



The Effect of Gut Microbiota Alteration, Probiotic Supplementation, and the Ketogenic Diet on Alzheimer's Disease Symptoms

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150 character summary

Investigated how microbiota changes, probiotic supplementation, and the ketogenic diet can affect Alzheimer's disease; analyzed 10+ studies.

Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disease that is shaped by several different inherent and lifestyle factors. Diet has the potential in modulating AD through gut microbiota modulation. In this review, we discuss how the gut microbiota impacts AD symptoms. Furthermore, we investigate the ability of two specific aspects of diet rising in popularity, probiotic supplementation and the ketogenic diet, to alter the gut microbiota and improve symptoms and biomarkers of AD. We hope that increased knowledge of how dietary adjustment affects AD can lead to novel treatments or key prevention methods for AD in the future.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that is characterized by memory loss, mood swings, and loss of independence in daily life. Memory loss in AD is typically episodic short-term memory loss, and involves difficulty with new information. AD patients typically remember long-term memories. Mood changes affect up to 90% of AD patients, and can include agitation, disinhibition, delusions, disrupted sleep, and depression. Over 7 million Americans are currently diagnosed with AD, and in 2022, it became the 7th leading cause of death, with over 120,000 deaths in the United States alone. AD does not just affect patients; in fact, around 11 million Americans provided over 19.2 billion hours of unpaid care for patients with Alzheimer's or other dementias in 2024 (Alzheimer's Association, 2024).

AD is characterized by the presence of extracellular amyloid-beta ($A\beta$) plaques, which are caused by the extracellular build-up of $A\beta$ peptides produced from the amyloid precursor protein (APP), a transmembrane protein involved in neuronal growth (Bamford et al., 2020). Normally, APP is cleaved by α -secretase and γ -secretase to form soluble peptides sAPP α , which is extracellular, and C-terminal fragment (CTF α), which is intracellular. CTF α is then cleaved by γ -secretase to produce 3-kDa peptide (p3) and intracellular domain AICD. The products formed through α -secretase and γ -secretase cleavage are non-toxic and may play roles in synapse plasticity and brain development (Chow et al., 2011). However, in the amyloidogenic pathway, APP is cleaved by β -secretase rather than α -secretase. β -secretase cleaves APP into sAPP β and a C-terminal fragment β (CTF β). When γ -secretase cleaves CTF β , amyloid-beta peptides and AICD are produced (Zhou et al., 2018). While these $A\beta$ peptides can have been suggested to have functional roles in protecting against infections, supporting recovery from injury, and regulating synaptic function (Brothers et al., 2018), toxicity occurs when a large amount of $A\beta$ peptides are released into the brain and form plaques. Extracellular plaques can disrupt neuronal communication, leading to chronic neuroinflammation, and eventually neuronal death.

A β accumulation happens gradually and can begin to deposit in the brain decades before symptoms begin appearing (National Institute of Aging, 2023).

Another key biomarker of AD are neurofibrillary tangles, which are formed by the aggregation of hyperphosphorylated tau proteins. Tau, a protein that binds to microtubules found in axons, helps stabilize microtubule structure (Chen and Yu, 2023). However, when tau becomes hyperphosphorylated, it prevents microtubule assembly and function and it begins to detach from microtubules and aggregates into insoluble tangles inside neurons (Iqbal et al., 2011). Furthermore, tau tangles can be released and received by other neurons, leading to the spread of pathogenic tau and propagation of AD progression (Zhang et al., 2021). Studies have shown that A β plaques may be a prerequisite for tau tangles (Bloom, 2014). The amyloid cascade hypothesis proposes that A β plaques cause tau hyperphosphorylation, which leads to neurofibrillary tangles and collectively driving AD progression (Roda, 2022).

In the last decade, aberrant activation of the resident brain immune cells, microglia, has also been attributed to AD progression (Liang et al., 2022). Microglia are cells in the brain that help maintain homeostasis, strengthen synaptic transmissions, and respond to injury or disease. Microglia respond to CNS injury or disease through phagocytosis, where foreign substances, dead cells, or protein aggregates that could be harmful to the brain are eliminated. Additionally, microglia release soluble factors such as chemoattractants, cytokines, and neurotropic factors that aid tissue repair in the CNS (Colonna and Butovsky, 2017). Toxic A β plaques and tau aggregates trigger microglial responses, which try to remove them through phagocytosis or the release of proteases that break down proteins. However, as AD progresses, microglia become unable to clear A β plaques and tau tangles due to their greater size and quantity (Miao et al., 2023). Microglia begin to overexpress proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6, leading to chronic neuroinflammation that can contribute to neurodegeneration (Muzio et al., 2021). Furthermore, many genetic risk factors for AD have been found in genes like TREM2, which influence microglia function, such as activating inflammatory response or phagocytosis (Qin et al., 2021), thus highlighting a key role for these cells in AD pathology.

While tau and A β have been classic molecular biomarkers of AD for many years, new research has introduced other aspects that can affect the progression of AD symptoms. One newer area of AD research concerns the relation between diet, the gut microbiome and the brain. The gut microbiome is a microbial community inside the gastrointestinal tract. The gut and the brain communicate via the gut-brain axis, which involves the brain, spinal cord, autonomic nervous system, enteric nervous system, and hypothalamic pituitary adrenal axis. Afferent signals travel from the gut's intestinal walls through vagal, spinal, and enteric nerves up to the CNS and efferent signals from the brain travel back to the gut (Carabotti et al., 2015). An example of gut-brain communication is the short-chain fatty acids-microglia pathway, where the gastrointestinal tract can regulate microglial development and activation through the release of

short-chain fatty acids (SCFAs). Gut-derived SCFAs can cross the blood-brain barrier and enter the brain via systemic circulation and directly influence damaged microglial cells or decrease inflammatory function (Cao et al., 2025). Diet can strongly influence the gut microbiome and the brain, via the gut-brain axis. One aspect of diet includes taking probiotics, which are live organisms such as bacteria or yeast that help maintain homeostasis in the gut microbiome by competing with harmful bacteria and promoting beneficial ones (Manan, 2025). Due to the rising popularity of probiotics, with an estimated 53% of Americans ingesting supplements, research into how probiotics affect AD is crucial (International Microbiota Observatory, 2025). Additionally, given the popularity of fad dieting in America, it is also of interest to investigate how popular diets such as the ketogenic diet, which has around 13 million American followers and involves high fat intake and low carbohydrate intake (UT Health San Antonio, 2024), might affect AD symptoms and progression. ***There has been increasing interest in how diet and the gut microbiome might influence the progression of AD. This review will examine how the gut microbiota is modulated in AD and how probiotic supplementation and the ketogenic diet can affect symptoms of AD.***

Alterations to the gut microbiome can improve symptoms in Alzheimer's disease

In a study by Elangovan and colleagues, researchers investigated whether fecal microbiota transplantation (FMT) could improve symptoms of both early and late stage AD in the 5xFAD mouse model, which is genetically engineered to overexpress mutations that lead to early amyloid deposition (Elangovan et al., 2022). Researchers divided the mice into a late-stage AD group (30-32 weeks old) and early-stage AD group (10-12 weeks old). FMT involved transferring stool from wildtype donors to the AD mice via oral gavage for 7 days. Following a 21-day incubation period, cognition assessments were administered and A β levels were measured. Results showed that all AD mice that received FMT from wildtype mice had around a 2.5 reduction in cortical amyloid load. Additionally, in the NORT, an assessment measuring a mouse's ability to distinguish between a novel object and a familiar one, the late-stage AD group showed an approximately 5-fold increase in discrimination index, where a greater number correlates to greater preference for a novel object and improved memory. Thus, this study demonstrates how modulating the gut microbiome via health WT stool transfers can induce significant improvements in both cognition and amyloid levels in an AD mouse model.

In a similar study, researchers investigated the effects of FMT on cognition in 5xFAD mice (Jiang et al., 2025). 3 groups were used: Wild-type, 5xFAD without no treatment, and 5xFAD receiving FMT from healthy human donors. FMT was administered every other day for 8 weeks after FMT mice had received an antibiotic treatment via oral gavage for 1 week to remove their original microbiota. After 8 weeks, behavioral tests were administered, and A β load was measured. Results showed that 5xFAD mice receiving FMT had improved cognitive function than untreated mice in the Morris water maze (MWM). In this test, mice were trained to find a hidden platform submerged under water and their escape latency, or time taken to reach the

platform, was measured. The 5xFAD mice that had received FMT had significantly shorter escape latencies of around 20 seconds compared to untreated 5xFAD mice that had escape latencies of around 40 seconds. FMT also increased the relative abundance of *Bifidobacterium*, *Lactobacillus*, *Faecalibaculum*, and *Desulfomicrobium* species in gut microbiomes of 5xFAD mice while decreasing hippocampal A β deposition. Since a lower escape latency correlates with better spatial learning and memory, this study further demonstrates how microbiota changes can improve disease hallmarks in an AD mouse model.

Upadhyay and colleagues investigated the effects of FMT on cognition, neuroinflammation, and oxidative stress in 5xFAD mice. This study utilized 5 different groups: an untreated 5xFAD group, a 5xFAD group receiving FMT from other 5xFAD mice, a 5xFAD group receiving FMT from wild-type mice, untreated wild-type mice, and wild-type mice receiving FMT from 5xFAD mice. Prior to treatment, antibiotics were administered to eliminate previous microbiota. FMT was administered daily for 8 weeks, and after day 50 of treatment, behavioral tests were administered and inflammatory cytokines were measured. Results showed that FMT from healthy donor mice to 5xFAD mice improved cognition and decreased inflammation. In the MWM, this group of mice had decreased escape latencies while 5xFAD mice receiving FMT from other 5xFAD mice had an unchanged escape latencies. 5xFAD mice receiving wild-type FMT also had a reduction in pro-inflammatory cytokines such as TNF- α , IFN- γ , IL-17, IL-1 β , IL-6, and IL-10, as well as reductions in oxidative stress biomarkers like lipid peroxidation, therefore demonstrating how microbiota changes can influence improvements in both cognition and AD biomarkers in 5xFAD mice (Upadhyay et al., 2025).

Probiotics alter the gut microbiome to improve symptoms in Alzheimer's disease

Rather than directly changing the gut microbiome, ingesting probiotics can also improve AD symptoms. In a study by Prajapati and colleagues, researchers investigated the effects of a human-origin probiotics cocktail on AD pathology in a APP/PS1 mouse model, which is a mouse line that models AD by expressing mutated human APP and PSEN1 genes (Prajapati et al., 2025). APP/PS1 mice aged 6-8 weeks were put into either a control or probiotics group, with the probiotics group receiving a cocktail of 5 *Lactobacillus* and 5 *Enterococcus* strains in their drinking water. After 16 weeks, cognitive tests showed that the probiotic drink significantly reduced cognitive decline. The probiotics group demonstrated shorter escape latencies in the MWM, with the probiotics group having 10 seconds as their average and the control group having 20 seconds. Mice who received the cocktail also showed decreased A β accumulation in the hippocampal region, as seen through an A β 42/40 ratio of around 2.5, compared to the control group's ratio of around 6, where A β 42 is considered more toxic and amyloidogenic compared to A β 40 (Qiu et al., 2015).

Hsu and colleagues researched the effects of probiotic supplements on AD patients using a 12-week randomized trial (Hsu et al., 2023). 32 AD patients between 50 and 90 years old with

mild to moderate dementia participated in the study, with 16 participants in a treatment and control group. The treatment group received probiotic supplements containing equal amounts of 5 strains daily. Researchers administered questionnaires and cognitive assessments before and after the 12-week trial. Although this study did not find significant improvements in cognitive function, demonstrated by no changes in cognition tests, results did show that the treatment group's inflammatory biomarkers were reduced. Specifically, pro-inflammatory cytokine IL-1 β levels decreased. Additionally, cortisol, which can enhance the effects of pro-inflammatory cytokines, decreased in the treatment group, where the fold change of decrease was 110.34%. . Therefore, the study proves how probiotics can alleviate neuroinflammation in AD patients.

Akhgarjand et al. investigated the effects of two strains of probiotics on AD symptoms in 90 patients ages 50-90 years old with mild to moderate AD (Akhgarjand et al., 2024). Using a 12-week trial, participants were divided into 3 groups: the control, which received a capsule without probiotics; intervention 1, which received a capsule with *Lactobacillus rhamnosus*; and intervention 2, which received a capsule with *Bifidobacterium longum*. Participants ingested the capsules twice every day. Researchers measured cognitive function, anxiety, and activities of daily living before and after the treatment. Results from the study show that the intervention 1 group had a significantly higher score difference than the two other groups on the Categorical Verbal Fluency Test , an assessment measuring cognition where patients have to come up with words given a certain parameter or category. Additionally, both intervention 1 and 2 groups showed significant improvement on the Generalized Anxiety Disorder Scale, where a higher score shows higher anxiety.. This study demonstrates how probiotics supplementation can not only improve cognition in AD patients, but also alleviate other behavioral symptoms such as stress.

Another study investigated the effects of probiotic and selenium co-supplementation on AD patients through a 12-week trial (Tamtaji et al., 2018). 79 participants between 55-100 years old who were diagnosed with AD were split into a probiotic with selenium group, a selenium-only group, and a placebo group. The probiotic with selenium group received 200 μ g/day of selenium along with a probiotic supplement containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*. Researchers also administered a cognitive assessment, the Mini-Mental State Examination (MMSE) at the start and end of the 12 weeks. Results showed that the probiotic and selenium co-supplementation group improved significantly in its MMSE score, with a difference of +1.5, compared to the placebo group's -.2 and selenium-only group's +.5. Since the MMSE measures cognitive functions including orientation, memory, attention, and language, this study shows how selenium supplementation with probiotics can improve cognition in AD patients.

In another study by Nimgampalle and colleagues, researchers investigated the effects of the probiotic strain *Lactobacillus plantarum* on albino rats with D-Galactose-induced AD

(Ningampalle et al., 2017). Researchers used 48 3-month old male albino rats who were injected with the monosaccharide D-Galactose, which induces characteristics of AD such as A β plaques, neurofibrillary tangles, and reduced levels of acetylcholine. It also causes AD-like symptoms such as decline in spatial memory and behavioral activity. The rats were divided into a control, AD group without *L. plantarum*, AD group that received *L. plantarum* for 60 days, and a control group that received only *L. plantarum* starting from the seventh week. Cognition and behavior were assessed on the 30th and 60th day. Results showed that the AD group receiving probiotics has improved spatial memory in the MWM. The AD group also demonstrated a significantly shorter average escape latency of around 10 seconds compared to the AD group without probiotics, which had an average escape latency of around 30 seconds. Additionally, the AD group, which demonstrated AD biomarkers such as amyloid plaques and tangles through D-Galactose, were restored to normal, pre-D-Galactose histopathological features following *L. plantarum* treatment. Therefore, this study shows how probiotics can improve cognition and physiological biomarkers in rats with AD-like symptoms.

The ketogenic diet improves symptoms of Alzheimer's disease

In addition to probiotic supplementation, “fad” diets are also a very popular dietary adaptation. Several studies have shown that the ketogenic diet (KD) improves symptoms of AD, both in APP/PS1 mouse models and human subjects. Jiang and colleagues investigated the effects of a KD on improving cognitive function and neuroinflammation in the early stages of AD (Jiang et al., 2023). They used 3 month old male APP/PS1 mice. The mice were given either the KD, which was low in carbohydrates, high in fat, and moderate in protein, or the control diet (CD), a typical laboratory diet (11.5% fat, 10.4% protein, 78.1% carbohydrate), with 12 mice in each group over a span of 3 months. After 3 months, the cognitive functions of mice in all groups were assessed through behavioral testing. Results showed that the KD treatment enhanced cognitive function while reducing neuroinflammation. During the NORT, APP/PS1 mice in the KD group demonstrated a significant increase in recognition index, demonstrating that cognition can improve with KD. Additionally, KD alleviated neuroinflammation by reducing A β plaque deposition and suppressing microgliosis. The study showed a reduction in A β 42 and a reduction in the number of IBA1-positive microglia in both the cortex and the hippocampus of the APP/PS1 mice under the KD treatment group. Since microglial and astrocyte activity are well-accepted measures of neuroinflammation, Jiang and colleagues conclude that amyloid pathology and neuroinflammation measures can be reduced through the ketogenic diet.

Brownlow et al. also investigated the efficacy of a ketogenic diet on mice (Brownlow et al., 2013). They used 60 mice, which included five months old APP/PS1 mice (a model of amyloid deposition), Tg4510 mice (a model of tau deposition), and control mice. Each type of mice was placed into experimental KD groups or control groups, with 10 mice in each group for 16 weeks. The KD included low carbohydrates and medium chain triglyceride-rich foods. Researchers assessed behavior and cognition after 14 weeks, and tests showed that mice on the KD showed

better motor skills compared to control diet mice in the rotarod test. Researchers measured average latency to fall off the rod, where a higher latency to fall off suggests better motor performance. In Tg4510 mice, the average latency to fall off was around 150 seconds for mice fed on a CD, but almost 200 seconds for KD. Therefore, this study demonstrates how the KD can improve symptoms of AD such as motor skills.

In a study done by Henderson and colleagues, the ketogenic compound AC-1202 was investigated as a potential treatment to improve cognition in patients with mild to moderate AD over 90 days (Henderson et al., 2009). Ketogenic compounds, which are produced by the body as an alternative to glucose while fasting or during KD, induce ketosis. This study was conducted at 23 sites and included 152 patients who were separated into placebo and treatment groups, with those in the treatment group receiving AC-1202 orally daily as a powder mixed with water, juice, or milk. Cognitive assessments and physiological measurements were administered at days 0, 45, 90, and 104 after administration of AC-1202. Results showed that AD Assessment Scale-Cognitive, which measures cognitive abilities such as memory, language, and orientation by requiring test-takers to perform tasks such as naming objects or recalling words, scores for the AC-1202 group was significantly higher than those of the placebo group. The AC-1202 group scored 5.33 points higher than the placebo group by the end of the study, thus showing how a ketogenic compound that induces a ketosis-like state can improve cognition in AD patients.

In a randomized crossover trial with 26 AD patients was performed to assess if a KD administered over 12 weeks could improve their cognition, daily function, or quality of life (Phillips et al., 2021). The KD included meal plans with an average macronutrient ratio of 58% fat (26% saturated, 32% non-saturated), 29% protein, 7% fiber, and 6% net carbohydrate, while the CDt included an average ratio of 11% fat (3% saturated, 8% non-saturated), 19% protein, 8% fibre, and 62% net carbohydrate. This study included two 12-week treatment periods separated by a 10-week washout period where participants ate according to their usual diets. Assessments evaluating quality of life, cognitive function, and daily function were given; a baseline assessment was given before each treatment period, and during weeks 6 and 12. Although the KD had no significant effects on cognitive functions, it did improve daily function and quality of life, increasing the scores on both tests by 3.13 ± 5.01 points and $+3.37 \pm 6.86$ points, respectively. Since decreased daily function and quality of life are both key aspects of AD, this study demonstrates that the ketogenic diet can potentially improve hallmarks of AD.

Researchers investigated the effects of a ketogenic medium chain triglyceride (kMCT) drink on patients with mild cognitive impairment (MCI) (Fortier et al., 2020). 56 participants diagnosed with MCI were placed into either an experimental group that received the ketogenic drink or a control group. The ketogenic drink was an emulsion providing 30g/day of kMCTs in 250 mL of lactose-free skim milk and was administered daily between two meals for six months. Patients'

cognition was assessed at baseline and at the end of the study, where tests included a neurocognitive battery measuring multiple domains such as episodic memory, executive function, attention, processing speed, and language ability. Results showed that the group with the ketogenic drink had significantly improved in certain cognitive domains. For instance, on the Rappel Libre/Rappel Indicé test, the French version of the 16-item free and cued word learning and recall test that assesses episodic memory, the kMCT group recalled 20% more words compared to the baseline. Therefore, this study shows how a ketogenic drink can improve cognitive functions of MCI patients.

Discussion

The continued investigation of AD has helped develop treatments ranging from symptomatic to multifactorial ones. Common types of treatments include cholinesterase (AChE) inhibitor drugs, such as donepezil or galantamine, and the NMDA receptor (NMDAR) antagonist memantine (Alzheimer's Society, 2014), along with the newly approved drug Donanemab (Alzheimer's Association, 2025). AD destroys neurons that produce the neurotransmitter acetylcholine (ACh), thus leading to low levels of this vital molecule. AChE inhibitors aim to block the breakdown of ACh in hopes of maintaining a healthy ACh level (Singh and Sadiq, 2023). While they improve certain symptoms such as memory, attention, apathy, and agitation during the milder stages of AD, their effectiveness decreases as the disease progresses. AChE inhibitors can also have side effects such as nausea or cardiac arrhythmia (Vecchio et al., 2021). Memantine, a partial NMDAR antagonist, prevents glutamate overactivation during AD and improves memory, mood, and cognition, allowing patients to better perform daily tasks (Olivares et al., 2016). However, memantine's side effects include hallucinations, confusion, headache, and dizziness and its benefits are limited to individuals with moderate to severe AD (Tang et al., 2023). Lastly, Donanemab, an anti-amyloid antibody, slows down early AD progression by binding to a specific form of A β called N3pE-A β and stimulates microglial cells to begin clearing those plaques (Alzheimer's Association, 2025). Common side effects include headaches and amyloid-related imaging abnormalities (ARIA), which can be characterized by cerebral edema or hemorrhage (Rabinovici et al., 2025). Currently, there is no cure for AD and thus, it is important to investigate physiological factors affecting AD, such as the gut microbiome, in order to work towards improved and novel treatments.

Due to the popularity of the ketogenic diet, there is growing consumer interest in the impact of it on not just weight loss, but all avenues of health, including the development and progression of brain health and neurodegenerative diseases such as AD. Probiotics, another popular product among consumers, is also worthy of investigation, since they have become increasingly integrated into the American diet in the forms of supplements or foods marketed as being probiotic-rich. Because these aspects of diet are already commonly present in the U.S., researchers should take advantage of their ubiquity to potentially investigate their effects on various populations or various stages and types of AD. Furthermore, current obesity rates in



America are high due to a diet filled with processed foods. As diet culture and patterns change, the health of Americans, from their microbiota to their brains, also change. Investigating the mechanisms of AD and diet will allow researchers to better create and apply novel treatments; thus, it is even more imperative to monitor the gut microbiome and its relationship to AD. Doing so may create new insights to the mechanisms and functions of the gut-brain axis in both health and disease, leading to the potential of novel treatments for AD.

Conclusion

Alzheimer's disease is a destructive and complex neurological disorder that is affected by multiple factors, including the relationship between the gut microbiome and the brain. This review specifically discussed how the gut microbiome is altered in AD, and how dietary interventions such as probiotics and the ketogenic diet influence AD symptoms. However, more research is needed to further refine the specific mechanisms in which the keto diet and probiotics affect AD and the gut-brain axis in order to develop new therapies.

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