REVIEW ARTICLE

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The role of gut microbiota in pathogenesis of Alzheimer Disease

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Abstract

Introduction and Objective. Recent insights point toward a complex interplay between gut microbiota and neurodegenerative processes in Alzheimer's disease (AD). The aim of the study is to explore how selected dietary patterns and microbiota-based interventions may affect cognitive function and neuroinflammation in AD by modulating the gut-brain axis.

Review Methods. research was conducted based on peer-reviewed studies published mainly between 2018 – 2024, focusing on the influence of Mediterranean, high-fibre, and ketogenic diets, as well as probiotics, prebiotics, and faecal microbiota transplantation (FMT) on cognitive outcomes and inflammatory markers in AD models and patients.

Brief description of the state of knowledge. Available evidence suggests that gut microbiota diversity and composition are altered in individuals with AD. Interventions, such as the Mediterranean or ketogenic diet, appear to enhance microbial richness and support anti-inflammatory pathways. Probiotic supplementation and FMT showed promising cognitive improvements in preclinical models, with limited but growing human data. However, considerable heterogeneity in study design and outcomes hinders firm conclusions.

Summary. Targeting gut microbiota through diet or microbiota-modulating therapies holds promise as an adjunctive approach in AD management. While preliminary results are encouraging, there remains a pressing need for longitudinal clinical trials to clarify which microbial profiles and interventions yield the most consistent cognitive benefits. In the meantime, nutritional strategies aimed at supporting a balanced gut ecosystem may serve as a low-risk complement to conventional AD treatment.

Key words

Alzheimer disease, gastrointestinal microbiome, brain-gut axis

INTRODUCTION AND OBJECTIVE

Alzheimer's Disease (AD), affecting millions of individuals annually worldwide, is the most prevalent neurodegenerative disorder and the leading cause of dementia [1]. It is estimated that approximately 50 million people globally currently suffer from AD, and the number continues to rise each year [1]. The disease is characterized by the extracellular deposition of plaques composed of beta-amyloid (Aβ) peptides and intracellular accumulation of hyperphosphorylated tau neurofibrillary tangles (NFTs). A chronic inflammatory state triggered by these pathological changes plays a central role in the pathogenesis of AD. Peripheral stimuli, including endotoxins, also contribute to the activation of neuroinflammation. Gradual cognitive decline ensues, accompanied by neuronal and synaptic loss. Progressive memory impairments, difficulties with recognition, and executive dysfunction are commonly observed [1, 2].

The population most at risk for AD includes individuals over the age of 65, although cases have also been documented in younger individuals [3]. AD poses a global health challenge due to the aging population. The number of diagnoses continues to increase annually [3, 4]. It is projected that by 2030, 82 million individuals will be affected by AD, and by 2050, this number is expected to nearly double [3]. Therefore, uncovering and understanding the underlying mechanisms and predisposing factors of this disease is of urgent importance to researchers. Although the pathogenesis of AD remains incompletely elucidated, numerous contributing factors have been identified. In addition to established factors such as age, family history, and genetic predisposition, environmental influences (including low educational attainment, smoking, and environmental pollution) are also considered relevant [3, 4].

Despite significant advancements in AD research in recent years, a highly effective therapy has yet to be developed. Numerous hypotheses and treatment strategies have been proposed, although many have failed to produce significant outcomes in clinical trials. Early diagnosis is widely regarded as critical. There is, however, potential to identify novel mechanisms that may enhance the current understanding of AD pathophysiology. The gut–microbiota–brain axis (GMBA) has gained increasing attention in recent clinical research. It has been proposed as a potential therapeutic target for individuals affected by neurodegenerative disorders of the central nervous system, including AD. The term 'gut microbiota' refers to a highly complex ecosystem of microorganisms – including trillions of bacteria, viruses,

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and fungi – that colonize the gastrointestinal tract and exist in a symbiotic relationship with the host [1].

The gut microbiota plays a vital role in both peripheral and central regulation of immune responses. Additionally, microorganisms can influence the integrity of the blood–brain barrier (BBB), which serves as a regulatory interface controlling immune cell infiltration into the brain. Although the brain was once considered an 'immune-privileged' organ, recent evidence supports the role of the gut microbiota in the bidirectional communication along the gut–brain axis. The composition of the gut microbiota is not static but is modifiable by numerous factors, such as diet, environmental influences, and lifestyle. Consequently, the microbiota varies between individuals. Age-related changes also occur, with an observed increase in Bacteroidetes and a decrease in Firmicutes abundance around the age of 65. Disruption of microbial homeostasis – referred to as gut dysbiosis – may lead to heightened immune stimulation, resulting in chronic inflammation [1, 4].

OBJECTIVE

The aim of this scoping review is to comprehensively discuss the significance of the human gut microbiota in the pathogenesis and progression of AD based on current scientific evidence. Information is provide about the microbiota and the central nervous system (CNS) in connection with AD.

MATERIALS AND METHOD

The review presents an integrated summary of the potential immunological, metabolic, and neurobiological mechanisms underlying the gut–brain axis, with particular emphasis on the role of dysbiosis. It also explores the interrelationships between aging, changes in microbiota composition, and susceptibility to AD, along with potential therapeutic approaches targeting gut microbiota modulation as an adjunct in the treatment of this disease.

Human gut microbiota. The human gut represents a low-oxygen environment colonized by a highly diverse microbial community, forming a dynamic ecosystem with high metabolic activity. These microorganisms inhabit various regions of the gastrointestinal tract, with the distal gut exhibiting the highest microbial density and the most favourable conditions for gut microbiota development. The small intestine is primarily inhabited by facultative anaerobes such as Streptococcus and Lactobacillus, whereas the large intestine – particularly the colon – is dominated by strictly anaerobic fermentative bacteria belonging to the families Ruminococcaceae, Lachnospiraceae, and Bacteroidaceae. Notably, the total mass of these microorganisms is estimated at approximately 1- 2 kilograms – comparable to the mass of an organ, or even the brain – which underscores their substantial biological significance. The collective genome of these microbes far exceeds the human genome in terms of gene count. The gut microbiota, through its considerable mass and metabolic activity, exerts an influence on the functioning of the entire human organism. The gut microbiota plays essential roles not only in digestion but also in metabolism, immune modulation, and interactions with the central nervous system. Although the latter remains incompletely understood, ongoing research aims to clarify the signalling pathways and nature of this communication. Over the years, perceptions of the significance of gut microbiota have evolved, with increasing interest in the factors shaping its composition and the functional roles of constituent microbes. The advent of modern DNA sequencing technologies, including shotgun metagenomics and metabolomics, has enabled in-depth characterization of the microbiota – formerly referred to as the 'black box' of the human body – and facilitated a broader understanding of its multifaceted influence on health and human physiology [5, 6].

Microbiota composition undergoes changes throughout life, beginning at birth. Already at this early stage, differences in microbial colonization may be observed depending on the mode of delivery. In newborns delivered vaginally, the microbiota resembles that of the maternal vaginal microbiome, whereas those delivered via caesarean section exhibit a microbiota enriched in skin and environmental microbes. Beyond the mode of delivery, genetic, dietary, environmental, and pharmacological factors – particularly antibiotic use – contribute to microbiota modifications. In healthy adults, bacteria are the dominant microorganisms, with over 1,000 different species identified. Among this vast population, Firmicutes and Bacteroidetes constitute the majority of gut microbiota. Other notable phyla include Actinobacteria and Proteobacteria, with Verrucomicrobia present in smaller quantities [5, 7].

The Firmicutes phylum includes genera such as Clostridium, Faecalibacterium, Lactobacillus, Ruminococcus, and Blautia. Notably, Faecalibacterium prausnitzii (Clostridium cluster IV) exhibits anti-inflammatory properties, and its depletion has been associated with neurodegenerative and inflammatory bowel diseases. Its beneficial effects are partly attributed to the production of butyrate, a key short-chain fatty acid (SCFA). Bacteria from the Bacteroides genus, belonging to the Bacteroidetes phylum, play a crucial role in fermenting complex polysaccharides, including dietary fibre and endogenous glycans [6, 8].

Within the Actinobacteria phylum, Bifidobacterium species – predominant in the infant gut microbiota, especially in breastfed infants – are notable for their capacity to ferment oligosaccharides and enhance immune function. Their abundance declines with age [9].

The Proteobacteria phylum includes opportunistic bacteria, such as Escherichia coli and Enterobacter, whose overgrowth is often observed in dysbiosis. Their increased presence correlates with elevated inflammation, intestinal barrier permeability, and cognitive decline [3].

A microbiological ecosystem rich in diverse species demonstrates greater resilience to external factors, including infections, dietary changes, and environmental stress. When this diversity decreases – as is often observed with aging and in patients with Alzheimer's disease – its protective function is also weakened. These alterations promote disruptions in homeostasis and may exacerbate neuroinflammatory processes [1].

In recent years, growing attention has been directed toward the gut–brain axis. This bi-directional communication involves the interaction of gut microbiota with the central nervous system via microbial metabolites, cytokines, and the vagus nerve. Disruptions in this communication are of particular importance in the context of neurodegenerative diseases, notably AD [10].

The microbiota-gut-brain (MGB) axis. The modern concept of the gut-brain axis emerged in the 1980s, when researchers

discovered that hormones produced by the gastrointestinal endocrine system could influence neurons and brain cells. In the 2000s, this idea expanded significantly with studies highlighting the contribution of the gut microbiota to this bidirectional communication system [11].

Today, the gut-brain axis – also referred to as the MGB axis – has become a dynamic area of research, particularly in the context of mental, metabolic, and neurological health. The MGB axis is a two-way communication system that operates through multiple interconnected pathways, including the vagus nerve, immune signalling, endocrine factors, and microbial metabolites such as SCFAs [12].

The CNS has a profound impact on the gastrointestinal system, influencing motility, enzyme secretion and other digestive functions [13]. Conversely, the gut microbiota influences the brain through various mechanisms, including stress-related activation of the hypothalamic-pituitary-adrenal (HPA) axis, vagus nerve stimulation, secretion of SCFAs, and their effects on blood-brain barrier permeability. Additionally, the microbiota can modulate neurotransmitter levels directly or via the biosynthetic pathways of the host [14–16].

Research identifies three key communication pathways between the gut and the brain: neuronal, immune, and endocrine. These pathways do not function independently but interact closely, influencing each other in a reciprocal manner [17].

The gut microbiota also plays a crucial role in the immune system. It modulates immune responses via microbial metabolites such as SCFAs, secondary bile acids, amino acid derivatives, and bioactive molecules like microbe-associated molecular patterns (MAMPs) [18]. These molecules fine-tune local immunity in the gut, influence the central nervous system through systemic circulation, and contribute to brain immune regulation, with microglia playing a central role [19].

It is particularly important to note that intestinal bacteria are capable of producing a wide range of neuroactive substances, including γ-aminobutyric acid (GABA) (produced by *Lactobacillus* spp. and *Bifidobacterium* spp.), acetylcholine (*Lactobacillus* spp.), serotonin (*Escherichia* spp., *Candida* spp., *Enterococcus* spp.), dopamine (*Bacillus* spp.), and noradrenaline (*Bacillus* spp., *Saccharomyces* spp.). These microbial metabolites play key roles not only in the internal communication of the gut microbiota but also in influencing systemic and peripheral physiological processes, including those that impact brain function. They are actively involved in regulating neurological development and can exert both direct and indirect effects on central nervous system activity [20].

Importantly, the gut microbiota interacts with neuroendocrine pathways, particularly the HPA axis. Stress activation of the HPA axis can modify gastrointestinal function and microbiota composition. On the other hand, depletion of the microbiota disrupts the HPA axis, evidenced by changes in glucocorticoid levels under both normal conditions and stress in microbiota-deficient mice [13].

Finally, hormones regulated by the microbiota and microbial products can directly interact with enteric neurons, influencing brain regions responsible for cognition, mood, anxiety, sensory perception, and feeding behaviours. The primary neural pathways connecting the gut and the brain include the vagus nerve and the enteric nervous system (ENS). The vagus nerve, which originates in the brainstem, innervates the internal organs, making it the fastest and most direct route through which the gut microbiota can influence the brain [21].

Vagal and spinal afferent signals carry these local messages to the brain, while efferent signals from the vagus and spinal systems exert effects on the gut, ensuring homeostasis through both direct and indirect interactions with the enteric nervous system. Studies have shown that approximately 90% of the signals within the brain–gut axis travel in a centripetal direction – from the gut to the brain – while only about 10% move from the brain to the gut. This complex interplay ultimately impacts gut physiology, immune function, and microbiota composition [22, 23]. Vagal afferent fibres terminate in both the muscle layer and the mucosal tissue of the intestines, where they detect mechanical stimuli, such as changes in luminal volume, as well as chemical signals, including neurotransmitters, hormones, and cytokines, all of which can be influenced by the gut microbiota [21].

Moreover, ENS forms an extensive network of over 100 million neurons and approximately 400 million enteric glial cells (EGCs), working together to regulate and coordinate various gastrointestinal functions. Beyond controlling motility and pain signalling, the ENS plays a critical role in maintaining epithelial barrier integrity, promoting epithelial regeneration, regulating mucus secretion, and modulating local immune responses [24].

Acting as an autonomous neuronal system, often referred to as the 'second brain', the ENS integrates signals from the gut microbiota, the immune system, and gut-derived hormones. Through this complex interplay, it influences smooth muscle activity, supports neurogenesis, and contributes to the maintenance of protective epithelial barriers [25].

Although the ENS can function independently, its physiological activity is regulated through reciprocal connections with the CNS, forming the so-called gut-brain axis. Enteric neurons are not typical autonomic neurons as most of them do not receive direct input from the vagus nerve. Instead, the ENS integrates signals from local gut circuits and from sympathetic and parasympathetic pathways, which primarily act on the ENS rather than directly on the structures of the gut wall, except for blood vessels and sphincters [26].

Recent studies highlight the critical role of microRNAs (miRNAs) in regulating key physiological processes within the gastrointestinal tract, such as motility, barrier integrity, immune modulation, and enteric nervous system activity. MiRNAs achieve this by influencing gene expression in gastrointestinal pacemaker cells, immune cells, and enteric neurons [27]. Beyond local effects, miRNAs also act as mediators of gut-brain communication, participating in shaping immune responses and maintaining blood-brain barrier integrity [28]. Recently, miRNAs have gained attention for their role in intercellular communication and their potential as biomarkers for various human diseases. Moreover, emerging evidence suggests that gut-derived miRNAs may actively contribute to dysbiosis associated with different pathological conditions [29, 30].

The gut microbiota profoundly influence host miRNA expression, both locally in the intestine and in distant organs such as the brain. *In vitro* studies have demonstrated that commensal bacteria can induce specific miRNA expression patterns in intestinal epithelial or dendritic cells, thereby affecting innate immunity and barrier function [31].

Additionally, microbial metabolites including tryptophan, butyrate, acetylcholine, norepinephrine, serotonin and dopamine, can indirectly modulate miRNA expression by influencing astrocyte activity, neurotransmission, and blood-brain barrier integrity [32].

MiRNAs are also secreted in association with extracellular vesicles (EVs), which serve as key carriers mediating intercellular communication within the gut-brain axis. Growing evidence highlights the role of EVs, whether host or microbiota-derived, as vehicles for miRNA transfer along this bidirectional communication pathway [32].

Altered gut microbiota in AD. The concept of 'healthy microbiota' has not yet been specifically defined. However, we can discuss the condition of 'intestinal dysbiosis' which is a microbial imbalance with an advantage of 'bad' bacteria in the intestines. Due to this disproportion, important mechanisms may be disrupted, such as production of essential metabolites or maintaining necessary immunological functions.

Many studies show the impact of the altered gut microbiota on cognitive decline. For that reason, it can be assumed that it has a direct influence on AD pathogenesis and progression. Patients with this disease often show increased levels of pro-inflammatory taxa, thereby reducing the number of anti-inflammatory taxa [33] (footnote added?). For example, in one study including patients with neurodegeneration (33 – AD, 32 mild cognitive impaired [MCI] and 32 controls) there was a significant decrease in Firmicutes along with a higher number of Proteobacteria, Gammaproteobacteria, and Enterobacteria [33]. Similar results were observed in studies by Vogt et al. which showed a significant reduction of Firmicutes and Bifidobacteria in faecal samples of patients with AD. Simultaneously, the decrease was balanced by an excessive growth of Bacteroidetes species [34].

Zhuang et al. reported a comparison of the 43 patients with AD with age- and gender-matched controls which showed the overgrowth of specific bacteria during neurodegeneration: increased number of Bacteroidetes and reduced Actinobacteria with enhanced Ruminococcaceae, Enterococcaceae, and Lactobacillaceae, together with less Lanchnospiraceae, Bacteroidaceae, and Veillonellaceae, at the family level [1].

The pattern of imbalance with the increase of proinflammatory bacteria and decrease of anti-inflammatory bacteria is similar to opportunistic species in various inflammatory bowel diseases and other neurologic disorders [35].

Studies by Cattaneo et al. showed that microbiota of patients with AD tends to have an escalated number of Bacteroidetes and reduced number of Actinobacteria, while featuring a decreasing trend in Ruminococcus and an increasing trend in Escherichia/Shigellla [3].

Compared to healthy individuals, approx. 85% of patients with dementia have changed gut microbiota, and in patients with AD the decreases of diversity and richness in gut microbiota were observed [36]. Additionally, there are specific bacterial species levels that demonstrated correlation with cerebrospinal fluid biomarkers of AD pathology [36].

Link between microbiota and neuro-inflammation. AD has a multifactorial etiology and is primarily associated with the accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles in the brain (NFTs). Neuroinflammation also plays a key role in the development of AD and cognitive decline in which activated microglia, reactive astrocytes, and an activated complement system, are involved, especially within amyloid plaques [37]. The occurrence of the inflammatory response in the brain is also influenced by the gut microbiota [38].

The presence of neuroinflammation does not always lead to neurodegenerative diseases. First of all, it is a process that helps to protect the brain from infection and injury; however, a prolonged response of inflammatory mediators can lead to brain cell damage [39]. In AD, microglial cells, which have phagocytic capacity and release numerous cytokines and chemokines, are of primary importance in the brain's inflammatory response. In normal conditions, microglia are responsible for neuroprotection and reduce the development of inflammation. However in AD patients, the presence of amyloid deposits and NFTs activates microglia, which initially accelerate phagocytosis and removal of Aβ plaques. Over time, increased activation of this system leads to a reduced ability to degrade Aβ plaques and exacerbation of AD as a result of the constant release of pro-inflammatory cytokines. This leads to the development of neuroinflammation and neuronal damage [37]. In addition, systemic inflammation may increase this effect [38].

The effect of compounds of bacterial origin on the development of AD is confirmed by studies on bacterial LPS [40] (footnote added?). This endotoxin produced by bacteria has strong immunomodulatory effects. It also causes an increase in intestinal permeability by damaging the intestinal epithelium. When it is released into the bloodstream, it disrupts the BBB by affecting its permeability. Upon reaching the brain LPS, by activating Toll-like receptors (TLRs) found on microglia, leads to the production of pro-inflammatory cytokines, in particular IL-1, IL-6, and tumour necrosis factor alpha (TNF-α). In this way, it contributes to the development of neuroinflammation [40].

In rat studies, LPS injected into the fourth ventricle of the brain induced inflammation and increased Aβ fibrillogenesis [41]. Another trial confirmed that even a single intraperitoneal injection of LPS in rats caused an increase in TNF-α and IL-18 in specific brain areas, with elevated levels persisting for up to 10 months after injection [42]. The importance of LPS in the development of AD is supported by studies that have shown an accumulation of LPS in the hippocampus and the superior temporal cortex of people with AD [43].

Another metabolite produced by gut bacteria and implicated in the development of neuroinflammation is trimethylamine (TMA), which is formed from dietary products containing methylamine and then converted to trimethylamine N-oxide (TMAO) in the liver. TMAO that reaches the brain can activate microglial cells, which increase the production of inflammatory cytokines [44].

Some of the bacterial metabolites, such as SCFAs, reduce inflammation in the brain. By weakening the ability of microglia to capture antigens, they reduce the production of pro-inflammatory cytokines. They also contribute to the inhibition of nuclear factor kappa B (NF-κB)-dependent pathways, thereby counteracting LPS-induced microglial induction. However, microbial dysbiosis limits the formation of SCFAs, limiting their beneficial effects [45].

Another important factor that can influence neuroinflammation is the vagus nerve which provides a two-way connection between the gut and the brain. The gut

Table 1. Treatments aimed at improving gut microbiota in AD [46]

Dietary therapy	Probiotics	Prebiotics	Synbiotics	FMT	TCM	Others
MD	SLAB51	FOS	Complementary synbiotic	From healthy donor	Huang-Lian-Jie-Du decotion	Antibiotics
High fibre, high	Lab4b	MOS	Synergistic synbiotic		Nano-Honokiol	GV-971
fermentation diet	*L. plantarum*	PUFAs			Patchouli alcohol	
Ketogenic diet	*S. boulardii*	Inulin			Icarin	
MMKD	*B. longum*	XOS				

AD – Alzheimer disease; FMT – faecal microbiota transplantation; TCM – traditional Chinese medicine MD – Mediterranean diet; MMKD – modified Mediterranean-ketogenic diet; FOS – fructooligosaccharides; MOS – mannan oligosaccharides; PUFAs – polyunsaturated fatty acids; XOS – xylooligosaccharides.

microbiota, through the production of neurotransmitters, such as dopamine, serotonin, and GABA, influence signals from the vagus nerve, the activation of which can modulate the levels of inflammatory factors in the brain. However, the exact mechanism of this process is unknown [38].

Although a growing body of research confirms the influence of the gut microbiota on the development of neuroinflammation, the exact mechanism of this process remains to be fully elucidated. There is a need for additional research that would provide a better understanding of the processes taking place.

Potential therapeutic strategies for AD targeting the gut microbiome. The exact role of the gut microbiome in AD pathogenesis is uncertain. However, there is growing evidence that treatments targetting the microbiome can significantly reduce the symptoms of AD. Potential treatment options that target intestinal microbiota are shown in Table 1 [46].

Diet. Studies suggest that dietary habits and gut microbiota may delay or prevent the course of AD. The Mediterranean diet (MD), rich in vegetables, fruits, legumes, and grains, plays a role in AD prevention and may reduce the risk of AD morbidity. Implementation of MD was linked to increase in beneficial microbial species, including *Bacteroides*, and anti-inflammatory metabolites. Consequently, reduction of gut inflammation resulted in neuroinflammation decrease and neurocognitive function enhancement. Moreover, a positive correlation was found between carbohydrate consumption and cerebral amyloid-beta protein load in 26% of participants with AD [3] (footnote added?). These findings imply that nutrition is a modifiable risk factor that can influence amyloid deposition in the brain, which links glucose metabolism to AD pathogenesis. Increased intake of vitamin B6, vitamin B12 and folic acid, while limiting a high fat diet, and saturated fatty acids (SFAs) may be favourable in AD patients [3].

Probiotics and prebiotics. Probiotics are known as live non-pathogenic bacteria and yeast, which consumed in proper amounts provide beneficial nutrients and help sustain a healthy gut microbiome. They affect human health by interactions with intestinal epithelial cells, the immune system and gut microbiota. In AD, probiotics control the inflammatory process and inhibit the precursor of oxidative stress. Moreover, they probably help reduce cognitive impairment during the course of the disease [47].

In animal models, strains including *Bifidobacterium longum* A1 and *Lactobacillus helveticus* Shirota efficiently prevented AD [3] (footnote added?). Additionally, a study by Leblhuber et al. showed that increased consumption of strains such as *Bifidobacterium*, *L. acidophilus*, *L. helveticus*, and fermented milk products enhanced gut microbiota diversity and Mini–Mental State Examination (MMSE) scores. On the contrary, another study revealed that the intake of two different probiotics did not substantially alter AD patients' cognitive performance or associated inflammatory markers. Hence, although there is some evidence that probiotics can improve cognitive function, further research is needed to demonstrate their therapeutic effectiveness [3].

Prebiotics, indigestible dietary fibres, serve as substrates for fermentation by intestinal bacteria. The products of this process, short-chain fatty acids (SCFAs), stimulate the immune system by promoting T-cell differentiation. Commonly used prebiotics in AD treatment include fructooligosaccharides (FOS) and mannan oligosaccharides (MOS), as well as substances derived from yacon, inulin, vegetables, herbs, and plants. According to recent studies, xylooligosaccharides (XOS) have a significant impact on the gut microbiota composition and alleviating AD symptoms [3, 47].

Liu et al. found that an 8-week treatment with MOS in 5xFAD transgenic AD mice model considerably improved cognitive abilities and spatial memory, while also reducing anxiety and compulsive behaviours [48] (footnote added?). MOS effectively counteracted LPS leakage and intestinal barrier damage, improved gut microbiota composition, and reduced inflammation [48]. Synbiotics, a mix of probiotics and prebiotics, enhance the viability and function of beneficial bacteria in the gastrointestinal tract [47].

Faecal microbiota transplantation (FMT). FMT involves the transplantation of gut microbiota from a healthy donor to rectify dysbiosis in patients in order to normalize its composition. In AD patients, FMT increases the level of Bacteroidetes and raises the number of Bacteroides species [3]. Dominant gut microbiome may lower pro-inflammatory cytokines, APP expression, and Aβ plaque deposition in the hippocampus, therefore re-establishing the balance of gut microbes [49].

An AD patient undergoing FMT from a healthy 47-year-old woman indicated substantial enhancements in cognitive function, reflected as both higher clinical dementia evaluation scores and MMSE scores [3]. Nonetheless, its clinical implementation remains problematic because of approval among recipients and donors, variability in immune response mechanisms, and the impact of lifestyle variables on gut microbiota composition. More research should be undertaken to address this method more thoroughly [3].

Others. Antibiotics and antiviral medicines are being investigated as possible therapeutics due to the fact that infection with pathogens, such as adenovirus, herpes simplex virus type 1, Chlamydia pneumonia, or Porphyromonas gingivalis, have been linked with AD onset. Moreover, antibiotics can be used not only to treat bacterial infections, but also to regulate the gut microbiome. By preventing excessive microglial activation and decreasing Aβ plaque

formation, antibiotics have an indirect effect on central nervous system pathology [49].

At present, antibiotics are used in preclinical experiments to assess the role of microbiota in AD. They are rarely applied in clinical settings due to their potential to disturb gut microbiology and eliminate beneficial microorganisms.

A new drug, the sodium oligomannate – GV-971 has shown efficacy in AD treatment [46]. Its effects include changing gut microbiota, blocking phenylalanine and isoleucine accumulation, reducing neuroinflammation, and reversing cognitive dysfunction.

Another AD treatment option is traditional Chinese medicine (TCM) which, based on a series of trials, proved to be helpful by altering the gut-brain axis and slowing its development [46]. Fan et al. found that administering Huang-Lian-Jie-Du decoction orally to a high fat diet-induced AD mice model for six months resulted in improved cognitive performance, reduced Aβ deposition in the brain, and altered gut microbiota [50]. In addition, TCM showed neuroprotective effects, improved neuroinflammatory and oxidative stress indicators, and regulated peripheral blood bile acids and SCFAs levels [50]. Studies have also shown that Danggui Shaoyao San enhanced cognition and learning abilities in AD rats by decreasing harmful gut bacteria and improving gut-brain metabolite interactions [46] (footnote added?). Yet currently, only preclinical research has been carried out on the function of TCM in the gut-brain axis and its impact on AD development [46].

CONCLUSIONS

Expanding the evidence base highlights the significant role of the gut microbiome in the development and treatment of AD. Alterations in the composition of microbiota can influence neuroinflammation, amyloid-beta accumulation, and cognitive function, opening up new therapeutic possibilities. MD, MMKD and ketogenic diets have shown beneficial effects on gut microbiota, promoting anti-inflammatory pathways and improving cognitive abilities. Probiotics, prebiotics, and FMT represent promising approaches that may modulate the gut-brain communication and support brain function.

Despite these promising results, further clinical studies are needed to precisely identify which specific microorganisms and metabolites are responsible for these changes. The use of gut microbiota as a therapeutic target for AD requires further validation in terms of both effectiveness and long-term safety. Research is also needed to optimize dietary and supplementation interventions that could support AD treatment.

Emerging therapeutic strategies that target the gut microbiome may offer an alternative or complementary approach to traditional AD treatments, providing a less invasive option with the potential to improve patients quality of life.

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