impairment [54], whereas transplanting microbiota from healthy wild-type mice into AD model mice substantially alleviates cognitive deficits and reduces A β deposition and neuroinflammation [55]. Other studies have shown that metabolites or inflammatory signals produced by the gut microbiota can influence the brain through the vagus nerve. In AD models, subdiaphragmatic vagotomy significantly increases cerebral levels of inflammatory factors such as IL-6, IL-1 β , and TNF- α and alters microbial diversity, indicating that the vagus nerve is an important pathway through which gut-derived bacterial and inflammatory signals may reach or influence the brain [56].

5.1. Evidence from Human Studies

Human cross-sectional studies consistently associate AD with an altered intestinal microbiome. Relative to healthy controls, patients with AD generally show lower fecal microbial richness and diversity and a distinctive community structure [26, 31], with fewer Firmicutes and butyrate-producing bacteria and a greater abundance of Proteobacteria [31]. This community structure can reduce production of butyrate and increase production of pro-inflammatory organisms, which may provide a plausible link between dysbiosis of the intestinal flora and systemic inflammation [32, 57]. The evidence from studies in humans is still limited, but small studies have shown changes in inflammatory markers and cognition. In a randomized study of 40 mild AD patients, the administration of probiotics for 6 weeks led to a decrease in serum LPS by 15% and TNF- α by 18%, and also improved cognitive function [58]. A separate 12-week RCT had positive effects on the oxidative stress, inflammatory markers, and quality of life in mild-to-moderate AD patients [59]. Fecal microbiota transplantation (FMT) is also a relatively new therapy, and preliminary studies have found cognitive improvement following FMT [60]. Small sample sizes and brief observation periods limit the conclusions that can be drawn from these studies and further research is needed to substantiate these observations in larger, randomized, long-term studies [60].

5.2. Limitations of Existing Studies

The gut–brain axis has been suggested as a piece of the puzzle in AD, but it is presently unclear whether dysbiosis leads to neurological changes or is a consequence of them, or if it plays an active role in both processes. The animal models allow for the direct testing of specific pathways, but their species-specific physiology and significant differences in their microbial composition preclude their use as representations of the diversity of human disease [61]. Human studies give more clinical relevance, and less experimental control. This association may be caused by factors that influence both the microbiome and the risk of dementia – diet, medications, age, lifestyle – or caused by other unknown factors. This is compounded by cross-sectional sampling, as this only captures the microbial and neurological state at a single moment. Large, long-term randomized studies are rare and the direction of the causality is not established yet [61]. Clinical translation is going to require standardisation of cohorts, repeated microbiome measurements, integration of multi-omics approaches and interventions targeting clearly defined patient subgroups.

6. Probiotics, Prebiotics, and Synbiotics

The definition of probiotics is “Live microorganisms that have a health-promoting effect on the host when consumed in suitable quantities” [62]. They communicate with the gut microorganisms and can help keep the balance of the gut microbiota in check. *Lactobacillus* and *Bifidobacterium* species can modulate the barrier function, immune activity and production of pro-inflammatory cytokines, which may affect several processes involved in AD [62]. During probiotic activity, metabolites are produced that increase the expression of tight-junction proteins and inhibit the NF- κ B signaling pathway, which can help to decrease intestinal permeability and inflammation [62]. In a humanized AD mouse model, Santosh Kumar Prajapati and collaborators found a probiotic cocktail to be effective in slowing down the pathological progression, and reducing inflammation, blood–brain barrier dysfunction, and intestinal permeability. In line with clinical translation, Camellia Akhgarjand and co-workers investigated the impact of a probiotic with a single strain in participants with both mild and moderate AD and found positive effects of probiotic supplementation on cognitive status [59]. Preliminary clinical trials and animal research indicate that probiotics could have some effect on cognition and gut–brain signaling, but the findings are only applicable to small numbers and there is significant inter-individual variation [64]. Therefore, treatment effects should be estimated separately in clinically relevant patient groups in larger trials.

6.1. Fecal Microbiota Transplantation

The idea of fecal microbiota transplantation (FMT) is to replace disrupted community by introducing a microbial ecosystem from the donor with AD [10]. FMT has been shown in animal models to be followed by a reduction in A β burden and neuroinflammation [55]. The suggested mechanism involves repair of the barrier and modulation of innate immune signaling through transplantation, which could repair the barrier, lower LPS in the circulation and mitigate toll-like receptor 4/NF- κ B activity [65]. The delivery is possible with colonoscopy or capsules. Other clinical studies indicate that either route may be useful, but capsules are less invasive and more appropriate for more frequent treatment. The data on which human conclusions are drawn for AD are preliminary and inconclusive compared to the definitive statistical data obtained from large random controlled trials [10]. Eligibility and dosage criteria for donors, as well as frequency of donations and measures of outcome vary across studies. FMT will need to be evaluated consistently and considered for routine AD care following international agreement on these procedures [61].

6.2. Lifestyle Interventions: Diet, Exercise, Stress Management, and Sleep

When the gut–brain axis is dysregulated, the ability of dietary intervention to modulate the microbiota–gut–brain axis via alterations in the substrates available to microorganisms, and the resulting metabolites, is relevant to both the prevention and management of AD. Both Mediterranean diet (MeDi) and Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diets provide good quantities of fibre and polyphenols. These components can stimulate the growth of good bacteria and restore the balance of good bacteria. They additionally have antioxidant and anti-inflammatory properties which have been linked to a reduced risk of dementia [64, 66]. The keto-enriched diet could also be beneficial in cases of impaired cerebral glucose utilization, by providing a substitute fuel [67]. Omega-3 fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid, may replenish neuronal membrane phospholipids, reduce mediators such as IL-1 β , and support cognition [68]. Unlike a single probiotic product, a broader dietary pattern delivers many bioactive compounds at once and may therefore exert a wider influence on microbial diversity and central nervous system health. Physical exercise can also increase beneficial microorganisms, including butyrate-producing bacteria, promote SCFA production, and strengthen intestinal barrier integrity and anti-inflammatory capacity, thereby alleviating AD symptoms [69]. In contrast, chronic stress excessively activates the HPA axis, releases stress hormones and inflammatory factors, disrupts microbial homeostasis, and weakens the intestinal barrier, thereby forming a pro-inflammatory vicious cycle [70]. Sleep deprivation is similarly harmful. It increases markers of neuronal injury and inflammation, accelerates amyloid- β deposition and tau pathological changes [71], and markedly impairs the clearance of A β by the glymphatic system. Through their coordinated effects on the microbiota–gut–brain axis, exercise, stress management, and sleep optimization therefore provide feasible non-pharmacological strategies for delaying AD progression.

7. Major Limitations

Acetylcholinesterase inhibitors are among the mainstream pharmacological treatments for AD. By inhibiting acetylcholinesterase (AChE) activity, they reduce the degradation of acetylcholine (ACh) in the synaptic cleft [72] and thereby increase its cerebral concentration to improve cognition. Memantine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with low-to-moderate affinity. It blocks calcium influx caused by excessive glutamatergic stimulation [72], suppresses excitotoxicity, and exerts neuroprotective effects. However, AD treatments represented by these two classes of drugs can only temporarily alleviate symptoms and cannot reverse neurodegeneration. Their adverse effects, short half-lives, and limited blood–brain barrier penetration also restrict their long-term efficacy [72]. Non-pharmacological interventions have potential but are limited by adherence and effect size [72]. The evidence available for the gut–brain axis is also distributed unevenly across study types. Mechanistic conclusions are drawn mainly from animal

experiments, whereas long-term human datasets remain limited [61]. Cross-sectional human studies cannot determine whether dysbiosis appears before AD or develops after neurological changes are underway [61]. Diet, age, sex, medication, and other disease-independent factors further obscure the specific contribution of AD to microbial variation. Intervention studies are also hard to compare due to variation in interventions. The selection of donors, mode of administration, surveillance of adverse effects and study of the mechanisms of action are not standardized in FMT studies, restricting synthesis and clinical translation [61]. Future studies in the field thus need to validate prospective cohorts and trials with interventions with standardized sampling, treatment, and outcome measures.

7.1. Future Research Directions

Future studies should link microbial composition to biological function, and not just catalog taxa. A combination of metagenomic, metabolomic and proteomic data can be used to link community structure to host pathways and to identify potential biomarkers [73]. In prospective cohorts that are recruited before symptoms occur, the same measurements should be repeated at different stages of the disease. This design would determine if changes in the microbiota come before cognitive changes or after the onset of neurological changes [33]. Another potential source of biological and therapeutic heterogeneity is the patients' genotype. The peripheral immune activation of APOE ϵ 4 carriers and disruption of the blood–brain barrier are associated with central neuroinflammation, such that carriers might be recruited into intervention studies with different immune and barrier state than non-carriers and might respond differently. Therapeutic development has begun to move beyond the traditional probiotics. The use of engineered bacteria, next generation probiotics and bacteriophages might allow for the manipulation of specific microbial populations [75], and the use of naturally occurring polyphenols and rifaximin might have the ability to inhibit undesirable microorganisms and promote beneficial microbial species [75]. A longitudinal observation and molecular profiling of the same subjects with targeted intervention in the same research framework would enable causal hypotheses to be tested directly.

8. Conclusion

Recent data suggest that the gut microbiota is involved in a two-way interaction between gut physiology and Alzheimer's disease. Dysbiosis can have an effect on peripheral inflammation, central neuroinflammation, A β deposition, and tau phosphorylation via neural, endocrine, immune and metabolic pathways. Vagal signaling, hypothalamic–pituitary–adrenal axis activity and microbial metabolites play key roles in this model. The interaction is likely to be two-way, as there is also a potential for injury to the nervous system to alter gut function and microbial makeup, and for the gut to affect the nervous system as well. However, the system isn't ready for everyday clinical use yet. Animal findings are not always reproduced in humans, most human datasets are cross-sectional, and confounding and inconsistent intervention protocols remain substantial. Stronger evidence will require cohorts followed from the preclinical stage, repeated metagenomic, metabolomic, and proteomic measurements, and direct testing of whether microbial markers predict later cognitive change. Trials of engineered bacteria, bacteriophages, or personalized probiotics should also account for modifiers such as the APOE ϵ 4 allele. A clinically useful gut–brain axis model will emerge only when mechanism, temporal sequence, and treatment response are demonstrated within a common research design.

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