Protective Roles of Probiotics against Alzheimer's Disease

Mariam Nasr Michael, Mohamed Sayed Ahmed Zamzam, Maher Nageb Ibrahim, Shimaa Elsayed hadhod

Medical Physiology Department, Faculty of Medicine - Zagazig University, Egypt
Corresponding author: Mariam Nasr Michael
E-mail: drmaro91@gmail.com, mariamnasr@medicine.zu.edu.eg
Conflict of interest: None declared.
Funding: No funding sources

Abstract

One of the leading causes of disability, death, and morbidity worldwide, Alzheimer's disease (AD) is a neurological disorder that worsens over time. There is an immediate and critical need to seek out fresh viewpoints due to the decades-long failure in medication discovery. Due to its strong associations with amyloids, systemic and focal inflammation, impairment of vascular homeostasis and gut barrier, mitochondrial dysfunction, etc., the gut microbiome (GM) has recently garnered a lot of attention in AD-related studies. The GM can communicate with the brain in both directions through the microbiome-gut-brain axis. As a result, probiotic supplementation, which regulates the GM, is a promising candidate for the treatment of AD. The goal of this article is to summarize the most recent findings on the efficacy of probiotics in the treatment and prevention of Alzheimer's disease, as well as the possible roles of genetic modification in the development of the disease.

Keywords: Probiotics, Alzheimer's Disease

Tob Regul Sci. ™ 2023 ;9(1): 8600-8614
DOI : doi.org/10.18001/TRS.9.1.609

Introduction

Cognitive impairment in one or more areas of cognition, such as learning, focus, memory, etc., typically coupled with behavioral and psychological abnormalities, is a hallmark of Alzheimer's disease (AD) [1]. From mild cognitive impairment (MCI) to dementia, there are various levels that can be categorized based on the severity of the condition [2]. As a result of its high rates of disability, mortality, and morbidity, AD has emerged as a major health concern and a major contributor to the worldwide financial burden [3]. Millions of older individuals are impacted by the increasing prevalence of AD, which reaches 23% in those over the age of 86 [4]. There is an immediate need for a more holistic view due to the fact that no medication has been able to significantly enhance the critical clinical outcomes of Alzheimer's disease (AD).

The gut microbiome (GM) is the collection of all the microbes and their DNA found in the gastrointestinal tract (GIT) [5]. Research has shown that GM is essential for maintaining homoeostasis and regulating the activities of nearly every major bodily system, including the CNS [6]. Over the last several decades, there has been a meteoric rise in studies investigating the role of GM in the aetiology of AD. Researchers are more optimistic about GM modification as a possible strategy to prevent or treat AD after discovering the microbiota-gut-brain axis, a communication link between GM and the brain [7]. As a result, probiotics, which are live bacteria that, when consumed in adequate quantities, can positively modify the GM, are now being considered as possible candidates for the therapy of Alzheimer's disease. Our current understanding of the gut microbiota's potential effects on Alzheimer's disease (AD) development and progression, as well as the potential protective functions of probiotics in this regard, is summarized in this article.

Gut microbiota and microbiota–gut–brain axis

The human gastrointestinal tract (GIT) is home to millions of genes and more than a thousand different kinds of microbes, such as viruses, helminth parasites, yeasts, single-celled eukaryotes, and bacteria [9]. Factors that can impact the genetic makeup of a population include things like age, nutrition, antibiotic exposure, stress, and the way a person is born, all of which can have an impact on the development of Alzheimer's disease [10]. The impact of genetic modification on human development and health has been the subject of an increasing amount of study. In addition to interacting with the human immune system through toll-like receptors (TLRs), GM can also participate in the immune system's maturation process [12], serve as a biological barrier to inhibit the invasion of aberrant microbiota [11], and so on. GMOs have been observed to influence microglia development and function [13,14]. Metabolic functions that GM may perform include modulating immune responses [16] and maintaining healthy levels of glucose and lipids [15]. Remarkably, the microbiota produces a number of significant metabolites, including neurotransmitters like dopamine, γ-aminobutyric acid (GABA), and serotonin (5-HT), as well as short-chain fatty acids (SCFAs), which have been linked to alterations in the host brain's activities [17,18].

The microbiome-gut-brain axis is a two-way street that connects the two systems via the vagus nerve, the enteric nervous system, the vascular system, and the immune system [19]. Abnormalities in behavior and emotion may result from changes in synaptic plasticity and transmission as well as changes in the concentration of different neurotransmitters (5-HT, dopamine, GABA, etc.) in germ-free (GF) mice that do not have GM [20]. Therefore, research on neurological illnesses, such as AD, has focused heavily on the axis.

Gut microbiota and AD

Pathological hallmarks of Alzheimer's disease (AD) include intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau and extracellular amyloid-β (Aβ) plaques [21]. Furthermore, it has been discovered that chronic neuroinflammation characterized by an overabundance of

proinflammatory cytokines and chemokines, hyperreactivity of astrocytes, and excessive microglial activation is a critical component of AD pathophysiology [22,23,24]. It has been found that neuroinflammation can both precede and impact the aggregation of Aβ and tau [13]. On the other hand, Aβ complexes have the ability to bind to pattern recognition receptors found in microglia and astrocytes, which can lead to dysregulation of neuroinflammation and the generation of reactive oxygen species (ROS), which in turn can cause the death of neurons and glial cells [22]. Additional factors that can raise the likelihood of developing AD include vascular risk factors, diabetes, atherosclerosis, and hypertension. Important early stages in the pathogenesis of Alzheimer's disease now include vascular lesions and dysfunction [25,26]. Clinical trials with medications targeting generally recognized chemicals, particularly Aβ, have failed because the cause and development of Alzheimer's disease are still not completely comprehended. Age, cerebrovascular risk factors, psychogenic illnesses [27], genetic mutations, and other variables all play a role in the development of Alzheimer's disease (AD).

The correlation between GM and AD is becoming stronger by the day. Both transgenic AD mice [28,29] and fecal samples from AD patients [6] have shown GM alterations. Research into the processes underlying this enlightening correlation may shed light on the development and treatment of Alzheimer's disease from many angles.

Gut microbiota and amyloid-related pathogenesis

Many different types of human GM, including Escherichia coli, Salmonella typhimurium, Bacillus subtilis, Staphylococcus aureus, Pseudomonas fluorescens, and others, are capable of secreting amyloids [30]. There are intricate connections between the immune system and amyloids created from genetic modification (GM) and humans. Despite differing amino acid sequences, microbial amyloids like CsgA still contain similar pathogen-associated molecular patterns (PAMPs). This means they could interact with the same Toll-like receptor (TLR2), leading to the production of IL-17A and IL-22, which are powerful inflammatory mediators, and ultimately activating the NF-κB signaling pathway and cyclooxygenase-2 (COX-2) [31,32,33]. Additionally, it has been discovered that bacterial amyloid proteins can cross-seed neuronal Aβ peptides, leading to their misfolding and aggregation [30,34,35]. Aβ has recently been shown to have antimicrobial properties and to be involved in the host immunological response to microorganisms via fibrillation, pathogen entrapment, and cell membrane disruption [36].

Gut microbiota dysbiosis and inflammation-driven pathogenesis

The role of GM in the development or worsening of AD may be explicable by the correlation between GM dysregulation and altered inflammatory states, according to mounting data. Changes in peripheral inflammation were associated with an upregulation of the proinflammatory taxon Escherichia coli and a downregulation of the anti-inflammatory taxon Escherichia rectale, according to research by Cattaneo et al. on GM taxa changes in patients with CI and brain amyloidosis [37]. Mice with

Alzheimer's disease (AD) and either the GF condition or prolonged antibiotic treatment show less insoluble amyloid plaques, less neuroinflammation, fewer microglia, and less astrocyte aggregation in the hippocampus [28,38,39].

An key mediator between GM dysbiosis and AD pathogenesis is lipopolysaccharide (LPS), which is found in the outer membrane of Gram-negative bacteria (Figure 1). By binding to CD14 and the TLR4-MD-2 complex on immune cells, it can set up powerful immunological responses. According to research [40-43], TLR4 has the ability to engage with TIRAP and MyD88, leading to the activation of NF-κB. NF-κB is a transcription factor that promotes inflammation and is recognized for initiating AD pathogenic pathways through the release of proinflammatory cytokines. An increase in blood monocyte/macrophage activation was positively associated with an increase in plasma LPS, according to research by Zhang et al. [44]. Additionally, AD patients had LPS found in their hippocampus and superior temporal lobe neocortex [45]. It was discovered that LPS and Aβ1-40/42 colocalize in amyloid plaques and the areas around blood vessels [46]. Amyloid standardised uptake value ratio absorption was favorably correlated with blood LPS levels, proinflammatory cytokine concentrations, and endothelial dysfunction, according to a study by Marizzoni et al. [47].

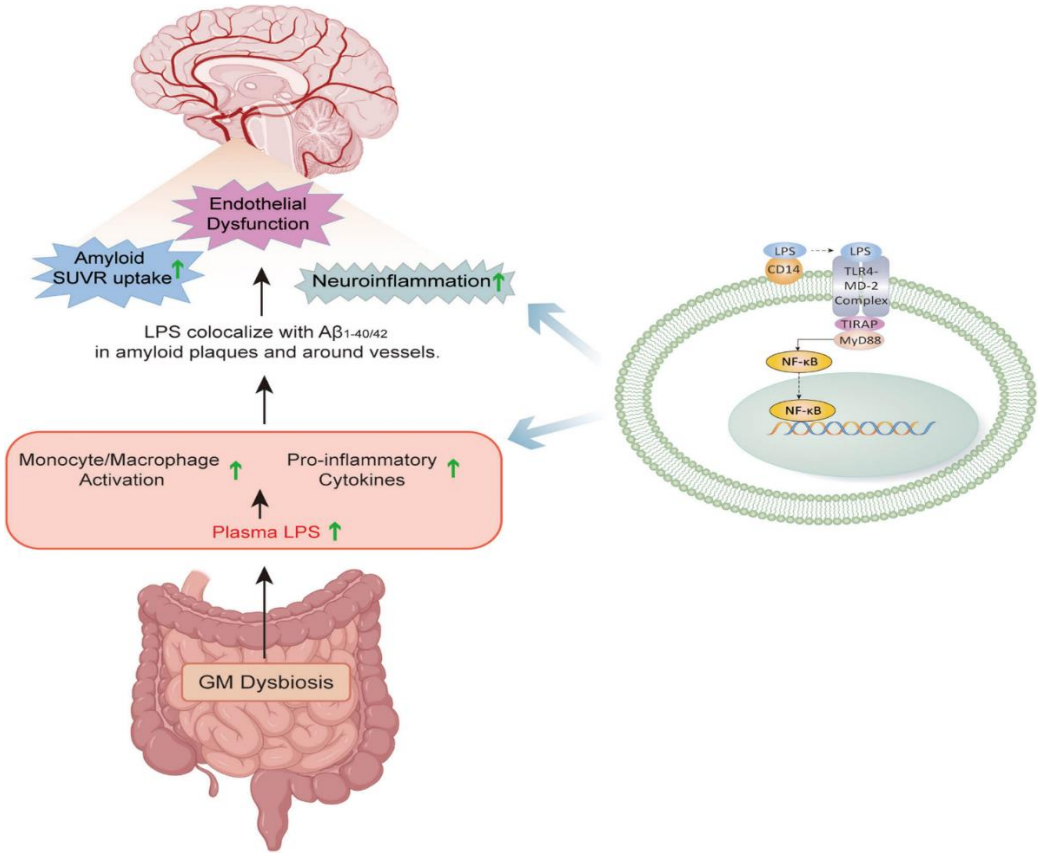

Figure 1: Proposed mechanism of LPS affecting the pathogenesis of AD. AD-related GM dysbiosis contributes to an increased level of plasma LPS, which promotes blood monocyte/macrophage activation and the secretion of pro-inflammatory cytokines mainly through NF-κB pathway. LPS can also cross the BBB, promote neuroinflammation and

colocalize with Aβ1-40/42 in amyloid plaques and around vessels in the brain, possibly affecting Aβ pathology and endothelial function.

Gut microbiota dysbiosis impairs vascular homeostasis and gut barrier

The importance of vascular homeostasis impairment in the etiology of Alzheimer's disease has long been recognized [25]. In addition, GM dysbiosis can impact the permeability of the gut epithelial barrier and the blood-brain barrier, both of which are critical for the invasion of GM and their metabolites into the brain [48]. Adult GF mice had their BBB permeability reduced and tight junction protein expression upregulated after receiving a transplant of fecal microbiota from pathogen-free mice [49]. There is a correlation between elevated proinflammatory GM and compromised gut barrier function, according to Engen et al. [50]. The BBB can be compromised by bacterial byproducts including amyloids and LPS, which cause long-term neuroinflammatory reactions [51]. Atherosclerosis, a prevalent risk factor for Alzheimer's disease, can develop as a result of GM dysbiosis because it affects levels of trimethylamine oxide, which control vascular microRNA [52].

Gut microbiota dysbiosis causes mitochondrial dysfunction

As a precursor to Alzheimer's disease, mitochondrial dysfunction can reduce energy metabolism and oxidative phosphorylation of important enzymes. Neuronal apoptosis and calcium homeostasis problems are also attributed to it [53]. A decline in PTEN-induced putative kinase 1 (PINK1) expression, aberrant brain metabolism, and diminished ATP production could be the outcome of an unbalanced mitochondrial/cellular antioxidant system [54,55]. The ability to supply energy to the host in aerobic and anaerobic environments is a result of the symbiotic interaction between mitochondrial metabolic diversity and primitive aerobic and anaerobic microorganisms. Mitochondrial failure, heightened oxidative stress, and an inflammatory response in the host may result from GM dysbiosis's altered bacterial composition and altered metabolite synthesis [56]. As a result, strategies that aim to avoid or lessen cognitive dysfunction by preventing mitochondrial failure and reducing oxidative stress have promise.

Other pathways

When it comes to learning and memory, glutamate is a big excitatory neurotransmitter [57]. Glutamate metabolism may be impacted by GM, according to recent research. GM includes Campylobacter jejuni and Bacteroides vulgatus. Additionally, GM-metabolized d-glutamate may affect cognitive function in AD patients through interactions with the glutamate N-methyl-D-aspartate receptor [58]. One important protective factor against neurodegeneration, especially in Alzheimer's disease, is brain-derived neurotrophic factor (BDNF) [59]. As the aberrant behavior and lowered BDNF level in GF mice may be normalized after colonization with probiotic treatment, it is claimed that GM can impact the amount of brain BDNF [60]. Acetate, butyrate, and propionate are saturated fatty acids (SCFAs) that can pass the blood-brain barrier (BBB) and influence the central nervous system (CNS). [61] in Since a microglia deficiency was observed in animals lacking the free fatty acid receptor 2 (FFAR2), one of the SCFA receptors, it follows that SCFAs can regulate microglia

homeostasis as well. There was a comparable shift in a GF setting [14]. Researchers found that AD mice whose sodium butyrate treatment began later in the disease showed improved memory function. This improvement may have occurred as a result of a restoration of histone acetylation and an increase in the expression of genes related to learning [62]. Intestinal cells rely on butyrate as an energy source, and it can increase the rate of mitochondrial respiration and ATP synthesis [63,64].

Probiotics as potential therapeutics for AD

There is mounting clinical evidence that suggests probiotics may have therapeutic potential in Alzheimer's disease (AD) through multiple pathways. Patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD) may benefit from taking probiotics, according to a 2019 meta-analysis [65]. This could be because probiotics have anti-inflammatory and antioxidative properties. Cognitive function in Alzheimer's disease patients was found to be considerably improved after 12 weeks of probiotic milk comprising Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum, according to a randomized, double-blind, controlled research. Although probiotics did not improve fasting plasma glucose, other lipid profiles, inflammation biomarkers, or oxidative stress biomarkers, they did have a positive effect on insulin resistance markers, plasma malondialdehyde levels, serum high-sensitivity C-reactive protein, triglyceride, and very low density lipoprotein levels (VLDL) [66]. over more solid proof, we need randomized controlled trials that are large-scale and run over an extended length of time.

The effects of probiotics on the pathophysiology and pathology of Alzheimer's disease have been the subject of research. Multiple probiotics have shown promise in reducing inflammation and improving cognitive function, according to previous research [67–70]. According to Bonfili et al., SLAB51 mixture, which includes Streptococcus thermophilus, bifidobacteria, and lactobacilli, can have a positive effect on plasma inflammatory cytokine levels, restore autophagy and the impaired ubiquitin proteasome system, decrease Aβ load, and improve cortical atrophy in Alzheimer's disease mice [69]. Past research has also shown that Lactobacillus johnsonii and Bifidobacterium infantis have anti-inflammatory properties [71,72]. This is because they modulate the kynurenine route of tryptophan breakdown, respectively. The effects of Aβ on the hippocampus's inflammation and immune-reactive gene expression could be reversed by Bifidobacterium breve A1, according to research by Kobayashi et al. Acetate, which may help mitigate some of the behavioral problems seen in AD model mice, was also shown to be more prevalent in the plasma [68].In the brains of 5xFAD transgenic mice, Lactobacillus plantarum C29 was found to control microglia activation, inhibit NF-κB activation, and decrease Aβ deposition [70].

Additional research is necessary to establish a safe and effective probiotic formulation for the prevention or treatment of AD, even if there is existing evidence that supports the therapeutic potential of probiotics. Due to a lack of stronger evidence-based verification of their health-promoting abilities and detrimental effects, major medical regulatory bodies have not approved any probiotic composition as a treatment method [73]. Warning: probiotics can cause sepsis and other dangerous side effects,

especially in susceptible populations like the elderly, the very sick, and those with impaired immune systems [61,73]. Several studies have shown that using probiotics following antibiotic therapy might cause a long-term dysbiosis, which can raise the risk of communicable infections [73-77]. Serotonergic syndrome, another notable side effect of probiotics, is commonly associated with the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression. In most cases, tryptophan-metabolizing probiotics on their own will not cause the syndrome, but when taken with powerful SSRIs, the risk increases dramatically [61,78]. People who have AD or are at risk for it are often elderly and may also be depressed, so it's important to be extra cautious while giving them probiotics.

Conclusion

Research on the link between GM and AD may provide fresh insights into the disease's pathophysiology, which is currently a barrier to effective AD treatment. Since GM dysbiosis has been linked to multiple AD indicators, addressing it by taking probiotics could be a way to treat AD. Further elucidation of the underlying mechanisms and development of a safe and effective probiotic formulation for AD prevention and therapy necessitates multiple well-designed mechanistic and clinical trials. To lessen associated hazards and improve their therapeutic efficacy, researchers are studying and developing new probiotic medications. Even if there are still a lot of obstacles, scientists all over the globe should be hopeful about the growing field that connects gut microbiota to AD.

References:

[1].Apostolova LG. Alzheimer disease. Contin (Minneap Minn). 2016;22(2 Dementia):419–34. [DOI] [PMC free article] [PubMed]; Apostolova LG. Alzheimer disease. Contin (Minneap Minn) 2016;22(2 Dementia):419–34. doi: 10.1212/CON.0000000000000307. [DOI] [PMC free article] [PubMed] [Google Scholar]

[2].Ljubenkov PA, Geschwind MD. Dementia. Semin Neurol. 2016;36(4):397–404. [DOI] [PubMed]; Ljubenkov PA, Geschwind MD. Dementia. Semin Neurol. 2016;36(4):397–404. doi: 10.1055/s-0036-1585096. [DOI] [PubMed] [Google Scholar]

[3].Sacuiu SF. Dementias. Handb Clin Neurol. 2016;138:123–51. [DOI] [PubMed]; Sacuiu SF. Dementias. Handb Clin Neurol. 2016;138:123–51. doi: 10.1016/B978-0-12-802973-2.00008-2. [DOI] [PubMed] [Google Scholar]

[4].Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I. Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. Neurologia. 2017;32(8):523–32. [DOI] [PubMed]; Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I. Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. Neurologia. 2017;32(8):523–32. doi: 10.1016/j.nrl.2016.02.016. [DOI] [PubMed] [Google Scholar]

[5].Cresci GAM, Izzo K. Chapter 4 – Gut microbiome. In Corrigan ML, Roberts K, Steiger E, editors. Adult Short Bowel Syndrome. United States: Academic Press; 2019. p. 45–54.; Cresci GAM, Izzo K. Corrigan ML, Roberts K, Steiger E. Adult Short Bowel Syndrome. United States: Academic Press; 2019. Chapter 4 – Gut microbiome; pp. p. 45–54. , editors. [Google Scholar]

[6].Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. Lancet Neurol. 2020;19(2):179–94. [DOI] [PubMed]; Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. Lancet Neurol. 2020;19(2):179–94. doi: 10.1016/S1474-4422(19)30356-4. [DOI] [PubMed] [Google Scholar]

[7].Collins SM, Bercik P. Gut microbiota: Intestinal bacteria influence brain activity in healthy humans. Nat Rev Gastroenterol Hepatol. 2013;10(6):326–7. [DOI] [PubMed]; Collins SM, Bercik P. Gut microbiota: Intestinal bacteria influence brain activity in healthy humans. Nat Rev Gastroenterol Hepatol. 2013;10(6):326–7. doi: 10.1038/nrgastro.2013.76. [DOI] [PubMed] [Google Scholar]
[8].Ambalam P, Raman M, Purama RK, Doble M. Probiotics, prebiotics and colorectal cancer prevention. Best Pract Res Clin Gastroenterol. 2016;30(1):119–31. [DOI] [PubMed]; Ambalam P, Raman M, Purama RK, Doble M. Probiotics, prebiotics and colorectal cancer prevention. Best Pract Res Clin Gastroenterol. 2016;30(1):119–31. doi: 10.1016/j.bpg.2016.02.009. [DOI] [PubMed] [Google Scholar]
[9].Cani PD. Human gut microbiome: hopes, threats and promises. Gut. 2018;67(9):1716–25. [DOI] [PMC free article] [PubMed]; Cani PD. Human gut microbiome: hopes, threats and promises. Gut. 2018;67(9):1716–25. doi: 10.1136/gutjnl-2018-316723. [DOI] [PMC free article] [PubMed] [Google Scholar]
[10].Khan MS, Ikram M, Park JS, Park TJ, Kim MO. Gut microbiota, its role in induction of Alzheimer's disease pathology, and possible therapeutic interventions: special focus on anthocyanins. Cells. 2020;9(4):853. [DOI] [PMC free article] [PubMed]; Khan MS, Ikram M, Park JS, Park TJ, Kim MO. Gut microbiota, its role in induction of Alzheimer's disease pathology, and possible therapeutic interventions: special focus on anthocyanins. Cells. 2020;9(4):853. doi: 10.3390/cells9040853. [DOI] [PMC free article] [PubMed] [Google Scholar]
[11].Okumura R, Takeda K. Maintenance of intestinal homeostasis by mucosal barriers. Inflamm Regen. 2018;38:5. [DOI] [PMC free article] [PubMed]; Okumura R, Takeda K. Maintenance of intestinal homeostasis by mucosal barriers. Inflamm Regen. 2018;38:5. doi: 10.1186/s41232-018-0063-z. [DOI] [PMC free article] [PubMed] [Google Scholar]
[12].Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Sci (N York, NY). 2005;307(5717):1915–20. [DOI] [PubMed]; Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Sci (N York, NY) 2005;307(5717):1915–20. doi: 10.1126/science.1104816. [DOI] [PubMed] [Google Scholar]
[13].Cerovic M, Forloni G, Balducci C. Neuroinflammation and the gut microbiota: possible alternative therapeutic targets to counteract Alzheimer's disease? Front Aging Neurosci. 2019;11:284. [DOI] [PMC free article] [PubMed]; Cerovic M, Forloni G, Balducci C. Neuroinflammation and the gut microbiota: possible alternative therapeutic targets to counteract Alzheimer's disease? Front Aging Neurosci. 2019;11:284. doi: 10.3389/fnagi.2019.00284. [DOI] [PMC free article] [PubMed] [Google Scholar]
[14].Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18(7):965–77. [DOI] [PMC free article] [PubMed]; Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E. et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18(7):965–77. doi: 10.1038/nn.4030. [DOI] [PMC free article] [PubMed] [Google Scholar]
[15].Duparc T, Plovier H, Marrachelli VG, Van Hul M, Essaghir A, Ståhlman M, et al. Hepatocyte MyD88 affects bile acids, gut microbiota and metabolome contributing to regulate glucose and lipid metabolism. Gut. 2017;66(4):620–32. [DOI] [PMC free article] [PubMed]; Duparc T, Plovier H, Marrachelli VG, Van Hul M, Essaghir A, Ståhlman M. et al. Hepatocyte MyD88 affects bile acids, gut microbiota and metabolome contributing to regulate glucose and lipid metabolism. Gut. 2017;66(4):620–32. doi: 10.1136/gutjnl-2015-310904. [DOI] [PMC free article] [PubMed] [Google Scholar]
[16].Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009;461(7268):1282–6. [DOI] [PMC free article] [PubMed]; Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D. et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009;461(7268):1282–6. doi: 10.1038/nature08530. [DOI] [PMC free article] [PubMed] [Google Scholar]

[17].Dinan TG, Cryan JF. Gut-brain axis in 2016: brain-gut-microbiota axis – mood, metabolism and behaviour. Nat Rev Gastroenterol Hepatol. 2017;14(2):69–70. [DOI] [PubMed]; Dinan TG, Cryan JF. Gut-brain axis in 2016: brain-gut-microbiota axis – mood, metabolism and behaviour. Nat Rev Gastroenterol Hepatol. 2017;14(2):69–70. doi: 10.1038/nrgastro.2016.200. [DOI] [PubMed] [Google Scholar]
[18].González-Arancibia C, Urrutia-Piñones J, Illanes-González J, Martinez-Pinto J, Sotomayor-Zárate R, Julio-Pieper M, et al. Do your gut microbes affect your brain dopamine? Psychopharmacology. 2019;236(5):1611–22. [DOI] [PubMed]; González-Arancibia C, Urrutia-Piñones J, Illanes-González J, Martinez-Pinto J, Sotomayor-Zárate R, Julio-Pieper M. et al. Do your gut microbes affect your brain dopamine? Psychopharmacology. 2019;236(5):1611–22. doi: 10.1007/s00213-019-05265-5. [DOI] [PubMed] [Google Scholar]
[19].Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99(4):1877–2013. [DOI] [PubMed]; Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M. et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99(4):1877–2013. doi: 10.1152/physrev.00018.2018. [DOI] [PubMed] [Google Scholar]
[20].Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. 2015;17(5):565–76. [DOI] [PMC free article] [PubMed]; Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. 2015;17(5):565–76. doi: 10.1016/j.chom.2015.04.011. [DOI] [PMC free article] [PubMed] [Google Scholar]
[21].Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomed. 2019;14:5541–54. [DOI] [PMC free article] [PubMed]; Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomed. 2019;14:5541–54. doi: 10.2147/IJN.S200490. [DOI] [PMC free article] [PubMed] [Google Scholar]
[22].Minter MR, Taylor JM, Crack PJ. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. J Neurochem. 2016;136(3):457–74. [DOI] [PubMed]; Minter MR, Taylor JM, Crack PJ. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. J Neurochem. 2016;136(3):457–74. doi: 10.1111/jnc.13411. [DOI] [PubMed] [Google Scholar]
[23].Price BR, Johnson LA, Norris CM. Reactive astrocytes: the nexus of pathological and clinical hallmarks of Alzheimer's disease. Ageing Res Rev. 2021;68:101335. [DOI] [PMC free article] [PubMed]; Price BR, Johnson LA, Norris CM. Reactive astrocytes: the nexus of pathological and clinical hallmarks of Alzheimer's disease. Ageing Res Rev. 2021;68:101335. doi: 10.1016/j.arr.2021.101335. [DOI] [PMC free article] [PubMed] [Google Scholar]
[24].Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015;16(6):358–72. [DOI] [PubMed]; Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 2015;16(6):358–72. doi: 10.1038/nrn3880. [DOI] [PubMed] [Google Scholar]
[25].Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC, et al. Vascular dysfunction-the disregarded partner of Alzheimer's disease. Alzheimers Dement. 2019;15(1):158–67. [DOI] [PMC free article] [PubMed]; Sweeney MD, Montagne A, Sagare AP, Nation DA, Schneider LS, Chui HC. et al. Vascular dysfunction-the disregarded partner of Alzheimer's disease. Alzheimers Dement. 2019;15(1):158–67. doi: 10.1016/j.jalz.2018.07.222. [DOI] [PMC free article] [PubMed] [Google Scholar]
[26].Vipin A, Loke YM, Liu S, Hilal S, Shim HY, Xu X, et al. Cerebrovascular disease influences functional and structural network connectivity in patients with amnestic mild cognitive impairment and Alzheimer's disease. Alzheimers Res Ther. 2018;10(1):82. [DOI] [PMC free article] [PubMed]; Vipin A, Loke YM, Liu S, Hilal S, Shim HY, Xu X. et al. Cerebrovascular disease influences functional and structural network connectivity in patients with amnestic mild cognitive impairment and Alzheimer's disease. Alzheimers Res Ther. 2018;10(1):82. doi: 10.1186/s13195-018-0413-8. [DOI] [PMC free article] [PubMed] [Google Scholar]

[27].Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's Dementia: J Alzheimer's Assoc. 2015;11(6):718–26. [DOI] [PubMed]; Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's Dementia: J Alzheimer's Assoc. 2015;11(6):718–26. doi: 10.1016/j.jalz.2015.05.016. [DOI] [PubMed] [Google Scholar]
[28].Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep. 2017;7:41802. [DOI] [PMC free article] [PubMed]; Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G. et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep. 2017;7:41802. doi: 10.1038/srep41802. [DOI] [PMC free article] [PubMed] [Google Scholar]
[29].Zhang L, Wang Y, Xiayu X, Shi C, Chen W, Song N, et al. Altered Gut microbiota in a mouse model of Alzheimer's disease. J Alzheimer's Disease: JAD. 2017;60(4):1241–57. [DOI] [PubMed]; Zhang L, Wang Y, Xiayu X, Shi C, Chen W, Song N. et al. Altered Gut microbiota in a mouse model of Alzheimer's disease. J Alzheimer's Disease: JAD. 2017;60(4):1241–57. doi: 10.3233/JAD-170020. [DOI] [PubMed] [Google Scholar]
[30].Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 2017;13(12):e1006654. [DOI] [PMC free article] [PubMed]; Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 2017;13(12):e1006654. doi: 10.1371/journal.ppat.1006654. [DOI] [PMC free article] [PubMed] [Google Scholar]
[31].Zhou Y, Blanco LP, Smith DR, Chapman MR. Bacterial amyloids. In: Sigurdsson EM, Calero M, Gasset M, editors. Amyloid proteins: methods and protocols. Totowa, NJ: Humana Press; 2012. p. 303–20.; Zhou Y, Blanco LP, Smith DR, Chapman MR. Sigurdsson EM, Calero M, Gasset M. Amyloid proteins: methods and protocols. Totowa, NJ: Humana Press; 2012. Bacterial amyloids; pp. p. 303–20. , editors. [Google Scholar]
[32].Nishimori JH, Newman TN, Oppong GO, Rapsinski GJ, Yen J-H, Biesecker SG, et al. Microbial amyloids induce interleukin 17 A (IL-17A) and IL-22 responses via toll-like receptor 2 activation in the intestinal mucos. Infect Immunit. 2012;80(12):4398. [DOI] [PMC free article] [PubMed]; Nishimori JH, Newman TN, Oppong GO, Rapsinski GJ, Yen J-H, Biesecker SG. et al. Microbial amyloids induce interleukin 17 A (IL-17A) and IL-22 responses via toll-like receptor 2 activation in the intestinal mucos. Infect Immunit. 2012;80(12):4398. doi: 10.1128/IAI.00911-12. [DOI] [PMC free article] [PubMed] [Google Scholar]
[33].Hill JM, Lukiw WJ. Microbial-generated amyloids and Alzheimer's disease (AD). Front Aging Neurosci. 2015;7(9). 10.3389/fnagi.2015.00009. [DOI] [PMC free article] [PubMed]; Hill JM, Lukiw WJ. Microbial-generated amyloids and Alzheimer's disease (AD) Front Aging Neurosci. 2015;7(9) doi: 10.3389/fnagi.2015.00009. [DOI] [PMC free article] [PubMed] [Google Scholar]
[34].Chen SG, Stribinskis V, Rane MJ, Demuth DR, Gozal E, Roberts AM, et al. Exposure to the functional bacterial amyloid protein curli enhances alpha-synuclein aggregation in aged fischer 344 rats and Caenorhabditis elegans. Sci Rep. 2016;6(1):34477. [DOI] [PMC free article] [PubMed]; Chen SG, Stribinskis V, Rane MJ, Demuth DR, Gozal E, Roberts AM. et al. Exposure to the functional bacterial amyloid protein curli enhances alpha-synuclein aggregation in aged fischer 344 rats and Caenorhabditis elegans . Sci Rep. 2016;6(1):34477. doi: 10.1038/srep34477. [DOI] [PMC free article] [PubMed] [Google Scholar]
[35].Friedland RP. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. J Alzheimers Dis. 2015;45(2):349–62. [DOI] [PubMed]; Friedland RP. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. J Alzheimers Dis. 2015;45(2):349–62. doi: 10.3233/JAD-142841. [DOI] [PubMed] [Google Scholar]
[36].Gosztyla ML, Brothers HM, Robinson SR. Alzheimer's amyloid-β is an antimicrobial peptide: a review of the evidence. J Alzheimer's Disease: JAD. 2018;62(4):1495–506. [DOI] [PubMed]; Gosztyla ML, Brothers HM, Robinson

SR. Alzheimer's amyloid-β is an antimicrobial peptide: a review of the evidence. J Alzheimer's Disease: JAD. 2018;62(4):1495–506. doi: 10.3233/JAD-171133. [DOI] [PubMed] [Google Scholar]
[37].Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017;49:60–8. [DOI] [PubMed]; Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C. et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017;49:60–8. doi: 10.1016/j.neurobiolaging.2016.08.019. [DOI] [PubMed] [Google Scholar]
[38].Dodiya HB, Kuntz T, Shaik SM, Baufeld C, Leibowitz J, Zhang X, et al. Sex-specific effects of microbiome perturbations on cerebral Aβ amyloidosis and microglia phenotypes. J Exp Med. 2019;216(7):1542–60. [DOI] [PMC free article] [PubMed]; Dodiya HB, Kuntz T, Shaik SM, Baufeld C, Leibowitz J, Zhang X. et al. Sex-specific effects of microbiome perturbations on cerebral Aβ amyloidosis and microglia phenotypes. J Exp Med. 2019;216(7):1542–60. doi: 10.1084/jem.20182386. [DOI] [PMC free article] [PubMed] [Google Scholar]
[39].Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang X, et al. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APP/PS1 murine model of Alzheimer's disease. Sci Rep. 2017;7(1):10411. [DOI] [PMC free article] [PubMed]; Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang X. et al. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APP/PS1 murine model of Alzheimer's disease. Sci Rep. 2017;7(1):10411. doi: 10.1038/s41598-017-11047-w. [DOI] [PMC free article] [PubMed] [Google Scholar]
[40].Beutler B. TLR4 as the mammalian endotoxin sensor. In: Beutler B, Wagner H, editors. Toll-like receptor family members and their ligands. Berlin, Heidelberg: Springer Berlin Heidelberg; 2002. p. 109–20.; Beutler B. Beutler B, Wagner H. Toll-like receptor family members and their ligands. Berlin, Heidelberg: Springer Berlin Heidelberg; 2002. TLR4 as the mammalian endotoxin sensor; pp. p. 109–20. , editors. [Google Scholar]
[41].Park BS, Lee JO. Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp Mol Med. 2013;45(12):e66. [DOI] [PMC free article] [PubMed]; Park BS, Lee JO. Recognition of lipopolysaccharide pattern by TLR4 complexes. Exp Mol Med. 2013;45(12):e66. doi: 10.1038/emm.2013.97. [DOI] [PMC free article] [PubMed] [Google Scholar]
[42].Ciesielska A, Matyjek M, Kwiatkowska K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. Cell Mol Life Sci. 2021;78(4):1233–61. [DOI] [PMC free article] [PubMed]; Ciesielska A, Matyjek M, Kwiatkowska K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. Cell Mol Life Sci. 2021;78(4):1233–61. doi: 10.1007/s00018-020-03656-y. [DOI] [PMC free article] [PubMed] [Google Scholar]
[43].LukiwWJ. Lipopolysaccharide and inflammatory signaling in Alzheimer's disease. Front Microbiol. 2016;7:1544. [DOI] [PMC free article] [PubMed]; Lukiw WJ. Lipopolysaccharide and inflammatory signaling in Alzheimer's disease. Front Microbiol. 2016;7:1544. doi: 10.3389/fmicb.2016.01544. [DOI] [PMC free article] [PubMed] [Google Scholar]
[44].Zhang R, Miller RG, Gascon R, Champion S, Katz J, Lancero M, et al. Circulating endotoxin and systemic immune activation in sporadic amyotrophic lateral sclerosis (sALS). J Neuroimmunol. 2009;206(1-2):121–4. [DOI] [PMC free article] [PubMed]; Zhang R, Miller RG, Gascon R, Champion S, Katz J, Lancero M. et al. Circulating endotoxin and systemic immune activation in sporadic amyotrophic lateral sclerosis (sALS) J Neuroimmunol. 2009;206(1-2):121–4. doi: 10.1016/j.jneuroim.2008.09.017. [DOI] [PMC free article] [PubMed] [Google Scholar]
[45].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. Front Cell Infect Microbiol. 2017;7:318. [DOI] [PMC free article] [PubMed]; 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. Front Cell Infect Microbiol. 2017;7:318. doi: 10.3389/fcimb.2017.00318. [DOI] [PMC free article] [PubMed] [Google Scholar]

[46].Zhan X, Stamova B, Jin L-W, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology. 2016;87(22):2324–32. [DOI] [PMC free article] [PubMed]; Zhan X, Stamova B, Jin L-W, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology. 2016;87(22):2324–32. doi: 10.1212/WNL.0000000000003391. [DOI] [PMC free article] [PubMed] [Google Scholar]
[47].Marizzoni M, Cattaneo A, Mirabelli P, Festari C, Lopizzo N, Nicolosi V, et al. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. J Alzheimers Dis. 2020;78(2):683–97. [DOI] [PubMed]; Marizzoni M, Cattaneo A, Mirabelli P, Festari C, Lopizzo N, Nicolosi V. et al. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. J Alzheimers Dis. 2020;78(2):683–97. doi: 10.3233/JAD-200306. [DOI] [PubMed] [Google Scholar]
[48].Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe. 2018;23(4):570. [DOI] [PMC free article] [PubMed]; Thevaranjan N, Puchta A, Schulz C, Naidoo A, Szamosi JC, Verschoor CP. et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. Cell Host Microbe. 2018;23(4):570. doi: 10.1016/j.chom.2018.03.006. [DOI] [PMC free article] [PubMed] [Google Scholar]
[49].Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6(263):263ra158. [DOI] [PMC free article] [PubMed]; Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M. et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6(263):263ra158. doi: 10.1126/scitranslmed.3009759. [DOI] [PMC free article] [PubMed] [Google Scholar]
[50].Engen PA, Dodiya HB, Naqib A, Forsyth CB, Green SJ, Voigt RM, et al. The Potential role of gut-derived inflammation in multiple system atrophy. J Parkinsons Dis. 2017;7(2):331–46. [DOI] [PubMed]; Engen PA, Dodiya HB, Naqib A, Forsyth CB, Green SJ, Voigt RM. et al. The Potential role of gut-derived inflammation in multiple system atrophy. J Parkinsons Dis. 2017;7(2):331–46. doi: 10.3233/JPD-160991. [DOI] [PubMed] [Google Scholar]
[51].Lin L, Zheng LJ, Zhang LJ. Neuroinflammation, gut microbiome, and Alzheimer's disease. Mol Neurobiol. 2018;55(11):8243–50. [DOI] [PubMed]; Lin L, Zheng LJ, Zhang LJ. Neuroinflammation, gut microbiome, and Alzheimer's disease. Mol Neurobiol. 2018;55(11):8243–50. doi: 10.1007/s12035-018-0983-2. [DOI] [PubMed] [Google Scholar]
[52].Komaroff AL. The microbiome and risk for atherosclerosis. JAMA. 2018;319(23):2381–2. [DOI] [PubMed]; Komaroff AL. The microbiome and risk for atherosclerosis. JAMA. 2018;319(23):2381–2. doi: 10.1001/jama.2018.5240. [DOI] [PubMed] [Google Scholar]
[53].Desler C, Lillenes MS, Tønjum T, Rasmussen LJ. The role of mitochondrial dysfunction in the progression of Alzheimer's disease. Curr Medicinal Chem. 2018;25(40):5578–87. [DOI] [PMC free article] [PubMed]; Desler C, Lillenes MS, Tønjum T, Rasmussen LJ. The role of mitochondrial dysfunction in the progression of Alzheimer's disease. Curr Medicinal Chem. 2018;25(40):5578–87. doi: 10.2174/0929867324666170616110111. [DOI] [PMC free article] [PubMed] [Google Scholar]
[54].Du F, Yu Q, Yan S, Hu G, Lue LF, Walker DG, et al. PINK1 signalling rescues amyloid pathology and mitochondrial dysfunction in Alzheimer's disease. Brain. 2017;140(12):3233–51. [DOI] [PMC free article] [PubMed]; Du F, Yu Q, Yan S, Hu G, Lue LF, Walker DG. et al. PINK1 signalling rescues amyloid pathology and mitochondrial dysfunction in Alzheimer's disease. Brain. 2017;140(12):3233–51. doi: 10.1093/brain/awx258. [DOI] [PMC free article] [PubMed] [Google Scholar]
[55].Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta. 2014;1842(8):1240–7. [DOI] [PMC free article] [PubMed]; Wang X, Wang W, Li L,

Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta. 2014;1842(8):1240–7. doi: 10.1016/j.bbadis.2013.10.015. [DOI] [PMC free article] [PubMed] [Google Scholar]
[56].Franco-Obregón A, Gilbert JA. The microbiome-mitochondrion connection: common ancestries, common mechanisms, common goals. mSystems. 2017;2(3):e00018–17. [DOI] [PMC free article] [PubMed]; Franco-Obregón A, Gilbert JA. The microbiome-mitochondrion connection: common ancestries, common mechanisms, common goals. mSystems. 2017;2(3):e00018–17. doi: 10.1128/mSystems.00018-17. [DOI] [PMC free article] [PubMed] [Google Scholar]
[57].Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. Behav Brain Res. 2003;140(1–2):1–47. [DOI] [PubMed]; Riedel G, Platt B, Micheau J. Glutamate receptor function in learning and memory. Behav Brain Res. 2003;140(1–2):1–47. doi: 10.1016/s0166-4328(02)00272-3. [DOI] [PubMed] [Google Scholar]
[58].Chang CH, Lin CH, Lane HY. d-glutamate and gut microbiota in Alzheimer's disease. Int J Mol Sci. 2020;21(8):2676. [DOI] [PMC free article] [PubMed]; Chang CH, Lin CH, Lane HY. d-glutamate and gut microbiota in Alzheimer's disease. Int J Mol Sci. 2020;21(8):2676. doi: 10.3390/ijms21082676. [DOI] [PMC free article] [PubMed] [Google Scholar]
[59].Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int J Mol Sci. 2020;21(20):7777. [DOI] [PMC free article] [PubMed]; Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int J Mol Sci. 2020;21(20):7777. doi: 10.3390/ijms21207777. [DOI] [PMC free article] [PubMed] [Google Scholar]
[60].Maqsood R, Stone TW. The gut-brain axis, BDNF, NMDA and CNS disorders. Neurochem Res. 2016;41(11):2819–35. [DOI] [PubMed]; Maqsood R, Stone TW. The gut-brain axis, BDNF, NMDA and CNS disorders. Neurochem Res. 2016;41(11):2819–35. doi: 10.1007/s11064-016-2039-1. [DOI] [PubMed] [Google Scholar]
[61].Arora K, Green M, Prakash S. The microbiome and Alzheimer's disease: potential and limitations of prebiotic, synbiotic, and probiotic formulations. Front Bioeng Biotechnol. 2020;8:537847. [DOI] [PMC free article] [PubMed]; Arora K, Green M, Prakash S. The microbiome and Alzheimer's disease: potential and limitations of prebiotic, synbiotic, and probiotic formulations. Front Bioeng Biotechnol. 2020;8:537847. doi: 10.3389/fbioe.2020.537847. [DOI] [PMC free article] [PubMed] [Google Scholar]
[62].Govindarajan N, Agis-Balboa RC, Walter J, Sananbenesi F, Fischer A. Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. J Alzheimer's Dis. 2011;26:187–97. [DOI] [PubMed]; Govindarajan N, Agis-Balboa RC, Walter J, Sananbenesi F, Fischer A. Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. J Alzheimer's Dis. 2011;26:187–97. doi: 10.3233/JAD-2011-110080. [DOI] [PubMed] [Google Scholar]
[63].Sochocka M, Donskow-Lysoniewska K, Diniz BS, Kurpas D, Brzozowska E, Leszek J. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease-a critical review. Mol Neurobiol. 2019;56(3):1841–51. [DOI] [PMC free article] [PubMed]; Sochocka M, Donskow-Lysoniewska K, Diniz BS, Kurpas D, Brzozowska E, Leszek J. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease-a critical review. Mol Neurobiol. 2019;56(3):1841–51. doi: 10.1007/s12035-018-1188-4. [DOI] [PMC free article] [PubMed] [Google Scholar]
[64].Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. Modified mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. EBioMedicine. 2019;47:529–42. [DOI] [PMC free article] [PubMed]; Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. Modified mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with

Alzheimer's disease markers in subjects with mild cognitive impairment. EBioMedicine. 2019;47:529–42. doi: 10.1016/j.ebiom.2019.08.032. [DOI] [PMC free article] [PubMed] [Google Scholar]
[65].Den H, Dong X, Chen M, Zou Z. Efficacy of probiotics on cognition, and biomarkers of inflammation and oxidative stress in adults with Alzheimer's disease or mild cognitive impairment – a meta-analysis of randomized controlled trials. Aging. 2020;12(4):4010–39. [DOI] [PMC free article] [PubMed]; Den H, Dong X, Chen M, Zou Z. Efficacy of probiotics on cognition, and biomarkers of inflammation and oxidative stress in adults with Alzheimer's disease or mild cognitive impairment – a meta-analysis of randomized controlled trials. Aging. 2020;12(4):4010–39. doi: 10.18632/aging.102810. [DOI] [PMC free article] [PubMed] [Google Scholar]
[66].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. Front Aging Neurosci. 2018;10:54. [DOI] [PMC free article] [PubMed]; 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. Front Aging Neurosci. 2018;10:54. doi: 10.3389/fnagi.2018.00054. [DOI] [PMC free article] [PubMed] [Google Scholar]
[67].Abraham D, Feher J, Scuderi GL, Szabo D, Dobolyi A, Cservenak M, et al. Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: role of microbiome. Exp Gerontol. 2019;115:122–31. [DOI] [PubMed]; Abraham D, Feher J, Scuderi GL, Szabo D, Dobolyi A, Cservenak M. et al. Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: role of microbiome. Exp Gerontol. 2019;115:122–31. doi: 10.1016/j.exger.2018.12.005. [DOI] [PubMed] [Google Scholar]
[68].Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, et al. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Sci Rep. 2017;7(1):13510. [DOI] [PMC free article] [PubMed]; Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A. et al. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Sci Rep. 2017;7(1):13510. doi: 10.1038/s41598-017-13368-2. [DOI] [PMC free article] [PubMed] [Google Scholar]
[69].Bonfili L, Cecarini V, Berardi S, Scarpona S, Suchodolski JS, Nasuti C, et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci Rep. 2017;7(1):2426. [DOI] [PMC free article] [PubMed]; Bonfili L, Cecarini V, Berardi S, Scarpona S, Suchodolski JS, Nasuti C. et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci Rep. 2017;7(1):2426. doi: 10.1038/s41598-017-02587-2. [DOI] [PMC free article] [PubMed] [Google Scholar]
[70].Lee HJ, Hwang YH, Kim DH. Lactobacillus plantarum C29-fermented soybean (DW2009) alleviates memory impairment in 5XFAD transgenic mice by regulating microglia activation and gut microbiota composition. Mol Nutr Food Res. 2018;62(20):e1800359. [DOI] [PubMed]; Lee HJ, Hwang YH, Kim DH. Lactobacillus plantarum C29-fermented soybean (DW2009) alleviates memory impairment in 5XFAD transgenic mice by regulating microglia activation and gut microbiota composition. Mol Nutr Food Res. 2018;62(20):e1800359. doi: 10.1002/mnfr.201800359. [DOI] [PubMed] [Google Scholar]
[71].Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic bifidobacteria infantis: an assessment of potential antidepressant properties in the rat. J Psychiatr Res. 2008;43(2):164–74. [DOI] [PubMed]; Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic bifidobacteria infantis: an assessment of potential antidepressant properties in the rat. J Psychiatr Res. 2008;43(2):164–74. doi: 10.1016/j.jpsychires.2008.03.009. [DOI] [PubMed] [Google Scholar]
[72].Valladares R, Bojilova L, Potts AH, Cameron E, Gardner C, Lorca G, et al. Lactobacillus johnsonii inhibits indoleamine 2,3-dioxygenase and alters tryptophan metabolite levels in BioBreeding rats. FASEB J. 2013;27(4):1711–20. [DOI] [PubMed]; Valladares R, Bojilova L, Potts AH, Cameron E, Gardner C, Lorca G. et al. Lactobacillus johnsonii

inhibits indoleamine 2,3-dioxygenase and alters tryptophan metabolite levels in BioBreeding rats. FASEB J. 2013;27(4):1711–20. doi: 10.1096/fj.12-223339. [DOI] [PubMed] [Google Scholar]
[73].Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. 2019;25(5):716–29. [DOI] [PubMed]; Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. 2019;25(5):716–29. doi: 10.1038/s41591-019-0439-x. [DOI] [PubMed] [Google Scholar]
[74].Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, Bashiardes S, et al. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. Cell. 2018;174(6):1406–23.e16. [DOI] [PubMed]; Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, Bashiardes S. et al. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. Cell. 2018;174(6):1406–23.e16. doi: 10.1016/j.cell.2018.08.047. [DOI] [PubMed] [Google Scholar]
[75].Grazul H, Kanda LL, Gondek D. Impact of probiotic supplements on microbiome diversity following antibiotic treatment of mice. Gut Microbes. 2016;7(2):101–14. [DOI] [PMC free article] [PubMed]; Grazul H, Kanda LL, Gondek D. Impact of probiotic supplements on microbiome diversity following antibiotic treatment of mice. Gut Microbes. 2016;7(2):101–14. doi: 10.1080/19490976.2016.1138197. [DOI] [PMC free article] [PubMed] [Google Scholar]
[76].Kabbani TA, Pallav K, Dowd SE, Villafuerte-Galvez J, Vanga RR, Castillo NE, et al. Prospective randomized controlled study on the effects of Saccharomyces boulardii CNCM I-745 and amoxicillin-clavulanate or the combination on the gut microbiota of healthy volunteers. Gut Microbes. 2017;8(1):17–32. [DOI] [PMC free article] [PubMed]; Kabbani TA, Pallav K, Dowd SE, Villafuerte-Galvez J, Vanga RR, Castillo NE. et al. Prospective randomized controlled study on the effects of Saccharomyces boulardii CNCM I-745 and amoxicillin-clavulanate or the combination on the gut microbiota of healthy volunteers. Gut Microbes. 2017;8(1):17–32. doi: 10.1080/19490976.2016.1267890. [DOI] [PMC free article] [PubMed] [Google Scholar]
[77].Spinler JK, Brown A, Ross CL, Boonma P, Conner ME, Savidge TC. Administration of probiotic kefir to mice with Clostridium difficile infection exacerbates disease. Anaerobe. 2016;40:54–7. [DOI] [PMC free article] [PubMed]; Spinler JK, Brown A, Ross CL, Boonma P, Conner ME, Savidge TC. Administration of probiotic kefir to mice with Clostridium difficile infection exacerbates disease. Anaerobe. 2016;40:54–7. doi: 10.1016/j.anaerobe.2016.05.008. [DOI] [PMC free article] [PubMed] [Google Scholar]
[78].Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112–20. [DOI] [PubMed]; Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352(11):1112–20. doi: 10.1056/NEJMra041867. [DOI] [PubMed] [Google Scholar]