

Review

Targeting the Microbiota–Butyrate–BHB Axis As a Potential Metabolic Therapeutic Strategy for Alzheimer’s Disease

Vijay Kumar^{1#}, Sinae Jang^{1#}, Yebeen Choi^{1#}, Sujin Kim^{1,3}, Yunkwon Nam¹,
MyeongHeon You¹, Minhoo Moon^{1,2*}

¹Department of Biochemistry, College of Medicine, Konyang University, Daejeon 35365, Korea. ²Research Institute for Dementia Science, Konyang University, Daejeon 35365, Korea. ³Division of Cardiovascular Disease Research, Department of Chronic Disease Convergence Research, Korea National Institute of Health, Cheongju-si 28159, Korea

[Received May 18, 2026; Revised July 16, 2026; Accepted July 17, 2026]

ABSTRACT: Alzheimer’s disease (AD) is increasingly linked to metabolic and microbial dysregulations, with butyrate and β -hydroxybutyrate (BHB) identified as key modulators. BHB is a ketone body primarily produced by the liver during periods of low glucose availability, and BHB levels are reduced in the AD brain and peripheral blood. Butyrate, a microbiota-derived short-chain fatty acid, is also reduced in the peripheral blood in association with gut microbiota dysbiosis. The reduction of butyrate and BHB, together with gut microbiota dysbiosis, is commonly observed in AD patients and correlates with cognitive decline and AD-related pathologies. Reduced levels of butyrate and BHB may impair energy metabolism, exacerbating amyloid-beta ($A\beta$) and tau pathologies. In contrast, preliminary evidence from interventional and ketogenic studies suggests that increasing butyrate and BHB levels may attenuate AD-related pathologies, such as $A\beta$ and tau abnormalities, while improving cognitive function. Emerging evidence suggests that both butyrate and BHB can cross the blood-brain barrier (BBB), suppressing oxidative stress and pro-inflammatory cytokines and potentially mitigating $A\beta$ aggregation and tau hyperphosphorylation. Accordingly, therapeutic strategies targeting the microbiota–butyrate–BHB axis represent a promising and biologically plausible approach that warrants further rigorous clinical investigation for the prevention and treatment of AD. This review comprehensively examines the roles of butyrate and BHB in ameliorating key AD-related pathologies, including $A\beta$ aggregation, tau hyperphosphorylation, neuroinflammation, and neurodegeneration. Additionally, the review explores the bidirectional association between butyrate/BHB and gut dysbiosis in AD, including how dysbiosis reduces butyrate/BHB levels while elevating them may reverse dysbiosis and improve gut-brain axis function. Collectively, these findings suggest that butyrate and BHB emerge as promising candidates for potential novel adjunctive therapies for AD, although supporting human evidence remains preliminary and heterogeneous.

Keywords: Alzheimer’s disease, β -hydroxybutyrate, Butyrate, AD-associated pathology, Microbiota dysbiosis

1. Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline, driven by multiple pathological

processes [1]. Diverse neuropathological hallmarks, including amyloid-beta ($A\beta$) and tau pathology, neuroinflammation, mitochondrial dysfunction, and synaptic and neuronal loss, have been observed in the brains of AD patients [2, 3]. In addition to these central

*Correspondence should be addressed to: Dr. Minhoo Moon, Department of Biochemistry, College of Medicine, Konyang University, Seo-gu, Daejeon 35365, Korea. E-mail: hominmoon@konyang.ac.kr. #These authors have contributed equally to this work.

Copyright: © 2026 Kumar V. et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

pathologies, recent research also implicates peripheral factors—particularly systemic metabolic dysfunction and gut microbiota dysbiosis—in the pathogenesis and progression of AD [4–7]. Importantly, complex crosstalk between the gut microbiome and systemic metabolic pathways can induce cerebral metabolic impairment, such as glucose hypometabolism in AD [8–10]. The disruption of glucose utilization in AD highlights the potential importance of alternative energy substrates to meet energy requirements [11–13]. While peripheral tissues can oxidize circulating fatty acids as an alternative fuel, the inability of bulky fatty acid molecules to easily cross the blood-brain barrier (BBB) limits their direct utility in the brain. Thus, instead of fatty acid utilization, the energy-deficient brain relies on alternative substrates that easily pass through the BBB. These include short-chain fatty acids (SCFAs) and ketone bodies, which can penetrate the BBB via carrier-mediated transport [14–16].

SCFAs are primarily produced by bacterial fermentation of dietary fibers in the colon [17]. The most abundant of these metabolites are butyrate, acetate, and propionate, of which butyrate mainly has beneficial effects by interrupting the progression of AD [18]. Notably, gut-derived butyrate not only serves as a direct energy substrate but can also contribute to hepatic ketogenesis and the production of β -hydroxybutyrate (BHB), particularly under low-carbohydrate conditions [19, 20]. This relationship is primarily supported by metabolic studies in healthy individuals, and its quantitative importance in AD patients remains to be fully clarified. Specifically, in the liver, butyrate is converted to butyryl-coenzyme A (butyryl-CoA) by acyl-coenzyme A (acyl-CoA) synthetase and undergoes β -oxidation to form acetyl-coenzyme A (acetyl-CoA) [21, 22]. During fasting or low-carbohydrate states, acetyl-CoA is transformed into acetoacetyl-coenzyme A (acetoacetyl-CoA) via thiolase, and then into 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) by HMG-CoA synthase. Subsequently, HMG-CoA is cleaved by HMG-CoA lyase to produce acetoacetate, which is sequentially reduced into BHB by β -hydroxybutyrate dehydrogenase [21, 22]. Indeed, among the various ketone bodies generated via this hepatic ketogenesis, which also include acetoacetate and acetone, BHB is the most abundant and stable circulating metabolite in the blood [23, 24]. Importantly, BHB levels can also be elevated independently through ketogenic diets, fasting, or medium-chain triglycerides (MCT) supplementation, which may not rely on gut-derived butyrate [25, 26]. Since brain regions with abnormal glucose metabolism in AD still efficiently uptake ketone bodies [27], these ketone bodies can be used as an alternative energy source instead of glucose [28]. However, the altered gut microbial environment in AD, characterized by dysbiosis,

suppresses the production of gut-derived butyrate [29–31]. Similarly, the depletion of butyrate in AD is closely associated with a decrease in gut microbial diversity, forming a vicious feedback loop [32, 33]. Additionally, a significant reduction in the levels of both butyrate and its downstream metabolite, BHB, has been observed in AD patients [34–36]. To address this detrimental depletion in AD, supplementing these metabolites has emerged as a potential therapeutic strategy. Interestingly, both butyrate and BHB share structural similarities and exert comparable pharmacological effects, improving glucose uptake and mitigating metabolic dysfunction in AD-affected brains [18, 37]. Moreover, exogenous administration of butyrate or BHB has been shown to be promising in preclinical studies to ameliorate AD-associated cognitive impairment and mitigate gut microbiota dysbiosis [38, 39]. In addition to these independent benefits, the synergistic effects of butyrate and BHB show therapeutic potential for AD and other metabolic disorder-associated brain diseases [19, 34]. Therefore, targeting the microbiota–butyrate–BHB axis may represent a biologically plausible metabolic strategy with the potential to restore cerebral energy homeostasis and mitigate the pathogenesis and progression of AD, pending validation in large-scale clinical trials.

Despite the growing body of evidence on gut microbiota dysbiosis, SCFAs, particularly butyrate, and ketone bodies such as BHB in AD, comprehensive reviews that integrate their complex and bidirectional interactions within a unified microbiota–butyrate–BHB axis remain limited. Several reviews have addressed aspects of the gut-brain axis in AD, the role of SCFAs in neuroinflammation and cognition, or the therapeutic potential of ketogenic diets or BHB independently. However, these works often treat butyrate and BHB as separate entities without fully exploring their metabolic linkage, particularly the potential contribution of butyrate to hepatic ketogenesis, their shared signaling pathways, such as G-protein-coupled receptor 109A (GPR109A) activation, histone deacetylase (HDAC) inhibition, and NLRP3 suppression, and their synergistic effects on restoring cerebral energy homeostasis and reversing dysbiosis.

The present review fills this gap by providing a focused synthesis of the microbiota–butyrate–BHB axis as a cohesive metabolic therapeutic strategy. We delineate (1) alterations in butyrate and BHB levels in AD patients and models; (2) their reciprocal relationship with gut dysbiosis, including how elevating these metabolites can reshape the microbiome, enriching beneficial taxa like *Akkermansia muciniphila* while suppressing pro-inflammatory ones; (3) overlapping and complementary mechanisms by which butyrate and BHB mitigate A β aggregation, tau hyperphosphorylation, neuro-

inflammation, oxidative stress, and synaptic/neurodegenerative changes; and (4) translational evidence from preclinical models of butyrate-targeted approaches and clinical trials of BHB-elevating interventions. By emphasizing the liver–gut–brain metabolic continuum and potential synergies such as high-fiber diets combined with ketogenic strategies, this review offers novel insights into a promising and metabolically grounded avenue that warrants further investigation. Taken together, we seek to provide insights into the therapeutic potential of modulating the microbiota–butyrate–BHB axis in AD.

2. The relevance of butyrate and BHB in AD

2.1 Alteration of butyrate level in AD

Although butyrate concentrations vary across studies, typical physiological levels in healthy adults are approximately 0.2–1.5 μM in peripheral blood, 0–2.8 μM in cerebrospinal fluid (CSF), and 4.44–11.9 $\mu\text{mol/g}$ in the gut lumen [17, 40–42]. Unfortunately, quantitative data comparing absolute butyrate concentrations between cognitively healthy controls and AD patients remain limited, highlighting the need for future studies. Nevertheless, existing evidence indicates that butyrate levels are substantially reduced in patients with AD compared with controls. Previous clinical observational studies have shown significantly altered butyrate levels in the feces and blood of AD patients compared to healthy controls [35, 36, 43]. The fecal concentration of butyrate was significantly decreased in mild cognitive impairment (MCI)-stage patients with AD compared to healthy controls. In particular, the mean fecal concentration of butyric acid, which is the protonated form of butyrate, was significantly decreased in MCI-stage AD patients at $825.28 \pm 544.49 \mu\text{g/g}$ compared with healthy controls at $1,156.32 \pm 583.59 \mu\text{g/g}$ [35]. Consistently, fecal levels of n-butyric acid, the acidic form of butyrate, were substantially reduced in AD patients compared to healthy controls, with mean concentrations of approximately 200 $\mu\text{g/g}$ in AD patients compared to 850 $\mu\text{g/g}$ in healthy controls [44]. In addition, serum n-butyric acid levels were significantly lower in AD patients compared to healthy controls, with mean concentrations of approximately 0.05 $\mu\text{g/ml}$ in AD patients compared with 0.2 $\mu\text{g/ml}$ in healthy controls [44]. Furthermore, plasma butyrate levels were measured in 67 participants: 10 cognitively unimpaired healthy controls (control group), 28 individuals with cognitive impairment due to AD (AD group), and 29 with cognitive impairment not due to AD (non-AD group). Plasma butyrate levels were significantly lower in the AD group compared to both the control group and the non-AD group [43]. These findings indicate that butyrate levels are selectively reduced in the

AD patient group. Furthermore, age-related changes in butyrate levels were examined in healthy control mice and amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice at multiple times up to 12 months of age [45]. Butyrate levels remained relatively similar between the two groups up to 4 months of age. However, starting from 5 months of age, APP/PS1 mice showed significantly lower butyrate levels in both feces and brain tissue compared to healthy controls. For example, at 5–6 months, fecal butyrate levels were $364 \pm 47 \mu\text{g/g}$ in APP/PS1 mice compared to $535 \pm 178 \mu\text{g/g}$ in control mice, while brain butyrate levels were $31 \pm 2 \text{ nmol/g}$ in APP/PS1 mice compared to $38 \pm 4 \text{ nmol/g}$ in control mice [45]. Taken together, butyrate is an important metabolite reflecting the relationship between gut microbiota and the gut–brain axis in patients with AD. Alterations in butyrate levels may play a critical role in the onset and progression of AD and highlight the potential of butyrate as a metabolic biomarker for AD.

2.2 Alteration of BHB level in AD

BHB levels are consistently lower in both animal models and patients with AD compared to wild-type control mice and healthy individuals, respectively, as observed in peripheral blood and brain tissue [34, 46]. Specifically, an investigation comparing brain metabolites between healthy and AD patients reported significantly reduced levels of BHB in the brain parenchyma of AD patients [34]. Consistently, a recent metabolomics study reported that BHB levels were markedly decreased more than glucose-derived metabolites such as fructose-6-phosphate and pyruvate in the prefrontal cortex of AD patients [47]. In AD, ketogenesis pathways are impaired or less efficient, which contributes to the reduced supply of brain energy [11, 48]. Although low-carbohydrate diets and fasting are not direct models of AD, they hold therapeutic relevance by stimulating ketogenesis. This approach is particularly appropriate for AD, where brain glucose hypometabolism is a well-established early feature [11]. The resulting impairment in brain energy metabolism can potentially be bypassed by ketone bodies, which serve as an alternative fuel source for the brain. Sprague–Dawley rats subjected to a low-carbohydrate diet or fasting exhibit markedly increased hepatic ketogenesis, thereby elevating BHB levels in plasma and CSF and providing ketone bodies as an alternative energy source to compensate for reduced glucose metabolism [49, 50]. Moreover, fasting-induced ketosis increased the levels of BHB in the occipital lobe and plasma of healthy adults [26]. In addition, BHB concentrations of blood reflect BHB levels in the CSF [50], and BHB levels in blood and brain are positively correlated [26]. In healthy individuals, the blood concentration of ketone bodies, including BHB and

acetoacetate, is approximately 0.1 mM and BHB constitutes the largest proportion [51]. However, the precise BHB concentrations in the brain, plasma, and CSF between healthy individuals and AD patients have yet to be established. Recent findings have shown that the level of BHB in plasma was 0.03 ± 0.04 mM, and the level of BHB in voxel was 0.05 ± 0.05 mM in healthy adults [26]. Fasting blood levels of BHB in patients with AD or MCI were 0.04 ± 0.02 mM in people without the apolipoprotein E $\epsilon 4$ gene (APOE $\epsilon 4$ non-carriers) and 0.08 ± 0.08 mM in people with the APOE $\epsilon 4$ gene (APOE $\epsilon 4$ carriers) [52]. Such variation in BHB concentrations may result from differences in measuring methods, experimental groups, and inter-individual differences. However, interpreting the causal role of reduced BHB levels in the brain, plasma, and CSF requires caution. Decreased BHB levels may act as pathogenic factors impairing cerebral bioenergetics, but they could also reflect secondary consequences of AD progression. Specifically, systemic depletion of these metabolites can be independently driven by confounding factors such as altered diet, frailty, comorbidities, medication use, altered gut transit, and disease-related reductions in food intake [53, 54]. Therefore, whether this deficiency represents a primary pathogenic factor or a secondary consequence of AD progression remains to be fully elucidated. Furthermore, current clinical evidence remains limited despite promising preclinical findings. Therefore, a strict hierarchy of evidence—from *in vitro* and *in vivo* models to human clinical trials—must be considered when evaluating their translational therapeutic potential. Collectively, the observed alterations in BHB levels among AD patients often characterized by lower circulating or brain concentrations may reflect disturbances in brain energy metabolism and reduced availability of ketone bodies as an alternative fuel. These findings suggest that BHB levels have potential as a metabolic biomarker for AD.

3. The association of butyrate and BHB with AD-related pathologies in the brain

3.1 Butyrate on AD-related pathologies

Butyrate has shown promising effects in preclinical models due to its multifaceted impact on AD. Butyrate targets A β accumulation, tau hyperphosphorylation, neuroinflammatory processes, and neurodegeneration, thereby slowing AD progression. This section reviews evidence on butyrate's effects in reducing AD-related pathologies in AD models.

Accumulation of A β peptides generated through sequential cleavage of APP by beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) and γ -secretase leads to neuronal dysfunction in AD [55].

Sodium butyrate (NaB) is a stable and water-soluble form of butyrate that is ideal for supplementation and research in mitigating AD pathologies [56]. NaB has been shown to significantly inhibit A β accumulation and BACE1 expression in high-cholesterol-induced AD models [55]. NaB reduced ROS levels by downregulating nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) and upregulating superoxide dismutase 1 (SOD1), thereby mitigating oxidative stress, a key contributor to A β toxicity [55]. In N2a neuroblastoma cells, NaB treatment enhanced cell viability and reduced ROS-mediated cellular injury caused by A β , demonstrating a protective effect against A β -induced damage [55]. Furthermore, NaB activated the GPR109A, which regulates the expression of AD-related genes, including APP, neuropeptidase, and brain-derived neurotrophic factor (BDNF) [57]. This activation promotes the expression of angiotensin-converting enzyme and BDNF, both of which exert neuroprotective effects by enhancing A β clearance and supporting neuronal survival [57]. Additionally, NaB attenuated A β -induced mitochondrial dysfunction in PC12 cells, preserving cellular energy metabolism and reducing oxidative damage [58]. In APP/PS1 transgenic mice, intragastric administration of *Clostridium butyricum* (CB), a butyrate-producing bacterium, reduced A β_{40} oligomerization, further supporting butyrate's role in decreasing A β burden [59]. Collectively, these findings highlight the potential of butyrate to mitigate A β pathology, including overproduction, aggregation, and impaired clearance of A β , in part through the alleviation of oxidative stress and mitochondrial dysfunction.

Tau pathology is characterized by hyperphosphorylated tau protein forming neurofibrillary tangles (NFTs) and disrupts microtubule stability and synaptic function, exacerbating AD progression. Butyrate acts as a potent HDAC inhibitor, promoting histone acetylation, which alters gene expression patterns associated with memory and cognitive function [60, 61]. This epigenetic regulation has been shown to reduce tau phosphorylation by modulating glycogen synthase kinase 3 β (GSK3 β) activity at lysine 15 in wild-type mice and *Caenorhabditis elegans* model of AD [62]. In these models, butyrate-mediated acetylation of GSK3 β decreased tau hyperphosphorylation, improving neuronal morphology and signaling [62]. Additionally, butyrate enhanced BDNF expression through H3K18ac acetylation at the BDNF promoter, which supports neuronal integrity, potentially ameliorating tau-related synaptic dysfunction [63]. In obese mouse models, butyrate alleviated cognitive impairment induced by quinolinic acid (QA) by restoring BDNF levels, which may indirectly reduce tau pathology by enhancing neuronal resilience [63]. NaB treatment in APP/PS1 mice reduced tau hyperphosphorylation via HDAC inhibition

and restored BDNF/tropomyosin receptor kinase B (TrkB) signaling, leading to improved memory performance [60]. Although direct evidence on tau dephosphorylation is limited, the ability of butyrate to modulate epigenetic pathways and support neuronal homeostasis suggests a promising role in mitigating tau pathology in AD.

Neuroinflammation, driven by over-activated microglia and elevated pro-inflammatory cytokines, amplifies neuronal damage and accelerates AD progression. In 5XFAD mice, NaB treatment suppressed microglia activation and significantly reduced levels of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , while decreasing A β accumulation [64]. Similarly, CB administration in APP/PS1 mice lowered microglial activation, as evidenced by reduced cluster of differentiation molecule 11b levels, and inhibited cyclooxygenase-2 (COX-2) and NF- κ B p65 phosphorylation in A β -induced BV2 microglial cells [59]. These anti-inflammatory effects were associated with reduced A β burden and improved cognitive function, highlighting butyrate's role in attenuating inflammation-driven pathology [59]. Butyrate modulates the gut-brain axis via free fatty acid receptor 3 signaling further contributing to anti-inflammatory effects, as disruptions in this pathway during aging exacerbate neuroinflammation and AD pathogenesis [65]. By restoring butyrate levels through microbial modulation, neuroinflammatory processes can be mitigated, supporting neuronal health and slowing disease progression [59].

Neurodegeneration in AD, characterized by synaptic loss and neuronal death, is associated with cognitive decline. Butyrate enhances synaptic plasticity, as demonstrated in 5XFAD mice treated with NaB for two weeks, which showed improved long-term potentiation (LTP) and depotentiation (DEP), critical mechanisms for learning and memory [64]. NaB increased dendritic spine density and synapse-associated proteins such as postsynaptic density protein 95 (PSD-95), synaptophysin (SYP), and NMDA receptor subunit 2B (NR2B), counteracting synaptic loss in AD mice [64]. In APPPS1-21 mice, prolonged NaB treatment acted as an HDAC inhibitor and increased associative memory by elevating hippocampal histone acetylation and upregulating genes related to learning [60]. Additionally, NaB treatment reduces A β by 40% in the brain and improves fear response by 25% in contextual and cued fear conditioning tests, indicating enhanced cognitive function at early AD stages [61]. Tributyrin, a butyrate prodrug that undergoes hydrolysis to butyrate in the intestine and liver, has shown potential in preventing cognitive decline in transgenic 3xTg-AD mice [66]. Butyrate also alleviated QA-induced neuronal lesions by restoring BDNF levels through

epigenetic mechanisms, reducing neuroinflammation and neurodegeneration in obese mice [61]. Additionally, butyrate stabilizes the glutamate/gamma-aminobutyric acid (GABA) system, reducing excitotoxicity and supporting neuronal metabolism, as seen with gamma-hydroxybutyrate in AD models [67, 68]. Butyrate regulates astrocyte metabolism to enhance energy homeostasis, supporting neuronal survival [69]. High-acetate and butyrate diets delayed cognitive decline, improved hippocampal neurogenesis, and influenced microglial morphology in 5XFAD mice, with transgenerational cognitive benefits observed in offspring of mothers on high-fiber diets rich in SCFAs [70]. The role of butyrate in ketone metabolism, overlapping with alternate day fasting effects, provides an alternative energy source for neurons, compensating for glucose hypometabolism in 3xTg-AD mice [71]. Although consistent preclinical evidence from 5XFAD, APP/PS1, and 3xTg-AD mouse models supports the therapeutic potential of butyrate and BHB, these promising findings require validation in human clinical studies. In addition, we have summarized important findings from the preclinical studies in Table 1. Future research should explore synergies between butyrate, dietary interventions like fasting, and other metabolic modulators to maximize therapeutic outcomes, offering hope for a comprehensive approach to managing AD.

3.2 BHB on AD-related pathologies

Previous preclinical studies have shown that BHB can ameliorate multiple core pathologies in AD models, including A β plaque deposition, tau toxicity, and neuroinflammatory responses, thereby slowing disease progression and preserving cognitive function. BHB has been suggested as a modulator of AD pathology in preclinical models, acting through multiple mechanisms. BHB treatment significantly reduced A β plaque burden, attenuated microglial overactivation, and improved cognitive performance in 5XFAD mice [72]. BHB also improved mitochondrial respiratory function and reduced A β toxicity in HT22 hippocampal neurons [72]. In addition, BHB activates the GPR109A, which downregulates APP and upregulates neprilysin (NEP) expression, thereby enhancing A β clearance in 5XFAD mice [72]. Similarly, oral administration of BHB to 5XFAD mice attenuated the activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, resulting in reduced NLRP3-dependent A β plaque formation and microgliosis [34]. BHB also protects neurons against A β -induced toxicity by preserving mitochondrial respiratory function, reducing oxidative stress, and inhibiting apoptotic pathways [73]. BHB mitigates A β neurotoxicity by upregulating tropomyosin

receptor kinase A (TrkA) in SH-SY5Y neuroblastoma cells, which suppresses HDAC1/3 expression and promotes histone acetylation, thereby ameliorating epigenetic dysregulation associated with AD [74]. Similarly, administration of a ketogenic diet composed of low carbohydrate and high saturated fat to transgenic APP V717I female mice showed approximately 25% reduction of total A β levels in brain [75]. In juvenile APP/PS1 knock-in mice, one month of high-fat, low-carbohydrate

ketogenic diet feeding improved motor coordination but produced no detectable changes in A β , β -C-terminal fragment of APP, or nitrotyrosine, an oxidative stress marker [76]. BHB-containing ketone treatment provided neuroprotection by inhibiting A β ₄₂ internalization into neurons [77]. This resulted in reduced intracellular A β ₄₂ accumulation, which restored mitochondrial complex I activity, suppressed oxidative stress, and improved synaptic plasticity [77].

Table 1. Preclinical evidence for the effects of butyrate and BHB on AD-related pathologies.

Mechanism/Pathology	Compound	Models	Key Findings	Reference(s)
Aβ plaque/accumulation	NaB	High-cholesterol AD models and N2a cells	A β accumulation ↓, BACE1 ↓, ROS via NOX2 ↓ & SOD1 ↑	[55]
	NaB/CB	APP/PS1 mice	A β 40 oligomerization ↓, GPR109A-mediated APP ↓ & NEP ↑	[57, 59]
	BHB	5XFAD mice and HT22 neurons	A β plaques ↓, Microgliosis ↓, GPR109A-mediated APP ↓ & NEP ↑	[34, 72]
	BHB	5XFAD mice	A β plaques ↓, NLRP3 inflammasome activation ↓	[34]
	BHB	SH-SY5Y cells	A β neurotoxicity ↓, TrkA ↑, HDAC1/3 ↓	[147]
	BHB/Ketones	APP/V717I, APP/PS1, and 3xTg-AD mice	Total A β ↓, Intracellular A β ₄₂ ↓, Restored mitochondrial complex-I	[75-78]
Tau pathology	Butyrate	Wild-type mice and C. elegans AD model	Tau phosphorylation via HDAC inhibition & GSK3 β acetylation ↓	[62]
	Butyrate	APP/PS1 mice	Tau hyperphosphorylation ↓, BDNF/TrkB signaling ↑	[60]
	BHB	ApoE ^{-/-} mice and 3xTg-AD mice	Tau tangles ↓, Hyperphosphorylated tau ↓	[80, 81]
Neuroinflammation	NaB	5XFAD mice and APP/PS1 mice	Microglia activation ↓, TNF- α /IL-6/IL-1 β ↓, NF- κ B p65 & COX-2 ↓	[59, 64]
	BHB	5XFAD mice, CCH rats and LPS-stimulated cells	Microglial activation ↓, IL-1 β /TNF- α /IL-6 ↓, NF- κ B ↓, NF- κ BIA/MAP3K8/TLR5 ↑	[34, 72, 87-90]
Mitochondrial function & oxidative stress	NaB	PC12 cells	A β -induced mitochondrial dysfunction ↓	[58]
	BHB	SH-SY5Y and 3xTg-AD mice	Preserved mitochondrial respiration, ROS/MDA ↓, TCA/glycolytic intermediates ↑	[73, 78]
Synaptic plasticity & neurodegeneration	NaB	5XFAD and APPPS1-21 mice	LTP/DEP ↑, Dendritic spines ↑, PSD-95/SYP/NR2B ↑, Histone acetylation ↑	[60, 61, 64]
	BHB	3xTg-AD mice	Synaptic plasticity ↑, Oxidative damage ↓	[78]
Cognitive function	NaB	5XFAD and APPPS1-21 mice	Associative memory ↑, Fear conditioning ↑, Hippocampal neurogenesis ↑	[60, 61, 64]
	BHB/Ketogenic diet	5XFAD, 3xTg-AD, CCH rats and D-gal mice	Spatial learning/memory ↑, Motor coordination ↑	[72, 76, 81, 87, 89]

Abbreviation: A β , amyloid- β ; APP, amyloid precursor protein; BACE1, beta-site APP-cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; BHB, β -hydroxybutyrate; C. elegans, Caenorhabditis elegans; CB, Clostridium butyricum; CCH, chronic cerebral hypoperfusion; COX-2, cyclooxygenase-2; DEP, depotentiation; GPR109A, G-protein-coupled receptor 109A; GSK3 β , glycogen synthase kinase 3 β ; HDAC, histone deacetylase; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; LTP, long-term potentiation; MAP3K8, mitogen-activated protein kinase kinase kinase 8; MDA, malondialdehyde; NaB, sodium butyrate; NEP, neprilysin; NF- κ B, nuclear factor- κ B; NF- κ BIA, nuclear factor- κ B inhibitor alpha; NLRP3, NLR family pyrin domain containing 3 (inflammasome); NOX2, NADPH oxidase 2; NR2B, NMDA receptor subunit 2B; PSD-95, postsynaptic density protein 95; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; SYP, synaptophysin; TCA, tricarboxylic acid (cycle); TLR5, toll-like receptor 5; TNF- α , tumor necrosis factor- α ; TrkA, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B.

Moreover, peripheral ketone injections reduce amyloid accumulation and significantly enhance cognitive function in the APP transgenic mice [77]. Furthermore, 3xTg-AD mice, which develop both A β and

tau pathologies, were fed a ketone ester containing BHB for eight months, after which brain tissues were analyzed [78]. The ketone ester diet significantly elevated levels of tricarboxylic acid cycle (TCA) cycle intermediates,

glycolytic intermediates, and the energy-linked biomarker while decreasing the levels of oxidized proteins and lipids and shifting mitochondrial redox potential toward a more reduced state in the hippocampus [78].

APOE $\epsilon 4$ gene is the most prevalent and strongest risk factor associated with AD and atherosclerosis [79]. In high-fat diet-fed APOE^{-/-} mice, BHB administration reduced amyloid plaque deposition in the substantia nigra pars compacta and inhibited both lipid accumulation and cluster of differentiation 68+ (CD68+) microglial infiltration in the choroid plexus. Additionally, BHB significantly reduced tau tangles in the hippocampal region of APOE^{-/-} mice [80]. The 3xTg-AD mice fed a ketone ester-based diet containing BHB exhibited reduced anxiety, improved performance on learning and memory tests, and decreased both A β deposition and hyperphosphorylated tau in the hippocampus, amygdala, and cerebral cortex [81]. Ketone ester-based diet can attenuate AD pathogenesis by reducing both A β and hyperphosphorylated tau deposition in the brains of mice [81]. Additionally, BHB supplementation in 5XFAD mice reduced A β plaque burden and improved synaptic plasticity by activating the GPR109A receptor and inhibiting NLRP3 inflammasome activation [34]. In conclusion, these preclinical findings indicate that BHB has the potential to regulate AD pathology and may serve as a candidate therapeutic agent.

In AD, neuroinflammation is strongly associated with A β and tau pathologies [82]. Soluble A β oligomers as well as fibrillar deposits, together with tau species, trigger microglia to shift from a homeostatic surveillant M2 state toward reactive and pro-inflammatory M1 states [83]. Activated microglia release inflammatory cytokines and elevate reactive oxygen species (ROS), which together promote neuronal death and progression of AD [84, 85]. BHB treatment attenuated the overactivation of microglia, as shown by decreased Iba-1 immunostaining, and suppressed the elevated mRNA levels of the pro-inflammatory cytokines interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) in the cortex and hippocampus of 5XFAD mice [72].

Consistently, BHB treatment significantly reduced microgliosis, as evidenced by a decrease in the total number of Iba-1⁺ activated microglia in the cortex/hippocampus of 5XFAD mice [34]. Chronic cerebral hypoperfusion (CCH), a long-term reduction in blood flow to the brain, is increasingly recognized as an important contributor to AD [86]. Animal models of CCH demonstrate that reduced cerebral blood flow can trigger AD-like pathologies, including A β accumulation, tau hyperphosphorylation, synaptic loss, and cognitive deficits, thus highlighting the important role of the CCH model in investigating AD-related mechanisms [86]. The intraperitoneal injection of BHB in rats with CCH

significantly decreased the levels of nuclear factor- κ B (NF- κ B), TNF- α , IL-1 β , and receptor for advanced glycation end products (RAGE) in the hippocampus, indicating its mitigating effect on neuroinflammation [87]. BHB treatment significantly inhibited microglial activation and reduced the production of pro-inflammatory mediators, including ROS, nitrite, IL-1 β , TNF- α , and IL-6 in BV2 microglial cells *in vitro* [88]. BHB alleviated learning and memory impairment by activating the silent information regulator 1 (SIRT1) pathway and decreasing the levels of IL-1 β , TNF- α and NLRP3 in the hippocampus of D-galactose-injured C57BL/6 mice, which serve as a well-established accelerated aging model [89]. Furthermore, BHB exerted anti-inflammatory and antioxidant effects in lipopolysaccharide (LPS)-stimulated macrophages [90]. BHB significantly suppressed the pro-inflammatory markers tumor necrosis factor superfamily member 6, TNF- α , phosphoinositide 3-kinase, NF- κ B, and Toll-like receptor 1, while upregulating the anti-inflammatory markers nuclear factor- κ B inhibitor alpha (NF- κ BIA), mitogen-activated protein kinase kinase kinase 8 (MAP3K8), and Toll-like receptor 5 (TLR5) in the BHB pretreatment group [90]. These results suggest that BHB may regulate multiple pathways to suppress neuroinflammation associated with AD.

Since cognitive impairment is a symptom of AD, improved cognitive ability indicates the therapeutic potential of the drug candidate. For instance, studies using APP/PS1, 3xTg-AD, and APP J20 mouse models of AD have shown that ketogenic diets or BHB supplementation significantly improve cognitive function [76, 81, 91]. Intraperitoneal injection of BHB for eight weeks significantly improved spatial learning and memory in CCH rats [87]. Similarly, BHB improved learning, memory, and cognitive abilities in D-gal-injured mice and 5XFAD mice [72, 89]. Additionally, BHB precursors MCTs and ketone ester have been associated with improvements in memory-based tasks and cognitive functions in mouse models of AD [52, 92]. Additionally, there is evidence from patients with mild-to-moderate AD that MCT supplementation improves cognitive function. Twenty patients with mild-to-moderate AD received an MCT-based ketogenic diet [93]. Subsequently, the cognitive test was conducted at 8 and 12 weeks, respectively. At 8 weeks of MCTs-based ketogenic diet, patients exhibited marked enhancement in both immediate and delayed logical memory assessments relative to their baseline scores. By 12 weeks, patients showed significant improvements in digit-symbol coding and immediate logical memory tests from baseline [93]. Consistently, MCTs show positive therapeutic effects on cognitive ability in mild-to-moderate AD patients with APOE $\epsilon 4$ ^{-/-} [94]. Although MCT does not contain BHB,

the liver quickly absorbs MCT and converts them into ketone bodies such as BHB [25]. Furthermore, BHB administration has been reported to ameliorate cognitive impairment in patients with type 2 diabetes, a major risk factor for AD [95]. Together, these findings suggest that BHB and BHB-elevating interventions may improve brain function by preventing A β and tau accumulation, reducing neuroinflammation, and oxidative stress that leads to enhanced cognitive ability in AD mouse models and patients. While preclinical findings are encouraging, translation to clinical settings requires caution due to differences between animal models and human AD patients.

3.3 Clinical evidence in humans

The emerging clinical evidence suggests potential benefits of butyrate and BHB in AD. While translation to humans with mild cognitive impairment (MCI) has been gradual, recent progress is supported by several randomized controlled trials.

3.3.1 Dietary ketogenic interventions

The largest study, BENEFIC (Brain ENergy, Functional Imaging, and Cognition) trial randomized 83 patients with mild-to-moderate AD to a 6-month modified Mediterranean-ketogenic diet (MMKD, <20 g carbohydrate/day) or a low-fat control diet recommended by the American Heart Association/Canadian nutritional guidelines [96]. The MMKD group achieved sustained mild nutritional ketosis with a mean plasma BHB of 0.6–0.95 mM and showed a clinically meaningful improvement of +4.1 points on the AD Assessment Scale-Cognitive Subscale, 11-item (ADAS-Cog11), compared with the control group, along with improved cognitive functions, preserved activities of daily living, and stabilization of cerebral glucose uptake on FDG-PET [96–98]. Cognitive benefits strongly correlated with adherence and plasma BHB concentration and were observed irrespective of APOE ϵ 4 status. Smaller trials, including a 12-week randomized crossover study of a modified ketogenic diet in 26 mild AD patients and a feasibility trial of the modified Atkins diet in MCI, reported improved daily function, quality of life, and trends toward better cognition with good adherence [99, 100]. However, long-term adherence to strict carbohydrate restriction can be challenging in older adults due to adherence burden, nutritional concerns, and side effects such as gastrointestinal discomfort, weight loss, and lipid profile alterations.

3.3.2 MCT supplementation

MCTs are rapidly converted to ketone bodies such as BHB in the liver. In a double-blind randomized controlled trial, daily intake of 30 g MCT improved ADAS-Cog scores in APOE ϵ 4 non-carrier patients with mild-to-moderate AD, with changes correlating with increased plasma concentrations of BHB [94]. Another study using an MCT-based ketogenic formula in mild-to-moderate AD patients showed marked enhancement in immediate and delayed logical memory at 8 weeks and improvements in digit-symbol coding at 12 weeks [93]. Meta-analyses indicate that MCT supplementation and ketogenic diets may improve global cognition in MCI and mild AD, with stronger effects often seen in APOE ϵ 4 non-carriers [101]. Results are heterogeneous; for example, a 3-month randomized trial with 152 mild-to-moderate AD patients using MCT supplementation did not reach statistical significance for the primary ADAS-Cog outcome, although secondary analyses showed modest benefits in APOE ϵ 4 non-carriers [93], highlighting the importance of patient selection, dose, and achieved BHB levels.

3.3.3 Exogenous ketone esters

A 90-day ketone monoester trial (20 g/day) in 23 patients with mild-to-moderate AD increased plasma BHB to 1–2 mM and improved working memory and processing speed [101]. Other studies using ketone esters have reported BHB elevation accompanied by cognitive trends. However, some trials showed no significant improvement in primary cognitive outcomes despite increased ketone levels. For example, a 6-month ketone ester trial in MCI patients found no significant cognitive benefit compared with placebo, although plasma BHB levels were elevated [102]. These approaches allow rapid and precise elevation of BHB independent of diet.

3.3.4 Butyrate-targeted approaches

Human clinical evidence for butyrate itself remains limited in AD. Nevertheless, butyrate-targeted strategies—including probiotics that enhance butyrate-producing bacteria, prebiotics, and butyrate prodrugs such as tributyrin—have yielded encouraging preliminary results [103, 104]. A small trial of butyrate-producing probiotics, such as multi-strain formulations containing *Lactobacillus* and *Bifidobacterium* species, has shown preliminary improvements in gut microbiota composition and cognitive markers in MCI/AD cohorts [102]. In addition, an ongoing clinical trial is evaluating the safety and efficacy of tributyrin (NCT06797817) supplementation in patients with mild AD, with preliminary results showing promising potential.

Collectively, the existing evidence base remains preliminary, characterized by small sample sizes, heterogeneous protocols, and limited direct measurement of butyrate levels or AD-specific biomarkers. Therefore, larger, longer-term randomized controlled trials are warranted to establish clinical efficacy, optimal formulations and dosing regimens, and potential synergies with butyrate-elevating approaches such as ketogenic diets or MCT supplementation. Patient stratification according to baseline gut microbiota composition, disease stage, and APOE genotype may further enhance therapeutic outcomes. The clinical phase status and NCT identifiers for butyrate- and BHB-enhancing agents are summarized in Table 2. Current human evidence remains limited and insufficient to establish definitive clinical efficacy.

3.4 Shared and divergent mechanisms of butyrate and BHB

Butyrate and BHB share several overlapping neuroprotective pathways in AD-related pathologies, as observed in preclinical AD models. These include inhibition of histone deacetylases, activation of the GPR109A receptor, and suppression of the NLRP3 inflammasome [34, 60, 72]. Collectively, these actions reduce neuroinflammation, oxidative stress, A β accumulation, and tau pathology. Nevertheless, the two metabolites also exert distinct effects. Butyrate primarily promotes gut microbial homeostasis and strengthens intestinal barrier integrity through peroxisome proliferator-activated receptor gamma (PPAR γ)-mediated regulation of oxygen levels and metabolic cross-feeding between bacterial species [105–108]. In contrast, BHB not only functions as an efficient alternative energy substrate for the brain but also exerts selective antimicrobial activity, including inhibition of *Bifidobacterium adolescentis* [109]. The efficacy observed in preclinical studies further differs according to the specific AD model employed. For example, stronger effects on tau pathology are often reported in 3xTg-AD mice compared with 5XFAD or APP/PS1 models [60, 78, 81]. The findings also vary by dose, route of administration, disease stage, and potentially sex. These differences highlight the need for more detailed mechanistic investigations and carefully designed translational studies.

4. The association of butyrate and BHB with gut microbiota dysbiosis in AD

Gut microbiota dysbiosis is a key pathogenic factor to AD and is characterized by reduced microbial diversity, depletion of butyrate-producing bacteria, and increased pro-inflammatory taxa. This imbalance contributes to

intestinal barrier dysfunction, systemic inflammation, and neuroinflammation via the gut-brain axis. Both butyrate and BHB, through direct microbial modulation and host signaling, may offer therapeutic potential to restore microbial homeostasis and mitigate AD progression.

4.1 Effects of butyrate on microbiota dysbiosis in AD

Butyrate, a microbiota-derived SCFA produced primarily by *Faecalibacterium*, *Roseburia*, and other *Clostridial* taxa through dietary fiber fermentation, is crucial for maintaining gut microbial homeostasis and gut-brain axis integrity [110, 111]. Longitudinal studies in 3xTg-AD mice have demonstrated that age-related loss of butyrate-producing bacteria coincides with increased dysbiosis and inflammation-associated genera, suggesting that reduced butyrate levels exacerbate microbial imbalance and establish a pro-inflammatory environment [31, 65]. Multiple studies in AD have reported a significant decrease in butyrate-producing bacteria such as *Faecalibacterium* and *Roseburia*, paralleled by lower fecal butyrate levels, often with an increase in pro-inflammatory taxa [29–31]. Accumulating evidence suggests a critical link between butyrate concentrations and the maintenance of a favorable gut microbiome composition, mediated by host-microbe metabolic interactions. In a healthy intestinal environment, butyrate functions as a signaling molecule that activates PPAR γ in human intestinal epithelial cells [106]. PPAR γ activation facilitates mitochondrial β -oxidation of fatty acids in surface colonocytes, a process that requires substantial oxygen consumption [108]. Consequently, this high oxygen utilization by colonocytes maintains luminal hypoxia, preserving a favorable niche for beneficial obligate anaerobes such as *Clostridia* (*Firmicutes*) and *Bacteroidia* (*Bacteroidetes*) [107]. These bacteria ferment dietary fiber into SCFAs, while microbial cross-feeding networks—rather than the metabolic capacity of individual species alone—further reinforce this anaerobic environment. Research utilizing co-culture models has shown that bacteria such as *Bifidobacterium adolescentis* degrade complex carbohydrates into intermediate such as lactate and acetate. These intermediates then serve as substrates for butyrate-producing anaerobes, including *Eubacterium hallii* and *Anaerostipes caccae*, which are unable to directly metabolize the original carbohydrate sources [105].

However, inflammatory signals disrupt this homeostatic balance by reprogramming colonocyte metabolism toward anaerobic glycolysis [112]. This metabolic shift markedly reduces epithelial oxygen consumption, allowing oxygen to leak from the microvasculature into the intestinal lumen [113, 114]. The resulting increase in luminal oxygen bioavailability

promotes the expansion of facultative anaerobic bacteria associated with colonic dysbiosis, particularly members of the phylum Proteobacteria, such as *Escherichia coli* and *Salmonella enterica* [113, 114]. This decline in beneficial bacteria increases intestinal permeability, enabling pro-inflammatory molecules to enter the systemic circulation and trigger neuroinflammation [115]. Specifically, reduced butyrate production impairs epithelial tight junctions integrity, thereby increasing permeability and facilitating the translocation of microbial products, such as LPS. This process destabilizes the microbial ecology and amplifies neuroinflammatory signaling [18, 116]. In human AD and MCI cohorts, butyrate depletion correlates with structural and functional gut microbiome changes, including reduced diversity and diminished SCFA synthesis capacity [32, 33]. Direct supplementation with NaB, butyrate-producing *Clostridium butyricum*, high-fiber diets, and prebiotic supplements has been shown in APP/PS1 mice to restore butyrate levels, rebalance microbiota, reduce A β burden, and improve cognitive performance [38, 59, 117]. Together, these findings establish butyrate depletion as a potential central feature of AD-associated gut dysbiosis. Microbiota-targeted interventions that enhance butyrate production therefore represent a promising strategy to stabilize gut microbial communities and mitigate downstream neuroinflammatory effects. In summary, BHB and butyrate converge on shared pathways including GPR109A activation, HDAC inhibition, and NLRP3 suppression to counteract AD-associated dysbiosis. While BHB primarily acts via ketogenic interventions to reshape microbiota and reduce inflammation, butyrate sustains the microbial niche through oxygen regulation and cross-feeding. Targeting this bidirectional gut-brain axis may broaden therapeutic efficacy in AD.

4.2 Effects of BHB on microbiota dysbiosis in AD

Emerging evidence indicates that the gut-brain axis is an important regulator of brain function and may contribute to neurological pathology. Specifically, the gut microbiota establishes and maintains the blood-CSF barrier, primarily by regulating the localization of tight junction proteins [118]. Metabolites of microbiota such as SCFAs can independently enhance gut barrier rigidity [119]. Evidence suggests that the administration of SCFAs strengthens the function of the blood-CSF barrier and attenuates the accumulation of A β in animal models of AD [120]. Conversely, disturbances in the gut-brain axis and alterations in microbial composition are increasingly recognized as factors that exacerbate neurodegenerative processes in AD. The gut microbiome in patients with AD and AD animal models is often

characterized by reduced microbial diversity and distinct compositional shifts [121, 122]. These microbial perturbations have been shown to correlate not only with CSF biomarkers [123] but also with peripheral inflammatory markers, such as elevated IL-1 β and NLRP3, alongside a reduction in the anti-inflammatory cytokine interleukin-10 [124]. In this context, BHB, a principal ketone body elevated during ketogenic states, has emerged as a crucial metabolic modulator capable of ameliorating neurodegenerative processes linked to gut-brain axis disruption [125, 126]. Beyond simply reshaping microbial composition, BHB exerts direct protective effects on intestinal integrity through specific signaling pathways. Mechanistically, BHB functions as an endogenous ligand for the GPR109A, also known as hydroxycarboxylic acid receptor 2, which is expressed on the surface of colonic epithelial cells and immune cells [127–129]. The activation of GPR109A by BHB induces potent anti-inflammatory signaling and promotes the assembly of tight junction proteins. This cascade reinforces the intestinal barrier, thereby mitigating leaky gut, which is commonly observed in AD pathology is often characterized by elevated permeability markers such as diamine oxidase [130–132].

In addition, BHB exerts epigenetic regulation by acting as an endogenous inhibitor of class I and IIa HDACs. By suppressing the activity of HDAC, BHB promotes histone acetylation at the promoters of key oxidative stress resistance genes, including forkhead box O3a and metallothionein 2 [133]. This epigenetic regulation augments the antioxidant capacity of the intestinal epithelium, thereby protecting the integrity of the gut barrier against oxidative damage associated with dysbiosis [133]. Furthermore, BHB serves as a key regulator of innate immunity within the gut microenvironment. BHB specifically inhibits the assembly and activation of the NLRP3 inflammasome in colonic macrophages, which in turn suppresses the release of pro-inflammatory cytokines, including IL-1 β and interleukin-18 [134]. BHB mitigates intestinal inflammation, thereby creating an environment that inhibits the proliferation of pro-inflammatory pathogenic bacteria, particularly those belonging to the *Proteobacteria* phylum [135]. Recent evidence further elucidates the selective antimicrobial properties of BHB. *In vitro* assays indicate that elevated concentrations of BHB inhibit the growth of *Bifidobacterium adolescentis* in a dose-dependent manner [109]. This specific microbial suppression is clinically relevant, as *B. adolescentis* is known to drive the accumulation of pro-inflammatory T-helper 17 (Th17) cells in the gut. Consequently, the BHB-mediated reduction of this bacterial strain leads to a decrease in intestinal Th17 cell populations, thereby dampening autoimmune-like responses [109].

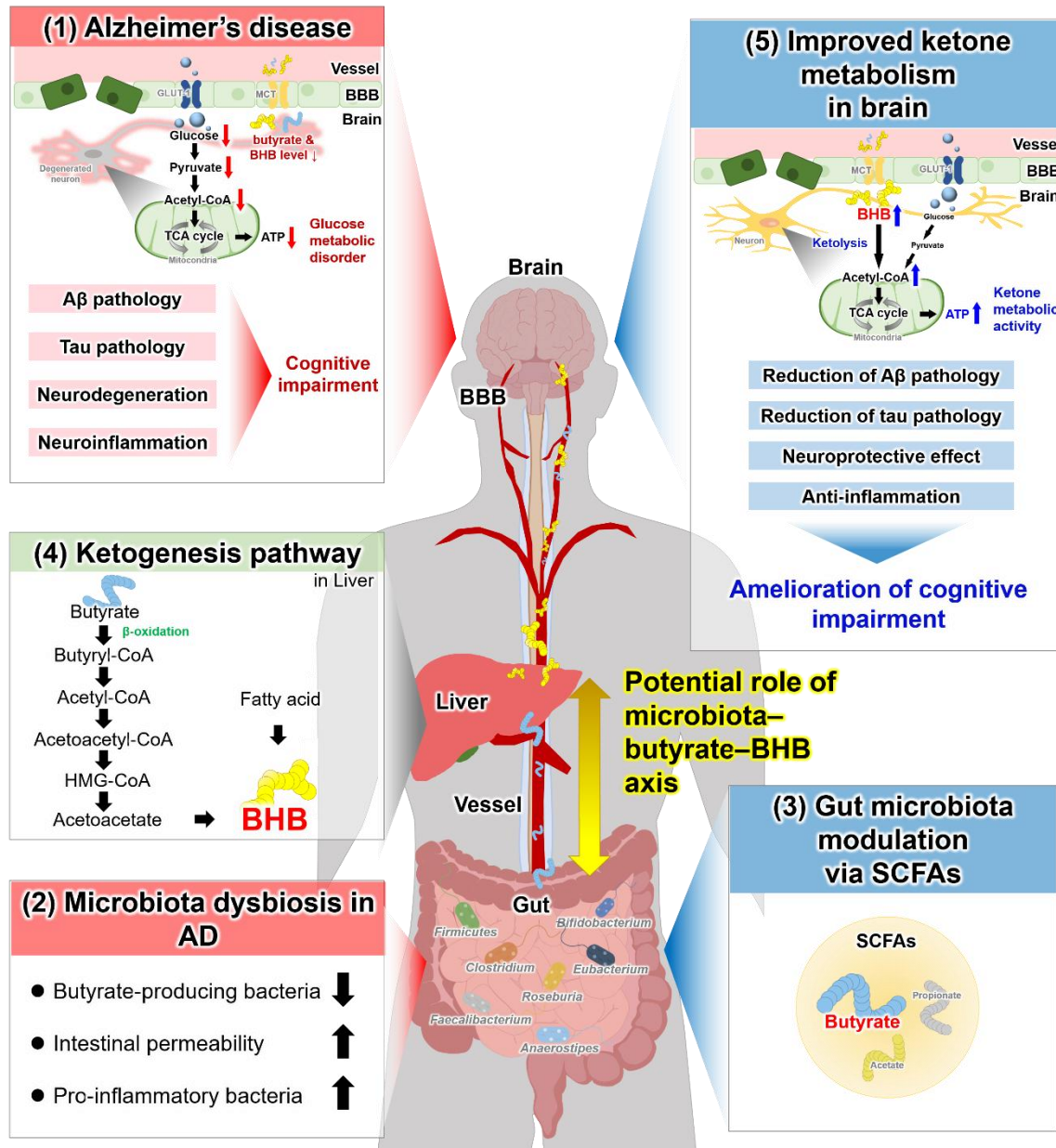


Figure 1. The microbiota–butyrate–BHB axis may ameliorate AD pathology by restoring impaired glucose metabolism and enhancing ketone metabolic activity. (1) AD involves Aβ accumulation, tau hyperphosphorylation, neurodegeneration, and neuroinflammation, and is accompanied by pathological features such as impaired glucose metabolism; these AD-related pathological features contribute to cognitive impairment. (2) In addition, gut microbiota dysbiosis occurs, and particularly, as butyrate-producing bacteria are reduced, gut butyrate levels decrease in AD. (3) However, restoration of gut microbiota balance through increased levels of SCFAs, particularly butyrate, offsets the dysbiosis observed in AD. (4) Subsequently, butyrate may support activated ketogenic pathways leading to the production of BHB in the liver. (5) Consequently, the increase in BHB may enhance brain ketone metabolism, alleviate AD-related pathological features such as Aβ and tau pathology, support neuroprotective functions and anti-inflammatory responses, and ultimately improve cognitive outcomes. Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; ATP, adenosine triphosphate; BBB, blood–brain barrier; BHB, β-hydroxybutyrate; CoA, coenzyme A; GLUT-1, glucose transporter-1; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A; MCT, monocarboxylate transporter; SCFAs, short-chain fatty acids; TCA cycle, tricarboxylic acid cycle.

Additionally, ketogenic diets have been shown to shift the gut microbial profile toward a greater relative abundance of beneficial taxa such as *Akkermansia*

muciniphila and *Lactobacillus*, while reducing pro-inflammatory genera, including *Desulfovibrio*, *Turicibacter*, and *Lachnobacterium*, in young healthy

mice [136]. Consistently, recent studies in transgenic AD mice have shown that ketogenic diets or MCT-enriched diets partially prevent or restore AD-induced microbial dysbiosis, preserving diversity and normalizing altered taxa effects that align with reduced A β pathology and improved cognition observed in 3xTg-AD and 5XFAD models [39]. Furthermore, *in vitro* assays further indicate that higher BHB concentrations slow the growth of *Bifidobacterium adolescentis* in a dose- and pH-dependent fashion, reducing intestinal Th17 cell populations, implying a selective antimicrobial action [109]. Such compositional shifts are hypothesized to attenuate systemic and neuroinflammatory cascades, consistent with findings from AD animal models and preliminary human studies [137–139]. The MMKD, in MCI cohorts, altered the gut microbiome and increased

SCFA production, correlating with favorable changes in AD biomarkers [140]. MMKD in MCI cohorts also decreased GABA-producing microbes *Alistipes sp. CAG:514* and GABA, and increased GABA-regulating microbes *Akkermansia muciniphila*, indicating that MCI modulates GABA levels [141]. Moreover, *A. muciniphila* plays a critical role in controlling host mucus turnover, enhancing intestinal wall integrity, thereby reducing metabolic endotoxemia [142]. A stronger barrier would limit the translocation of inflammatory bacterial components, such as LPS, into circulation, thereby reducing a key peripheral trigger for central A β and tau accumulation. These findings suggest that BHB-mediated modulation of the gut microbiota may serve as a key mechanistic link between ketogenic diets and improved neurocognitive outcomes in AD.

Table 2. Summary of human studies evaluating butyrate- and BHB-enhancing agents as therapeutics for AD.

Agent	Therapeutic purpose	Mechanism of action	Subject characteristics	Clinical Status	Reference
Tributylin (butyrate prodrug)	Disease-targeted small molecule	Metabolism and bioenergetics via gut-brain axis	Mild AD	Phase 3; recruiting (NCT06797817)	-
Multi-strain probiotics	Disease-targeted supplement	Microbiota modulation and butyrate production	Mild-to-moderate AD/MCI	Phase 2; recruitment completed (IRCT201511305623N60)	[102]
Intranasal insulin	Disease-targeted biologic	Metabolism and bioenergetics	Preclinical and Prodromal	Phase 2; completed (NCT05081219)	[148]
Tricaprillin (AC-1204)	Disease-targeted small molecule	Metabolism and bioenergetics	Mild-to-moderate dementia	Phase 2/3; completed (NCT01741194)	[149]
Nicotinamide riboside	Disease-targeted small molecule	Metabolism and bioenergetics	Prodromal	Not Applicable; completed (NCT04078178)	[150]
Nicotinamide riboside	Disease-targeted small molecule	Metabolism and bioenergetics	Mild-to-moderate AD/MCI	Early phase 1; active not recruiting (NCT04430517)	[151]
Nicotinic acid	Disease-targeted small molecule	Inflammation /Immunity	Mild-to-moderate dementia	Phase 1/2; recruiting (NCT06582706)	-
Ketone monoester (KME)	-	Metabolism and bioenergetics	Healthy volunteers	Not Applicable; completed (NCT04421014)	[152]
Octanoic (C8:0) and Decanoic (C10:0) acids	-	Metabolism and bioenergetics	Healthy volunteers	Not Applicable; completed (NCT03830268)	[153]
Modified Mediterranean-Ketogenic Diet (MMKD)	Disease-targeted dietary intervention	Metabolism and bioenergetics	Mild-to-moderate AD/MCI	Not Applicable; completed (NCT02984540)	[154]
Medium-Chain Triglycerides (MCT)	Disease-targeted supplement	Metabolism and bioenergetics	Mild-to-moderate AD	Other; not recruiting (ChiCTR-IOR-16009737)	[94]

"Not Applicable" indicates that this trial has not yet been assigned a traditional clinical phase.

5. Limitations and future directions

Promising preclinical and emerging clinical evidence supports the microbiota–butyrate–BHB axis as a potential metabolic therapeutic target for AD; however, several limitations warrant further consideration. At present, the majority of mechanistic evidence is derived from cellular and transgenic mouse models (Table 1). These models

only partially recapitulate the complexity of human sporadic AD, which is both age-dependent and associated with multiple risk factors. Similarly, differences between rodents and humans in gut microbiome composition, metabolic regulation, BBB function, and immune responses further constrain direct translatability [33]. In addition, quantitative data on absolute butyrate and BHB concentrations in the AD brain, CSF, and periphery

remain limited and inconsistent due to methodological variability, highlighting the need for standardized analytical methods. Direct human evidence for butyrate supplementation or butyrate-producing probiotics remains limited [43, 143]. The precise contribution of gut-derived butyrate to hepatic BHB production in AD is incompletely quantified, and potential synergies between high-fiber and ketogenic approaches are largely unexplored [19]. Establishing definitive causality in the bidirectional microbiota–butyrate–BHB–AD relationship is challenging, as dysbiosis and metabolite depletion may represent consequences rather than primary causes [144, 145]. Confounding factors such as diet, comorbidities, medications, and lifestyle further complicate interpretation. Clinical evidence for BHB-elevating interventions such as ketogenic diets, MCTs, and ketone esters is encouraging but remains heterogeneous, collectively characterized by small sample sizes, short durations, variable adherence, and differential effects according to APOE genotype, AD stage, and baseline metabolic status (Table 2). Furthermore, the cognitive and energetic benefits of these BHB-elevating interventions are often modest or confined to secondary outcomes, while their long-term safety, sustainability, and effects on key AD biomarkers—including A β , phospho-tau, and PET imaging—require further validation [140]. Additionally, long-term ketogenic interventions are associated with several side effects, including gastrointestinal discomfort, nutrient deficiencies, and muscle loss, all of which require careful monitoring [146].

Future studies should focus on well-powered, long-term randomized controlled trials in diverse populations with MCI and mild AD. These trials should use personalized approaches based on APOE genotype, baseline gut microbiome composition, metabolomic profiles, and the severity of reduced brain glucose metabolism. Integrating multi-omics approaches such as gut metagenomics, metabolomics, neuroimaging, and inflammatory markers may help clarify underlying mechanisms and identify which patients are most likely to respond to treatment. In addition, combining high-fiber diets or butyrate-producing probiotics with ketogenic strategies, such as MCTs or exogenous ketone esters, may create synergistic benefits. These approaches warrant rigorous evaluation in future studies. Longitudinal studies that track the microbiota–butyrate–BHB axis from the preclinical AD stage onward could help clarify the temporal relationships and identify reliable biomarkers. In addition, preclinical research should use more human-relevant models, such as animals with humanized microbiota or age-related comorbidities, and should pay greater attention to sex differences. Finally, the development of targeted butyrate delivery systems or selective modulators of the HDAC-, GPR109A-, or NLRP3-mediated signaling pathways

could overcome key limitations of current dietary approaches, such as poor bioavailability, variable patient response, gastrointestinal side effects, and difficulty maintaining long-term adherence. Addressing these gaps may clarify whether modulation of the microbiota–butyrate–BHB axis can progress from a promising strategy to a clinically validated adjunctive therapy for the prevention and treatment of AD.

6. Conclusion

AD is a multifaceted neurodegenerative disorder driven by A β and tau pathologies, neuroinflammation, synaptic loss, and profound metabolic dysregulation, particularly cerebral glucose hypometabolism. This review synthesizes emerging evidence on the microbiota–butyrate–BHB axis as a potential integrative pathway linking gut dysbiosis, peripheral metabolism, and brain pathology. Gut microbiota dysbiosis in AD is characterized by reduced microbial diversity and depletion of butyrate-producing microbial taxa such as *Faecalibacterium prausnitzii*, *Roseburia*, and *Eubacterium*, which contributes to reduced butyrate levels. Butyrate depletion correlates with increased intestinal permeability, elevated peripheral inflammation, and neuroinflammatory signaling in the brain. Butyrate supports gut homeostasis through HDAC inhibition, GPR109A activation, tight junction reinforcement, and metabolic cross-feeding that supports beneficial anaerobes. BHB, elevated during ketosis, modulates the gut microbiota through selective antimicrobial effects—primarily inhibiting *Bifidobacterium adolescentis* and certain pro-inflammatory taxa—while promoting relative enrichment of beneficial microbes such as *Akkermansia muciniphila*. Concurrently, BHB reinforces intestinal barrier integrity via GPR109A signaling, HDAC inhibition, and NLRP3 inflammasome suppression, which collectively attenuate systemic inflammation that promotes AD progression.

Preclinical studies in cellular and animal models of AD consistently show that both butyrate and BHB can ameliorate key pathologies, including A β plaque burden, tau hyperphosphorylation, microglial activation, oxidative stress, and cognitive deficits. Ketogenic interventions and butyrate-producing probiotics have been shown to improve AD-related biomarkers in AD models. In humans, clinical evidence—primarily from randomized trials of ketogenic diets, MCT supplementation, and ketone esters—indicates that interventions elevating BHB to mild ketosis levels may improve cognition, stabilize brain glucose uptake, and enhance daily function in individuals with MCI or mild-to-moderate AD. These effects often correlate with achieved plasma BHB concentrations, although their

dependence on APOE ϵ 4 status varies across studies. The synergistic interplay within the microbiota–butyrate–BHB axis, which may include microbiota-derived butyrate contributing to hepatic ketogenesis and BHB production in specific metabolic contexts, while BHB supports microbial homeostasis (Fig. 1), may represent a biologically plausible and metabolically grounded approach. However, ketogenic interventions can raise circulating BHB largely independently of gut-derived butyrate, although this distinction is primarily supported by general metabolic studies rather than direct evidence from AD models or patients. Targeting the microbiota–butyrate–BHB axis through high-fiber/prebiotic interventions, ketogenic diets, MCTs, exogenous ketone esters, or butyrate-producing probiotics may simultaneously address gut dysbiosis and cerebral energy deficits while mitigating core AD pathologies. Overall, although preclinical data are encouraging, human evidence remains preliminary and insufficient to establish ketogenic strategies as clinically effective therapies for AD. The results are heterogeneous, with benefits varying substantially by disease stage, APOE genotype, adherence, intervention duration, and achieved plasma BHB levels. Some trials have also shown no significant cognitive improvement on primary outcomes. Future research should prioritize well-powered longitudinal human trials, personalized approaches based on baseline microbiota and metabolic profiles, and the evaluations of synergistic combinations to better define their potential role in AD.

Acknowledgements

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number RS-2023-KH138733 to M.M.). This research was also supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (grant numbers RS-2023-00240010 to M.M. and RS-2024-00450135 to Y.N.). This work was further supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government, Ministry of Science and ICT, in 2026 (grant number RS-2026-25523040 to M.M.).

Authors' contributions

V.K., S.J., and Y.C. wrote the draft of the manuscript and conducted the literature search. V.K., S.J., Y.C., S.K., Y.N., and M.H.Y. conducted the literature search and interpreted the data and also contributed to figure

preparation. M.M. supervised the project, designed the review, and revised the manuscript. All authors have read and approved the article.

Competing interests

The authors declare no conflict of interest.

References

- [1] Wilson DM, 3rd, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I (2023). Hallmarks of neurodegenerative diseases. *Cell*, 186:693-714.
- [2] D'Alessandro MCB, Kanaan S, Geller M, Pratico D, Daher JPL (2025). Mitochondrial dysfunction in Alzheimer's disease. *Ageing Res Rev*, 107:102713.
- [3] DeTure MA, Dickson DW (2019). The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*, 14:32.
- [4] Bostancikliglu M (2019). The role of gut microbiota in pathogenesis of Alzheimer's disease. *J Appl Microbiol*, 127:954-967.
- [5] Seo DO, Holtzman DM (2024). Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. *Exp Mol Med*, 56:86-94.
- [6] Song D, Li Y, Yang LL, Luo YX, Yao XQ (2025). Bridging systemic metabolic dysfunction and Alzheimer's disease: the liver interface. *Mol Neurodegener*, 20:61.
- [7] Suswiantoro V, Tang KS, Rahman K, Puteri MU, Wahyuni T, Ariestanti DM, et al. (2026). Metabolic Drivers of Alzheimer's Disease: Integrating brain Hypometabolism, insulin Resistance, and systemic dysregulation. *Front Neuroendocrinol*, 81:101248.
- [8] Iozzo P, Guzzardi MA (2019). Imaging of brain glucose uptake by PET in obesity and cognitive dysfunction: life-course perspective. *Endocr Connect*, 8:R169-R183.
- [9] Li X, Liu F, Zhu Y, Shi H (2026). Gut Microbiota, Insulin Resistance, and Alzheimer's Disease: A Narrative Review of Mechanistic Links and Therapeutic Perspectives. *Int J Gen Med*, 19:593664.
- [10] Li ZH, Jiang YY, Long CY, Peng Q, Yue RS (2023). The gut microbiota-astrocyte axis: Implications for type 2 diabetic cognitive dysfunction. *CNS Neurosci Ther*, 29 Suppl 1:59-73.
- [11] Ramezani M, Fernando M, Eslick S, Asih PR, Shadfar S, Bandara EMS, et al. (2023). Ketone bodies mediate alterations in brain energy metabolism and biomarkers of Alzheimer's disease. *Front Neurosci*, 17:1297984.
- [12] Kumar V, Kim SH, Bishayee K (2022). Dysfunctional Glucose Metabolism in Alzheimer's Disease Onset and Potential Pharmacological Interventions. *Int J Mol Sci*, 23.

- [13] Henderson ST (2008). Ketone bodies as a therapeutic for Alzheimer's disease. *Neurotherapeutics*, 5:470-480.
- [14] Oldendorf WH (1973). Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. *Am J Physiol*, 224:1450-1453.
- [15] Pollay M, Alan Stevens F (1980). Starvation-induced changes in transport of ketone bodies across the blood-brain barrier. *J Neurosci Res*, 5:163-172.
- [16] Hasselbalch SG, Knudsen GM, Jakobsen J, Hageman LP, Holm S, Paulson OB (1995). Blood-brain barrier permeability of glucose and ketone bodies during short-term starvation in humans. *Am J Physiol*, 268:E1161-1166.
- [17] Silva YP, Bernardi A, Frozza RL (2020). The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. *Front Endocrinol (Lausanne)*, 11:25.
- [18] Chen H, Meng L, Shen L (2022). Multiple roles of short-chain fatty acids in Alzheimer disease. *Nutrition*, 93:111499.
- [19] Cavaleri F, Bashar E (2018). Potential Synergies of beta-Hydroxybutyrate and Butyrate on the Modulation of Metabolism, Inflammation, Cognition, and General Health. *J Nutr Metab*, 2018:7195760.
- [20] Li H, Gao Z, Zhang J, Ye X, Xu A, Ye J, et al. (2012). Sodium butyrate stimulates expression of fibroblast growth factor 21 in liver by inhibition of histone deacetylase 3. *Diabetes*, 61:797-806.
- [21] Bourassa MW, Alim I, Bultman SJ, Ratan RR (2016). Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health? *Neurosci Lett*, 625:56-63.
- [22] Schonfeld P, Wojtczak L (2016). Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. *J Lipid Res*, 57:943-954.
- [23] Dabek A, Wojtala M, Pirola L, Balcerzyk A (2020). Modulation of Cellular Biochemistry, Epigenetics and Metabolomics by Ketone Bodies. Implications of the Ketogenic Diet in the Physiology of the Organism and Pathological States. *Nutrients*, 12.
- [24] Dhillon KK, Gupta S. 2025. Biochemistry, Ketogenesis. In *StatPearls*. Treasure Island (FL).
- [25] Heidt C, Fobker M, Newport M, Feldmann R, Fischer T, Marquardt T (2023). Beta-Hydroxybutyrate (BHB), Glucose, Insulin, Octanoate (C8), and Decanoate (C10) Responses to a Medium-Chain Triglyceride (MCT) Oil with and without Glucose: A Single-Center Study in Healthy Adults. *Nutrients*, 15.
- [26] Pan JW, Rothman TL, Behar KL, Stein DT, Hetherington HP (2000). Human brain beta-hydroxybutyrate and lactate increase in fasting-induced ketosis. *J Cereb Blood Flow Metab*, 20:1502-1507.
- [27] Cunnane SC, Courchesne-Loyer A, Vandenberghe C, St-Pierre V, Fortier M, Hennebelle M, et al. (2016). Can Ketones Help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health during Aging and the Treatment of Alzheimer's Disease. *Front Mol Neurosci*, 9:53.
- [28] Zilberter Y, Zilberter T (2020). Glucose-Sparing Action of Ketones Boosts Functions Exclusive to Glucose in the Brain. *eNeuro*, 7.
- [29] Yamashiro K, Takabayashi K, Kamagata K, Nishimoto Y, Togashi Y, Yamauchi Y, et al. (2024). Free water in gray matter linked to gut microbiota changes with decreased butyrate producers in Alzheimer's disease and mild cognitive impairment. *Neurobiol Dis*, 193:106464.
- [30] Kachoueian F, Kalkhoran NY, Kalkhoran AY, Kyada A, Rekha MM, Chaudhary K, et al. (2025). Butyrate: a key mediator of gut-brain communication in Alzheimer's disease. *Metab Brain Dis*, 40:189.
- [31] Chilton PM, Ghare SS, Charpentier BT, Myers SA, Rao AV, Petrosino JF, et al. (2024). Age-associated temporal decline in butyrate-producing bacteria plays a key pathogenic role in the onset and progression of neuropathology and memory deficits in 3xTg-AD mice. *Gut Microbes*, 16:2389319.
- [32] Ling Z, Zhu M, Yan X, Cheng Y, Shao L, Liu X, et al. (2020). Structural and Functional Dysbiosis of Fecal Microbiota in Chinese Patients With Alzheimer's Disease. *Front Cell Dev Biol*, 8:634069.
- [33] Liang C, Pereira R, Zhang Y, Rojas OL (2024). Gut Microbiome in Alzheimer's Disease: from Mice to Humans. *Curr Neuropharmacol*, 22:2314-2329.
- [34] Shippy DC, Wilhelm C, Viharkumar PA, Raife TJ, Ulland TK (2020). beta-Hydroxybutyrate inhibits inflammasome activation to attenuate Alzheimer's disease pathology. *J Neuroinflammation*, 17:280.
- [35] Gao C, Li B, He Y, Huang P, Du J, He G, et al. (2023). Early changes of fecal short-chain fatty acid levels in patients with mild cognitive impairments. *CNS Neurosci Ther*, 29:3657-3666.
- [36] Wu L, Han Y, Zheng Z, Peng G, Liu P, Yue S, et al. (2021). Altered Gut Microbial Metabolites in Amnesic Mild Cognitive Impairment and Alzheimer's Disease: Signals in Host-Microbe Interplay. *Nutrients*, 13.
- [37] Taylor MK, Sullivan DK, Keller JE, Burns JM, Swerdlow RH (2022). Potential for Ketotherapies as Amyloid-Regulating Treatment in Individuals at Risk for Alzheimer's Disease. *Front Neurosci*, 16:899612.
- [38] Cuervo-Zanatta D, Syeda T, Sanchez-Valle V, Irene-Fierro M, Torres-Aguilar P, Torres-Ramos MA, et al. (2023). Dietary Fiber Modulates the Release of Gut Bacterial Products Preventing Cognitive Decline in an Alzheimer's Mouse Model. *Cell Mol Neurobiol*, 43:1595-1618.
- [39] M'Bra PEH, Suarez-Urbe I, Avino M, Ng Kwan Lim E, Mayhue M, Balthazar P, et al. (2025). Medium-chain triglycerides and ketogenic diet prevent alterations of the gut microbiome in transgenic Alzheimer's disease mice. *Commun Biol*.
- [40] O'Riordan KJ, Collins MK, Moloney GM, Knox EG, Aburto MR, Fulling C, et al. (2022). Short chain fatty

- acids: Microbial metabolites for gut-brain axis signalling. *Mol Cell Endocrinol*, 546:111572.
- [41] Singh V, Lee G, Son H, Koh H, Kim ES, Unno T, et al. (2022). Butyrate producers, "The Sentinel of Gut": Their intestinal significance with and beyond butyrate, and prospective use as microbial therapeutics. *Front Microbiol*, 13:1103836.
- [42] Saban Guler M, Arslan S, Agagunduz D, Cerqua I, Pagano E, Berni Canani R, et al. (2025). Butyrate: A potential mediator of obesity and microbiome via different mechanisms of actions. *Food Res Int*, 199:115420.
- [43] Marizzoni M, Coppola L, Festari C, Luongo D, Salamone D, Naviglio D, et al. (2025). Circulating short chain fatty acids in Alzheimer's disease: A cross-sectional observational study. *J Alzheimers Dis*, 106:38-43.
- [44] Wang Z, Wang C, Yuan B, Liu L, Zhang H, Zhu M, et al. (2025). Akkermansia muciniphila and its metabolite propionic acid maintains neuronal mitochondrial division and autophagy homeostasis during Alzheimer's disease pathologic process via GPR41 and GPR43. *Microbiome*, 13:16.
- [45] Zhang L, Wang Y, Xiayu X, Shi C, Chen W, Song N, et al. (2017). Altered Gut Microbiota in a Mouse Model of Alzheimer's Disease. *J Alzheimers Dis*, 60:1241-1257.
- [46] Wan L, Lu J, Fu J, Huang J, Yang Q, Xin B, et al. (2018). Acetylcholinesterase Inhibitor Donepezil Effects on Plasma beta-Hydroxybutyrate Levels in the Treatment of Alzheimer's Disease. *Curr Alzheimer Res*, 15:917-927.
- [47] Patel V, Mill J, Okonkwo OC, Salamat S, Li L, Raife T (2024). Global Energy Metabolism Deficit in Alzheimer Disease Brain. *J Prev Alzheimers Dis*, 11:171-178.
- [48] Liu H, Wang S, Wang J, Guo X, Song Y, Fu K, et al. (2025). Energy metabolism in health and diseases. *Signal Transduct Target Ther*, 10:69.
- [49] Brownlow ML, Jung SH, Moore RJ, Bechmann N, Jankord R (2017). Nutritional Ketosis Affects Metabolism and Behavior in Sprague-Dawley Rats in Both Control and Chronic Stress Environments. *Front Mol Neurosci*, 10:129.
- [50] Wang X, Liu Q, Zhou J, Wu X, Zhu Q (2017). beta hydroxybutyrate levels in serum and cerebrospinal fluid under ketone body metabolism in rats. *Exp Anim*, 66:177-182.
- [51] Robinson AM, Williamson DH (1980). Physiological roles of ketone bodies as substrates and signals in mammalian tissues. *Physiol Rev*, 60:143-187.
- [52] Reger MA, Henderson ST, Hale C, Cholerton B, Baker LD, Watson GS, et al. (2004). Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging*, 25:311-314.
- [53] Dissanayaka DMS, Jayasena V, Rainey-Smith SR, Martins RN, Fernando W (2024). The Role of Diet and Gut Microbiota in Alzheimer's Disease. *Nutrients*, 16.
- [54] Panza F, Lozupone M, Solfrizzi V, Sardone R, Dibello V, Di Lena L, et al. (2018). Different Cognitive Frailty Models and Health- and Cognitive-related Outcomes in Older Age: From Epidemiology to Prevention. *J Alzheimers Dis*, 62:993-1012.
- [55] Kim SY, Chae CW, Lee HJ, Jung YH, Choi GE, Kim JS, et al. (2020). Sodium butyrate inhibits high cholesterol-induced neuronal amyloidogenesis by modulating NRF2 stabilization-mediated ROS levels: involvement of NOX2 and SOD1. *Cell Death Dis*, 11:469.
- [56] Kruh J (1982). Effects of sodium butyrate, a new pharmacological agent, on cells in culture. *Mol Cell Biochem*, 42:65-82.
- [57] Sun J, Yuan B, Wu Y, Gong Y, Guo W, Fu S, et al. (2020). Sodium Butyrate Protects N2a Cells against Abeta Toxicity In Vitro. *Mediators Inflamm*, 2020:7605160.
- [58] Yuan B, Liu M, Gong Y, Wang Z, Jin X, Xie G, et al. (2022). Sodium butyrate exerts antioxidant stress effects and attenuates Abeta(25-35)-induced cytotoxicity in PC12 cells. *Arch Biochem Biophys*, 731:109448.
- [59] Sun J, Xu J, Yang B, Chen K, Kong Y, Fang N, et al. (2020). Effect of Clostridium butyricum against Microglia-Mediated Neuroinflammation in Alzheimer's Disease via Regulating Gut Microbiota and Metabolites Butyrate. *Mol Nutr Food Res*, 64:e1900636.
- [60] Govindarajan N, Agis-Balboa RC, Walter J, Sananbenesi F, Fischer A (2011). Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. *J Alzheimers Dis*, 26:187-197.
- [61] Fernando W, Martins IJ, Morici M, Bharadwaj P, Rainey-Smith SR, Lim WLF, et al. (2020). Sodium Butyrate Reduces Brain Amyloid-beta Levels and Improves Cognitive Memory Performance in an Alzheimer's Disease Transgenic Mouse Model at an Early Disease Stage. *J Alzheimers Dis*, 74:91-99.
- [62] Ge X, Zheng M, Hu M, Fang X, Geng D, Liu S, et al. (2023). Butyrate ameliorates quolinic acid-induced cognitive decline in obesity models. *J Clin Invest*, 133.
- [63] Zhang Y, Shen Y, Liufu N, Liu L, Li W, Shi Z, et al. (2023). Transmission of Alzheimer's disease-associated microbiota dysbiosis and its impact on cognitive function: evidence from mice and patients. *Mol Psychiatry*, 28:4421-4437.
- [64] Jiang Y, Li K, Li X, Xu L, Yang Z (2021). Sodium butyrate ameliorates the impairment of synaptic plasticity by inhibiting the neuroinflammation in 5XFAD mice. *Chem Biol Interact*, 341:109452.
- [65] Mishra SP, Jain S, Wang B, Wang S, Miller BC, Lee JY, et al. (2024). Abnormalities in microbiota/butyrate/FFAR3 signaling in aging gut impair brain function. *JCI Insight*, 9.
- [66] Chilton PM, Ghare SS, Charpentier BT, Myers SA, Rao AV, Greenwell JC, et al. (2023). Oral tributyrin supplementation attenuates Alzheimer's disease-

- associated neuropathology and prevents cognitive and behavioral deficits in the 3xTg-AD mouse model. *Alzheimer's & Dementia*, 19.
- [67] Maitre M, Klein C, Mensah-Nyagan AG (2016). A proposed preventive role for Gamma-hydroxybutyrate (Xyrem(R)) in Alzheimer's disease. *Alzheimers Res Ther*, 8:37.
- [68] Calvo-Flores Guzman B, Vinnakota C, Govindpani K, Waldvogel HJ, Faull RLM, Kwakowsky A (2018). The GABAergic system as a therapeutic target for Alzheimer's disease. *J Neurochem*, 146:649-669.
- [69] Wang C, Zheng D, Weng F, Jin Y, He L (2022). Sodium butyrate ameliorates the cognitive impairment of Alzheimer's disease by regulating the metabolism of astrocytes. *Psychopharmacology (Berl)*, 239:215-227.
- [70] Zhou Y, Xie L, Schroder J, Schuster IS, Nakai M, Sun G, et al. (2023). Dietary Fiber and Microbiota Metabolite Receptors Enhance Cognition and Alleviate Disease in the 5xFAD Mouse Model of Alzheimer's Disease. *J Neurosci*, 43:6460-6475.
- [71] Ye Y, Fu C, Li Y, Sun J, Li X, Chai S, et al. (2024). Alternate-day fasting improves cognitive and brain energy deficits by promoting ketone metabolism in the 3xTg mouse model of Alzheimer's disease. *Exp Neurol*, 381:114920.
- [72] Wu Y, Gong Y, Luan Y, Li Y, Liu J, Yue Z, et al. (2020). BHBA treatment improves cognitive function by targeting pleiotropic mechanisms in transgenic mouse model of Alzheimer's disease. *FASEB J*, 34:1412-1429.
- [73] Xie G, Tian W, Wei T, Liu F (2015). The neuroprotective effects of beta-hydroxybutyrate on Abeta-injected rat hippocampus in vivo and in Abeta-treated PC-12 cells in vitro. *Free Radic Res*, 49:139-150.
- [74] Li X, Zhan Z, Zhang J, Zhou F, An L (2020). beta-Hydroxybutyrate Ameliorates Abeta-Induced Downregulation of TrkA Expression by Inhibiting HDAC1/3 in SH-SY5Y Cells. *Am J Alzheimers Dis Other Dement*, 35:1533317519883496.
- [75] Van der Auwera I, Wera S, Van Leuven F, Henderson ST (2005). A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab (Lond)*, 2:28.
- [76] Beckett TL, Studzinski CM, Keller JN, Paul Murphy M, Niedowicz DM (2013). A ketogenic diet improves motor performance but does not affect beta-amyloid levels in a mouse model of Alzheimer's disease. *Brain Res*, 1505:61-67.
- [77] Yin JX, Maalouf M, Han P, Zhao M, Gao M, Dharshaun T, et al. (2016). Ketones block amyloid entry and improve cognition in an Alzheimer's model. *Neurobiol Aging*, 39:25-37.
- [78] Pawlosky RJ, Kemper MF, Kashiwaya Y, King MT, Mattson MP, Veech RL (2017). Effects of a dietary ketone ester on hippocampal glycolytic and tricarboxylic acid cycle intermediates and amino acids in a 3xTgAD mouse model of Alzheimer's disease. *J Neurochem*, 141:195-207.
- [79] Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC (2022). ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. *Mol Neurodegener*, 17:72.
- [80] Krishnan M, Hwang JS, Kim M, Kim YJ, Seo JH, Jung J, et al. (2020). beta-hydroxybutyrate Impedes the Progression of Alzheimer's Disease and Atherosclerosis in ApoE-Deficient Mice. *Nutrients*, 12.
- [81] Kashiwaya Y, Bergman C, Lee JH, Wan R, King MT, Mughal MR, et al. (2013). A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease. *Neurobiol Aging*, 34:1530-1539.
- [82] Povala G, Bellaver B, Bastiani MA, Ferrari-Souza JP, Aguzzoli CS, Leffa DT, et al. (2025). Amyloid beta and tau are associated with the dual effect of neuroinflammation on neurodegeneration. *Alzheimers Dement*, 21:e70746.
- [83] Gao C, Jiang J, Tan Y, Chen S (2023). Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Target Ther*, 8:359.
- [84] Thakur S, Dhapola R, Sarma P, Medhi B, Reddy DH (2023). Neuroinflammation in Alzheimer's Disease: Current Progress in Molecular Signaling and Therapeutics. *Inflammation*, 46:1-17.
- [85] Simpson DSA, Oliver PL (2020). ROS Generation in Microglia: Understanding Oxidative Stress and Inflammation in Neurodegenerative Disease. *Antioxidants (Basel)*, 9.
- [86] Zhao Y, Gong CX (2015). From chronic cerebral hypoperfusion to Alzheimer-like brain pathology and neurodegeneration. *Cell Mol Neurobiol*, 35:101-110.
- [87] Wang Z, Li T, Du M, Zhang L, Xu L, Song H, et al. (2023). beta-hydroxybutyrate improves cognitive impairment caused by chronic cerebral hypoperfusion via amelioration of neuroinflammation and blood-brain barrier damage. *Brain Res Bull*, 193:117-130.
- [88] Xu X, Zhang Q, Tu J, Ren Z (2011). D-β-hydroxybutyrate inhibits microglial activation in a cell activation model in vitro. *Journal of Medical Colleges of PLA*, 26:117-127.
- [89] Yang X, Wang R, Zhou H, Wang L, Wang R, Li H, et al. (2021). beta-hydroxybutyrate Alleviates Learning and Memory Impairment Through the SIRT1 Pathway in D-Galactose-Injured Mice. *Front Pharmacol*, 12:751028.
- [90] Qiao G, Lv T, Zhang M, Chen P, Sun Q, Zhang J, et al. (2020). beta-hydroxybutyrate (beta-HB) exerts anti-inflammatory and antioxidant effects in lipopolysaccharide (LPS)-stimulated macrophages in *Liza haematocheila*. *Fish Shellfish Immunol*, 107:444-451.
- [91] Newman J, Kroll F, Ulrich S, Palop J, Verdin E (2017). Betahydroxybutyrate Suppresses Epileptiform Spikes and Improves Cognition in

- Alzheimer's Mouse Model. *Innovation in Aging*, 1:1151.
- [92] Pawlosky RJ, Kashiwaya Y, King MT, Veech RL (2020). A Dietary Ketone Ester Normalizes Abnormal Behavior in a Mouse Model of Alzheimer's Disease. *Int J Mol Sci*, 21.
- [93] Ota M, Matsuo J, Ishida I, Takano H, Yokoi Y, Hori H, et al. (2019). Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. *Neurosci Lett*, 690:232-236.
- [94] Xu Q, Zhang Y, Zhang X, Liu L, Zhou B, Mo R, et al. (2020). Medium-chain triglycerides improved cognition and lipid metabolomics in mild to moderate Alzheimer's disease patients with APOE4(-/-): A double-blind, randomized, placebo-controlled crossover trial. *Clin Nutr*, 39:2092-2105.
- [95] Jensen NJ, Nilsson M, Ingerslev JS, Olsen DA, Fenger M, Svart M, et al. (2020). Effects of beta-hydroxybutyrate on cognition in patients with type 2 diabetes. *Eur J Endocrinol*, 182:233-242.
- [96] Cunnane S, Fortier M, Castellano CA, Pierre VS, Morin MC, Langlois F, et al. (2020). Improved brain energetics and cognition after a 6-month ketogenic intervention in mild cognitive impairment: Final results of the Benefic Trial: Brain energy rescue interventions to treat or delay Alzheimer's disease. *Alzheimer's & Dementia*, 16:e037961.
- [97] Fortier M, Castellano CA, Croteau E, Langlois F, Bocti C, St-Pierre V, et al. (2019). A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment. *Alzheimers Dement*, 15:625-634.
- [98] Myette-Cote E, St-Pierre V, Beaulieu S, Castellano CA, Fortier M, Plourde M, et al. (2021). The effect of a 6-month ketogenic medium-chain triglyceride supplement on plasma cardiometabolic and inflammatory markers in mild cognitive impairment. *Prostaglandins Leukot Essent Fatty Acids*, 169:102236.
- [99] Phillips MCL, Deprez LM, Mortimer GMN, Murtagh DKJ, McCoy S, Mylchreest R, et al. (2021). Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. *Alzheimers Res Ther*, 13:51.
- [100] Buchholz A, Deme P, Betz JF, Brandt J, Haughey N, Cervenka MC (2024). A randomized feasibility trial of the modified Atkins diet in older adults with mild cognitive impairment due to Alzheimer's disease. *Front Endocrinol (Lausanne)*, 15:1182519.
- [101] Gabuzyan R, Lee C, Nygaard HB (2024). Ketogenic Approaches for the Treatment of Alzheimer's Disease. *J Alzheimers Dis*, 101:S443-S453.
- [102] Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, et al. (2016). Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front Aging Neurosci*, 8:256.
- [103] Duysburgh C, Verstrepen L, Van Meulebroek L, Marzorati M (2025). Tributyrin (CoreBiome®) enhances butyrate levels and modulates the gut microbiota, barrier function, and immune response in vitro. *Front Nutr*, 12:1712993.
- [104] Cavaleri F, Bashar E (2018). Potential Synergies of β -Hydroxybutyrate and Butyrate on the Modulation of Metabolism, Inflammation, Cognition, and General Health. *J Nutr Metab*, 2018:7195760.
- [105] Belenguer A, Duncan SH, Calder AG, Holtrop G, Louis P, Lobley GE, et al. (2006). Two routes of metabolic cross-feeding between *Bifidobacterium adolescentis* and butyrate-producing anaerobes from the human gut. *Appl Environ Microbiol*, 72:3593-3599.
- [106] Alex S, Lange K, Amolo T, Grinstead JS, Haakonsson AK, Szalowska E, et al. (2013). Short-chain fatty acids stimulate angiopoietin-like 4 synthesis in human colon adenocarcinoma cells by activating peroxisome proliferator-activated receptor gamma. *Mol Cell Biol*, 33:1303-1316.
- [107] El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B (2013). The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat Rev Microbiol*, 11:497-504.
- [108] Duszka K, Oresic M, Le May C, Konig J, Wahli W (2017). PPARgamma Modulates Long Chain Fatty Acid Processing in the Intestinal Epithelium. *Int J Mol Sci*, 18.
- [109] Ang QY, Alexander M, Newman JC, Tian Y, Cai J, Upadhyay V, et al. (2020). Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells. *Cell*, 181:1263-1275 e1216.
- [110] Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF (2016). The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? *Neurochem Int*, 99:110-132.
- [111] Mirzaei R, Bouzari B, Hosseini-Fard SR, Mazaheri M, Ahmadyousefi Y, Abdi M, et al. (2021). Role of microbiota-derived short-chain fatty acids in nervous system disorders. *Biomed Pharmacother*, 139:111661.
- [112] Byndloss MX, Baumler AJ (2018). The germ-organ theory of non-communicable diseases. *Nat Rev Microbiol*, 16:103-110.
- [113] Rivera-Chavez F, Zhang LF, Faber F, Lopez CA, Byndloss MX, Olsan EE, et al. (2016). Depletion of Butyrate-Producing *Clostridia* from the Gut Microbiota Drives an Aerobic Luminal Expansion of *Salmonella*. *Cell Host Microbe*, 19:443-454.
- [114] Litvak Y, Byndloss MX, Baumler AJ (2018). Colonocyte metabolism shapes the gut microbiota. *Science*, 362.
- [115] Kang JW, Vemuganti V, Kuehn JF, Ulland TK, Rey FE, Bendlin BB (2024). Gut microbial metabolism in Alzheimer's disease and related dementias. *Neurotherapeutics*, 21:e00470.
- [116] Marizzoni M, Cattaneo A, Mirabelli P, Festari C, Lopizzo N, Nicolosi V, et al. (2020). Short-Chain Fatty Acids and Lipopolysaccharide as Mediators

- Between Gut Dysbiosis and Amyloid Pathology in Alzheimer's Disease. *J Alzheimers Dis*, 78:683-697.
- [117] Ticinesi A, Mancabelli L, Carnevali L, Nouvenne A, Meschi T, Del Rio D, et al. (2022). Interaction Between Diet and Microbiota in the Pathophysiology of Alzheimer's Disease: Focus on Polyphenols and Dietary Fibers. *J Alzheimers Dis*, 86:961-982.
- [118] Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Toth M, et al. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*, 6:263ra158.
- [119] Peng L, Li ZR, Green RS, Holzman IR, Lin J (2009). Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *J Nutr*, 139:1619-1625.
- [120] Xie J, Bruggeman A, De Nolf C, Vandendriessche C, Van Imschoot G, Van Wenterghem E, et al. (2023). Gut microbiota regulates blood-cerebrospinal fluid barrier function and A β pathology. *Embo j*, 42:e111515.
- [121] Li H, Cui X, Lin Y, Huang F, Tian A, Zhang R (2024). Gut microbiota changes in patients with Alzheimer's disease spectrum based on 16S rRNA sequencing: a systematic review and meta-analysis. *Front Aging Neurosci*, 16:1422350.
- [122] Chandra S, Sisodia SS, Vassar RJ (2023). The gut microbiome in Alzheimer's disease: what we know and what remains to be explored. *Mol Neurodegener*, 18:9.
- [123] Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. (2017). Gut microbiome alterations in Alzheimer's disease. *Sci Rep*, 7:13537.
- [124] Cattaneo A, Cattane N, Galluzzi S, Provati S, Lopizzo N, Festari C, et al. (2017). Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging*, 49:60-68.
- [125] Kaviyarasan S, Chung Sia EL, Retinasamy T, Arulsamy A, Shaikh MF (2022). Regulation of gut microbiome by ketogenic diet in neurodegenerative diseases: A molecular crosstalk. *Front Aging Neurosci*, 14:1015837.
- [126] Rawat K, Singh N, Kumari P, Saha L (2021). A review on preventive role of ketogenic diet (KD) in CNS disorders from the gut microbiota perspective. *Rev Neurosci*, 32:143-157.
- [127] Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, Muller-Fielitz H, et al. (2014). The beta-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. *Nat Commun*, 5:3944.
- [128] Bhatt B, Zeng P, Zhu H, Sivaprakasam S, Li S, Xiao H, et al. (2018). Gpr109a Limits Microbiota-Induced IL-23 Production To Constrain ILC3-Mediated Colonic Inflammation. *J Immunol*, 200:2905-2914.
- [129] Gao K, Mu CL, Farzi A, Zhu WY (2020). Tryptophan Metabolism: A Link Between the Gut Microbiota and Brain. *Adv Nutr*, 11:709-723.
- [130] Stadlbauer V, Engertsberger L, Komarova I, Feldbacher N, Leber B, Pichler G, et al. (2020). Dysbiosis, gut barrier dysfunction and inflammation in dementia: a pilot study. *BMC Geriatr*, 20:248.
- [131] Pei Y, Lu Y, Li H, Jiang C, Wang L (2023). Gut microbiota and intestinal barrier function in subjects with cognitive impairments: a cross-sectional study. *Front Aging Neurosci*, 15:1174599.
- [132] Kowalski K, Mulak A (2019). Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J Neurogastroenterol Motil*, 25:48-60.
- [133] Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, et al. (2013). Suppression of oxidative stress by beta-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science*, 339:211-214.
- [134] Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, et al. (2015). The ketone metabolite beta-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med*, 21:263-269.
- [135] Zeng MY, Inohara N, Nunez G (2017). Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunol*, 10:18-26.
- [136] Ma D, Wang AC, Parikh I, Green SJ, Hoffman JD, Chlipala G, et al. (2018). Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. *Sci Rep*, 8:6670.
- [137] Sridharan B, Lee MJ (2022). Ketogenic Diet: A Promising Neuroprotective Composition for Managing Alzheimer's Diseases and its Pathological Mechanisms. *Curr Mol Med*, 22:640-656.
- [138] Mazandarani M, Lashkarbolouk N, Ejtahed HS, Qorbani M (2023). Does the ketogenic diet improve neurological disorders by influencing gut microbiota? A systematic review. *Nutr J*, 22:61.
- [139] Jang J, Kim SR, Lee JE, Lee S, Son HJ, Choe W, et al. (2023). Molecular Mechanisms of Neuroprotection by Ketone Bodies and Ketogenic Diet in Cerebral Ischemia and Neurodegenerative Diseases. *Int J Mol Sci*, 25.
- [140] Nagpal R, Neth BJ, Wang S, Craft S, Yadav H (2019). 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*, 47:529-542.
- [141] Dilmore AH, Martino C, Neth BJ, West KA, Zemlin J, Rahman G, et al. (2023). Effects of a ketogenic and low-fat diet on the human metabolome, microbiome, and foodome in adults at risk for Alzheimer's disease. *Alzheimers Dement*, 19:4805-4816.
- [142] Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. (2013). Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*, 110:9066-9071.
- [143] Salman B, Haidar R, Faour V, Abou Ali W, Aridi L, Harb F, et al. (2025). Microbiota Gut-Brain Axis Dysfunction in Alzheimer's Disease: From

- Pathogenesis to Potential Treatments—A Review. *Health Sciences Review*:100251.
- [144] Chen A, Wang Y, Hu YQ (2024). Exploring Causal Relationships Between Gut Microbiota and Alzheimer's Disease: A Bidirectional Mendelian Randomization Study. *J Alzheimers Dis Rep*, 8:1031-1040.
- [145] Kumari S, Desai V, Sivakumar S, Sikri K, Kumar M (2025). Association between gut microbial dysbiosis and Alzheimer's disease: An umbrella review. *npj Dementia*, 1:41.
- [146] Yakupova EI, Bocharnikov AD, Plotnikov EY (2022). Effects of Ketogenic Diet on Muscle Metabolism in Health and Disease. *Nutrients*, 14.
- [147] Li X, Zhan Z, Zhang J, Zhou F, An L (2020). β -Hydroxybutyrate Ameliorates $A\beta$ -Induced Downregulation of TrkA Expression by Inhibiting HDAC1/3 in SH-SY5Y Cells. *Am J Alzheimers Dis Other Demen*, 35:1533317519883496.
- [148] Erichsen JM, Register TC, Sutphen C, Ma D, Gaussoin SA, Rudolph M, et al. (2025). A phase 2A/B randomized trial of metabolic modulators intranasal insulin and empagliflozin for MCI and early AD. *Alzheimers Dement*, 21:e70704.
- [149] Henderson ST, Morimoto BH, Cummings JL, Farlow MR, Walker J (2020). A Placebo-Controlled, Parallel-Group, Randomized Clinical Trial of AC-1204 in Mild-to-Moderate Alzheimer's Disease. *J Alzheimers Dis*, 75:547-557.
- [150] Wu CY, Kupferschmid AC, Chen L, McManus AJ, Kivisakk P, Galler JA, et al. (2025). Cognitive and Alzheimer's disease biomarker effects of oral nicotinamide riboside (NR) supplementation in older adults with subjective cognitive decline and mild cognitive impairment. *Alzheimers Dement (N Y)*, 11:e70023.
- [151] Dolle C, Tzoulis C (2025). NAD augmentation as a disease-modifying strategy for neurodegeneration. *Trends Endocrinol Metab*, 36:1072-1083.
- [152] Aygerinos KI, Mullins RJ, Egan JM, Kapogiannis D (2022). Ketone Ester Effects on Biomarkers of Brain Metabolism and Cognitive Performance in Cognitively Intact Adults ≥ 55 Years Old. A Study Protocol for a Double-Blinded Randomized Controlled Clinical Trial. *J Prev Alzheimers Dis*, 9:54-66.
- [153] Vandenberghe C, St-Pierre V, Fortier M, Castellano CA, Cuenoud B, Cunnane SC (2020). Medium Chain Triglycerides Modulate the Ketogenic Effect of a Metabolic Switch. *Front Nutr*, 7:3.
- [154] Brinkley TE, Leng I, Register TC, Neth BJ, Zetterberg H, Blennow K, et al. (2022). Changes in Adiposity and Cerebrospinal Fluid Biomarkers Following a Modified Mediterranean Ketogenic Diet in Older Adults at Risk for Alzheimer's Disease. *Front Neurosci*, 16:906539.