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Insights into Emerging Trends of Gut Dysbiosis in Alzheimer's Disease: Exploring Potential of Pre and Probiotics

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Abstract: First discovered by Alois Alzheimer in 1906, Alzheimer's disease (AD) is the most common cause of dementia. It is characterized by memory loss, gradual cognitive decline, and neuroinflammation linked to tau protein tangles and β-amyloid plaque buildup. Effective treatment is still difficult despite the fact that there are many ideas that attempt to explain its complex genesis, such as cholinergic, amyloid, tau propagation, neurovascular, mitochondrial, inflammatory, and gut microbiota dysbiosis theories. Recent research identifies the gut microbiota–brain axis (GMBA) as a key modulator of AD pathogenesis, affecting amyloid-β metabolism through microbial metabolites and neurotransmitters, neuroinflammatory responses, and blood–brain barrier integrity. Microbes in the gut create short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, which are essential for immunological modulation, metabolic control, and neuronal function. Neurodegeneration is linked to gut microbial imbalance, which is disrupted by dysbiosis. Probiotics, prebiotics, dietary changes, and fecal microbiota transplantation all target the GMBA, which presents a potential approach to managing AD and merits more research to prove causality and therapeutic efficacy.

Keywords: Alzheimer's disease, gut microbiota, brain health and illness, dysbiosis, prebiotics, probiotics.

INTRODUCTION

Alzheimer's disease (AD) is primarily linked to various factors, resulting in changes to both brain function and behavior, for instance cognitive decline and memory loss. Alois Alzheimer, a psychiatrist and neuropathologist, initially identified AD in 1906. He presented his findings at the 37th Meeting of South-West German Psychiatrists, which were based on observations of plaques and neurofibrillary tangles in the brain histology of a patient experiencing memory loss, aggression, confusion, and paranoia. Soon afterwards, the illness associated with Alzheimer was officially named "Alzheimer's disease" by his associate, Emil Kraepelin [1]. Currently, Alzheimer's disease is the leading cause of dementia, impacting 5.8 million individuals in the US. It is forecast that Alzheimer's disease cases in the United States will increase to 13.8 million by the year 2050 [2]. The pathological characteristics of AD are marked by the gradual accumulation of beta-amyloid (Aβ) plaques and tangles of overly phosphorylated tau neurofibrils, resulting in

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neuroinflammation and continuous cognitive deterioration [3]. Dysfunction of synapses, persistent activation of the immune system and traumatic events impacting on brain leads to disrupt central immune homeostasis and hasten disease progression through substantial neuronal loss in the hippocampus [4].

Despite significant research efforts to understand the pathogenesis of the disease, the cause-and-effect relationships of the complex biological processes involved in Alzheimer's disease are not yet fully understood.Although, several hypothesis have been put forward to explain the Etiopathogenesis of AD; these includes- Cholinergic hypothesis [5], Amyloid hypothesis [6,7], Tau propagation hypothesis [8,9,10], Neurovascular hypothesis [11,12], Gut microbiota dysbiosis hypothesis, Inflammatory hypothesis [13,14], Metal ion hypothesis [15], Lymphatic system hypothesis [16,17] and Mitochondrial cascade and related hypothesis [18-20]. Researchers have been working to develop various therapeutic strategies to combat AD, which have been formulated to understand the causes of AD pathogenesis and progression. These strategies describe that AD is a complex and multifaceted disease, and therefore, different therapeutic options have been proposed. Many of these options have failed in clinical trials and have not been found to produce significant benefits, which highlights the need for further research and development of more effective treatments [21-23]. The inability to fully comprehend the illness makes it difficult to create successful treatments, highlighting the necessity of a thorough and multifaceted strategy to address it. Reliable and consistent biomarkers are still a ways off from being used practically in clinical settings, despite the fact that early disease identification is frequently seen as essential for intervention in its early phases [24, 25].

Varied population of microorganisms, known as the gut microbiota, including bacteria, fungi, and viruses, inhabit the gastrointestinal tract. This microbial balance is disrupted by dysbiosis, which has been connected to a number of neurological conditions. Multiple routes, including peripheral neurotransmitters, microbial metabolites, and immunological signalling molecules, may be involved in gut–brain communication, according to emerging data [26]. There is mounting evidence that gut dysbiosis is regularly seen in animal models and AD patients, highlighting its possible involvement in the development and course of the illness. According to mechanistic studies, the gut microbiota may affect AD pathology through a number of interrelated pathways, such as the generation of neuroactive metabolites, changes in systemic and neuroinflammatory responses, control of the integrity of the blood–brain barrier, and impacts on the aggregation and clearance of amyloid-β. The idea that altering the microbiome may help control AD is supported by early therapeutic strategies such dietary changes, fecal microbiota transplantation, probiotics, and prebiotics. However, the study of the microbiota–gut–brain axis is still in its early stages, with significant obstacles such as inter-individual variation in microbiome profiles, a lack of conclusive evidence, and an inadequate comprehension of the interactions between microbial metabolites and their hosts. In order to prove causation and make it possible to logically develop clinically successful microbiome-based treatments for AD, these gaps must be filled [27]. A potential therapeutic target for conditions affecting the central nervous system, like Alzheimer's disease, the gut microbiota brain axis (GMBA) has gained prominence in biomedical research in recent years [28-30].

Establishment & Composition of GM:

The complex ecology known as the gut microbiota serves as a home for a wide variety of microorganisms that have mutually beneficial interactions with their human host. In addition to offering many benefits and resistance to the development of new species, the gut microbiome is made up of a variety of bacteria that maintain a mutually beneficial relationship with the host. The recolonization of dangerous bacteria could result from an imbalance in this intricate ecosystem, which could then cause inflammatory reactions and the emergence of various diseases [31]. The gut microbiota plays a crucial role in maintaining a state of balance within the human intestine [32]. This substance offers numerous effects including defense against pathogens, carbohydrate breakdown and control of fat storage, the production of vital vitamins, and the regulation of the immune response, signifying an environmental factor of great significance in human homeostasis [33]. GM plays a significant role in several metabolic processes through the fermentation of undigested carbohydrates and the production of short-chain fatty acids (SCFAs), with a range of beneficial systemic impacts [34]. The three most commonly produced SCFAs are acetate, propionate, and butyrate [35]. These substances may regulate hepatic processes such as lipogenesis and cholesterol production, according to evidence. While butyrate is mostly utilized by the gastrointestinal mucosa as an energy source, propionate is engaged in gluconeogenesis in the liver, and acetate is the SCFA with the highest concentration in plasma and has been connected to low plasma insulin levels [36]. Furthermore, the gut microbiota promotes the creation of ketone bodies and carbon dioxide, and also helps regulate energy balance by stimulating the intestinal enteroendocrine cells [36-38]. In addition to its metabolic roles, the gut microbiome helps prevent the establishment of pathogenic microorganisms. Process entails creation

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of bacteriocins or antimicrobial peptides [39]. As a result, there is a competition for nutrients, which in turn stimulates innate immunity through the secretion of IgA and the activation of Toll-like receptors (TLR) [40, 41]. These compounds are able to detect molecular patterns found in microorganisms that consist of bacterial-derived lipopolysaccharides (LPS), lipoproteins, flagellin, and DNA from pathogens [34].

Intestinal microbiota's immunomodulatory activity plays a role in its interaction with the immune system, influencing both the activation of innate immunity and the maturation and subsequent refinement of adaptive immunity [42, 43]. The intestinal microbiota's activity at the neurological level is of utmost importance and is achieved through a two-way communication process between the gut and the brain via the Gut-Brain axis (GBA) [44]. GM influences the enteric nervous system by regulating the synthesis, release, and degradation of neurotransmitters and neurotrophic factors, preserving the sensory barrier, adjusting enteric sensory signals, producing bacterial byproducts, and controlling mucosal immunity [34-45]. Phycological relationship was observed as a connection between mood disorders and an imbalance of gut bacteria [46]. Effect is primarily attributed to neurotransmitters viz., serotonin and dopamine, which are produce by native GM, influencing brain alertness, mood regulation, memory, and learning process [45, 47].

Effectiveness of intestinal microbiota activities largely hinges on its composition, which evolves with age through various life stages. Microbiota development commences during gestation and concurrently advances alongside the host, performing the essential roles required for homeostasis preservation as illustrated in (Table -1).

Table 1: Common species of gut microbiota and effects of their metabolites on the central nervous system

Gut microbiota	Metabolites	Effects on the central nervous system function	Ref.
Lactobacillus, Bifidobacterium	Gamma-aminobutyric acid (GABA)	The primary inhibitory neurotransmitter is responsible for controlling mood, behavioural and cognitive processes.	(49)
Bifidobacterium infantis, Streptococcus, Escherichia, Enterococcus, Lactococcus, Lactobacillus,)	Candida Serotonin (5-HT	Neurotransmitters, control emotional responses.	(50)
Escherichia, Bacillus, Lactococcus, Lactobacillus, Streptococcus	Dopamine	Regulate both mental and physical activities, including cognitive functions like learning and memory.	(50)
Lactobacillus, Bacillus	Acetylcholine	Cognitive, memory, social interaction, self-care capacity, and emotional well-being.	(51)
Bacteroides, Bifidobacterium, Propionibacterium, Eubacterium, Lactobacillus, Clostridium, Roseburia, Prevotella	Short-chain fatty acids (SCFA)	Enhance the blood-brain barrier's permeability reduction, stimulate the production and release of neurotransmitters.	(52)
Lactococcus, Lactobacillus, Streptococcus, Enterococcus	Histamine	Manage sleep patterns and cognitive functions.	(53) (54)

Additionally, the human gastrointestinal tract is a hospitable environment that is home to more than 100 trillion microbes, thereby classifying the microbiome as the body's largest "virtual organ." This, in turn, affects and regulates the host's overall fitness, appearance, and well-being [48]. As a result, significant efforts have been focused on countering the impact of intestinal dysbiosis in neurodegenerative disease.

Gut -Brain Axis:

Through microbial–metabolite, immunological, endocrine, and neurological pathways, the "gut–brain axis" is a two-way communication system that connects the central nervous system and the gastrointestinal tract. It affects behavior, emotions, and thought processes in addition to coordinating intestinal processes including

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motility and secretion. Intestinal permeability modulation, enteroendocrine hormone secretion, immunological activation with cytokine release, vagal and enteric nervous system signalling, and microbial synthesis of neuroactive metabolites such short-chain fatty acids are important pathways. A disturbance of this intricately regulated network leads to neuroinflammation, barrier dysfunction, and altered neurotransmission—processes that are becoming more and more linked to neurodegenerative diseases like Alzheimer's [55]. Within this communication network, the brain influences gut movement, sensory, and secretion processes, while signals from the gut in turn impact brain function [56]. Maintaining gut homeostasis relies heavily on this relationship, which has also been linked to the development of various metabolic and mental health issues, including psychiatric and neurological disorders [57, 58].

Different routes of communication between the gut microbiota and the brain have been proposed:

- The vagus nerve serves as the primary modulatory pathway, with its influence exerted through both incoming and outgoing branches [59, 60].
- Through the production of metabolites and bioactive peptides, including short-chain fatty acids, as well as the regulation of neurotransmitters, like serotonin and acetylcholine, the gut microbiota affects the host [59-61].
- The HPA system releases cortisol in response to stress, which can affect intestinal motility, health, and mucus production. Ultimately, this can lead to changes in the gut microbiota's composition. By altering the levels of stress hormones, this alteration may have an impact on the central nervous system. [61].
- The immune response is mediated through the release of pro-inflammatory cytokines and chemokines [62].
- Immunity plays a critical role in this process. Specifically, toll-like receptors (TLRs) and peptidoglycans (PGNs) act as sensors of microbial components, mediating the immune response towards microbes [63, 64].

Local immune activation can, through various pathways, result in immune activation in different organs, including the brain [65]. This low-grade immune activation has been linked to the underlying causes of certain forms of depression and neurodegenerative disorders, including AD and Parkinson's disease (PD) [59]. The intricate relationship between various factors is not unexpected, considering that the gut–brain axis is directly or indirectly linked to neuropsychiatric illnesses, with the gut microbiota serving as a primary component of this communication [66].

Gut dysbiosis & AD

The role of gut microbiota and GMBA in AD is of utmost importance. GM plays a crucial role in overall health and function of the brain, and alterations in the GM have been linked to various neurological disorders, including AD. GMBA, a member of the gut microbiota, has been shown to have a significant impact on the development and progression of AD [67]. Gut bacteria composition has a dramatic impact on any age-related neurological disorder. External factors such as diet, lifestyle, and pro-inflammatory insults, as well as internal components including genetic variations, the immune system, metabolites, and hormones, significantly impact the makeup of the gut microbiome, which subsequently produces signalling compounds viz., SCFAs, tryptophan, choline, and hormones (including ghrelin, leptin) in the gastrointestinal tract capable of regulating central nervous system functions [68]. Aging has a significant impact on the composition of GM, which tends to favor the development of pro-inflammatory bacteria. These include *Bacillus fragilis, Faecalibacteriumprausnitzii, Eubacterium rectale, Eubacterium hallii,* and *Bacteroides fragilis*. Local and systemic inflammation come from the reduction of anti-inflammatory bacterial numbers. This inflammation damages the blood-brain barrier (BBB) and increases the permeability of the gastrointestinal system. A compromised blood-brain barrier encourages neuroinflammation.

According to research by Cattaneo et al., patients with amyloid-positive illnesses have more pro-inflammatory microorganisms than healthy individuals [69]. Although infection with *Salmonella enterica* or *Candida albicans* enhanced susceptibility to subsequent infections in transgenic mice expressing mutant human APP and in Caenorhabditis elegans models harboring human Aβ42, these animals outlived wild-type controls with prolonged survival. Aβ's antibacterial qualities are responsible for this contradiction, as its heparin-binding motif makes it easier for it to interact with the glycosylated parts of microbial cell walls. By promoting microbial agglutination and disrupting pathogen adherence to host cells, this binding helps the host defend against infection even if the host is generally more susceptible [70]. Bacteria-derived amyloids have been identified as potential causative factors for Aβ peptide aggregation in AD. Specifically, amyloids produced by certain bacteria, such as curli from *E. coli*, TasA from *Bacillus subtilis*, CsgA from *S. Typhimurium*, FapC from *Pseudomonas fluorescens*, and phenol soluble modulins from *Staphylococcus aureus*, have been shown to contribute to the development of Alzheimer's disease pathology by promoting the formation of Aβ oligomers and fibrils [71].

Amyloids originating from bacteria, other factors are involved in the onset and progression of Alzheimer's disease. The administration of lipopolysaccharides (LPS) from bacteria to experimental animals in the fourth ventricle of

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the brain resulted in a symptom profile that closely resembled Alzheimer's disease [72]. Even the injection of LPS in mice leads to an increase in Aβ levels in the hippocampal area, resulting in cognitive defects. This supports the role of LPS in the formation of amyloid fibrils [73,74]. Upon being in use, LPS has been discovered to initiate the TLR4 pathway, causing immune cells to produce pro-inflammatory cytokines and IgM/IgA, leading to an intensification of systemic inflammation [75-78]. From this viewpoint, gut inflammation could be a reason why AD develops. The connection between the GM's composition, inflammation, additional neuroinflammation, and the onset of AD, is a key point of contention in understanding the causes of Alzheimer's disease. Several investigations have found pathogens in the brain tissue of patients who died from AD [79-82].

Among the viruses and bacteria that have been linked to AD are herpes simplex virus type 1 and various bacterial species, including *Chlamydophila pneumoniae, Borrelia burgdorferi*, and other spirochetes [83-85]. Evidence also indicates a substantial rise in levels of *Helicobacter pylori*-specific IgG antibodies in both the cerebrospinal fluid and the serum of individuals with AD [86]. New therapeutic strategies may be developed by exploring the key function of specific gut microbiota compositions associated with AD, in an effort to increase the presence of beneficial microorganisms, while also modifying both dietary habits and lifestyle, which could help to prevent the progression of AD as shown in **(Figure 1)** [87-89].

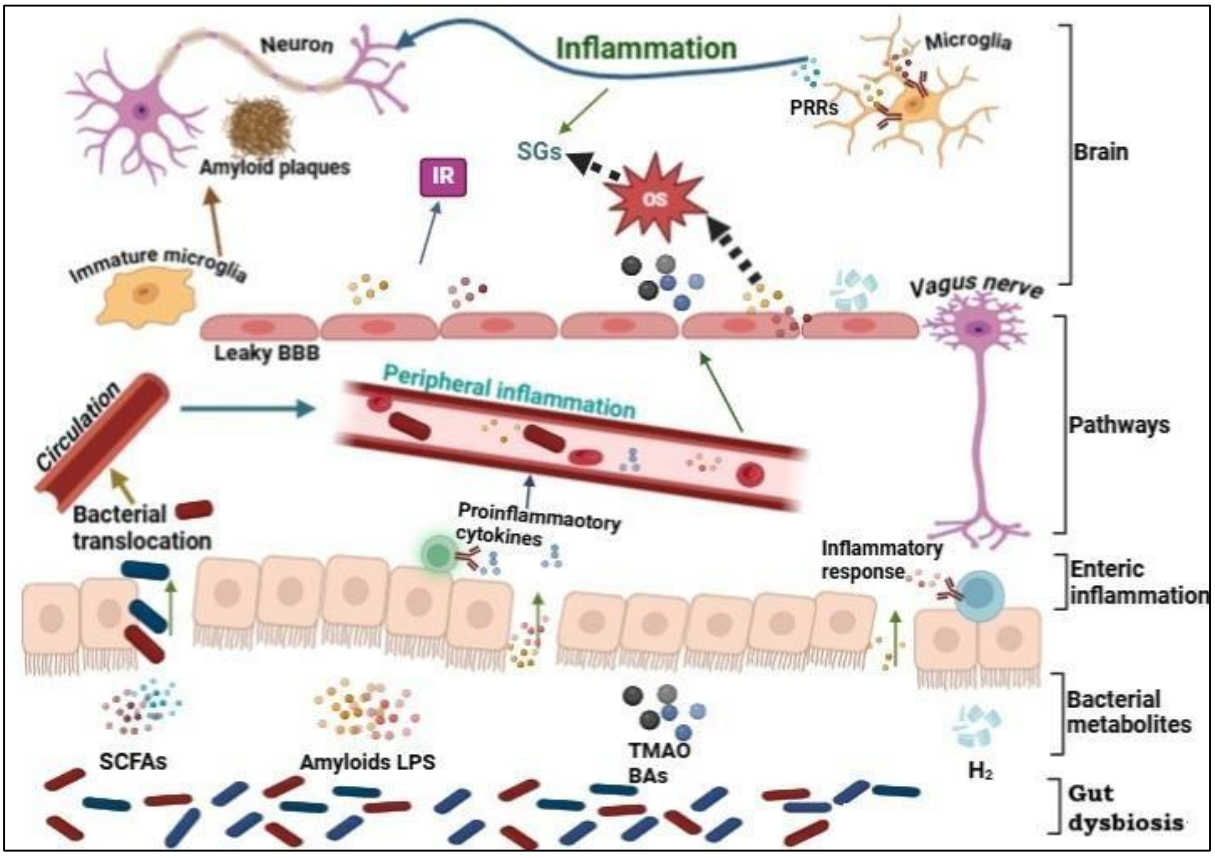

Figure 1: Depicts the effects of an imbalance in the gut microbiome in AD. Gut dysbiosis results in a decrease of beneficial compounds, including SCFAs and H2, and an increase of harmful compounds, such as amyloids and Trimethylamine N-oxide (TMAO), which leads to increased permeability of the intestinal mucosal barrier and BBB, activation of peripheral immune responses, and elevated levels of peripheral and central oxidative stress. The progression of AD pathology is furthered by gut dysbiosis, which leads to enhanced amyloid plaque formation, increased neuroinflammation, SGs, and IR.

Probiotics and Prebiotics as a Potential treatment strategy for AD:

Probiotics:

First used in 1974, the term "probiotics" today refers to "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." Immune response modulation, stress protection, pathogen colonization inhibition, and intestinal epithelial barrier function augmentation are some of their positive benefits. In models of neurodegenerative diseases, probiotic supplementation has been demonstrated to improve spatial memory, lower the load of amyloid plaque in the hippocampus, and restore synaptic plasticity and long-term potentiation in rats treated with Aβ [90-93]. These effects are partially mediated by the brain's inhibition of NF-κB

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signaling that is dependent on TLR4 and RIG-I. There isn't much clinical data, but one randomized study found that probiotics helped AD patients' cognitive performance and lipids and malondialdehyde levels, two plasma indicators. Although these results point to the therapeutic potential of probiotics in halting or reducing the course of AD, there is currently not enough clinical evidence to support their routine usage in AD care [94-95].

The exact mechanism by which probiotics display effects in AD remains unclear. According to 16s rRNA sequencing, supplementation with probiotics in humans did not appear to alter the types of bacteria in the intestinal flora, yet it did cause the benefits of probiotics to manifest on behaviour by temporarily modifying the state of gene expression in the collective microbiome, a phenomenon that was later validated in germ-free mice and identical twins [96]. Therefore, metatranscriptomic and metabolomic technologies are needed to assess the effects of probiotic intervention on gut microbiota in the host. Although probiotics have been widely promoted among the general public, many probiotic strains and formulations have yielded contradictory clinical results [91]. More attention should be paid to the adverse effects of probiotics. These include: - Systemic infection, GI side effects, Gene transfer from probiotics to normal microbiota, Harmful metabolic effects of probiotics, Immune system stimulation and other potential negative consequences [97]. However, future probiotic treatments for Alzheimer's disease necessitate the creation of methods to overcome colonization resistance [91].

Prebiotics:

The existing definition of prebiotics is "a substrate that selectively benefits from being used by the host's micro-organisms and can lead to a reduction in cognitive impairments and decreased Aβ deposition in the brains of animals with Alzheimer's disease" [98]. Prebiotics are non-digestible organic compounds, specifically short-chain carbohydrates that can selectively promote the growth and/or activity of one or a small set of beneficial gut bacteria [99]. The gut microbiota serves as a source of food, which in turn triggers the production of short-chain fatty acids (SCFAs), ultimately impacting both gastrointestinal and extra intestinal functions [100]. A body of research is indicating their potential usefulness as additional therapy options for various neurological and psychiatric disorders, including anxiety, depression, and Parkinson's disease [101]. Current research into AD prevention and treatment is also exploring the potential benefits of prebiotics, yielding encouraging outcomes [99,101-110]. Yeast beta glucans administration to mouse models of Alzheimer's disease (AD) has been shown to be effective in several ways. It helps to re-establish a balance between pro-inflammatory and anti-inflammatory gut microbiome species. This balance is crucial for the production of short-chain fatty acids (SCFAs), which in turn limits neuroinflammation and insulin resistance [102]. Reduced neuroinflammation and improved short-term memory and cognitive ability in mice that resembled features of Alzheimer's disease were also reported after pre-treatment with lactulose and melibiose, two trehalose analogues. This improvement may be attributed to enhanced autophagy function [104]. Furthermore, 5xFAD mice that were fed a diet supplemented with mannan oligosaccharide for eight weeks were able to promote the growth of Lactobacillus species and reduce the abundance of Helicobacter. This resulted in a decrease in LPS leakage and helped to prevent dysfunctions in the intestinal epithelial barrier and the blood-brain barrier. This prebiotic-driven reshaping of the gut microbiota was accompanied by several notable effects, including reduced Aβ accumulation in various brain regions such as the cortex, hippocampus, and amygdala, reestablishment of redox homeostasis, and increased levels of butyrate [105]. Comparable outcomes were achieved in both rat and mouse models of Alzheimer's disease through the oral administration of oligosaccharides derived from Marinda officinalis, which resulted in enhanced memory and learning capabilities, as well as reduced plaque formation, oxidative stress, and overall inflammation [109-110].

The exact mechanism by which the aforementioned prebiotics work is still unclear, but their ability to maintain a diverse and stable gut microbiota may underlie these observed benefits [102, 107, 109]. Recent studies support this hypothesis by indicating that the combination of probiotics and prebiotics, often referred to as synbiotics, appears to be more beneficial than prebiotics alone in promoting neurogenesis and decreasing both local and systemic inflammation, with its effects being more pronounced [107]. Findings from a large, multi-ethnic longitudinal study involving 1837 elderly individuals without signs of neurodegeneration have demonstrated that regular consumption of fructan, a well-established prebiotic, decreases the likelihood of developing AD, supporting previous research conducted in mice [106]. Despite the study's comprehensive normalization for factors such as age, gender, recruitment time, ethnicity, daily caloric intake, education, and APOE genotype, other authors argue that the evidence supporting the use of prebiotics in clinical practice remains insufficient [108]. These data collectively imply that prebiotics could be beneficial as a preventative or supplementary treatment for AD, but further human clinical trials are required to form a definitive conclusion illustrated in **(Table 2)**.

Table 2: Effects of probiotics/prebiotics on AD

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SR.NO.	GUT MICROBIOTA[Probiotics/Prebiotics]	MODEL	FINDING	Ref.
1.	*Collinsella*	PRS mode [PRSice-2 software]	Previous research has linked certain microorganisms to neuroinflammatory processes within the MGBA, whereas protective species such as Gordonibacter are understood to produce metabolites that foster gut and brain well-being.	111
2.	C rodentium	female germ-free Swiss Webster mice[Study design C57BL/6 mice were]	Observations in this study showed a decrease in BDNF levels within the hippocampi of mice infected with C rodentium, implying that an enteric bacterial infection can negatively affect memory by decreasing hippocampal BDNF.	112
3.	a Lactobacillus, L. rhamnosus	BALB/c mice	The administration led to a decrease in both anxiety and stress response, accompanied by alterations in central gamma-aminobutyric acid (GABA) receptors expression.	113
4.	*Bifidobacterium infantis*, 552 *Lactobacillus rhamnosus* strain R0011 (95%) and 553 *L. helveticus* strain R0052 (5%), *L. rhamnosus* (JB-1), 554 and *Lactobacillus farciminis*	RAT MODEL	An imbalance has developed between the 565 pro-inflammatory and anti-inflammatory responses, with the entire immune system now predominantly shifting 566 toward inflammation. This shift is characterised by a significant 567 increase in the release of pro-inflammatory cytokines and a corresponding 568 decrease in the release of anti-inflammatory cytokines, leading to 569 further exacerbation of the inflammation.	114
5.	*L. acidophilus, Bifidobacterium langum*, and *L. case*	CLINICAL TRAIL	In individuals who are overweight, levels of inflammatory cytokines have decreased.	115
6.	*Erysipelatoclostridium*	AD model mice (i.e., APP/PS1 mice),	Erysipelatoclostridium plays a crucial role in the development of AD, acting as microorganisms associated with inflammation.54 In mice with AD, they act as a central bacterial taxon, significantly contributing to the synthesis of DCA in the gut.	116
7.	Dubosiella	wild-type (WT) mice	Dubosiella exhibits anti-aging effects in AD mice by enhancing the bacterial genus, which includes reducing oxidative stress, improving endothelial function, and modifying the GM.	116
8	Gram-negative bacilli, and *Escherichia coli* (E. coli)	Drosophila as a Model	Researchers led by Zhan et al. discovered that fragments from Escherichia coli (E. coli) and lipopolysaccharide, a compound produced by certain bacteria, were found together in areas of the brain known as A plaques in deceased Alzheimer's disease (AD) patients. Additionally, lipopolysaccharide was found in the brain's perivascular areas, which suggests that the breakdown of the blood-brain barrier due to microbial activity may be contributing to the neurodegeneration seen in AD.Reports suggest that systemic inflammation and gut permeability are significant factors in the development of Alzheimer's disease.	117
9.		Mouse model	Research utilizing mouse models has shown the effects of gut microbiota on amyloid-beta accumulation, neuroinflammation, and cognitive	118

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			deterioration. Evidence from these results suggests a link between the gut microbiome and the development of dementia.	
10.	*C. butyricum*	AD animal models	Butyricum triggers the release of GLP-1, which safeguards the BBB, possibly through the regulation of tight junctions. Similarly, C. butyricum has been shown to prevent brain endothelial barrier dysfunction, as indicated by reduced brain water content and the reinstatement of normal tight junction protein levels.	119
11.	*Lactobacillus plantarum* MTCC 1325	3-month-old male albino rats (Wistar strain)	The following effects have been observed: 1. Improved spatial memory. 2. Enhanced gross behavioral activity. 3. The formation of hyperchromatic nuclear chromatin in the cytoplasm. 4. An increased level of acetylcholine (Ach) in the hippocampus and cerebral cortex. 5. A decreased level of amyloid plaques and neurofibrillary tangles (NFT) in the hippocampus and cerebral cortex.	120
12.	*Lactobacillus acidophilus, Bifidobacterium bifidum* and *Bifidobacterium longum*	Adult normal reared male Wistar rats	The provided data lists several benefits associated with a particular treatment or intervention. These benefits include: 1. Improved spatial learning and memory. 2. Restoration of synaptic plasticity in the brain's hippocampus. 3. Prevention of the accumulation of Aβ peptide in the brain's hippocampus. 4. Decrease in malondialdehyde (MDA) levels in the brain. 5. Increase in total antioxidant capacity in the plasma.	121
13.	SLAB51	3xTg-AD mice	The analysis of brain homogenates revealed several key findings: 1. A decrease in p53 levels was observed. 2. An increase in RARβ levels was detected. 3. Elevated levels of antioxidant enzymes were found, including: - Glutathione S-transferase (GST) - Glutathione peroxidase (GPx) - Superoxide dismutase (SOD) - Catalase (CAT) 4. A decrease in poly-ADP ribose polymerase (PARP) levels was observed. 5. A decrease in 8-Oxoguanine glycosylase (OGG1) levels was detected in the brain.	122
14.	*SLAB51 (Streptococcus thermophilus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii* subsp. *bulgaricus* and *Lactobacillus brevis)*	8-week-old male 3xTg-AD mice	There are several key findings related to glucose and insulin signaling in the brain: 1. Increased levels of glucose transporter 3 (GLUT3) and glucose transporter 1 (GLUT1) were observed in the hippocampal CA1 region. 2. Reduced levels of phosphorylated tau protein were found in the brain, which may indicate a decrease in tau aggregation. 3. Elevated levels of HbA1c, a marker of long-term glucose control, were detected in the plasma. 4. Increased expression of the insulin-like growth factor-I receptor (IGF-IRβ) was observed in the brain.	123
15.	*Lactobacillus plantarum, Lactobacillus delbrueckii subsp. Bulgaricu, Lactobacillus paracasei, Lactobacillus acidophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis* and *Streptococcus salivarius*	6–8-month-old female AppNL−G−F and C57BL/6 (wild type	The provided data suggests several key findings related to the effects of a particular treatment or intervention. These findings include: 1. Elevated levels of short chain fatty acids (SCFAs) in the brain's hippocampus, specifically: - Acetate - Butyrate - Lactate 2. Increased levels of SCFAs in the serum, including: - Propionate - Isobutyrate 3. Enhanced c-fos immunoreactivity	124

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	subspecies, *thermophilus*		in the brain, which is indicative of increased neuronal activity. 4. Reduced anxiety-like behavior in individuals undergoing this treatment or intervention.	
16.	*Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Bifidobacterium longum*	Male Sprague-Dawley rats	The following effects have been observed: 1. Enhanced spatial learning and memory capabilities. 2. An increase in the amplitude of field excitatory postsynaptic potentials (fEPSPs) within the hippocampus. 3. An increase in long-term potentiation in the CA1 region of the hippocampus. 4. Reduced paired-pulse facilitation in neurons. 5. Lower levels of nitric oxide in the serum.	125
17.	*Lactobacillus reuteri*, *Lactobacillus rhamnosus* and *Bifidobacterium infantis*	Male Wistar rats	The following effects have been observed: 1. Improved spatial learning and memory. 2. Reduced accumulation of Aβ (amyloid-beta) in the hippocampus. 3. Lower levels of MDA (malondialdehyde), a marker of oxidative stress, in the brain. 4. Increased levels of SOD (superoxide dismutase), an antioxidant enzyme, in brain homogenates. 5. Decreased levels of IL-1β (interleukin-1 beta) and α-TNF (tumor necrosis factor-alpha) in hippocampal tissue.	126
18.	Bifidobacterium breve strain A1	10-week-old male ddY mice	The effects of the treatment on cognitive function and related biological markers include: 1. Enhanced spatial learning and memory capabilities. 2. Elevated plasma acetate levels. 3. Reduced expression of genes induced by amyloid beta (Aβ) in the hippocampus. 4. Prevention of cognitive dysfunction caused by amyloid beta (Aβ).	127
19.	*Lactobacillus acidophilus* 1688FL431-16LA02, *Lactobacillus fermentum* ME3, *Bifidobacterium lactis* 1195SL609-16BS01 and *Bifidobacterium longum* 1152SL593-16BL03	8-week-old male Wistar rats	The following effects have been observed: 1. Enhanced memory and spatial learning abilities. 2. An increase in superoxide dismutase (SOD) levels in hippocampal tissue. 3. A decrease in malondialdehyde (MDA) levels in the hippocampus. 4. A reduction in the number and size of amyloid-beta (Aβ) plaques in the brain.	128
20.	*Lactobacillus rhamnosus* UBLR-58	Female Swiss albino mice	Observations in Brain Tissue: 1. Decreased MDA level: MDA (Malondialdehyde) is a marker of lipid peroxidation, which is a process that can lead to cell damage. A decrease in MDA level suggests a reduction in oxidative stress in the brain. 2. Increased SOD level: SOD (Superoxide Dismutase) is an enzyme that helps to neutralize superoxide radicals, which are a type of free radical that can cause cell damage. An increase in SOD level indicates an enhanced ability to counteract oxidative stress in the brain. 3. Increased GPx level: GPx (Glutathione Peroxidase) is an enzyme that helps to reduce oxidative stress by neutralizing hydrogen peroxide and other peroxides. An increase in GPx level suggests an improved ability to mitigate oxidative damage in the brain. 4. Increased CAT level: CAT (Catalase) is an enzyme that helps to break down hydrogen peroxide into water and oxygen, thereby reducing oxidative stress. An increase in CAT level indicates an enhanced ability to neutralize	129

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			hydrogen peroxide in the brain. 5. Reduced amyloid plaques deposition: Amyloid plaques are abnormal protein deposits that are associated with neurodegenerative diseases such as Alzheimer's. A reduction in amyloid plaques deposition suggests a decrease in the progression of neurodegenerative disease in the brain.	
21.	*Bacillus subtilis* NCIB3610 and *Escherichia coli* OP50	Not relevent	The provided data appears to describe several potential benefits of a particular treatment or intervention. These benefits include: 1. Improved cognitive function 2. Reduced expression of Aβ peptides 3. Relief from behavioral deficits 4. Enhanced chemotactic response	130
22.	*Bifidobacterium longum*, *Lactobacillus acidophilus lysates*, vitamins A, vitamin D, omega 3 fatty acids in cod liver oil, vitamins B1, B3, B6, B9, B12, and Interval treadmill running	Male APP/PS1 transgenic mice (B6C3-Tg(APPswe, PSEN1dE9) 85Dbo/Mmjax; APP/PS1TG)	Observations Indicative of Potential Neuroprotective Effects: 1. Increased exploratory activity 2. Reduced Aβ plaques in the hippocampus 3. Increased microglia in the brain 4. Elevated OGG1 levels in the brain 5. Increased presence of Lactobacillus reuteri in the gut 6. Enhanced cognitive performance	131
23.	*Bifidobacterium longum*, *Lactobacillus acidophilus lysates*, vitamins A, vitamin D, omega 3 fatty acids in cod liver oil, vitamins B1, B3, B6, B9, B12, and Interval treadmill running	3-month-old, male APP/PS1 transgenic mice (B6C3-Tg (APPswe, PSEN1dE9) 85Dbo/Mmjax; APP/PS1TG) and six wild types	Observations of Oxidative Stress Markers: 1. Elevated levels of Superoxide Dismutase (SOD) were found in the hippocampus. 2. An increase in the concentration of Nuclear Factor-Erythroid Factor 2-Related Factor 2 (NRF-2) was observed in the liver. 3. A higher level of 8-oxodG, a marker of oxidative DNA damage, was detected in the hippocampus.	132
24.	*Lactobacillus helveticus* IDCC3801	Male Sprague Dawley rats and ICR mice	The following effects have been observed: 1. An increase in memory and cognitive function. 2. A decrease in the activity of β-secretase in the brain. 3. A decrease in the amount of intracellular APPβ. 4. An increase in the amount of intracellular APPα. 5. A decrease in the production of Aβ40 in the brain.	133
25.	*Lactobacillus Pentosus* and *Lactobacillus plantarum* C29.	Male ICR mice	Research has shown several key effects of a particular treatment or intervention: 1. Enhanced spatial learning and memory capabilities. 2. Elevated levels of cAMP response element-binding protein (CREB) in the hippocampus. 3. Increased activation of brain-derived neurotrophic factor (BDNF) in the hippocampus.	134
26.	*Lactobacillus casei, Lactobacillus plantarum, Lactobacillus salivarius, Lactobacillus acidophilus, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium bifidum, Bifidobacterium*	male and female 3xTg mice	The study revealed several key findings related to cognitive function and neurodegeneration. These include: 1. Enhanced spatial learning and memory capabilities. 2. Reduced levels of Aβ40 and Aβ42 peptides in the hippocampus. 3. Decreased levels of amyloid and tau proteins in	135

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	infantis, Bifidobacterium longum, and *Bifidobacterium breve*		the basal forebrain and frontal cortices. 4. Lower expression of the microglial marker arginase 1 (ARG1) in the brain.	
27.	Prebiotic mannan oligosaccharide	5XFADmice	There is a reduction observed in cognitive deficits, amyloid plaques, oxidative stress, and microglial activation, accompanied by changes in the gut microbiome.	136
28.	Prebiotic R13		TrkB receptor kinase blocked the pro-inflammatory pathway in the gut, resulting in decreased amyloid production and oxidative stress.	137
29.	prebiotic sodium oligo-mannate (GV-971)		The goal is to improve mental faculties and manage mild to moderate Alzheimer's disease. Studies indicate that GV-971 has the potential to counteract cognitive decline by correcting gut imbalances; reducing brain inflammation; and crossing the blood-brain barrier to directly interact with Aβ, preventing the formation of Aβ fibrils.	138

CONCLUSION

Our knowledge of health, illness, and the creation of innovative biotherapeutics has significantly increased as a result of research on the human microbiota. Considerable advancements have been made in the identification and characterization of particular probiotic strains and prebiotics, as well as in the validation of their possible health benefits. Despite these developments, there is still mistrust in the medical world, mostly because of the shortcomings of recent studies. Variability in illness models frequently affects results, and there are still few large-scale, randomized, controlled clinical trials that support the purported advantages of probiotics and prebiotics. Live probiotic cells' ability to survive and operate is further hampered by the harsh circumstances of the gastrointestinal track. Although it is frequently challenging to demonstrate their specificity, prebiotics get around this problem by preventing enzymatic breakdown and favorably encouraging the growth of good gut microorganisms. Microencapsulation of probiotics is one of the newer techniques that optimizes delivery selectivity and cell viability throughout gastrointestinal transit. Future approaches are probably going to combine prebiotics (synbiotics) and microencapsulated probiotics, which will have synergistic effects. Creating physiologically appropriate models to investigate host-microbiota interactions and designing targeted delivery systems that guarantee effectiveness and repeatability in clinical settings are two of the major challenges that lie ahead.

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REFERENCES:

1. V.I. Gavrilov. Acta Virol. 1975 Nov;19(6):510.
2. Durbin RP. Letter: Acid secretion by gastric mucous membrane. Am J Physiol. 1975 Dec;229(6):1726.
3. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004 Aug 5;430(7000):631-9.
4. Ashraf GM, Tarasov VV, Makhmutova A, Chubarev VN, Avila-Rodriguez M, Bachurin SO, Aliev G. The possibility of an infectious etiology of Alzheimer disease. Molecular neurobiology. 2019 Jun;56:4479-91.
5. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. The Lancet. 1976 Dec 25;308(8000):1403.
6. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron. 1991 Apr 1;6(4):487-98.
7. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends in pharmacological sciences. 1991 Jan 1;12:383-8.
8. Braak H, Braak E. Evolution of the neuropathology of Alzheimer's disease. Acta Neurologica Scandinavica. 1996 Apr;94(S165):3-12.
9. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer?. European archives of psychiatry and clinical neuroscience. 1999 Dec;249:S14-22.
10. Nukina N, Ihara Y. One of the antigenic determinants of paired helical filaments is related to tau protein. The Journal of Biochemistry. 1986 May 1;99(5):1541-4.
11. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008 Jan 24;57(2):178-201.
12. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. Neuron. 2010 Jul 29;67(2):181-98.

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13. Bagyinszky E, Van Giau V, Shim K, Suk K, An SS, Kim S. Role of inflammatory molecules in the Alzheimer's disease progression and diagnosis. Journal of the neurological sciences. 2017 May 15;376:242-54.
14. Latta CH, Brothers HM, Wilcock DM. Neuroinflammation in Alzheimer's disease; A source of heterogeneity and target for personalized therapy. Neuroscience. 2015 Aug 27;302:103-11.
15. Qian X, Xu Z. Fluorescence imaging of metal ions implicated in diseases. Chemical Society Reviews. 2015;44(14):4487-93.
16. Tammela T, Petrova TV, Alitalo K. Molecular lymphangiogenesis: new players. Trends in cell biology. 2005 Aug 1;15(8):434-41.
17. Zhao Z, Sagare AP, Ma Q, Halliday MR, Kong P, Kisler K, Winkler EA, Ramanathan A, Kanekiyo T, Bu G, Owens NC. Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. Nature neuroscience. 2015 Jul;18(7):978-87.
18. Matilainen O, Quirós PM, Auwerx J. Mitochondria and epigenetics–crosstalk in homeostasis and stress. Trends in cell biology. 2017 Jun 1;27(6):453-63.
19. Mastroeni D, McKee A, Grover A, Rogers J, Coleman PD. Epigenetic differences in cortical neurons from a pair of monozygotic twins discordant for Alzheimer's disease. PloS one. 2009 Aug 12;4(8):e6617.
20. Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, Rogers J. Epigenetic changes in Alzheimer's disease: decrements in DNA methylation. Neurobiology of aging. 2010 Dec 1;31(12):2025-37.
21. Oxford AE, Stewart ES, Rohn TT. Clinical trials in Alzheimer's disease: a hurdle in the path of remedy. International Journal of Alzheimer's Disease. 2020;2020(1):5380346.
22. Yaari R, Hake A. Alzheimer's disease clinical trials: past failures and future opportunities.
23. Rosenblum WI. Why Alzheimer trials fail: removing soluble oligomeric beta amyloid is essential, inconsistent, and difficult. Neurobiology of aging. 2014 May 1;35(5):969-74.
24. Ausó E, Gómez-Vicente V, Esquiva G. Biomarkers for Alzheimer's disease early diagnosis. Journal of Personalized Medicine. 2020 Sep;10(3):114.
25. Rasmussen J, Langerman H. Alzheimer's disease–why we need early diagnosis. Degenerative neurological and neuromuscular disease. 2019 Dec 24:123-30.
26. Evenepoel P, Poesen R, Meijers B. The gut–kidney axis. Pediatric Nephrology. 2017 Nov;32:2005-14.
27. Mosterd CM, Kanbay M, Van Den Born BJ, Van Raalte DH, Rampanelli E. Intestinal microbiota and diabetic kidney diseases: the role of microbiota and derived metabolites inmodulation of renal inflammation and disease progression. Best Practice & Research Clinical Endocrinology & Metabolism. 2021 May 1;35(3):101484.
28. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE. The microbiota-gut-brain axis. Physiological reviews. 2019 Aug 28.
29. Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, Kim DK, Kim HJ, Choi H, Hyun DW, Lee JY. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut. 2020 Feb 1;69(2):283-94.
30. Long-Smith C, O'Riordan KJ, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota-gut-brain axis: new therapeutic opportunities. Annual review of pharmacology and toxicology. 2020 Jan 6;60(1):477-502.
31. Gibson MK, Pesesky MW, Dantas G. The yin and yang of bacterial resilience in the human gut microbiota. Journal of molecular biology. 2014 Nov 25;426(23):3866-76.
32. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012 Mar 16;148(6):1258-70.
33. Martínez I, Muller CE, Walter J. Long-term temporal analysis of the human fecal microbiota revealed a stable core of dominant bacterial species. PloS one. 2013 Jul 16;8(7):e69621.
34. Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cellular and Molecular Life Sciences. 2019 Feb 15;76:473-93.
35. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. Applied and environmental microbiology. 2007 Feb 15;73(4):1073-8.
36. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut microbes. 2016 May 3;7(3):189-200.
37. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, Pettersson S. Host-gut microbiota metabolic interactions. Science. 2012 Jun 8;336(6086):1262-7.
38. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nature reviews immunology. 2016 Jun;16(6):341-52.
39. Iimura M, Gallo RL, Hase K, Miyamoto Y, Eckmann L, Kagnoff MF. Cathelicidin mediates innate intestinal defense against colonization with epithelial adherent bacterial pathogens. The journal of immunology. 2005 Apr

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15;174(8):4901-7.
40. Kau AL, Planer JD, Liu J, Rao S, Yatsunenko T, Trehan I, Manary MJ, Liu TC, Stappenbeck TS, Maleta KM, Ashorn P. Functional characterization of IgA-targeted bacterial taxa from undernourished Malawian children that produce diet-dependent enteropathy. Science translational medicine. 2015 Feb 25;7(276):276ra24-.
41. Wu W, Sun M, Chen F, Cao AT, Liu H, Zhao Y, Huang X, Xiao Y, Yao S, Zhao Q, Liu Z. Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43. Mucosal immunology. 2017 Jul 1;10(4):946-56.
42. Perez-Cano FJ, Gonzalez-Castro A, Castellote C, Franch A, Castell M. Influence of breast milk polyamines on suckling rat immune system maturation. Developmental & Comparative Immunology. 2010 Feb 1;34(2):210-8.
43. Odenwald MA, Turner JR. The intestinal epithelial barrier: a therapeutic target?. Nature reviews Gastroenterology & hepatology. 2017 Jan;14(1):9-21.
44. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology. 2015 Apr;28(2):203.
45. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PW. Psychobiotics and the manipulation of bacteria–gut–brain signals. Trends in neurosciences. 2016 Nov 1;39(11):763-81.
46. Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, Zeng L, Chen J, Fan S, Du X, Zhang X. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Molecular psychiatry. 2016 Jun;21(6):786-96.
47. Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, Neher JJ, Fåk F, Jucker M, Lasser T, Bolmont T. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Scientific reports. 2017 Feb 8;7(1):41802.
48. Bercik P, Collins SM, Verdu EF. Microbes and the gut-brain axis. Neurogastroenterology & Motility. 2012 May;24(5):405-13.
49. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. Journal of applied microbiology. 2012 Aug 1;113(2):411-7.
50. Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis. Microbial endocrinology: the microbiota-gut-brain axis in health and disease. 2014 Jun 9:195-219.
51. Kawashima K, Misawa H, Moriwaki Y, Fujii YX, Fujii T, Horiuchi Y, Yamada T, Imanaka T, Kamekura M. Ubiquitous expression of acetylcholine and its biological functions in life forms without nervous systems. Life sciences. 2007 May 30;80(24-25):2206-9.
52. Russell WR, Hoyles L, Flint HJ, Dumas ME. Colonic bacterial metabolites and human health. Current opinion in microbiology. 2013 Jun 1;16(3):246-54.
53. Landete JM, De Las Rivas B, Marcobal A, Munoz R. Updated molecular knowledge about histamine biosynthesis by bacteria. Critical reviews in food science and nutrition. 2008 Aug 25;48(8):697-714.
54. Thomas CM, Hong T, Van Pijkeren JP, Hemarajata P, Trinh DV, Hu W, Britton RA, Kalkum M, Versalovic J. Histamine derived from probiotic Lactobacillus reuteri suppresses TNF via modulation of PKA and ERK signaling. PloS one. 2012 Feb 22;7(2):e31951.
55. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology. 2015 Apr;28(2):203.
56. Kaur G, Behl T, Bungau S, Kumar A, Uddin MS, Mehta V, Zengin G, Mathew B, Shah MA, Arora S. Dysregulation of the gut-brain axis, dysbiosis and influence of numerous factors on gut microbiota associated Parkinson's disease. Current Neuropharmacology. 2021 Feb 1;19(2):233-47.
57. Wang HX, Wang YP. Gut microbiota-brain axis. Chinese medical journal. 2016 Oct 5;129(19):2373-80.
58. Pascale A, Marchesi N, Govoni S, Barbieri A. Targeting the microbiota in pharmacology of psychiatric disorders. Pharmacological Research. 2020 Jul 1;157:104856.
59. Margolis KG, Cryan JF, Mayer EA. The microbiota-gut-brain axis: from motility to mood. Gastroenterology. 2021 Apr 1;160(5):1486-501.
60. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences. 2011 Sep 20;108(38):16050-5.
61. Heijtz RD, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, Hibberd ML, Forssberg H, Pettersson S. Normal gut microbiota modulates brain development and behavior. Proceedings of the National Academy of Sciences. 2011 Feb 15;108(7):3047-52.
62. Rea K, Dinan TG, Cryan JF. The microbiome: A key regulator of stress and

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neuroinflammation. Neurobiology of stress. 2016 Oct 1;4:23-33.
63. Dichter GS, Damiano CA, Allen JA. Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: animal models and clinical findings. Journal of neurodevelopmental disorders. 2012 Dec;4:1-43.
64. Banks WA, Erickson MA. The blood–brain barrier and immune function and dysfunction. Neurobiology of disease. 2010 Jan 1;37(1):26-32.
65. Silver J, Schwab ME, Popovich PG. Central nervous system regenerative failure: role of oligodendrocytes, astrocytes, and microglia. Cold Spring Harbor perspectives in biology. 2015 Mar 1;7(3):a020602.
66. Kim YK, Shin C. The microbiota-gut-brain axis in neuropsychiatric disorders: pathophysiological mechanisms and novel treatments. Current neuropharmacology. 2018 Jun 1;16(5):559-73.
67. Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. Science China Life Sciences. 2016 Oct;59:1006-23.
68. Mancuso C, Santangelo R. Alzheimer's disease and gut microbiota modifications: the long way between preclinical studies and clinical evidence. Pharmacological research. 2018 Mar 1;129:329-36.
69. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, Bianchetti A. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiology of aging. 2017 Jan 1;49:60-8.
70. Kumar DK, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE, Moir RD. Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Science translational medicine. 2016 May 25;8(340):340ra72-.
71. Kesika P, Suganthy N, Sivamaruthi BS, Chaiyasut C. Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. Life sciences. 2021 Jan 1;264:118627.
72. Hauss-Wegrzyniak B, Vraniak PD, Wenk GL. LPS-induced neuroinflammatory effects do not recover with time. Neuroreport. 2000 Jun 5;11(8):1759-63.
73. Kahn MS, Kranjac D, Alonzo CA, Haase JH, Cedillos RO, McLinden KA, Boehm GW, Chumley MJ. Prolonged elevation in hippocampal Aβ and cognitive deficits following repeated endotoxin exposure in the mouse. Behavioural brain research. 2012 Apr 1;229(1):176-84.
74. Asti A, Gioglio L. Can a bacterial endotoxin be a key factor in the kinetics of amyloid fibril formation?. Journal of Alzheimer's disease. 2014 Jan 7;39(1):169-79.
75. Lucas K, Maes M. Role of the Toll Like receptor (TLR) radical cycle in chronic inflammation: possible treatments targeting the TLR4 pathway. Molecular neurobiology. 2013 Aug;48(1):190-204.
76. Mohammad S, Thiemermann C. Role of metabolic endotoxemia in systemic inflammation and potential interventions. Frontiers in immunology. 2021 Jan 11;11:594150.
77. Maes M, Twisk FN, Kubera M, Ringel K, Leunis JC, Geffard M. Increased IgA responses to the LPS of commensal bacteria is associated with inflammation and activation of cell-mediated immunity in chronic fatigue syndrome. Journal of affective disorders. 2012 Feb 1;136(3):909-17.
78. Maes M, Mihaylova I, Leunis JC. Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut–intestinal permeability. Journal of affective disorders. 2007 Apr 1;99(1-3):237-40.
79. Frost B, Diamond MI. Prion-like mechanisms in neurodegenerative diseases. Nature Reviews Neuroscience. 2010 Mar;11(3):155-9.
80. Emery DC, Shoemark DK, Batstone TE, Waterfall CM, Coghill JA, Cerajewska TL, Davies M, West NX, Allen SJ. 16S rRNA next generation sequencing analysis shows bacteria in Alzheimer's post-mortem brain. Frontiers in aging neuroscience. 2017 Jun 20;9:261413.
81. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer's disease brain tissue. Journal of Alzheimer's Disease. 2013 Aug 5;36(4):665-77.
82. Zhao Y, Jaber V, Lukiw WJ. Secretory products of the human GI tract microbiome and their potential impact on Alzheimer's disease (AD): detection of lipopolysaccharide (LPS) in AD hippocampus. Frontiers in cellular and infection microbiology. 2017 Jul 11;7:318.
83. Hammond CJ, Hallock LR, Howanski RJ, Appelt DM, Little CS, Balin BJ. Immunohistological detection of Chlamydia pneumoniae in the Alzheimer's disease brain. BMC neuroscience. 2010 Dec;11:1-2.
84. Miklossy J. Bacterial amyloid and DNA are important constituents of senile plaques: further evidence of the spirochetal and biofilm nature of senile plaques. Journal of Alzheimer's Disease. 2016 Aug 8;53(4):1459-73.
85. Carter C. Alzheimer′ s Disease: APP, Gamma Secretase, APOE, CLU, CR1, PICALM,

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ABCA7, BIN1, CD2AP, CD33, EPHA1, and MS4A2, and Their Relationships with Herpes Simplex, C. Pneumoniae, Other Suspect Pathogens, and the Immune System. International Journal of Alzheimer's Disease. 2011;2011(1):501862.
86. Kountouras J, Boziki M, Gavalas E, Zavos C, Deretzi G, Grigoriadis N, Tsolaki M, Chatzopoulos D, Katsinelos P, Tzilves D, Zabouri A. Increased cerebrospinal fluid Helicobacter pylori antibody in Alzheimer's disease. International Journal of Neuroscience. 2009 Jan 1;119(6):765-77.
87. Shabbir U, Arshad MS, Sameen A, Oh DH. Crosstalk between gut and brain in Alzheimer's disease: the role of gut microbiota modulation strategies. Nutrients. 2021 Feb 21;13(2):690.
88. Goyal D, Ali SA, Singh RK. Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2021 Mar 2;106:110112.
89. Zhu F, Li C, Chu F, Tian X, Zhu J. Target dysbiosis of gut microbes as a future therapeutic manipulation in Alzheimer's disease. Frontiers in aging neuroscience. 2020 Oct 6;12:544235.
90. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, Scott K, Stanton C, Swanson KS, Cani PD, Verbeke K. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature reviews Gastroenterology & hepatology. 2017 Aug;14(8):491-502.
91. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nature medicine. 2019 May;25(5):716-29.
92. Asl ZR, Sepehri G, Salami M. Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. Behavioural brain research. 2019 Dec 30;376:112183.
93. Abraham D, Feher J, Scuderi GL, Szabo D, Dobolyi A, Cservenak M, Juhasz J, Ligeti B, Pongor S, Gomez-Cabrera MC, Vina J. Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: role of microbiome. Experimental gerontology. 2019 Jan 1;115:122-31.
94. Yang X, Yu D, Xue L, Li H, Du J. Probiotics modulate the microbiota–gut–brain axis and improve memory deficits in aged SAMP8 mice. Acta Pharmaceutica Sinica B. 2020 Mar 1;10(3):475-87.
95. Leblhuber F, Egger M, Schuetz B, Fuchs D. Commentary: effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Frontiers in Aging Neuroscience. 2018 Mar 6;10:54.
96. McNulty NP, Yatsunenko T, Hsiao A, Faith JJ, Muegge BD, Goodman AL, Henrissat B, Oozeer R, Cools-Portier S, Gobert G, Chervaux C. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. Science translational medicine. 2011 Oct 26;3(106):106ra106-.
97. Sotoudegan F, Daniali M, Hassani S, Nikfar S, Abdollahi M. Reappraisal of probiotics' safety in human. Food and Chemical Toxicology. 2019 Jul 1;129:22-9.
98. Sun J, Xu J, Ling Y, Wang F, Gong T, Yang C, et al. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl Psychiatry. 2019 Aug 5;9(1):189.
99. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, Berenjian A, Ghasemi Y. Prebiotics: definition, types, sources, mechanisms, and clinical applications. Foods. 2019 Mar 9;8(3):92.
100. Den Besten G, Van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of lipid research. 2013 Sep 1;54(9):2325-40.
101. Rajanala K, Kumar N, Chamallamudi MR. Modulation of gut-brain axis by probiotics: a promising anti-depressant approach. Current Neuropharmacology. 2021 Jul 1;19(7):990-1006.
102. Xu M, Mo X, Huang H, Chen X, Liu H, Peng Z, Chen L, Rong S, Yang W, Xu S, Liu L. Yeast β-glucan alleviates cognitive deficit by regulating gut microbiota and metabolites in Aβ1–42-induced AD-like mice. International journal of biological macromolecules. 2020 Oct 15;161:258-70.
103. Varesi A, Pierella E, Romeo M, Piccini GB, Alfano C, Bjørklund G, Oppong A, Ricevuti G, Esposito C, Chirumbolo S, Pascale A. The potential role of gut microbiota in Alzheimer's disease: from diagnosis to treatment. Nutrients. 2022 Feb 5;14(3):668.
104. Lee YS, Lai DM, Huang HJ, Lee-Chen GJ, Chang CH, Hsieh-Li HM, Lee GC. Prebiotic lactulose ameliorates the cognitive deficit in Alzheimer's disease mouse model through macroautophagy and chaperone-mediated autophagy pathways. Journal of agricultural and food chemistry. 2021 Feb 22;69(8):2422-37.
105. Liu Q, Xi Y, Wang Q, Liu J, Li P, Meng X, Liu K, Chen W, Liu X, Liu Z. Mannan oligosaccharide attenuates cognitive and behavioral disorders in the 5xFAD Alzheimer's disease mouse model via regulating the gut

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microbiota-brain axis. Brain, Behavior, and Immunity. 2021 Jul 1;95:330-43.
106. Nishikawa M, Brickman AM, Manly JJ, Schupf N, Mayeux RP, Gu Y. Association of dietary prebiotic consumption with reduced risk of Alzheimer's disease in a multiethnic population. Current Alzheimer Research. 2021 Oct 1;18(12):984-92.
107. Deng SM, Chen CJ, Lin HL, Cheng IH. The beneficial effect of synbiotics consumption on Alzheimer's disease mouse model via reducing local and systemic inflammation. Iubmb Life. 2022 Aug;74(8):748-53.
108. Barbosa RS, Vieira-Coelho MA. Probiotics and prebiotics: focus on psychiatric disorders–a systematic review. Nutrition reviews. 2020 Jun 1;78(6):437-50.
109. Xin Y, Diling C, Jian Y, Ting L, Guoyan H, Hualun L, Xiaocui T, Guoxiao L, Ou S, Chaoqun Z, Jun Z. Effects of oligosaccharides from Morinda officinalis on gut microbiota and metabolome of APP/PS1 transgenic mice. Frontiers in Neurology. 2018 Jun 15;9:412.
110. Chen D, Yang X, Yang J, Lai G, Yong T, Tang X, Shuai O, Zhou G, Xie Y, Wu Q. Prebiotic effect of fructooligosaccharides from Morinda officinalis on Alzheimer's disease in rodent models by targeting the microbiota-gut-brain axis. Frontiers in aging neuroscience. 2017 Dec 8;9:403.
111. Cammann D, Lu Y, Cummings MJ, Zhang ML, Cue JM, Do J, Ebersole J, Chen X, Oh EC, Cummings JL, Chen J. Genetic correlations between Alzheimer's disease and gut microbiome genera. Scientific Reports. 2023 Mar 31;13(1):5258.
112. Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, MacQueen G, Sherman PM. Bacterial infection causes stress-induced memory dysfunction in mice. Gut. 2011 Mar 1;60(3):307-17.
113. Savignac HM, Tramullas M, Kiely B, Dinan TG, Cryan JF. Bifidobacteria modulate cognitive processes in an anxious mouse strain. Behavioural brain research. 2015 Jul 1;287:59-72.
114. Liang S, Wang T, Hu X, Luo J, Li W, Wu X, Duan Y, Jin F. Administration of Lactobacillus helveticus NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience. 2015 Dec 3;310:561-77.
115. Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA, Salami M. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. Frontiers in aging neuroscience. 2016 Nov 10;8:229544.
116. Chen Y, Li Y, Fan Y, Chen S, Chen L, Chen Y, Chen Y. Gut microbiota-driven metabolic alterations reveal gut–brain communication in Alzheimer's disease model mice. Gut Microbes. 2024 Dec 31;16(1):2302310.
117. Zhan X, Stamova B, Jin LW, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology. 2016 Nov 29;87(22):2324-32.
118. Filatov A. The Gut Microbiome: Unveiling its Potential Role in Dementia Risk. SVOA Neurology. 2023;4(6):195-7.
119. Stoeva MK, Garcia-So J, Justice N, Myers J, Tyagi S, Nemchek M, McMurdie PJ, Kolterman O, Eid J. Butyrate-producing human gut symbiont, Clostridium butyricum, and its role in health and disease. Gut microbes. 2021 Jan 1;13(1):1907272.
120. Nimgampalle M, Kuna Y. Anti-Alzheimer properties of probiotic, Lactobacillus plantarum MTCC 1325 in Alzheimer's disease induced albino rats. Journal of clinical and diagnostic research: JCDR. 2017 Aug 1;11(8):KC01.
121. Asl ZR, Sepehri G, Salami M. Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. Behavioural brain research. 2019 Dec 30;376:112183.
122. Bonfili L, Cecarini V, Cuccioloni M, Angeletti M, Berardi S, Scarpona S, Rossi G, Eleuteri AM. SLAB51 probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. Molecular Neurobiology. 2018 Oct;55:7987-8000.
123. Bonfili L, Cecarini V, Gogoi O, Berardi S, Scarpona S, Angeletti M, Rossi G, Eleuteri AM. Gut microbiota manipulation through probiotics oral administration restores glucose homeostasis in a mouse model of Alzheimer's disease. Neurobiology of Aging. 2020 Mar 1;87:35-43.
124. Kaur H, Golovko S, Golovko MY, Singh S, Darland DC, Combs CK. Effects of probiotic supplementation on short chain fatty acids in the App NL-GF mouse model of Alzheimer's disease. Journal of Alzheimer's Disease. 2020 Jan 1;76(3):1083-102.
125. Rezaeiasl Z, Salami M, Sepehri G. The effects of probiotic Lactobacillus and Bifidobacterium strains on memory and learning behavior, long-term potentiation (LTP), and some biochemical parameters in β-amyloid-induced rat's model of Alzheimer's disease. Preventive Nutrition and Food Science. 2019 Sep 30;24(3):265.
126. Mehrabadi S, Sadr SS. Assessment of probiotics mixture on memory function,

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inflammation markers, and oxidative stress in an Alzheimer's disease model of rats. Iranian biomedical journal. 2020 Feb 29;24(4):220.
127. Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, Kondo T, Abe K, Xiao JZ. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Scientific reports. 2017 Oct 18;7(1):13510.
128. Athari Nik Azm S, Djazayeri A, Safa M, Azami K, Ahmadvand B, Sabbaghziarani F, Sharifzadeh M, Vafa M. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β-amyloid (1–42) injected rats. Applied Physiology, Nutrition, and Metabolism. 2018;43(7):718-26.
129. Patel C, Pande S, Acharya S. Potentiation of anti-Alzheimer activity of curcumin by probiotic Lactobacillus rhamnosus UBLR-58 against scopolamine-induced memory impairment in mice. Naunyn-Schmiedeberg's Archives of Pharmacology. 2020 Oct;393(10):1955-62.
130. Cogliati S, Clementi V, Francisco M, Crespo C, Arganaraz F, Grau R. Bacillus subtilis delays neurodegeneration and behavioral impairment in the Alzheimer's disease model Caenorhabditis elegans. Journal of Alzheimer's Disease. 2020 Jan 1;73(3):1035-52.
131. Abraham D, Feher J, Scuderi GL, Szabo D, Dobolyi A, Cservenak M, Juhasz J, Ligeti B, Pongor S, Gomez-Cabrera MC, Vina J. Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: role of microbiome. Experimental gerontology. 2019 Jan 1;115:122-31.
132. Téglás T, Ábrahám D, Jókai M, Kondo S, Mohammadi R, Fehér J, Szabó D, Wilhelm M, Radák Z. Exercise combined with a probiotics treatment alters the microbiome, but moderately affects signalling pathways in the liver of male APP/PS1 transgenic mice. Biogerontology. 2020 Dec;21:807-15.
133. Yeon SW, You YS, Kwon HS, Yang EH, Ryu JS, Kang BH, Kang JH. Fermented milk of Lactobacillus helveticus IDCC3801 reduces beta-amyloid and attenuates memory deficit. Journal of Functional Foods. 2010 Apr 1;2(2):143-52.
134. Jung IH, Jung MA, Kim EJ, Han MJ, Kim DH. Lactobacillus pentosus var. plantarum C29 protects scopolamine-induced memory deficit in mice. Journal of applied microbiology. 2012 Dec 1;113(6):1498-506.
135. Wolf AB, Braden BB, Bimonte-Nelson H, Kusne Y, Young N, Engler-Chiurazzi E, Garcia AN, Walker DG, Moses GS, Tran H, LaFerla F. Broad-based nutritional supplementation in 3xTg mice corrects mitochondrial function and indicates sex-specificity in response to Alzheimer's disease intervention. Journal of Alzheimer's Disease. 2012 Jan 1;32(1):217-32.
136. Liu Q, Xi Y, Wang Q, Liu J, Li P, Meng X, Liu K, Chen W, Liu X, Liu Z. Mannan oligosaccharide attenuates cognitive and behavioral disorders in the 5xFAD Alzheimer's disease mouse model via regulating the gut microbiota-brain axis. Brain, Behavior, and Immunity. 2021 Jul 1;95:330-43.
137. Chen GF, Xu TH, Yan Y, Zhou YR, Jiang Y, Melcher K, Xu HE. Amyloid beta: structure, biology and structure-based therapeutic development. Acta pharmacologica sinica. 2017 Sep;38(9):1205-35.
138. Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, Xie Z, Chu X, Yang J, Wang H, Chang S. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell research. 2019 Oct;29(10):787-803.

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