*Special Article*

# Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease

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*It has been hypothesized that alterations in the composition of the gut microbiota might be associated with the onset of certain human pathologies, such as Alzheimer disease, a neurodegenerative syndrome associated with cerebral accumulation of amyloid-β fibrils. It has been shown that bacteria populating the gut microbiota can release significant amounts of amyloids and lipopolysaccharides, which might play a role in the modulation of signaling pathways and the production of proinflammatory cytokines related to the pathogenesis of Alzheimer disease. Additionally, nutrients have been shown to affect the composition of the gut microbiota as well as the formation and aggregation of cerebral amyloid-β. This suggests that modulating the gut microbiome and amyloidogenesis through specific nutritional interventions might prove to be an effective strategy to prevent or reduce the risk of Alzheimer disease. This review examines the possible role of the gut in the dissemination of amyloids, the role of the gut microbiota in the regulation of the gut–brain axis, the potential amyloidogenic properties of gut bacteria, and the possible impact of nutrients on modulation of microbiota composition and amyloid formation in relation to the pathogenesis of Alzheimer disease.*

## INTRODUCTION

The gut microbiota plays a fundamental role in the modulation of the bidirectional signaling underlying the gut–brain axis.[1,2] Dysbiosis and alterations of the gut microbiome composition have been shown to contribute to the development of several diseases in humans, such as inflammatory bowel disease, type 2 diabetes, metabolic syndrome, obesity, allergies, colorectal cancer, and Alzheimer disease (AD).[3–5] Alzheimer disease is a progressive neurodegenerative syndrome associated with the accumulation of proteinaceous misfolded amyloid-$\beta$ (A$\beta$) fibrils and oligomers, together with neurofibrillary tangles consisting of hyperphosphorylated tau protein, in the cerebral cortex and other brain regions.[6] It has been suggested that type 2 diabetes, metabolic syndrome, and AD might be deeply interconnected.[7–9] In particular, alterations of the gut microbiome can activate proinflammatory cytokines and increase intestinal permeability, leading to the development of insulin resistance, which has also been associated with AD.[4] Additionally, bacteria populating

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the gut microbiome are known to excrete immunogenic mixtures of amyloids, lipopolysaccharides (LPSs), and other microbial exudates into their surrounding environment.[10–15] Bacterial amyloids might activate signaling pathways known to play a role in neurodegeneration and AD pathogenesis, while the gut microbiome might enhance inflammatory responses to cerebral accumulation of A$\beta$.[16]

It has been suggested that diet and specific nutrients can affect the composition of the gut microbiota[17] and might influence the production or aggregation of amyloid proteins.[16,18–23] This suggests that modulating the gut microbiome through specific nutritional interventions and the use of prebiotics and probiotics might represent an effective strategy to reduce the level of chronic inflammation and A$\beta$ associated with AD, possibly preventing or ameliorating AD symptoms.

This review examines recent scientific literature addressing the possible role of the gut in the dissemination of amyloid and prion-like proteins, the role of the gut microbiota in the regulation of the gut–brain axis, the potential amyloidogenic effects of gut bacteria, and the possible impact of certain foods and plant-related viruses on microbiota composition and amyloid formation, highlighting some of the limitations of these studies as well as the beneficial effects of certain plant-derived nutrients for the prevention of AD.

## THE GUT–BRAIN AXIS AND THE ROLE OF THE GUT IN DISSEMINATION OF AMYLOID PROTEINS

The gut and the brain are deeply interconnected through the gut–brain axis. The central nervous system (CNS) and, in particular, the hypothalamic–pituitary–adrenal axis are activated in response to environmental-related factors. Additionally, the CNS communicates with the enteric nervous system, the gut muscle layers, and the intestinal mucosa through bidirectional (ie, afferent and efferent) autonomic pathways, thus modulating permeability, mucus secretion, motility, and immunity.[24] Inputs from the CNS can modify gut functions, while inputs from the gut to the CNS can modulate specific symptoms.[25] Alterations of these bidirectional communications may contribute to neuroinflammation and the pathogenesis of CNS disorders.[1,2] In particular, the gut has been shown to play a role in the transmission of prionic proteins,[26] which are responsible for mammalian transmissible spongiform encephalopathies.[27] Increasing evidence suggests that clumping of proteins with prion-like behavior might be a phenomenon shared by many of the major CNS diseases, like AD, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. According to this hypothesis, AD-related A$\beta$ should be reconceived as prion-like proteinaceous nucleating particles, and AD as a prion-like disease.[27–29] Protein degradation pathways are normally able to degrade small amounts of prions; however, when prions accumulate and exceed a certain threshold, they are able to self-propagate, thereby compromising CNS functions.[28]

It has been reported that, upon oral administration, prions can withstand the process of digestion and may become incorporated by microfold cells or villous columnar epithelial cells in the gut. Upon entering the intestinal epithelium, prions, by interacting with dendritic cells or macrophages, might accumulate in follicular dendritic cells within Peyer's patches (important sites of mucosal immunity induction) and other lymphoid follicles. Then, by interacting with follicular dendritic cells, prion-like proteins might move to the enteric nervous system, which governs gastrointestinal functions, finally spreading to the CNS.[26] This might occur through the endocrine, humoral, and immune links that characterize the gut–brain axis.

Considering the unifying "prion concept"[29] and the role played by the gut in prion transmission,[26] it is conceivable that the gastrointestinal tract might also play a role in A$\beta$ formation and transmission, possibly contributing to the pathogenesis of AD.

Systemic senile amyloid proteins have been identified in Peyer's patches in a senescence-accelerated mouse model (SAM-P/1), as shown by immunohistochemical staining and electron microscopy.[30] Another study found that A$\beta$ fused with the enhanced green fluorescent protein, when administered to mice before weaning, accumulated in the cytoplasm of columnar epithelial cells, in the crypt, in Peyer's patches, and in the spleen, starting at 3 hours after administration.[31] However, whether Peyer's patches play a direct role in A$\beta$ propagation and AD initiation in humans still needs to be confirmed.

Moreover, homologous or heterologous amyloidogenic precursors might serve as amyloid-enhancing factors and might be transmitted by oral ingestion or parenteral administration.[32] The activity of amyloid-enhancing factor and the levels of total ubiquitin and ubiquitin-protein conjugates were greater in brain samples of AD patients than in normal brain samples.[33] Serum amyloid A proteins, a family of apolipoproteins expressed either constitutively at different levels in different normal human tissues (eg, breast, stomach, small and large intestine, prostate, lung, pancreas, kidney, tonsil, thyroid, pituitary, placenta, skin epidermis, and brain[34]) or in response to inflammatory stimuli, have been found localized within senile plaques in the brains of AD patients.[35,36] Furthermore, in vitro treatment

with serum amyloid A was found to stimulate glial cell reactivity, as shown by the upregulation of several cytokine genes (eg, *IL-6, TNF-α, IL-12 p40, IL-23 p19,* and *IL-10*) and of inducible nitric oxide synthase, particularly in microglial cells and, to a lesser extent, in astrocytes.[37] This suggests that serum amyloid A might play a role in the pathogenesis of AD.

Together, these studies suggest that the gut and the gut–brain axis might play a role in the cross-seeding of amyloid-enhancing factors such as serum amyloid A and misfolded A$\beta$ and, for this reason, might be implicated in the onset of AD.

## ROLE OF GUT MICROBIOTA IN REGULATION OF THE GUT–BRAIN AXIS AND IN GENERATION OF AMYLOID PROTEINS

The gut–brain axis is controlled by the gut microbiota,[1,2] which is composed of as many as $10^{14}$ microorganisms, mainly bacteria belonging to about 1000 different species, but also bacteriophage particles, viruses, fungi, and archaea.[3,38,39] The gut microbiome plays an essential role in preserving a normal gut physiology and in modulating signaling along the gut–brain axis, thus contributing to the health of the individual.[40,41]

When perturbations of gut microbiota (ie, dysbiosis) occur as a consequence of exposure to antibiotics, especially during infancy,[42–44] or to dietary changes,[17,45] use of probiotics,[46] food additives,[47] nonsteroidal anti-inflammatory drugs,[48] and a variety of health conditions,[49–53] colonization by intrinsic pathogens can perturb the gut–brain axis, triggering inflammatory host responses and pathogen-mediated disease.[3] In the opposite way, high CNS stress levels might affect gut physiology and perturb the gut microbiota composition.[40,41]

In line with the proposal that chronic dysbiosis can compromise the physiological bidirectional signaling that characterizes the gut–brain axis, it has been hypothesized that persons affected by irritable bowel syndrome might suffer from comorbid neurological dysfunctions in addition to respiratory, neuromuscular, sleep-related, and psychological disorders.[25] Analogously, nonceliac gluten sensitivity, known to trigger gut dysbiosis, has also been linked to neuroinflammation and a higher risk of dementia.[50] Additionally, persons affected by irritable bowel syndrome seem to be at increased risk of developing Parkinson's disease, as shown in a cohort of Taiwanese patients with newly diagnosed irritable bowel syndrome.[54]

Moreover, species that populate the microbiome, such as bacteria and fungi, excrete complex and immunogenic mixtures of functional LPSs, amyloids, and other microbial exudates from their outer membranes into their surrounding environment.[10–15] In particular, LPSs may modify gut homeostasis, gut inflammation, and gut permeability, as shown in inflammatory bowel disease and necrotizing enterocolitis[55] as well as in sepsis.[56] Additionally, microbial amyloids are implicated in molecular and cellular adaptation, stimulation of adhesion, aggregation, formation of biofilm, tissue invasion, bacterial colonization, and infectivity of pathogens.[13] *Escherichia coli, Salmonella enterica, Salmonella typhimurium, Bacillus subtilis*, *Mycobacterium tuberculosis*, and *Staphylococcus aureus* are some of the many bacterial strains that produce functional extracellular amyloid fibers.[13,14] These bacteria might interact with the host environment in multiple ways. In particular, the *E. coli* endotoxin was found to potentiate the formation of A$\beta$ fibrils in vitro and, for this reason, might be implicated in the pathogenesis of AD.[57]

Monomeric LPSs and amyloids are generally soluble, although they might polymerize over time into insoluble fibrous protein aggregates. These aggregates might be responsible for alteration of proteostasis, induction of oxidative stress, and cross-seeding phenomena; for example, by acting as aggregation nuclei, amyloid proteins can seed their own polymerization, as shown both in vitro and in vivo.[16,58] This has been postulated along with the concept of molecular mimicry, which was formulated in recent decades to explain commonalities of biological structures developed in response to evolutionary pressures.[16] Bacterial amyloids might prime the innate immune system, thus enhancing inflammatory responses to cerebral A$\beta$.[16] The following section describes how gut-bacteria-derived amyloids might contribute to the pathogenesis of AD.

## CONTRIBUTION OF GUT MICROBIOTA AND GUT-BACTERIA-DERIVED AMYLOIDS TO THE ONSET OF ALZHEIMER DISEASE

Considering there are undefined amounts of LPSs and amyloids in the human gut, it is possible that the human gut microbiota might play a role in the etiopathogenesis of neurological disorders characterized by amyloidogenic features, such as AD,[59–63] even though this has not been confirmed.[14,64] In particular, alterations of the gut microbiota and an increase in the gut's permeability might lead to an overall increase in systemic inflammation, neuroinflammation, and dysfunction of specific brain regions, such as the cerebellum and the hippocampus,[25,65] and to the development of insulin resistance, which is correlated with AD pathogenesis.[4,66,67] The contribution of gut microbiota to amyloid

formation and dissemination becomes even more important during aging, when both the gastrointestinal tract epithelium and the blood–brain barrier become more permeable to small molecules.[59–61,68] Amyloid brain influx through the blood–brain barrier is known to be mediated by the receptor for advanced glycosylation products (RAGE)[69] and is dependent on amyloid chaperones and apolipoproteins E and J,[70] while amyloid clearance is controlled by the low-density lipoprotein receptor-related protein 1.[71] These transportation mechanisms are known to be altered in AD patients.[72] Additionally, prion-like proteins (in particular, $PrP^{C}$) may also contribute to monocyte transendothelial infiltration by forming an alternative junctional adhesion molecule,[73] possibly inducing or aggravating inflammation (Figure 1).

Moreover, during aging, the composition of the gut microbiota changes, with numbers of *Bacteroidetes* increasing over those of *Firmicutes* and *Bifidobacteria*, even though high interindividual variations among the elderly can be found. This variability can be influenced by different dietetic regimens and different residential situations (ie, day-hospital, community, rehabilitation, or long-term residential care).[74–76]

To explain how gut microbiota might contribute to the pathogenesis of AD, it has been hypothesized that bacteria-derived amyloids might leak from the gastrointestinal tract and accumulate at the systemic and brain level.[62] This might cause an increase in reactive oxygen species and the activation of nuclear factor-κB (NF-κB) signaling, which upregulates the proinflammatory microRNA-34a (miRNA-34a). As a consequence, miRNA-34a would downregulate the expression of *TREM2* (triggering receptor expressed in microglial/myeloid cells-2), leading to impairment of phagocytosis that contributes to accumulation of $A\beta_{42}$ peptide.[62,77]

Additionally, bacterially derived LPSs and amyloids can further exacerbate the gut's leakiness and can increase the levels of cytokines and other small proinflammatory molecules, such as interleukin (IL) 17A and IL-22, which are directly associated with AD.[68,78] These cytokines might transit through both the gastrointestinal tract and the blood–brain barrier, accessing the brain and further triggering immunogenic reactions, reactive oxygen species release, and signaling of toll-like receptor 2/1, CD14, and NF-κB,[16,62] which are known to play a role in neurodegeneration (Figure 1).

To date, the contributions of specific bacterial species in the gut to the onset or consolidation of dementia and cognitive impairment have not been clearly defined. However, some bacterial species, such as *Lactobacillus* and *Bifidobacterium* (both gram-positive facultative anaerobic or microaerophilic bacteria), can metabolize glutamate to produce γ-aminobutyric acid

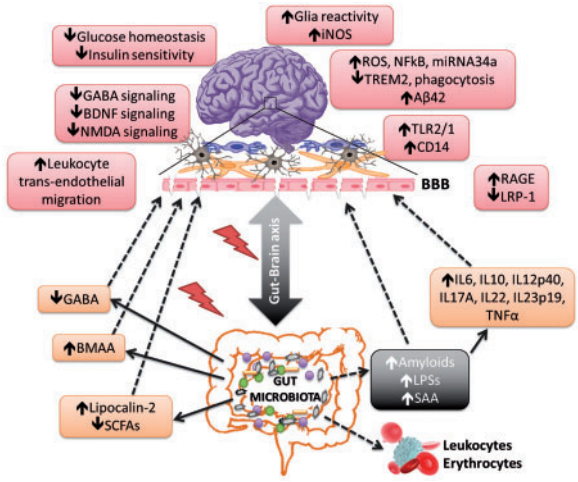


*Figure 1* **Gut–brain axis perturbations and bacteria-derived amyloidogenesis at the onset of Alzheimer disease.** Under conditions of gut chronic inflammation, the gut microbiome might release high amounts of amyloid-enhancing factors (ie, amyloids, LPSs, and SAA), which may leak from the gastrointestinal tract and increase the levels of proinflammatory cytokines (ie, IL6, IL10, IL12p40, IL17A, IL22, IL23p19, TNFα). Leukocytes and amyloid proteins may transit more easily through the BBB because of the altered expression of RAGE, LRP-1 receptors, and tight junctions, contributing to neuroinflammation. Additionally, cytokines may transit through both the gastrointestinal tract and the BBB (both more permeable with aging), thus entering the CNS, and may further TLR2/1, CD14 signaling, glia reactivity, and iNOS increase. Increase of reactive oxygen species levels and activation of NF-κB signaling may occur. As a consequence, miRNA34a is upregulated, causing downregulation of TREM2 and, consequently, accumulation of Aβ42 peptides and reduction of phagocytosis. Perturbations of gut microbiota can also lead to impairment of GABA formation, accumulation of the neurotoxin BMAA (known to disrupt NMDA signaling and found accumulated in the AD brain), increase of lipocalin-2 (an intestinal adipokine associated with inflammation and insulin resistance), and decrease of SCFAs (which modulate glucose homeostasis and insulin sensitivity). As a consequence, signaling of GABA, BDNF, and NMDA becomes perturbed, glucose homeostasis becomes impaired, and insulin sensitivity is reduced. Moreover, coccus-shaped bacteria have been found near or within erythrocytes and near leukocytes in blood samples of AD patients. *Abbreviations*: AD, Alzheimer disease; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BMAA, β-*N*-methylamino-L-alanine; CD14, cluster of differentiation 14; CNS, central nervous system; GABA, γ-amino butyric acid; IL, interleukin; iNOS, inducible nitric oxide synthase; LPSs, lipopolysaccharides; LRP-1, low density lipoprotein receptor-related protein 1; miRNA, micro RNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, *N*-methyl-D-aspartate; RAGE, receptor for advanced glycosylation products; ROS, reactive oxygen species; SAA, serum amyloid A; SCFAs, short-chain fatty acids; TLR2/1, toll-like receptor 2/1; TNFα, tumor necrosis factor α; TREM2, triggering receptor expressed in microglial/160myeloid cells-2.

(GABA), the major inhibitory neurotransmitter,[11] and alterations of gut microbiota might compromise the endogenous production of GABA and short-chain fatty acids (ie, acetate, butyrate, and propionate). Alterations

of GABA signaling are linked to cognitive impairment, AD, anxiety, depression, and synaptogenesis impairments,[79–82] while lower levels of short-chain fatty acids might negatively affect brain glucose and energy homeostasis, immune responses, and epithelial cell growth, possibly impacting the functioning of both the central and peripheral nervous systems[83,84] (Figure 1).

Remarkably, brain-derived neurotrophic factor (BDNF) signaling was decreased in both the brain and the serum of patients affected by AD,[85,86] and BDNF expression was reduced in the hippocampus of a germ-free mouse model (ie, mice that have not been naturally colonized by microorganisms).[87] Considering that gnotobiotic rodent models may have intrinsic limitations,[88,89] may lack some human-specific gut bacteria, and may have different proportions of gut bacteria and different immune responses than those found in humans,[90–92] it would be worthwhile to assess the possible effects of gut dysbiosis in humans in vitro and in vivo.

Moreover, gut cyanobacteria are known to produce the nonproteinogenic amino acid *β*-*N*-methylamino-L-alanine, a neurotoxin known to elicit excitotoxicity by interacting with the *N*-methyl-D-aspartate glutamate receptor, and *N*-methyl-D-aspartate signaling is known to be disrupted in AD and other neuropathologies.[93] Accordingly, high levels of *β*-*N*-methylamino-L-alanine have been found in the brains of persons affected by AD and amyotrophic lateral sclerosis[94] (Figure 1).

Finally, gut microorganisms might also translocate from the gastrointestinal tract through microfold cells overlaying the Peyer's patches and into the blood and other tissues, a phenomenon known as atopobiosis. This may contribute to the dynamics of inflammatory diseases such as irritable bowel syndrome, necrotizing enterocolitis, and neuroinflammatory diseases.[95] Analogously, coccus-shaped bacteria have been found in blood samples of AD patients, particularly on the cell surface of both leukocytes and erythrocytes as well as within erythrocytes, as shown by transmission electron microscopy[96] (Figure 1).

Altogether, these studies suggest that gut microbiota and gut-microbiota products might represent modulators of gene–environment interactions, affecting chromatin plasticity within the brain and modulating neuronal transcription and, eventually, neuronal functions. For these reasons, the gut microbiota itself might represent an epigenetic entity, as recently hypothesized.[97]

## EFFECTS OF DIET ON MICROBIOTA COMPOSITION

Diet plays a fundamental role in health, and specific dietary patterns, mainly characterized by low intakes of plant-derived foods, have been associated with the risk of type 2 diabetes, metabolic syndrome, and some forms of cancer and AD.[98,99] While foods such as fructose- and purine-rich foods can stimulate the generation of uric acid, thus causing insulin resistance and fat accumulation, others (eg, plant foods, antioxidants, probiotics, nuts, soybeans, and n-3 fatty acids) can positively modulate mitochondrial biogenesis.[100] In particular, n-3 polyunsaturated fatty acids are known to have important anti-inflammatory and immunomodulatory properties and have been used for the prevention and treatment of diseases characterized by chronic gut inflammation (eg, irritable bowel syndrome and rheumatoid arthritis)[101–103] and neurodegeneration (eg, AD),[104,105] as recently highlighted.[106]

Importantly, diet can also affect the composition of the gut microbiota (Figure 2).[17,45] Diets characterized by high intakes of fruit and vegetables (eg, rural, Mediterranean, plant-rich, or plant-based diets) and a low or null consumption of meat are associated with a greater abundance of *Prevotella* than *Bacteroides* organisms.[107] Bacteria from the genus *Prevotella* are known to express genes controlling cellulose and xylan hydrolysis,[108] whereas *Bacteroides* bacteria are enriched with genes necessary for breaking down amino acids. For this reason, *Bacteroides* species seem more prevalent in Western populations that follow a Western-style diet, rich in animal proteins and fats and low in fiber,[109] confirming the key role of diet as a modulator of the gut microbiota composition.[107]

Moreover, changes in the intake of specific nutrients such as fatty acids, carbohydrates, micronutrients, prebiotics, and probiotics not only affect the gut microbiota but can also modulate the expression of genes and proteins specifically present in liver, adipose tissue, intestine, and muscle cells, as shown by studies of metagenomics and integrative metabolomics.[46] Diet-dependent alterations of the gut microbiota composition can have consequences in the context of obesity, type 2 diabetes, and metabolic syndrome,[38,46] and may affect brain physiology[110] and influence the risk of AD.[4]

Specifically, probiotics and prebiotics (typically nondigestible fiber compounds), by modulating gut microbiota composition, may ameliorate or prevent intestinal (and systemic) inflammation, thereby modulating immunity and neurobiology.[111,112] In particular, most intervention studies in elderly subjects have shown that probiotics and prebiotics can stimulate the growth of *Bifidobacterium* populations while concomitantly decreasing the growth of enterobacteria.[74] Probiotics were also found to decrease levels of proinflammatory cytokines such as IL-5, IL-6, IL-1*β*, IL-8, and TNF-*α*,[113,114] which are upregulated in the elderly,[115] and to increase levels of natural killer cells, activated lymphocytes, and phagocytosis,[116] suggesting

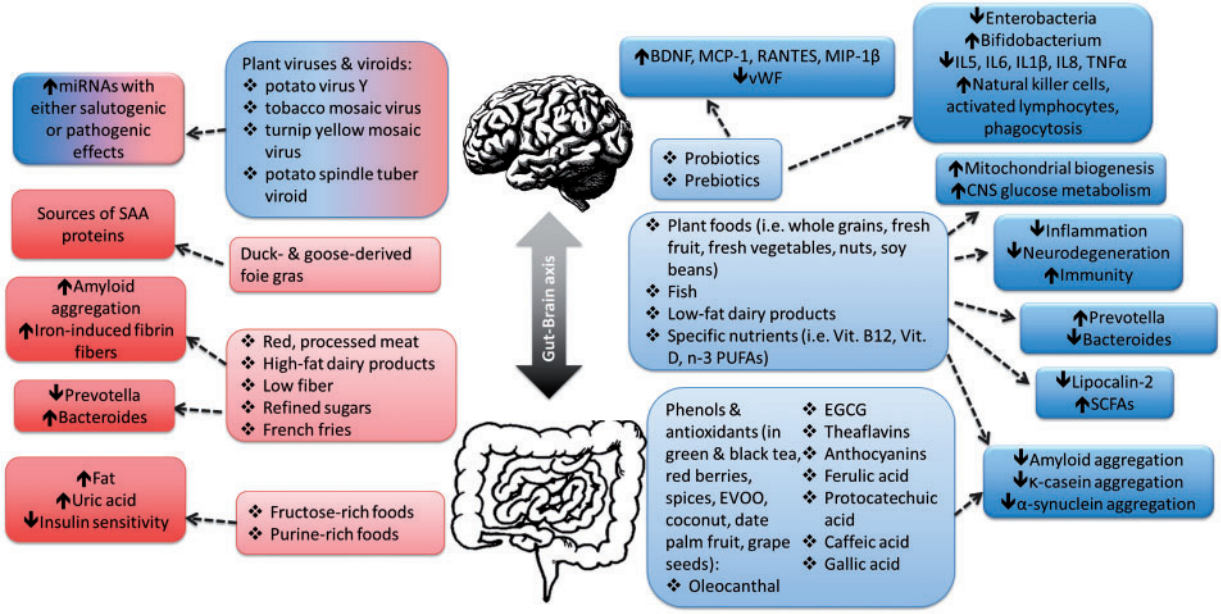


*Figure 2* **Effects elicited by nutrients and foods on either gut microbiota composition or amyloid formation.** Protective, antiamyloidogenic foods and nutrients and their salutogenic effects are shown on the right side of the figure; proamyloidogenic foods and nutrients and their pathogenic effects are indicated on the left side. Plant viruses and viroids can increase the levels of miRNAs with either salutogenic or pathogenic effects. *Abbreviations*: CNS, central nervous system; BDNF, brain-derived neurotrophic factor; EGCG, (−)-epi-gallocatechin gallate; EVOO, extra virgin olive oil; IL, interleukin; MCP-1, monocyte chemotactic protein-1; MIP-1$\beta$, macrophage inflammatory protein-1$\beta$; miRNA, micro RNA; PUFAs, polyunsaturated fatty acids; RANTES, regulated on activation, normal T cell expressed and secreted; SAA, serum amyloid A; SCFAs, short-chain fatty acids; TNF$\alpha$, tumor necrosis factor $\alpha$; Vit B12, vitamin $B_{12}$; vWF, Von Willebrand factor.

improvement of the adaptive immune response and reduction of inflammation.

Additionally, probiotics, prebiotics, and changes in diet seem to positively affect brain functions and brain neurochemistry.[110,117,118] In particular, supplementation with probiotics was reported to reduce the levels of von Willebrand factor (a blood glycoprotein found elevated in cardiovascular, cancer, and connective-tissue-related diseases[119]) and to significantly upregulate the protein BDNF and the cytokines MCP-1 (monocyte chemotactic protein-1) and CCL5/RANTES (chemokine [C-C motif] ligand 5/regulated on activation, normal T cell expressed and secreted), both related to IL-17, as well as the chemokine MIP-1$\beta$ (macrophage inflammatory protein-1$\beta$), in schizophrenia patients, reducing gastrointestinal leakage.[120] Notably, BNDF was downregulated in the brains of AD patients.[85]

Plant-based dietary interventions can also ameliorate gut dysbiosis and its associated health conditions. A clinical intervention trial involving 6 obese subjects with type 2 diabetes and/or hypertension who followed a strict vegetarian diet for 1 month showed that the vegetarian diet promoted a reduction of gut inflammation, with a decrease of pathobionts (ie, *Enterobacteriaceae*) and an increase of commensal microbes (ie, *Bacteroides fragilis* and *Clostridium* species belonging to clusters XIVa and IV).[121] This resulted in a reduction of intestinal lipocalin-2, an adipokine associated with the development of inflammation and insulin resistance,[122] and higher levels of short-chain fatty acids,[121] which are associated with improved glucose homeostasis and insulin sensitivity[84] as well as modulation of CNS functions,[83] as reported above. Large randomized controlled trials are needed to define the possible role of prebiotics, probiotics and plant-based dietary interventions in the management of gut dysbiosis, cognitive dysfunction, and AD-related symptoms.

## NUTRIENTS AND FOODS AS MODULATORS OF AMYLOID AGGREGATION OR AS SOURCES OF AMYLOIDS

Certain nutrients can also affect amyloid production or represent a source of amyloids, possibly affecting neuroinflammation and dementia-related risk[16,18] (Figure 2). Clinically and cognitively normal individuals with and without AD risk factors, following dietary patterns characterized by high intakes of whole grains, fresh fruits, vegetables, legumes, fish, and low-fat dairy products (which provide higher intakes of vitamin $B_{12}$, vitamin D, and n-3 polyunsaturated fatty acids) and by low intakes of refined sugars, French fries, high-fat dairy products, butter, and processed meat, show lower accumulation of A$\beta$ in the brain and higher

cerebral glucose metabolism, as evidenced by neuroimaging analysis of gray matter volumes (a marker of brain atrophy), $^{11}$C-Pittsburgh compound B (to measure the accumulation of fibrillar A$\beta$), and $^{8}$F-fluorodeoxyglucose (to assess brain glucose metabolism).[19,123]

Several studies have described the beneficial effects of natural phenols present in plant-derived foods, such as green tea, red berries, spices, extra virgin olive oil, red wine, and aromatic herbs, in reducing amyloid aggregation and the incidence of amyloid-related diseases.[20–22] In particular, oleuropein aglycone and oleocanthal, two phenolic components of extra virgin olive oil, have been shown to promote A$\beta$ clearance and autophagy as well as inhibition of tau aggregation and neuroinflammation.[124] Oleocanthal has been found to stimulate A$\beta$ clearance by upregulating two major transporters of A$\beta$ expressed in the blood–brain barrier (ie, P-glycoprotein and low-density lipoprotein receptor-related protein 1), consequently increasing the brain efflux rate, as shown in murine brain endothelial cells in vitro and in C57BL/6 wild-type mice in vivo.[125] However, considering there are significant interpecies differences between the mouse and the human blood–brain barrier with regard to A$\beta$ clearance and degradation,[126] the actual suitability of oleocanthal and other extra virgin olive oil phenols in reducing amyloid deposits in humans should be confirmed.

Analogously, the polyphenol (−)-epi-gallocatechin gallate, mainly present in green tea, and theaflavins, found in fermented black tea, are known to inhibit the formation of amyloid fibrils. Both (−)-epi-gallocatechin gallate and theaflavins have shown neuroprotective action against A$\beta$ toxicity. They have also been shown to inhibit the fibrillogenesis of both A$\beta$ and $\alpha$-synuclein as well as the maturation of A$\beta$ and $\alpha$-synuclein fibrils into larger toxic aggregates in vitro.[23,127–129] For this reason, they might have preventive effects against both AD and Parkinson disease. Coconut-derived phenols and phytohormones (ie, cytokinins) might also be suitable to prevent the aggregation of A$\beta$ proteins, as suggested by in vitro observations.[130]

Date palm fruits represent a good source of dietary fiber and contain large amounts of total phenols and other natural antioxidants (eg, anthocyanins, ferulic acid, protocatechuic acid, and caffeic acid) that have been shown to reduce A$\beta$ in vivo.[131]

Similarly, gallic acid, the most active component in grape seed extracts, has been shown to inhibit fibrillary aggregation of both A$\beta$ peptides and $\kappa$-casein (a milk protein known to spontaneously form amyloid fibrils under physiological conditions) in vitro.[132]

Several other plant-derived nutrients, such as garlic extracts,[133] walnut extract,[134] and resveratrol,[135,136] as well as plants such as turmeric, *Salvia miltiorrhiza*, *Panax ginseng*, rosemary, cinnamon, ginger, sage, and many others,[137] have been shown to inhibit aggregation of amyloid proteins and subsequent plaque formation. Importantly, phytochemicals and their metabolic products can modulate gut microbiota composition by exerting prebiotic-like effects, inhibiting pathogenic bacteria and stimulating the growth of beneficial bacteria.[138] For instance, tea phenolics and their aromatic metabolites have been reported to elicit bacteriostatic or antimicrobial activities on gut microbiota, specifically inhibiting the growth of some pathogenic bacteria (ie, *Clostridium perfringens*, *Clostridium difficile,* and *Bacteroides* species).[139] These modulatory effects may have important consequences on the level of release of microbial-derived LPSs and amyloids.

Animal-derived foods, such as red and processed meat that contains large amounts of trivalent iron, can contribute to the formation of iron-induced fibrin fibers, which have been shown to entangle erythrocytes, thus preventing oxygen delivery to the CNS, and to interact with A$\beta$,[140–142] possibly contributing to AD pathogenesis.[96] On the other hand, chlorophyll-derived magnesium, like plant-derived polyphenols, has been shown to disaggregate erythrocyte-associated fibrin.[96]

Additionally, some animal-derived foods, such as duck- or goose-derived foie gras, contain fibrillary material composed of serum amyloid A–related proteins that induced extensive systemic amyloid pathological deposits in a transgenic mouse model of secondary amyloidosis.[32] However, extrapolating these data to humans might be questionable, considering the very high dose of foie gras administered and the unnatural (from a human perspective) routes of administration (ie, oral gavage and tail injection).[32]

Another aspect to consider is the possible transmission of amyloid-like molecules from plant viruses. Plant viruses, such as the potato virus Y,[143] the tobacco mosaic virus,[144] and the turnip yellow mosaic virus,[145] harbor RNAs that may mimic the nucleotide sequences of human miRNAs. Plant viral RNAs might be taken up through the intestine and distributed to the brain, thereby representing possible sources of amyloidogenesis.[16] One hypothesis is that nucleotide sequence homologies between plant viral RNAs and human miRNAs, and also between plant viroids (eg., potato spindle tuber viroid) and human miRNAs, could modulate the production of miRNAs in the host, influencing protein expression,[146–148] even in salutogenic ways.[16] This hypothesis would explain the lower incidence of AD in sub-Saharan Africa and in India (compared with Western countries), where the consumption of potatoes infected with potato virus Y is much higher.[16] However, some miRNA populations associated with AD have been found in cerebrospinal fluid,[149] in different brain

anatomical compartments, and in extracellular fluid[150] and may play a role in the onset and establishment of an AD phenotype.[151]

## DISCUSSION

The gut–brain axis plays a key role in regulating the physiology of both the gut and the brain. The fact that metabolic-related syndromes and AD share common traits such as insulin resistance and chronic inflammation[8,9,152] and correlate with similar impairments of brain anatomy and function[99,153–159] further confirms the important role played by the gut–brain axis in the regulation of host metabolism, immune response, and brain physiology.[66] The bidirectional communications that characterize the gut–brain axis are modulated by the presence of the gut microbiome. Under conditions of dysbiosis, the gut microbiota becomes perturbed and, as a consequence, chronic inflammation occurs, together with a plethora of metabolic and immunogenic reactions that might contribute to the onset of obesity, type 2 diabetes, metabolic syndrome, and AD.3–5,25,40,41,50

Bacteria populating the microbiome have been shown to produce amyloids, LPSs, and other immunogenic compounds[10–15] that might contribute to the regulation of signaling pathways implicated in neuroinflammation, brain A$\beta$ deposition, and AD pathogenesis.[16] Knowing the cellular and molecular mechanisms underlying gut dysbiosis and inflammation might enable the discovery of biomarkers suitable for the early diagnosis of AD and the design of novel therapeutics and preventive strategies.[67] In particular, this knowledge will provide insight into the complex multifactorial etiopathology of late-onset AD, the most prevalent form of AD (constituting nearly 95% of all AD cases[65]), which is related to genetic alleles (eg, *APOE*-$\varepsilon$4 [apolipoprotein $\varepsilon$4][160] and an allelic variant of *TREM2*[161]) and, notably, multiple environmental risk factors.

Nutritional interventions associated with the use of probiotics, prebiotics, and plant-derived nutrients and phytocompounds, by ameliorating gut inflammation and dysbiosis, might stimulate a positive modulation of the gut–brain axis, reduce neuroinflammation, and retard or regress cognitive impairments associated with AD.[25] Additionally, nutritional patterns characterized by a high intake of plant foods and specific plant-derived compounds have been shown to reduce A$\beta$ aggregation and, for this reason, are currently considered suitable for the prevention of AD.[19–23,123,124,127,128,130,131,133–137] Knowing the effects and functions of specific phytocompounds, prebiotics, and probiotics could aid the design of novel oral therapies for AD and other CNS diseases.[6,83,162]

The recommendation of frequent intakes of nutraceuticals or isolated nutrients, however, might not be beneficial, considering the possible oxidative-stress-related events that follow interactions between nutraceutical supplements and metal ions.[163] A more favorable strategy would be to encourage higher intakes of low-fat, plant-derived foods and lower or null intakes of meat products as a general strategy to prevent AD, type 2 diabetes, and metabolic syndrome.[99]

Several studies conducted in animals have described the effects that antibiotics, prebiotics, and probiotics might have on the gut microbiota composition.[164–167] The extrapolation of these data to humans, however, is unclear and requires further investigation.[5,168] Importantly, translatability of this knowledge into human-relevant treatments should be assessed through human-based (rather than animal-based) strategies.[169,170] Some compounds tested on animal models and/or in vitro have been reported to elicit unpredictable and opposite effects. As an example, $\alpha$-mangostin, a xanthone found in mangosteen fruit, has been reported to promote dysbiosis in mice in vivo, elevating serum levels of granulocyte colony-stimulating factor, IL-6, and serum amyloid A,[171] while inhibiting A$\beta$ aggregation in rat cortical neurons in vitro.[172] Moreover, considering the interspecies differences in the brain efflux and the clearance of A$\beta$, in murine and human blood–brain barriers,[126] and in gut microbiota composition and immune responses,[90–92] human gut dysbiosis and the actual antiamyloidogenic effects of phytocompounds should be assessed in human subjects by means of neuroimaging tools and dyes. Additionally, brain-on-a-chip[173,174] and gut-on-a-chip[175,176] models might represent promising novel in vitro tools to explore gut–brain relations and the role of the microbiome in neurodegeneration.

## CONCLUSION

Understanding the early causes of gut microbiota dysbiosis and the correlations between gut microbiota and brain physiology might help prevent or reduce sequelae related to chronic gut and brain inflammation.


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