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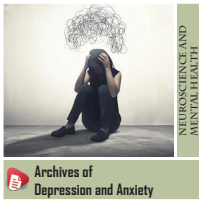

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Review Article

Crosstalk of Gastrointestinal Pathogen Infection, Food Allergy, and Neuroinflammation in Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD), the most common cause of dementia worldwide, is underrecognised as a systemic disorder that extends beyond the central nervous system. Emerging evidence highlights the critical role of the Gut–Brain Axis (GBA), a bidirectional communication network linking intestinal microbes, immune responses, and neural pathways. Perturbations in this axis, such as enteric microbial dysbiosis and food allergy, may contribute to immune dysregulation, gut microbial alterations, and intestinal barrier dysfunction, which are hypothesised to influence β-amyloid aggregation, tau pathology, and ultimately cognitive decline. These insights underscore the importance of intestinal homeostasis in modulating susceptibility to neurodegeneration. Several factors contribute to the pathogenesis of AD; however, this review focuses on food allergies and Gastrointestinal Pathogens (GIPs). Despite decades of research, there is currently no curative treatment; existing pharmacological therapies provide only modest symptomatic relief and slow disease progression. Consequently, clinical interest has grown in complementary and integrative approaches, particularly traditional herbal medicines and acupuncture, which have long histories of use in maintaining systemic balance and preventing AD progression. Preclinical and clinical studies suggest that such interventions may regulate gut microbiota composition, enhance barrier integrity, suppress pro-inflammatory signalling, and confer direct neuroprotective effects. In this review, we discuss the therapeutic potential of traditional medicine-based interventions as adjunctive strategies for AD management, with emphasis on their ability to target the GBA, modulate immune responses, and improve neuroprotection. These perspectives may provide insight for future preventive and therapeutic frameworks for AD.

Abbreviations

AD: Alzheimer's Disease; GBA: Gut-Brain Axis: TLR: Toll-Like Receptor: IL: Interleukin; EED: Environmental Enteric Dysfunction; Aβ: Amyloid-β; BBB: Blood–Brain Barrier; FPIES: Protein-Induced Enterocolitis Syndrome; ILC2s: Type 2 Innate Lymphoid Cells; CSF: Cerebrospinal Fluid; EPEC: Entero Pathogenic E. coli; PI-IBS: Post-Infectious Irritable Bowel Syndrome; SCFAs: Short-Chain Fatty Acids; Treg: Regulatory T Cell; CNS: Central Nervous System; EGIDs: Eosinophilic Gastrointestinal Disorders; GP: Gut Pathogen; GIP: Gastrointestinal Pathogen; OBA: Organ-Brain Axis

Introduction

Alzheimer's Disease (AD) is the most common cause of dementia worldwide, affecting more than 55 million people as of 2023, and its prevalence is characterised by progressive cognitive decline and behavioural impairment. AD has long been understood primarily as a Central Nervous System (CNS) disorder marked by extracellular amyloid-β (Aβ) deposition, intracellular tau hyperphosphorylation, synaptic dysfunction, and neuronal death. Growing evidence implicates systemic factors—particularly immune dysfunction and gut disturbances in shaping AD risk and progression [1-3]. This review highlights the potential indirect roles of food allergy and GIP infection in the development of AD, distinct from established genetic and environmental influences.

Several FDA-approved drugs now target amyloid plaques in Alzheimer's disease, including lecanemab (Leqembi) and donanemab (Kisunla). These therapies are indicated for patients in the early stages of Alzheimer's and are designed

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to slow disease progression by promoting amyloid clearance from the brain. However, their use is limited by significant safety concerns. The most notable adverse effect is amyloid-related imaging abnormalities (ARIA), which may present as oedema (swelling) or microhemorrhages (bleeding). Additional side effects include headaches, dizziness, and infusion-related reactions. Given these challenges, there is an urgent need to develop safer and more effective strategies for the prevention and treatment of Alzheimer's disease [4-6].

Current findings

Intestinal dysfuncionin AD

One of the key intestinal abnormalities in AD is gut barrier impairment. Both human and animal studies reveal increased intestinal permeability ("leaky gut") in [7]. The Zou group found reduced expression of tight junction proteins (occludin, claudin-1, and ZO-1) in AD mouse models, which allowed bacterial products like Lipopolysaccharide (LPS) to enter systemic circulation [8]. Elevated LPS levels have been detected in postmortem AD brains and colocalise with Aβ plaques, suggesting translocation from the gut contributes to neuroinflammation [9]. Compromised gut integrity facilitates chronic systemic inflammation, which accelerates neuronal injury and cognitive decline.

Microbiota dysbiosis of AD

AD patients frequently exhibit altered gut microbiota composition. Metagenomic studies show reduced abundance of beneficial taxa such as *Bifidobacterium* and *Faecalibacterium prausnitzii*, alongside enrichment of proinflammatory species including *Escherichia/Shigella* [10]. These shifts reduce production of short-chain fatty acids (SCFAs) like butyrate, which normally maintain epithelial barrier integrity and support regulatory T cell (Treg) differentiation. Butyrate deficiency has been associated with increased neuroinflammation and accelerated Aβ pathology [11]. Dysbiosis also alters bile acid metabolism, producing neurotoxic secondary bile acids implicated in cognitive decline.

Immune dysregulation of AD

Intestinal dysfunction in AD includes dysregulated mucosal immunity. Microbial metabolites and antigens activate gut immune cells, promoting a Th1/Th17-skewed response. This results in systemic release of IL-6, TNF-α, and IL-1β, which cross the blood–brain barrier (BBB) and exacerbate neuroinflammation; this latter can also be triggered by IL-8 and IL-18 [12,13]. Evidence also suggests that intestine -derived immune cells can migrate to the CNS. In APP/PS1 mice, activated intestinal T cells infiltrated the brain and worsened amyloid pathology [14]. Thus, intestinal immune dysregulation links peripheral dysfunction with central AD pathology.

In summary, intestinal dysfunction plays a critical role in AD pathogenesis by disrupting the Gut–Brain Axis (GBA), impairing barrier integrity, altering microbial composition, and driving immune dysregulation, which collectively promote neuroinflammation and accelerate the accumulation of amyloid and tau pathology.

Gastrointestinal pathogens

Infection may contribute to alzheimer's disease pathogenesis through intestinal dysfunction

GIP infections, caused by bacteria, viruses, and parasites, remain a leading cause of gastrointestinal morbidity worldwide. Common pathogens include *Escherichia coli, Salmonella, Shigella, Clostridium diffcile*, rotavirus, norovirus, and protozoa such as *Giardia lamblia*. While many infections are acute and self-limiting, they often trigger persistent alterations in intestinal physiology. These infections may cause intestinal dysfunction, defined as impaired barrier integrity, altered immune signalling, intestinal dysbiosis, and long-term sequelae such as post-infectious irritable bowel syndrome (PI-IBS) or malabsorption, and Environmental Enteric Dysfunction (EED) in adults, as a result indirectly contributing to AD pathogenesis through intestinal, BBB, and GBA dysfunction.

Enteric pathogens lead to barrier dysfunction

One major effect of enteric pathogens is damage to the epithelial barrier. Pathogens deploy toxins and virulence factors that disrupt tight junction proteins, increasing permeability ("leaky gut"). For example, *Enteropathogenic E. coli* (EPEC) injects effector proteins via a type III secretion system, leading to pedestal formation, epithelial injury, and barrier leakage (Martinez-Argudo et al., 2010). Similarly, *C. difficile* toxins A and B cause cytoskeletal disruption and epithelial apoptosis, resulting in codiarrhoea [15] and non-structured protein (NSP4) [16]. Barrier disruption permits translocation of bacterial products such as LPS into the lamina propria and circulation. This amplifies immune activation and perpetuates inflammation, contributing to chronic dysfunction beyond acute infection.

Enteric pathogens trigger immune dysregulation

Enteric infections provoke strong innate and adaptive immune responses. Pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) detect microbial products, activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and inflammasome pathways. This induces proinflammatory cytokines (IL-1β, IL-8, IL-18, TNF-α, IL-6) that recruit neutrophils and macrophages to infection sites [17,18] and may contribute to AD pathogenesis, as elevated levels of several of these cytokines have been detected in the serum and cerebrospinal fluid (CSF) of AD patients [12,13,19].

Enteric pathogens disrupt healthy intestinal microbiota

Also disturb the gut microbiota, resulting in dysbiosis. Antibiotic-associated *C. difficile* infection exemplifies how pathogen overgrowth following microbiome disruption causes recurrent colitis. Viral infections such as rotavirus also induce long-term shifts in microbial ecology, reducing beneficial commensals and enabling pathogen persistence [20] and also

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exacerbate EED in low-resource settings. Repeated childhood infections contribute to chronic villous blunting, impaired absorption, stunted growth, and poor oral vaccine responses [21]. Microbiota perturbation impairs colonisation resistance, facilitating recurrent infections and chronic inflammation. Furthermore, reduced production of SCFAs, such as butyrate, weakens epithelial barrier function and regulatory immune responses, reinforcing dysfunction.

In summary, enteric pathogens disrupt gut–brain axis homeostasis by damaging the intestinal barrier, inducing immune dysregulation, and reducing microbial diversity. These alterations stimulate the release of pro-inflammatory cytokines, facilitate their translocation across the BBB, and exacerbate neuroinflammation, thereby contributing to Alzheimer's disease pathogenesis through systemic–central immune crosstalk.

Food allergy may contribute to alzheimer's disease pathogenesis through intestinal dysfunction

Food allergy promotes asthma, atopic dermatitis, and immune-mediated adverse reactions to dietary antigens, affecting approximately 6–8% of children and up to 4% of adults worldwide. It can be life-threatening in anaphylaxis. The intestinal tract, as the primary site of exposure to food antigens, plays a central role in both the initiation and manifestation of allergic responses. Atopic diseases—including asthma, allergic rhinitis, and atopic dermatitis—are significantly and dose-dependently associated with increased dementia risk [22] and food allergy was also found to increase phosphorylation of tau protein in the brain [23].

Food allergy has recently been recognised as a driver of intestinal dysfunction, characterised by barrier disruption, altered microbial ecology, and dysregulated immune responses.

Food allergy may promote intestinal dysfunction

The intestinal epithelium forms a physical and biochemical barrier that regulates antigen passage from the lumen to systemic circulation. In food allergy, epithelial barrier integrity is compromised. Studies demonstrate increased intestinal permeability ("leaky gut") in allergic individuals, attributed to disrupted tight junction proteins such as occludin and claudins [24,25]. This impaired barrier allows excessive penetration of food antigens and microbial products, perpetuating allergic sensitisation and systemic inflammation.

Additionally, epithelial cells in allergic intestines often secrete higher levels of thymic stromal lymphopoietin (TSLP) and IL-33, which activate dendritic cells and type 2 innate lymphoid cells (ILC2s). This creates a pro-Th2 microenvironment that promotes IgE class switching and mast cell activation, amplifying allergic responses [26].

Immune dysregulation

Food allergy reflects a breakdown of oral tolerance, the process by which the immune system normally develops non-reactivity to dietary antigens. Instead, allergic individuals mount Th2-skewed immune responses, producing cytokines such as IL-4, IL-5 [Su et al., personal communication], and IL-13. These cytokines drive eosinophil recruitment, mucus hypersecretion, and mast cell degranulation in the intestinal mucosa, all of which contribute to dysfunction.

Chronic allergic inflammation can remodel the intestinal mucosa, leading to villus atrophy, goblet cell hyperplasia, and increased smooth muscle contractility [27]. These changes impair nutrient absorption and promote motility disturbances, contributing to clinical symptoms such as abdominal pain, diarrhoea, and malabsorption, which may ultimately contribute to EED.

Microbiota alterations

The gut microbiota plays a crucial role in shaping immune tolerance. Dysbiosis, imbalance in gut microbes, reduced microbial diversity with depletion of beneficial taxa such as *Bifidobacterium* and *Faecalibacterium,* has been consistently observed in food-allergic patients [28]. Loss of SCFA-producing bacteria diminishes butyrate and propionate levels, which normally strengthen epithelial barrier function and promote regulatory T-cell differentiation. Animal studies provide causal evidence: transplantation of microbiota from food-allergic infants into germ-free mice increases susceptibility to allergic responses, whereas restoring specific Clostridia strains restores tolerance [29]. This suggests that food allergy–related intestinal dysfunction is tightly linked to microbial imbalance.

Clinical manifestations of intestinal dysfunction

In practice, intestinal dysfunction in food allergy manifests as both acute and chronic gastrointestinal symptoms. Acute IgE-mediated reactions may trigger nausea, vomiting, abdominal pain, and diarrhoea shortly after allergen ingestion. Non-IgE–mediated forms, such as food protein-induced enterocolitis syndrome (FPIES) or eosinophilic gastrointestinal disorders (EGIDs), result in persistent inflammation, leading to malabsorption, growth retardation, and intestinal remodelling [30].

In summary, food allergy can trigger gut dysbiosis, which can then influence the gut-brain axis and potentially contribute to AD pathogenesis. This occurs through increased intestinal permeability, systemic inflammation, and impaired blood-brain barrier function, ultimately promoting AD hallmarks like neuroinflammation and amyloid-beta accumulation. Compared with gut dysbiosis and chronic intestinal inflammation, the relationship between food allergy and Alzheimer's disease remains relatively underexplored. Several epidemiological studies have reported increased dementia risk among individuals with allergic diseases, including asthma, allergic rhinitis, and atopic dermatitis, while experimental studies have demonstrated that allergic inflammation can enhance tau phosphorylation and neuroinflammatory responses. Nevertheless, direct evidence specifically implicating food allergy in Alzheimer's disease is currently limited, and most proposed mechanisms are inferred from studies of intestinal

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barrier dysfunction, systemic inflammation, and gut-brain axis dysregulation. Therefore, food allergy should presently be regarded as a potential contributor rather than an established causal factor in AD pathogenesis.

Taken together, intestinal dysfunction in AD encompasses barrier breakdown, microbiota dysbiosis, immune dysregulation, and gastrointestinal symptoms, all of which reinforce systemic and neuroinflammation. Both food allergy and GIP infection can lead to intestinal dysfunction. These mechanisms link intestinal dysfunction with central nervous system pathology. Thus, both food allergy and GIP infection represent peripheral drivers of chronic inflammation and barrier dysfunction that, over time, may increase susceptibility to AD (Table 1).

Gut–brain axis in alzheimer's pathogenesis

The gut–brain axis is a bidirectional communication network involving the gastrointestinal tract, its resident microbiota, immune and endocrine pathways, and the CNS. Increasingly, researchers have recognised that AD is not a purely brain-localised pathology but is influenced by systemic changes, particularly those originating in the gut and peripheral organs.

The intestinal microbiota regulates digestion, energy metabolism, immune development, and production of bioactive metabolites such as SCFAs, bile acids, and tryptophan derivatives [31,32]. Perturbations in this microbial community, termed dysbiosis, have been implicated in ageing, metabolic diseases, and neurodegeneration [33,34]. In the context of AD, dysbiosis is hypothesised to accelerate pathological processes by altering metabolite availability, increasing systemic and CNS inflammation, and compromising the integrity of the gut barrier and BBB [11,35].

Evidence indicates that AD patients exhibit specific microbial shifts, including reduced abundance of beneficial SCFA-producing bacteria (e.g., Faecalibacterium prausnitzii, Roseburia spp.) and enrichment of potentially pro-inflammatory taxa (e.g., Escherichia/ Shigella) [36].

The immune system provides a major communication route between gut and brain. Dysbiosis can increase intestinal permeability ("leaky gut"), allowing translocation of microbial products such as LPS into circulation. Elevated LPS has been detected in AD brains and is thought to prime microglia toward a pro-inflammatory state that impairs amyloid clearance and exacerbates neurotoxicity [37]. Thus, gut-driven systemic inflammation directly contributes to neuroinflammation, one of the central drivers of AD pathology.

Organ–brain axis extensions

Other organ systems are tightly connected to gut–brain communication and are increasingly implicated in AD, including: 1). Gut–Liver–Brain Axis: Microbial metabolites such as bile acids are processed in the liver, and altered bile acid pools have been observed in AD patients. Dysregulated bile acid signalling affects cholesterol homeostasis, neuronal metabolism, and even tau phosphorylation [38]; 2). Gut–Immune–Brain Axis: Peripheral immune cells, shaped by gut microbial composition, infiltrate the brain and influence microglial responses. Regulatory T–cell populations are particularly influenced by SCFA levels, linking dietary fibre intake to neuroimmune outcomes [32] and 3). Gut–Metabolic–Brain Axis: Insulin resistance, lipid metabolism, and systemic inflammation, all strongly influenced by gut microbiota, are recognised AD risk factors.

In summary, dysbiosis can affect the CNS via microglial activation, highlighting the importance of the intestinal microbiota-brain axis in AD pathogenesis. These organ axes

Table 1: Food allergy, GIP infection and Alzheimer's disease.

Category	Food Allergy	GIP Infection	Alzheimer's Disease
Key Mechanisms (e.g., intestinal barrier disruption)	Epithelial barrier disruption (⍰ permeability), loss of oral tolerance, Th2-skewed responses, mast cell/eosinophil activation, chronic mucosal remodelling.	Pathogen-mediated epithelial injury and toxin effects, PRR/TLR activation, inflammasome-driven inflammation, villous atrophy or cytoskeletal disruption.	Gut barrier impairment (reduced tight junction proteins), chronic low-grade systemic inflammation, microbiota-driven metabolic and immunologic shifts.
Microbiota Changes	Reduced diversity. Depletion of protective taxa (e.g., Bifidobacterium, Faecalibacterium). Loss of SCFA-producing bacteria contributing to sensitisation and impaired tolerance.	Acute pathogen overgrowth (e.g., Salmonella, Shigella, C. difficile) and post-infectious dysbiosis.Loss of colonisation resistance and reduced commensals.	Dysbiosis characterized by ⍰ Bifidobacterium, ⍰ Faecalibacterium, ⍰Proteobacteria/Escherichia–Shigella; altered bile acid metabolism and reduced butyrate.
Immune Dysregulation	Dominant Th2 cytokines (IL-4, IL-5, IL-13), IgE-mediated mast cell degranulation, eosinophilia; impaired regulatory T cell induction due to low SCFA.	High innate cytokine release (IL-1β, TNF-α, IL-6), neutrophil influx, oxidative tissue damage; potential for chronic mucosal immune activation.	Peripheral proinflammatory cytokines (IL-6, TNF-α), Th1/Th17 skewing in some contexts. Microglial priming and infiltration of peripheral immune cells into CNS.
Clinical Manifestations	Acute GI allergy (nausea, vomiting, diarrhoea); Chronic forms include FPIES, EGIDs with malabsorption and growth issues; food-triggered systemic reactions.	Acute gastroenteritis (diarrhoea, vomiting); chronic sequelae such as post-infectious IBS (PI-IBS), environmental enteric dysfunction (EED), recurrent C. difficile colitis.	GI symptoms common in AD (constipation, dysmotility, appetite change); Association with increased dementia risk in chronic intestinal inflammatory conditions.
References	[25,28,30]	[21]	[9,11,35]

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underscore AD as a multi-system disorder where peripheral biology profoundly influences central pathology.

Application of gba in traditional chinese medicine for ad

Traditional Chinese medicine conceptualises health and disease through the dynamic interplay of organs, channels (meridians), and vital substances (Qi, Blood, Yin, and Yang). Increasing evidence suggests that TCM organ theories may parallel mechanisms of peripheral organ–brain communication elucidated in contemporary neuroscience, immunology, and microbiome research. The integration of these perspectives offers a novel lens for understanding AD and related neurodegenerative disorders.

TCM organ theory and brain function

Fatty-producing Kidney essence and closely linked to the Heart, signalling ageing and a fatty deena fatty Lisignalling (Each organ system in TCM has both physiological and psychoemotional attributes, creating a holistic framework of organ–brain interaction, including: Kidney–Brain Axis: The TCM Kidney is considered the root of essence and marrow production. Deficiency in Kidney Jing is linked to cognitive production loss and premature ageing. Evidence suggests that dysfunction and impaired clearance of metabolic toxins may accelerate neurodegeneration [39-42]. 2). Spleen–Brain Axis: The concepts parallel the gut–brain axis, where impaired intestinal function and dysbiosis contribute to systemic inflammation, altered short-chain fatty acid production, and compromised BBB integrity [32,38]. 3). Liver–Brain Axis: In TCM, Liver Qi stagnation manifests as irritability, depression, and restlessness. Evidence has been implicated in AD pathogenesis [43]. 4). Heart–Brain Disturbances: Heart Qi or Yin may present as insomnia, anxiety, or memory deficits. Modern research aligns with this by highlighting the contribution of vascular health, cardiac output, and neurovascular coupling to brain function and dementia risk [44].

Evidence-based research supporting tcm concepts of organ–brain interaction

Interaction Concept Ding Id Nourishment: kidney Cognitive ceCognitiharmonisingng: 1). Kidney and Cognitivssignalling [40]. This parallels the nourishment-kidney deficiency weakening. 2). Intestinal Dysbiosis (including also TCM-Spleen) and AD: Numerous studies show that intestinal dysbiosis contributes to systemic inflammation, BBB permeability, and amyloid pathology (36, 35). [45]. 3). Liver Metabolism and Neurodegeneration: Altered bile acid pools and hepatic metabolic dysprogression are observed in AD patients [43]. 4). Cardiovascular and Cognitive Function: Cerebral perfusion and vascular integrity are critical determinants of AD progression, which may be associated with an increased risk of dementia [43].

Focusing on the gut–brain/organ–brain axis offers not only mechanistic insights but also therapeutic opportunities. Unlike amyloid plaques within the brain, the gut microbiome is modifiable through diet, probiotics, prebiotics, herbal formulations, and lifestyle changes. This makes it a compelling target for both prevention and treatment strategies in AD. Moreover, the convergence of modern biomedical research with traditional clinical practices such as TCM, which has long emphasised organ interconnections and the importance of digestive health for mental function, opens a fertile space for integrative approaches.

In summary, the convergence of TCM theory and modern organ–brain axis research offers valuable insights into AD pathogenesis and therapy. While TCM describes functional organ–brain interactions [38]. Biomedical science is now uncovering mechanistic correlates involving the gut microbiome, hepatic metabolism, immune regulation, and vascular function. Integrating these paradigms may guide innovative prevention and treatment strategies that target systemic health to protect the brain.

TCM interventions therapies targeting organ–brain regulation

TCM employs herbal medicine, acupuncture, and dietary therapy to harmonise organ systems and restore brain health. For examples, herbal formulas for Kidney-tonifying, *for* Blood-nourishing, and for Liver-Qi regulating which have been shown to improve cognition and reduce neuroinflammation in preclinical AD models [46] and TCM dietary therapy to emphasize balanced digestion and avoid excessive damp-forming foods (e.g., greasy, sweet foods), parallel modern dietary recommendations such as the Mediterranean diet, which supports microbiome diversity and lowers AD risk [51]. Foods that tonify the Kidney (e.g., black sesame, walnuts) and strengthen the Spleen (e.g., yam, barley) are prescribed for memory and cognitive resilience [47].

Faecal microbiota transplantation (FMT), historically rooted in TCM as "yellow soup" described in the 4th-century *Handbook of Emergency Medicine* by Ge Hong [48-54], was originally used to treat severe diarrhoea and food poisoning. This ancient therapy laid the foundation for modern FMT. Recent studies show that FMT from healthy or young donors can restore gut microbiota composition, reduce neuroinflammation, and improve cognition in an Alzheimer's disease model. Hazan and colleagues reported a case of improvement in Alzheimer's disease symptoms following faecal microbiota transplantation [50].

TCM employs herbal formulas and dietary interventions that not only nourish specific organs but also regulate the gut microbiome and immune system. Modern pharmacological studies confirm that many classical formulations exert microbiota-modulating and neuroprotective effects. For examples, animal studies show a kidney-tonifying formula, widely used for cognitive decline, can restores gut microbiota diversity, increases SCFA levels, and improves learning and memory in AD models [51]; a kidney-tonifying and brain-strengthening prescription that reduces amyloid deposition in APP/PS1 mice, partly by modulating gut microbial composition

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[52]; herbs can promote synaptic plasticity and shift gut microbiota toward beneficial taxa [53]; herbs can clear heat and dampness, anti-inflammatory effects on microglia and modulates intestinal flora [54], and herbs have prebiotic-like effects that enhance SCFA production, regulate immunity, and reduce neuroinflammation [55,56].

Acupuncture and acupressure are promising complementary therapies for treating both intestinal dysfunction and AD. Preclinical and clinical studies suggest that acupuncture modulates the gut-microbiota-brain axis by improving gut barrier integrity, reducing pro-inflammatory bacteria or fungi, lowering serum LPS and inflammatory cytokines, and restoring blood–brain barrier function [57]. These effects are linked to reductions in β-amyloid deposition, oxidative stress, and neuronal damage, along with improved cognimodulating neuroinflammatory, improving gut microbiota, and enhancing cerebral perfusion [58,59]. Clinical evidence also shows that adjunctive acupuncture enhances cognitive outcomes in mild AD and mild cognitive impairment, possibly via gut microbiota regulation [60,61]. Together, evidence points toward gut-mediated mechanisms as central to acupuncture's benefits in AD.

In summary, Traditional Chinese Medicine offers holistic strategies to prevent and treat AD by regulating the gut–brain axis and intestinal function. However, further well-designed clinical trials are essential to validate these findings and strengthen their integration into clinical practice, particularly in FMT application.

Limitations and future perspectives

Despite growing evidence supporting the role of the gut-brain axis in Alzheimer's disease, several important limitations should be acknowledged. First, much of the mechanistic evidence linking gastrointestinal pathogens, food allergy, and neurodegeneration is derived from animal models. Although these studies provide valuable biological insights, their translation to human Alzheimer's disease remains uncertain. Second, epidemiological studies investigating allergic diseases and dementia are heterogeneous with respect to study populations, diagnostic criteria, follow-up duration, and adjustment for confounding variables. Consequently, the observed associations should not be interpreted as evidence of causality. Third, studies investigating gut microbiota are often limited by relatively small sample sizes, cross-sectional designs, and substantial interindividual variability influenced by diet, medication use, geography, and ageing. Fourth, while acupuncture, herbal medicine, and faecal microbiota transplantation have demonstrated encouraging findings in experimental models and preliminary clinical studies, most human trials remain limited by small sample sizes, heterogeneous treatment protocols, inadequate blinding, and short follow-up periods.

Large multicenter randomised controlled trials are still required before these interventions can be recommended for routine clinical practice.

Finally, Alzheimer's disease is a multifactorial disorder involving genetic susceptibility, ageing, vascular disease, metabolic dysfunction, and environmental factors. Gastrointestinal dysfunction should therefore be considered one component within a complex pathogenic network rather than a single causal mechanism.

Conclusions and future research directions

Accumulating evidence suggests that gastrointestinal pathogen infections and, to a lesser extent, food allergy may contribute to systemic inflammation and gut-brain axis dysregulation associated with Alzheimer's disease. However, current evidence remains largely associative, and additional mechanistic investigations and well-designed longitudinal clinical studies are needed to establish causality and determine the therapeutic value of targeting these pathways (Figure 1 and Tables 1,2).

Author contributions

Conceptualization: BBS; Validation BBS; resources BBS; writing—review and editing: BBS and.; project administration: BBS. CX: Reviewed and edited. All authors have read and agreed to the published version of the manuscript.

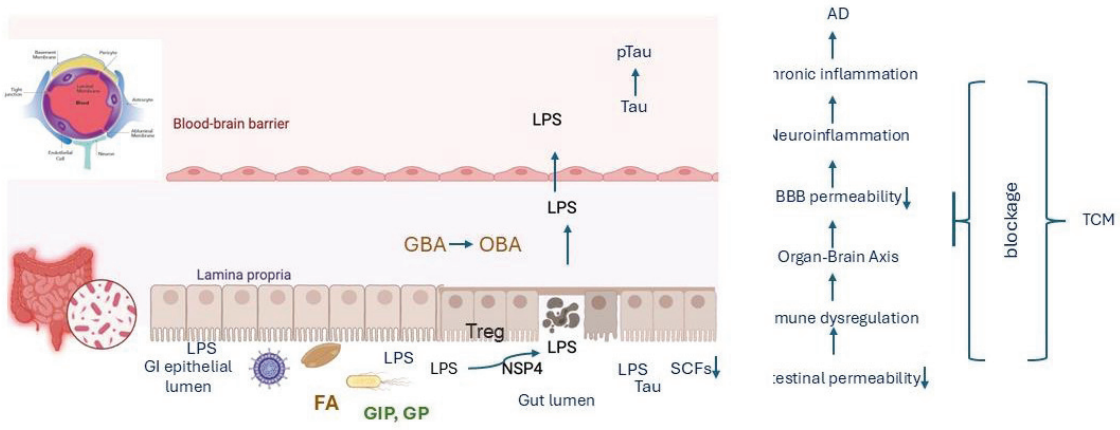

Figure 1: Intraoperative image, Complete section of the pancreas body.

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Table 2: A comparative table (Conventional Medicine vs TCM) focused on gut/organ–brain–axis approaches to prevention and treatment of Alzheimer's disease.

Approach		Primary gut/organ–brain mechanisms targeted	Typical interventions/examples	Evidence level (gut/brain axis relevance)	Representative references (short)
Conventional	**Lifestyle & Dietary Interventions**	Modulate gut microbiota composition, increase SCFAs, reduce systemic inflammation, improve metabolic health (gut–metabolic–brain).	Mediterranean diet, ketogenic/mod-Med diets, increased dietary fibre, physical activity, glycemic control.	Moderate: epidemiology & intervention trials show cognitive benefit; microbiome mediation supported by cohort and mechanistic studies.	[31]
	Amyloid-targeting Therapies	Indirect modulation via reduction of cerebral amyloid; limited direct gut effects but systemic inflammation and BBB interactions relevant to efficacy and safety (ARIA).	Lecanemab (Leqembi), Donanemab (Kisunla); symptomatic drugs (cholinesterase inhibitors, memantine).	High for amyloid-lowering efficacy in early AD; safety concerns (ARIA) and unclear translation into long-term functional benefit; limited gut-directed evidence.	[5]
	Microbiome-directed Therapies	Restore eubiosis, increase beneficial metabolites (IPA, SCFAs), reduce endotoxemia and peripheral inflammation, modulate immune–microglial signalling.	Probiotic strains (Bifidobacterium, Lactobacillus), prebiotic fibres, symbifaecal microbiota transplantation (experimental).	Early clinical & preclinical evidence: small RCTs and mechanistic studies show metabolite changes (IPA, SCFAs) and inflammatory modulation.	[14]
		FMT			
TCM	**Herbal Formulas**	Tonify organs (Kidney/Spleen), reduce phlegm-dampness and inflammation; many formulas shown to modulate gut microbiota and SCFA/bile acid profiles in models.	Liuwei Dihuang Wan, Bushen Yizhi, formulas containing Ginseng, Astragalus, Scutellaria; polysaccharide-rich herbal extracts.	Preclinical and some clinical data: animal studies show microbiota modulation and neuroprotection; clinical evidence emerging but heterogeneous.	[45]
	Acupuncture	Modulates the autonomic improves gut motility and microbiota composition, reduces neuroinflammation, and enhances cerebral perfusion.	Acupuncture at GV20 (Baihui), ST36 (Zusanli), scalp acupuncture protocols used in cognitive impairment trials.	Preclinical and small clinical trials suggest autonomic, anti-inflammatory, and microbiome effects; larger trials needed.	[59]
	Dietary	Improve digestion/'Spleen' function, support microbiota via prebiotic foods, reduce damp/phlegm; parallels Mediterranean-like dietary effects on microbiome.	Foods/herbs to 'tonify' Kidney/Spleen: walnuts, black sesame, yam; emphasis on warm, easily digestible foods; avoidance of greasy/sweet 'damp'-forming foods.	Traditional use supported by mechanistic studies showing prebiotic and anti-inflammatory effects of certain foods; clinical trial evidence limited but promising.	*[45]*
	Therapy				

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