Chapter 3

Modulation of the microbiota-gut-brain axis by bioactive food, prebiotics, and probiotics decelerates the course of Alzheimer's disease

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Chapter Outline

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The origin of Alzheimer´s disease may be placed outside the brain

Alzheimer´s disease (AD) is considered as a syndrome that mainly affects older people in a progressive manner, causing deterioration in memory, thinking, behavior, and the ability to perform everyday activities. It is estimated that 50 million people worldwide are living with dementia, and it is projected to increase to 82 million in 2030, and 152 million by 2050 [1]. Aging is the main risk factor for this condition and the percentage of cases with AD increases to 3% in people aged 65–74, 17% in people aged 75–84, and 32% in people aged 85 and older [2].

There are two major neuropathological hallmarks in AD patients: amyloid-beta peptide (Aβ), which tend to accumulate extracellularly as Aβ plaques, and the intracellular hyperphosphorylation of tau protein causing impairment in the cytoskeleton function causing neuronal death [3–5]. In addition, neuroinflammation and degeneration of neuronal processes and synapses are observed at the early stages of the disease [6]. AD is a multifactorial condition with only 2%–4% of the cases of familiar origin associated with specific protein mutations, whereas the remaining 98% are of sporadic type [1]. The apolipoprotein ε4 allele (APOE4) is the strongest genetic risk factor for AD; however, both familiar- and sporadic-AD types present an accumulation of Aβ plaques and tau hyperphosphorylation with specific disease progression patterns in selected brain regions [7,8]. Therefore, drugs in the AD pipeline include agents intended to intervene in the pathological hallmarks of the disease. Despite the huge budget invested by the pharmaceutical companies, there are overwhelming negative results in clinical trials [9]. Notwithstanding, the current Food and Drug Administration Agency (FDA, USA) approved medications include only symptomatic cognitive enhancers, and drugs to treat neuropsychiatric symptoms [10]. This panorama evidences the urgent need to develop disease-modifying therapies (DMT) capable of preventing, delaying the onset, or slowing the progression of AD.

It is widely accepted that brain and body alterations related to AD initiate decades before clinical symptoms of dementia appear [11], with undetected changes in the brain of the person to be affected years later with AD. Examples of these include abnormal levels of Aβ in the brain, in cerebrospinal fluid (CSF), and decreased metabolism of glucose as shown on positron emission tomography (PET) scans [12]. These brain changes are actually considered clinical biomarkers; however, some aged persons without dementia may also show similar brain alterations [13,14]. Therefore, caution must be taken to define AD clinical diagnostic tests based on those biomarkers.

Interestingly, years before AD clinical symptoms are developed, people frequently report gastrointestinal disorders [15], present systemic chronic low-grade inflammation [16], and increased levels of inflammatory cytokines in serum [17–19]. Moreover, peripheral chronic low-grade inflammation

is associated with shortened latency for AD onset in ApoE4 carriers [20]. In the 19th century, the German psychiatrist Alois Alzheimer described a higher incidence of syphilis infection in AD patients [21]. Also, systemic and recurrent infections enhance the possibility to develop cognitive impairment and dementia [22,23]. Recently, epidemiological studies have shown that high titers of antiviral antibodies correlate with the development of AD [24], as well as antibody titers versus common infectious bacteria, such as *Borrelia burgdorferi, Chlamydophila,* and *Helicobacter pylori* are higher in AD patients compared to nondemented subjects. Interestingly, enhanced antibody titers are associated with higher Aβ levels in plasma of AD patients, who also showed higher life-span exposure to pathogens [25,26]. Moreover, *H. pylori*-infected AD patients present higher tau concentrations in CSF, lower scores in the Mini-Mental State Examination (MMSE), and tend to develop more severe dementia compared to noninfected AD patients [27]. From this, there is a notion that harmful substances derived from microbial constituents cause inflammation. The relationship between chronic infections and dementia may be related to an aberrantly active systemic and central immune reaction. Bacterial peptidoglycan cell wall can activate both innate and adaptive arms of the host mucosal immune system [28], triggering the production of proinflammatory cytokines such as interleukin (IL)-6 and IL-1β. Gram-negative bacteria release lipopolysaccharide (LPS) component of their cell wall, activate toll-like receptors (TLRs) expressed in monocytes, macrophages, and microglia [29] with a concomitant production of IL-1β and IL-6 that generates an inflammatory reaction in the body and brain [30]. IL-1β induces activation of both astrocytes and microglia [31] and generates neuroinflammation, a hallmark of AD [32]. Furthermore, physiological doses of IL-6 induce phosphorylation of tau protein in hippocampal neurons by deregulating the cdk5/p35 pathway [33]. Interestingly, central nervous system (CNS)-infected persons develop AD histopathologic hallmarks, such as Aβ aggregation, neuroinflammation, and cognitive impairment [34], while systemic inflammation during midlife is associated with cognitive decline over a 20-year period [35]. Therefore, chronic systemic infections can trigger an immune response, systemic low-grade inflammation, and neuroinflammation, with a concomitant aggregation of proteins related to AD pathology in the brain.

It is observed that older individuals have elevated levels of inflammatory cytokines, such as IL-6 and tumor necrosis factor-α (TNF-α), compared to younger ones [36]. This age-related proinflammatory condition has been named as "inflammaging," associated with several age-related diseases [37]. Nonetheless, AD patients had a stronger systemic inflammation [22,38], and a strong neuroinflammation in brain regions related to cognition [39] compared to age-matched nondemented subjects. Similarly, transgenic mice (Tg-mice) overexpressing genes associated with familiar AD, such as mutations in amyloid precursor protein (APP) and tau protein, had an over-activation of B- and T-lymphocytes and

increased IgG plasma levels [40], mirroring the peripheral immune system activation observed in AD patients [6]. What factors might cause this strong peripheral and central inflammation, even years before dementia diagnosis, is yet not clear. However, the recent investigations may help to elucidate a path toward a better understanding of the possible origin of this neurodegenerative disease. Several groups have convincingly reported a predominance of proinflammatory bacteria in fecal samples of AD patients compared to age-matched controls [41–45]. The relative abundance of *Escherichia* spp. and *Shigella* spp. was found increased, and the abundance of *Eubacterium rectale* was decreased in fecal samples from cognitive-impaired elders positive for Aβ plaques, in comparison to Aβ-negative cognitive-impaired subjects or controls [41]. Another study found decreased amounts of Phylum Firmicutes and *Bifidobacterium*, but increased Bacteroidetes in the fecal samples of AD patients [43], while others have found increased Actinobacteria in AD fecal samples [45]. Fecal microbiota had qualitative similarities, but quantitative differences compared to microbiota from the cecum [46,47]. Hence, fecal microbiota analysis may well represent gut-microbiota (GM) variations related to health or disease. AD-associated GM alterations are reproducible in animal models. Tg-mice developed a predominant proinflammatory GM during aging, compared to the control mice (i.e., APP/PS1, 3xTgAD, and 5xFAD models) [48–51]. GM dysbiosis alters gut epithelium permeability and increases the levels of circulating proinflammatory cytokines, LPS, and other substances into the plasma [52]. Moreover, dysbiosis may also contribute to bacterial translocation [53]. Recent investigations show the presence of different microorganisms in AD brain samples, such as bacteria (i.e., *Chlamydophila pneumoniae, Clostridium perfringens, B. burgdorferi*) [54–56], viruses (i.e., *Cytomegalovirus, herpes simplex virus*) [57,58], and fungi (i.e., *Trichoderma viride, Candida albicans, C. glabrata, C. orthopsis, Saccharomyces cerevisiae, Sclerotinia borealis*) [55,59], which are more frequently observed in brains from diseased subjects than controls. It is hard to perceive how those microorganisms could penetrate into the brain. However, blood–brain barrier (BBB) breakdown is an early biomarker of human cognitive dysfunction [60], associated with free passage of bacterial and other external agents into the brain [61].

The gene encoding APP is an ancient and highly conserved gene expressed in neuronal and nonneuronal tissues [62]. In vertebrates, alternate splicing of the APP transcript generates eight isoforms, from which the 695 amino acid form is expressed predominantly in the CNS, and the 751 and 770 amino acid forms are more ubiquitously expressed [63]. APP could be cleaved by α-secretase, and then γ-secretase, but this does not generate Aβ. The by-products could be reinternalized in clathrin-coated pits into endosomal compartments containing the proteases BACE1 and γ-secretase, resulting in the production of Aβ [64]. Notably, APP overexpression and Aβ aggregation could be detected not only in the brain parenchyma, but also in the intestinal submucosa [65], being more expressed in AD patients and

Tg-mice compared to age-paired controls [66,67]. Aβ aggregation and APP overexpression are also observed in the intestine [67,68] and fat tissue from obese subjects [69]. Contrary, $APP^{-/-}$ mice are resistant to diet-induced obesity [70] and develop an attenuated inflammatory profile compared to controls [65]; this data suggest that APP and its by-products may regulate the host defense and immune system. In support of this idea, several studies have demonstrated a potent microbicidal effect of Aβ peptide [71–73]. In 2010, Soscia and coworkers tested the antimicrobial activity of amyloid aggregates obtained from cortex samples of AD patients versus different microorganisms, including bacteria and fungi. They reported lower growth of colonies when AD tissue was present compared to the control-treated samples [72]. Synthetic Aβ1-40 and Aβ1-42 also showed equivalent or greater antimicrobial potency than LL-37 (an antimicrobial peptide) for eight different pathogens tested (*C. albicans, Escherichia coli, Streptococcus epidermidis, S. pneumoniae, S. aureus, S. pyogenes, Listeria monocytogenes, Enterococcus faecalis, Pseudomonas aeruginosa, Staphylococcus mitis,* and *Salivarius salivarius*) [72]. Additional studies have shown that amyloidogenic Aβx-42 binds stronger to bacterial surface than Aβ1-40, producing agglutination of different microorganisms (*C. albicans, E. faecalis, E. coli, S. aureus,* and *L. monocytogenes*) [73], causing physical immobilization and facilitating their phagocytosis [74]. Aβ per se could act as opsonin to enable the lysis process by macrophages and microglia [75]. It was shown experimentally that infection with *Salmonella typhimurium* [76], *Herpes viridae* [77], *Porphyromonas gingivalis* [78], or LPS [79] promotes a greater Aβ aggregation in AD-mice models. These evidences suggest that Aβ aggregation may mediate a host-innate immune defense mechanism against invading pathogens that could be detected in organs highly exposed to microorganism (i.e., intestine). Thus, AD-related dysbiosis characterized by an abundance of proinflammatory bacteria may promote intestinal Aβ production and peripheral inflammation that eventually affects brain functions. Data presented in this review may offer a new perspective to understand the etiology of the AD, placing peripheral infections, systemic immune activation, and Aβ aggregation, as therapeutic targets to combat the development of this neurodegenerative disease.

Microbiota-gut-brain axis and the influence of bacterial-released substances on brain function

In humans, the GM consists of millions of microorganisms inhabiting in the gastrointestinal tract, and bacteria represent 90% of the GM population [80,81]. This complex ecosystem includes up to 100 trillion bacteria [82]. Most of these bacteria belong to the Firmicutes and Bacteroidetes phyla [83]. Proteobacteria, Actinobacteria, and Verrucomicrobia are also found in the gut, but in lower proportions [84]. The diversity of the microbial

communities is different between sections of the gastrointestinal tract, as few microorganisms could withstand the low pH levels in the stomach and small intestine. Contrary, the conditions found in the large intestine promote the growth of diverse anaerobic bacteria [85]. GM diversity and composition are also substantially different between individuals [86], and this complex gut ecosystem plays essential roles in maintaining health of the host: regulation of food digestion, providing energy substrates for colonic epithelial cells, modulation of immunological processes [87], and regulation of the gut-brain axis [88,89]. Alteration in the composition of this dynamic bacterial community is known as gut dysbiosis, and has been associated with the development of diseases, such as irritable bowel syndrome [90], colorectal cancer [91], cardiovascular diseases, fatty liver [92], allergies, metabolic syndrome, diabetes [93], and obesity [94]. Furthermore, it has been recently proposed that GM is involved in the emergence of mental disorders, such as depression [95], anxiety [96], Parkinson's, and recently, AD [97]. Consequently, a bidirectional communication between the GM/gastrointestinal system and the brain has been proposed, and it has led to the concept of *microbiota-gut-brain axis* [98].

As outlined in the previous section, latest investigations report alterations in the composition and diversity of GM in fecal samples of AD subjects [26,41,43,44]. AD dysbiosis seems to be characterized by a predominance of proinflammatory bacteria and a decreased bacteria diversity compared to age-matched healthy controls [41,44,99–101]. Particularly, Cattaneo et al. [41] showed a significant increase in *Escherichia* and *Shigella* abundances, but a decrease in *E. rectale*, the former being both proinflammatory bacteria and the later, an antiinflammatory or commensal bacteria [41]. Tg-mice also showed similar GM alterations, with an increased proinflammatory, but decrease antiinflammatory bacteria abundances [48–51]. Above all, bacterial products could also be detected in plasma or even in brain samples of AD patients: LPS [102], *E. coli* K99 [44], and several bacteria antigens are higher in AD brain tissue compared to controls [103–105]. It is important to highlight that GM featured in AD patients is already detected in mild-cognitive impaired (MCI) individuals [106]. MCI is the prodromal state to AD; with slight cognitive dysfunctions already 8–10 years before the onset of dementia symptoms [107]. Similarly, longitudinal studies in Tg-mice showed an age-associated dysbiosis, culminating with a strong proinflammatory environment and the appearance of severe AD pathological hallmarks [50,51,108]. Based on those previous findings, Bolmont and coworkers aimed to prove that amyloid aggregation in the brain relates to GM alterations by using germ-free Tg-mice [109]. In addition, Minter et al. [110,111] treated Tg-mice with an antibiotic cocktail and determined the rate of Aβ aggregation in different brain regions [110,111]. Under both experimental conditions, Tg-mice had lower Aβ burden and less microglia activation compared to the control Tg-mice. These culminating results clearly show an association

between gut bacteria and brain amyloidosis that might be related to the microbicidal properties of the Aβ peptide as described in the previous section. Whether this microbiota-gut-brain communication affects memory in Tg-mice has not been described; however, germ-free Swiss Webster mice show impairments in nonspatial and working memory compared to mice with an intact GM [112]. Similarly, antibiotics-treated mice have lower cognitive scores than controls [113,114]. In humans, antibiotic combination therapies associate with some neurological disorders such as anxiety, delirium, confusional state, mania, and psychosis [115]. Therefore, antibiotic treatment might not be a viable therapeutic option to treat AD.

Aging is the main risk factor for AD [116] and it is characterized by a strong gut dysbiosis with increased abundance of facultative anaerobes, decreased of beneficial organisms [117], increased permeability of intestinal- [118] and blood-brain barriers (BBB) [61], and reduced capacity of the body to eliminate toxic compounds. These age-related factors contribute to the free passage of some intestinal bacterial-derived products to the blood circulation and even into the brain [119]. Some bacterial-derived products, such as LPS [120], activate an inflammatory reaction [121], and trigger chronic neuroinflammation [122,123]. In the following paragraphs, we have briefly described the impact of some GM-released substances in the brain function.

Lipopolysaccharide

Lipopolysaccharide (LPS) is present in the outer membrane of Gram-negative bacteria, and it has been proposed as a causal factor for chronic degenerative conditions [94,124]. LPS plays key roles in the host-pathogen interactions and innate immune system [125,126]. Alterations in GM composition/abundance are associated with enhanced plasma levels of LPS [127,128], which may result in an exacerbated metabolic endotoxemia [124], a condition characterized by inflammation and increased release of proinflammatory cytokines. Both, LPS and proinflammatory cytokines, affect the function of the BBB by interacting with TLR4 [125], found on the surface of brain endothelial cells [129]. In response to such inflammatory stimulus, brain cells produce cytokines as a defense mechanism, resulting in neuroinflammation. LPS has been detected in the parenchyma and blood vessels of nondemented elders and AD brain samples; however, LPS is greater in AD subjects [44,97,121]. Similarly, exacerbated LPS plasma levels are found in Tg-mice compared to wild-type animals [50]. LPS administration drives the generation of Aβ1-42 in the brain [79,121,125,130], and results in memory impairment and astrocyte activation [79]. Moreover, LPS induced depressive-like behaviors followed by upregulation of TNF-alpha and Iba-1 expression was observed in the hippocampus of conventional mice, but not in germ-free animals [131]. Also, colonic lumen filtrate of neomycin and polymyxin B-treated

mice has less inflammatory properties and results in reduced LPS content, events related to an increase in propionate: acetate ratio in the colonic lumen filtrate of control mice [132]. Therefore, LPS could be clearly linked to GM dysbiosis, inflammation, amyloid aggregation, and memory impairments.

Short-chain fatty acids

Short-chain fatty acids (SCFAs) are simple carboxylic acids from 1 to 6 carbon atoms produced through fermentation of undigested polysaccharide and oligosaccharides by saccharolytic bacteria in the gut [133,134]. Among these bacteria, *Bacteroides* spp., *Faecalibacterium* spp., *Bifidobacterium* spp., *Clostridium* spp., *Eubacterium* spp., *Lactobacillus* spp., and *Ruminococcus* spp. have been reported as the best producers [135]. The most abundant SCFA produced by GM are acetic, propionic, and butyric acids with molar ratios in humans of 60:20:20, respectively [136]. These volatile molecules have important roles in health and nutrition [137], besides influencing pH, nutrient uptake, and microbial balance in the gut environment [138]. On the one hand, SCFAs are essential energy sources for colonocytes (i.e., butyrate), and other peripheral organs (i.e., acetate and propionate) [139], supplying almost 10% of the energy requirements of the host [140]. The colonic epithelium receives about 70% of its energy from SCFAs, mainly from butyric acid [141]. Therefore, SCFAs are important modulators of host metabolism. Moreover, propionate is a precursor of protein synthesis, gluconeogenesis, and liponeogenesis in the liver [142]. Acetate is a substrate for cholesterol synthesis [143], as well as a suppressor of appetite through a central hypothalamic mechanism [144]. Acetate improves glucose homeostasis [145], while propionate impairs insulin action [146], but butyrate enhances insulin sensitivity and energy expenditure [147]. Insulin resistance impairs glucose uptake, and insulin resistance has been demonstrated in *postmortem* brain tissue from AD patients, even in the absence of diabetes [148]. Apparently, the amyloid load could be the principal triggering factor that causes the insulin resistance in AD brains [149–152]. Thus, SCFAs availability may help to alleviate impaired brain glucose uptake and rescue brain function.

It is important to note that despite one-carbon difference between acetate (C2), propionate (C3), and butyrate (C4), SCFAs have substantially different effects on brain cells. Intracerebroventricular (i.c.v.) infusion of propionate induced neuroinflammation [153], progressive development of limbic-kindled seizures, oxidative stress (e.g., lipid peroxidation), microglial activation associated with decreased glutathione activity in adult rats [154]), and impairments in social behavior and working memory in younger animals [155]. Contrary, intraperitoneal (i.p.) injection of phenyl-butyrate restores dendritic spines density of hippocampal CA1 pyramidal neurons [156], and decreases activation of human primary astrocyte culture [157]. Butyrate reverses stress-induced reduction in neurotrophic factors and rescues the memory

impairments observed in an animal model of maternal deprivation [158]. Acetate consolidates weak learning and rescues amyloid-induce impaired memory in chicks [159]. In addition, SCFAs could also act as signaling molecules and epigenetic regulators [160]. Among SCFA, butyrate inhibits histone deacetylase (HDAC), and increases the availability of histone acetyl transferase (HAT), which increases histone acetylation. This inhibition has been reported to improve memory function, neuroprotection, and neuro-regeneration in a mouse model of AD [161]. Hence, propionate has substantially a neurotoxic effect, while butyrate and acetate rather neuroprotective effects. Therefore, overall production of SCFAs (propionate, butyrate, and acetate) may cause opposing effects on brain function. Hence, direct modulation of butyrate production, but reduction in propionate might result in lower neuroinflammation and improved brain function.

Ketone bodies

Ketone bodies (KBs) are synthesized in the liver through 3-ketothiolase and mitochondrial HMG-CoA synthase from fatty acids β-oxidation-derived acetyl-CoA [162]. Certain conditions, such as starvation and exercise [163], low-carbohydrate (∼10%) intake, moderate-protein (∼20%), and high-fat (∼70%) diets [164] promote KB generation. β-hydroxybutyrate, acetoacetate, and acetone are KB originated from SCFAs oxidation. Similar to SCFAs, KBs have important actions on body metabolism, as acetoacetate diminishes glucose uptake and oxidation [165], and β-hydroxybutyrate decreases glucose consumption [166]. Both, SCFAs and KB, regulate sympathetic nervous system (SNS), as propionate promotes sympathetic outflow, while β-hydroxybutyrate suppresses SNS activity, triggering and antagonizing G protein-coupled receptor 41 (GPR41) [167]. KBs also show important neuroprotective effects [168], as acetoacetate protects against glutamate-mediated neurotoxicity in hippocampus [169] and β-hydroxybutyrate increases mitochondrial pyruvate´s metabolism, decreases glucose consumption and glycolysis stimulation in hippocampal astrocytes [170]. β-Hydroxybutyrate inhibits nucleotide-binding leucine-containing protein receptor family member 3 (NLRP3) inflammasome [171], which is defined as a "critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines IL-1β/IL-18 in response to microbial infection and cellular damage" [172], suppressing glial activation and increasing NeuN-positive cells proliferation [173]. β-Hydroxybutyrate also increases oxygen consumption and adenosine triphosphate (ATP) production through mitochondrial activation, and induces brain-derived neurotrophic factor (BDNF) gene expression [174]. The impact of ketogenic diets on cognition has been related to beneficial effects [175–177] mainly associated with KB´s histone deacetylase inhibition properties [178]. Ketone ester-based diets have also been shown to improve learning and to decrease Aβ deposition in amygdala and hippocampus [176]

being β-hydroxybutyrate particularly relevant to AD therapy [179], as it has been shown to attenuate neurodegeneration and neuroinflammation in a mouse model of Huntington´s disease [180].

Other bacterial metabolites

GM also has the capacity to produce neurotransmitters such as gamma-aminobutyric acid (GABA), norepinephrine (NE), dopamine (DA), acetylcholine (AC) and 5-hydroxy tryptamine (5-HT), or serotonin [181]. *Lactobacillus* spp. and *Bifidobacterium* spp. produce GABA from glutamate. GABA is an inhibitory neurotransmitter, and dysfunction in GABA signaling has been reported in AD [182]. *Escherichia* spp., *Bacillus* spp., and *Saccharomyces* spp. produce NE that promotes microglia degradation and phagocytosis of Aβ in mice [183]. *Bacillus* spp. produces DA, which has neuroprotective role as it possesses antiamyloidogenic and antioxidant actions in Tg-mice brain [184]. *Lactobacillus* spp. produces AC, which is decreased along with muscarinic and nicotinic cholinergic receptors in AD [185], and AC bioavailability helps to restore cognition in AD patients (H [186].). 5-HT is mainly produced by *Candida* spp., *Streptococcus* spp., *Escherichia* spp., and *Enterococcus* spp., and increased serotonin signaling in the synaptic cleft could slowdown the progression of AD pathological hallmarks in Tg-mice [187]. Overall, GM and its released substances, such as SCFA, KB, and neurotransmitters might play a vital role against AD development. We will discuss further how to selectively increase the release of some bacterial substances by the diet.

Modulating the course of Alzheimer´s disease by diet

Metabolic disorders such as obesity, diabetes, and metabolic syndrome are associated with a 20% higher risk to develop AD [188]. The Lancet Commission on Dementia Prevention, Intervention, and Care has documented that modifications in lifestyle may reduce the incidence of AD up to 30% [116]. Available data showed an evidence of a possible benefit of controlling modifiable risk factors and promoting protective factors (such as healthy diet) to avoid upward worldwide estimates of dementia. Clinical trials have concluded that diet could modify the course of AD pathology, as ingestion of vegetables and fruits diminishes the onset and incidence of AD [189,190], and the consumption of specific nutrients (i.e., vitamin E, decosahexaenoic acid, folate, lutein, beta-carotene, nuts, fish, vegetables, leafy greens, and extra virgin olive oil) is associated with neuroprotection. The Mediterranean diet (MED diet) is characterized by high consumption of fruits, vegetables, cereals, legumes, olive oil, nuts, seeds, moderate consumption of fish, average consumption of wine, and low intake of red meats [191]. MED diet has been associated with lower risk for AD [192,193], reduced risk of developing MCI or

progression from MCI to AD [194], reduction in AD biomarker burden [195], better learning, greater memory performance and larger bilateral dentate gyrus volumes [196], lower PET scan measurements of Aβ deposition, and higher brain glucose metabolism [197]. In addition, the consumption of rich vegetable-based foods and fiber results in delayed predementia stages [198]. The dietary approaches to stop hypertension (DASH) diet by the National Heart, Lung, and Blood Institute (NHLBI) consist of ingestion of nuts, fruits, vegetables, fish, whole cereal products, low-fat dairy products, and poultry, all of which are rich in blood pressure-deflating nutrients such as potassium, calcium, "lean" proteins, minerals, and fiber [198]. Greater adherence and long-term DASH score have been associated with better average cognitive function in aged American women [199]. Moreover, the Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet [198], constituted by green leafy vegetables, berries, nuts, olive oil, whole grains, fish, beans, poultry, wine and limited consumption of red meat, fried foods, butter, cheese, pastries, and sweets [200], delays cognitive decline [199] and AD [182].

Recently, International Consortia have initiated joint efforts to delay the onset of AD and dementias based on multi-domain intervention programs, with preliminary positive results. Physical activity promotion, healthy diet, improvement of self-management of cardio metabolic risk factors, and cognitive stimulation have a potentialized effect to delay or avoid dementia. The Finnish Geriatric Intervention study to prevent cognitive impairment and disability (FINGER) was a 2-year intervention project that enrolled 1260 older adults aged 60–77 years and included: nutritional counseling, cognitive training, and management of vascular and metabolic risk factors, as well as physical activity. FINGER results suggest that multi-domain interventions may stop cognitive decline in older adults at risk of dementia [201–203]. Based on FINGERS´s preliminary results, similar multimodal intervention projects (World-Wide-FINGERS, U.S. POINTER, HATICE, LipiDiDiet, MIND-ADMINI) are currently being conducted in several countries [204].

AD patients show low levels of vitamin A [205], vitamin B6 [206], B12 [207], vitamin D [208], vitamin E [209], vitamin K [210], and folate [211]. Hence, supplements have also been suggested as an alternative therapy in the treatment of AD. Vitamin A intake has shown to protect neurons and improve memory performance, as well as spatial learning in rats [212]. Takasaki et al. [213] reported that vitamin A inhibits the oligomerization of Aβ. In addition, vitamin E acts as a scavenger for reactive oxygen species (ROS), it is involved in superoxide dismutase (SOD) regeneration, and inhibits inflammation induced by increased glutamate [214]. In AD patients, the treatment with α-tocopherol tends to slow the progression of the disease [215]. Moreover, the use of multivitamin supplements (vitamins B6, B9, and B12) in AD patients reduces the level of homocysteine, an amino acid associated with an enhanced risk to develop dementia [216]. Nevertheless, supplement intake has furnished limited and inconsistent results in clinical settings [217].

The "medical foods" are composed of a formula that meets the specific nutritional requirements against a disease. Even though these formulas contain ingredients safe for human consumption, their use is not as heavily regulated by the FDA as drugs used for AD treatment. Some formulas available in the United States and Europe are proven to have mild-beneficial effects; among them are: Souvenaid, Axona, and CerefolinNAC [218]. Souvenaid is a combination of uridine monophosphate, phospholipid, vitamins, antioxidants, omega-3 fatty acids, and choline; these nutrients help in the formation and maintenance of the synaptic membranes and the formation of synapse [219]. In patients with AD, the administration of Souvenaid for 12 weeks improved memory performance [220]. CerefolinNAC consists of methyl-cobalamin (vitamin B12), L-methylfolate, and *N*-acetylcysteine. These components act against metabolic imbalances of hyper-homocysteinemia and neurovascular oxidative stress linked to progressive memory loss [218]. Finally, Axona is a medical food that targets metabolic deficiencies (by reducing glucose metabolism) associated to AD. Axona contains caprylic acid, which is metabolized to β-hydroxybutyrate. This KB crosses the BBB and is intended to enter the neurons where it is used to produce ATP and other substrates for the electron transport chain. As mentioned above, ketogenic diets could improve memory [221]. However, the consumption of Axona might produce side effects such as diarrhea, flatulence, and dyspepsia, although no interactions have been observed with AD medications. Thus, the best path to prevent cognitive decline are multidomain lifestyle intervention, highlighting the intake of healthy diet rich in fruits, seeds, and vegetables among older individuals at risk to develop dementia.

Bioactive food and modulation of gut microbiota composition and brain function

A common factor on the multimodal intervention projects described in the previous section is the control of the diet, as they promote the intake of vegetables, fruits, and seeds. As opposed to single nutrients (i.e., omega-3 polyunsaturated fatty acids, vitamins B6 and B12, folate, vitamin D, and vitamins A, C, or E), the role of healthy and balanced dietary patterns may be more relevant because nutrients have cumulative and synergistic effects. Moreover, it is proven that manipulation of gut community structure by the diet is a useful strategy to combat metabolic disorders [222], and as mentioned before, metabolic alterations are important risk factors for AD. In 1980, Japan accepted the use of "foods for specific use in health," known as FOSHU (an acronym that comes from English: Foods of Specified Health Use), being considered as drugs from the legal point of view. In Europe, some nutraceuticals considered as new foods, and regulated by the European Community Commission under the European Food Safety Authority (EFSA) are considered as functional food

or bioactive food. Bioactive food is food that in natural or processed forms, in addition to offering nutritious components, contains some *bioactive* components that are beneficial for human health [223]. Plant-based food is characterized by a high content of polyphenols, such as flavonoids, isoflavones, phenolic acids, stilbenoids, and tannins, among others [224], with strong antioxidant properties. These antioxidant properties provide important benefits to the brain, as this organ is highly susceptible to the damage caused by oxidative stress. The brain possesses higher levels of transition metals (iron, copper), polyunsaturated fatty acids, and had a moderate activity of antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase), relatively lower levels of glutathione [225], and higher oxygen utilization [226]. Then, reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced as the result of oxidative stress could damage cellular components such as proteins, carbohydrates, lipids, and nucleic acids. A sustained activation of glial cells is one of the main causes of increased ROS, nitric oxide (NO), and proinflammatory cytokine levels in the brain [227]. Recently, there has been much interest in the neuroprotective properties of polyphenols, from bioactive food, as they have been associated with protection against age-related cognitive and motor decline in rodents [228], improved memory in older adults [229], neuronal signaling, and behavior in Tg-mice [230]. Mixing extracts with different phenolic compositions result in a synergistic effects in reducing total content of Aβ in the brain, and rescue cognitive damage in Tg-mice [231]. Flavonoid-rich foods reduce the levels of NO, TNF-α, IL-1β, and ROS [232], while mulberry extract rich in anthocyanins reduces lipid oxidation, and increases antioxidant enzyme activity in the brain of senescence-accelerated mice [233]. Polyphenols are also capable of inducing the activation of cAMP-response element-binding protein (CREB) and increasing the levels of brain-derived neurotrophic factor (BDNF) in the hippocampus, in addition to change the phosphorylation of the extracellular signal-related kinase (ERK1/2) [234]. Oral administration of grape seed polyphenol extract to rats during 11 days increased the levels of two phenolic acids [3-hydroxybenzoic acid and 3(3′-hydroxyphenyl) propionic acid] in the brain, and *in vitro* assay demonstrated that these phenolic acids interfere with the self-assembly of Aβ peptide into neurotoxic Aβ aggregates [235]. Hence, the neuroprotective actions of bioactive food are highly related to their antioxidant and antiinflammatory effects, to the interaction with self-assembling proteins in the brain, and recently demonstrated, to the modulation of gut bacterial communities. For example, cranberry fruit-derived oligosaccharides have important bacterial antiadhesion properties, inhibition of biofilm formation, and reduces bacterial growth [236–238], acting then as prebiotic. Gibson and Roberfroid [239] introduced the concept of prebiotics as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or of a limited number of bacterial species resident in the

colon, improving the host health" [239]. Prebiotics act as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" according to the International Scientific Association for Probiotics and Prebiotics (ISAPP) [240]. Thus, prebiotics may act as nutrients for microorganisms harbored by the host [240]. The prebiotic effect of polyphenols has been demonstrated as they modify the Bacteroides/Firmicutes balance [241]. Polyphenols promote the growth of specific bacterial species linked to health benefits such as *Lactobacillus acidophilus* [242], *Faecalibacterium* [243], and *Akkermansia muciniphila*, which is an intestinal mucin-degrading bacteria [244]. Colonization with *A. muciniphila* reduces the motor degeneration in transgenic mice prone to amyotrophic lateral sclerosis [245]. However, most polyphenols could not be absorbed due to their complex chemical structure (polymers, glycosides, or esters). Gut bacteria metabolize complex phenolic compounds into phenolic acids, with even greater biological activity than the native form (polymers). GM-derived phenolic metabolites are then capable of crossing the BBB, producing an antioxidant and antiinflammatory effect in the brain, and modulating signaling pathways involved in neuroinflammation [246].

Most dietary fibers (defined as carbohydrate polymers with three or more monomeric units that are resistant to the endogenous digestive enzymes, and thus neither hydrolyzed nor absorbed in the small intestine) [247] are also subjected to bacterial fermentation in the gastrointestinal (GI) tract producing fermentative end products [248]. There are important modifications in GM composition depending on the kind of dietary fiber [249]: growth of *Bifidobacterium* species could be achieved by the ingestion of oligosaccharides, as these bacteria possess the enzymatic machinery and the metabolic profile to efficiently utilize this substrate [250]. Nondigestible inulin-type fiber-rich diets modify and enrich bacterial genera such as *Bacteroides* and *Faecalibacterium* [251], *Coprococcus, Ruminococcus* [252], and *Clostridium* [253]. Chicory-derived inulin-type fructans increase *Anaerostipes and Bifidobacterium*, and decrease *Bilophila* relative abundances in humans [254]. Furthermore, different types of fibers generates diverse GM-related health benefits, for example, inulin-type fructans from asparagus, leek, onions, banana, wheat, garlic, chicory, and artichoke [251] modulate the lipids profile and glucose metabolism [255], and associate with improved cognition [256]. Oligosaccharides from *Morinda officinalis* ameliorate cognitive impairment and the pathological hallmarks in Tg-mice by modulation of GM composition [257]. Inulin intake enhances systemic metabolism and reduces neuroinflammation in an APOE4 mouse model, increasing beneficial microbiota and decreasing harmful microbiota in feces [258].

As mentioned before, butyrate is related to neuroprotection, while propionate is rather a neurotoxic substance [259–262]. The proximal large intestine is considered as the gut portion with highest bioavailability of carbohydrates,

and therefore highest SCFAs concentration. In addition, long-transit times could favor an increased contribution to colon SCFAs pools mainly due to protein breakdown and amino acid fermentation, among other effects on bacterial physiology and metabolism [263]. SCFA production by anaerobic bacteria [249] relies on metabolic pathways such as Wood-Ljungdahl pathway for acetate production [264], acylate, succinate, and propanediol pathways for propionate production, and butyrate kinase as well as CoA-transferase for butyrate production [252]. Oligofructose and fructooligosaccharides-rich diets modify SCFA concentration in the cecum, increasing acetate and butyrate, but decreasing propionate molar percentages compared with a control diet [265]. Other fermentation products such as methane and lactate could be further converted to butyrate by other bacteria taxa promoting its growth and proliferation, including *Roseburia intestinalis* and lactate-utilizing butyrogenic species [266]. Therefore, GM modulation by specific type of diets could favor the growth of butyrate-producing bacteria or reduce the abundance of propionate-producing species. In Tg-mice, it has been demonstrated that the intake of bioactive food [dried nopal (*Opuntia ficus*), soy (*Glycine max*), chia (*Salvia hispanica*) seed oil, and turmeric (*Curcuma long*) mix] increases the abundances of antiinflammatory bacteria but reduces the presence of proinflammatory and propionate-producing bacteria. This bioactive food intake was associated with improved cognitive performance, decreased neuroinflammation, and tau-hyper phosphorylation in female Tg-mice [50]. Microbial metabolism of dietary fibers by bacteria ferulic acid-esterase gene+, such as *Lactobacillus fermentum*, leads to the release of this metabolite, which has antioxidant and antiinflammatory properties and could be considered as a potential therapeutic treatment for various chronic pathologies such as neurodegeneration, obesity, diabetes, and cancer [247]. Its administration is also able to reverse AD behavioral deficits in Tg-mice, restore Aβ load, neuroinflammation, and oxidative stress to control values [267]. In addition, xylo-oligosaccharides supplemented diet improved brain plasticity, reduced brain mitochondrial dysfunction and oxidative stress, apoptosis, and microglial activation, leading to restored cognitive functions in obese-insulin-resistant rats [268]. Thus, bioactive food intake may result in important neuroprotective effects mainly through the modulation of GM composition. Currently, there are no reports about negative effects after the intake of prebiotics. However, there is currently an ongoing discussion of the benefit of probiotics over prebiotics to combat a specific disease. In the following section, we would offer the recent data on those therapeutic strategies based on probiotics aimed to combat AD.

Intake of probiotics to modify the AD course

The term probiotics comes from the Greek language and means “for life,” being originally used for growth stimulation substances produced by microorganisms

and later as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [269]. Recent reports show beneficial effects of probiotics on AD pathology by using Tg-mice models. A probiotic formulation made of *Streptococcus thermophilus*, Bifidobacteria (*Bifidobacterium longum, B. breve,* and *B. infantis*), and Lactobacilli (*L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subspecie *Bulgaricus,* and *L. brevis)* could influence plasma concentration of ghrelin (a hormone involved in learning and memory) and IL-1 (an inflammatory cytokine), restore impaired neuronal proteolytic pathways (ubiquitin proteasome system and autophagy), and decrease cognitive decline related to a reduction in brain damage, and reduced accumulation of Aβ aggregates in Tg-mice [270]. A very similar probiotic mixture of *S. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei,* and *L. delbrueckii* induced important GM composition changes in aged rats with an increase in the abundance of *Actinobacteria* and *Bacteroidetes*, which was reduced in control-treated aged rats. This probiotic mixture was also able to modulate the expression of a considerable number of genes in brain tissue related with inflammatory and neuronal plasticity processes, downregulating genes involved in neurodegeneration (Alox15, Nid2 and PLA2G3), attenuating the age-related deficit in long-term potentiation (LTP), decreasing microglial activation, and increasing the expression of BDNF and synapsin [271]. In addition, *L. paracasei* improved hippocampal plasticity, attenuated brain mitochondrial dysfunction, and decreased hippocampal apoptosis, oxidative stress, and microglial activation, leading to restored cognitive function in high-fat diet (HFD) fed rats [268]. *Clostridium butyricum* intake attenuated cognitive dysfunction, decreased histopathological changes, increased BDNF, induced Akt phosphorylation, reduced neuronal apoptosis, and restored butyrate content in feces and brain in a mouse model of vascular dementia. Likewise, intragastrical pretreatment with *C. butyricum* in a mouse model of cerebral ischemia/reperfusion injury improved neurological deficit, relieved histopathologic change, increased SOD activity, and decreased malondialdehyde (MDA) concentration in relation with a butyrate content in the brain [272]. Some strains of *L. fermentum* potently secrete ferulic acid, capable of reducing Aβ fibril formation, neuroinflammation, and learning deficits in Tg-mice [273]. Some bacterial taxa such as *Clostridium autoethanogenum, C. thermoaceticum*, *Ruminococcus hidrogenotroficus*, *Acetobacterium woodi*, *Bifidobacterium lactis,* and *Bacteroides thetaiotaomicron* are able to produce acetate through Wood-Ljungdahl metabolic pathway, whereas other species such as *E. rectale*, *Roseburia* spp., *Coprococcus catus*, *Faecalibacterium prausnitzii*, *Anaerostipes* spp., *Eubacterium hallii*, *Coprococcus eutactus*, *Coprococcus comes*, *B. infantis,* and *Bacteroides fragilis* are able to produce butyrate through CoA-transferase and butyrate

kinase metabolic pathways, while *Megasphera* spp., Bacteroidetes, *Veillonella* spp., *Dialister succinatiphilus*, *Phascolarctobacterium succinatutens*, *Ruminococcus obeum*, *Blautia wexeri*, *Roseburia inulinivorans*, *Bifidobacterium pseudocatenulatum,* and *Bacteroides intestinalis* are able to produce propionate through acrylate, succinate, and propanediol metabolic pathways [252,264,274]. Thus, ingestion of probiotics alone or in combination may impact body and brain function by the release of metabolites and other bacterial products. Notwithstanding, the efficacy of probiotics in the treatment and prevention of disease is still controversial. The European Food Safety Authority and the US FDA have not yet approved any probiotic formulation as therapeutic substance [275,276]. Lack of peer-reviewed scientific reports and missing data about side effects from probiotics use [277,278] led to the conclusion that probiotics interventions are not safe yet to fight against onset of dementia, as no important reporting safety data are available yet.

Conclusion and perspectives

Clinical biomarkers provide a powerful approach to understand the etiology and to follow the progression of a disease. Currently, no single biomarker can accurately diagnose AD, but they may use to initiate pharmacological interventions. It is widely accepted that a more effective therapeutic outcome might be obtained when body´s and brain´s alterations are on the early stage of AD, which means, decades before onset of dementia. This requires clinical validation of early biomarkers. Current data demonstrate an important role of GM, bacteria/virus/fungi infections, Aβ microbicidal´s effect, and systemic inflammation, as critical factors related to the onset of dementia. Due to the association between those peripheral factors and AD onset, they may be considered as clinical biomarkers of the early stages of AD. More importantly, the design of therapies aimed to restore GM composition, reducing systemic inflammation, and the production of neurotoxic bacterial substances could represent a promising approach and effective DMT to overcome the overwhelming number of AD cases in the World. Dietary interventions have proven to delay onset of AD and other dementias. Bioactive food and prebiotics can be responsible for this neuroprotective effect by modulation of the gut-brain axis. Prebiotics can promote the release of specific protective substances able to reach the brain, reducing neuroinflammation and improving cognitive and memory functions (i.e., butyrate). Prebiotics may also modulate gut microbiota composition reducing the release of neurotoxic substances associated with brain dysfunction (i.e., propionate, LPS). Therefore, dietary interventions rich in prebiotics may be able to modulate the course of AD by restoration of the gut-microbiota-brain axis (Fig. 3.1).

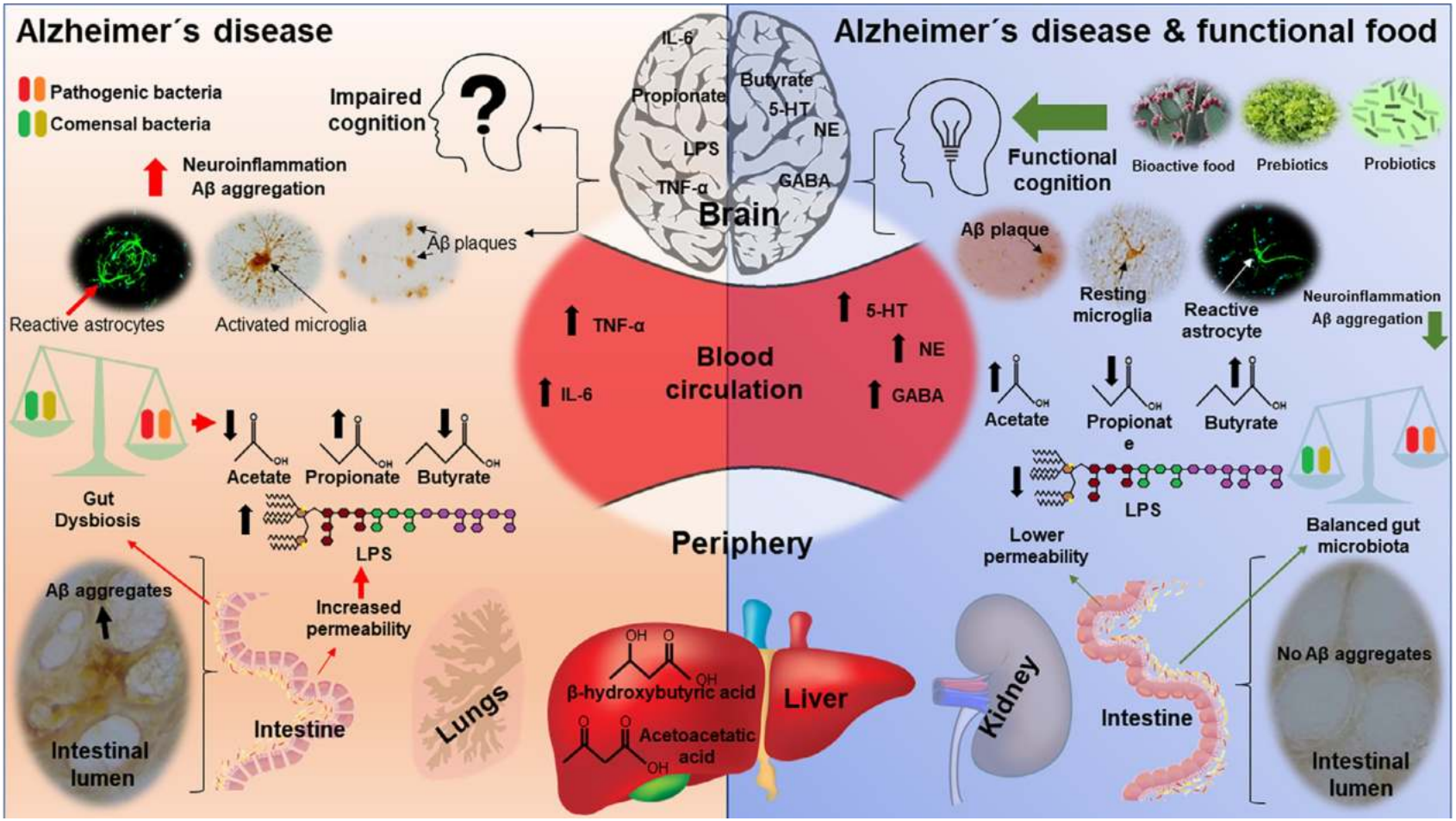

FIG. 3.1 Left side: brain and body alterations observed in AD patients include Aβ aggregates in the brain, and in the periphery. pTau in the brain and CSF. Gut dysbiosis with a predominant proinflammatory bacterium that release neurotoxin substances (i.e., LPS, propionate). Aβ is a microbicidal peptide that can regulate the host-immune system. Its accumulation might respond to its physiological action against invading pathogens, causing inflammation. Right side: ingestion of bioactive food (i.e., nopal, *Opuntia ficus*), prebiotics (i.e., chicory, *Cichorium intybus*), or probiotics (i.e., *Lactobacillus paracasei*) modulates gut microbiota composition, restoring the abundance of antiinflammatory bacteria and reducing the release of neurotoxic substances into the circulation. Intake of bioactive food, prebiotics, or probiotics associates with a reduced neuroinflammation and an enhanced cognitive performance in demented patients and in persons at risk to develop AD.

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Conflict of interest

The authors declare no competing financial interests.

Abbreviations

5-HT	5-hydroxy tryptamine
Aβ	amyloid-beta peptide
AC	acetylcholine
AD	Alzheimer's disease
ApoE4	apolipoprotein ε4 allele
APP	amyloid precursor protein
ATP	adenosine triphosphate
BBB	blood–brain barrier
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
CREB	cAMP-response element-binding protein
CSF	cerebrospinal fluid
DA	dopamine
DASH	dietary approaches to stop hypertension
DMT	disease-modifying therapies
EFSA	European Food Safety Authority
ERK1/2	extracellular signal-related kinase
FDA	Food and Drug Administration Agency
FINGER	Finnish Geriatric Intervention study to prevent cognitive impairment and disability
FOSHU	Foods of Specified Health Use
GABA	gamma-aminobutyric acid
GI	gastrointestinal
GM	gut microbiota
GPR	G protein-coupled receptor
HAT	histone acetyl transferase
HDAC	histone deacetylase
i.c.v.	intracerebroventricular
i.p.	intraperitoneal
Ig	immunoglobulin
IL	interleukin

ISAPP	International Scientific Association for Probiotics and Prebiotics
KB	ketone bodies
LPS	lipopolysaccharide
LTP	long-term potentiation
MCI	mild-cognitive impaired
MED-diet	Mediterranean diet
MIND	Mediterranean-DASH intervention for neurodegenerative delay
MMSE	Mini-Mental State Examination
NE	norepinephrine
NHLBI	National Heart, Lung, and Blood Institute
NLRP3	nucleotide-binding leucine-containing protein receptor family member 3
NO	nitric oxide
PET	positron emission tomography
RNS	reactive nitrogen species
ROS	reactive oxygen species
SCFA	short-chain fatty acids
SNS	sympathetic nervous system
SOD	superoxide dismutase
Tg	transgenic
TLRs	toll-like receptors
TNF-α	tumor necrosis factor-α

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