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Review

Comprehensive Review of Nutraceuticals against Cognitive Decline Associated with Alzheimer's Disease

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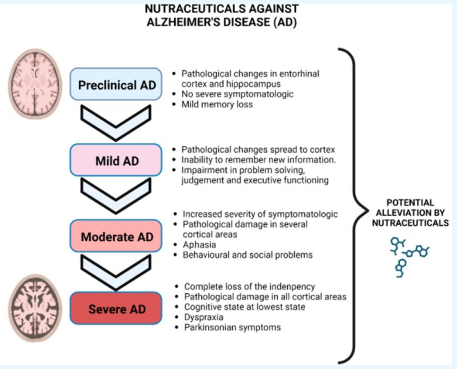
ABSTRACT: Nowadays, nutraceuticals are being incorporated into functional foods or used as supplements with nonpharmacological approaches in the prevention and management of several illnesses, including age-related conditions and chronic neurodegenerative diseases. Nutraceuticals are apt for preventing and treating such disorders because of their nontoxic, non-habit-forming, and efficient bioactivities for promoting neurological well-being due to their ability to influence cellular processes such as neurogenesis, synaptogenesis, synaptic transmission, neuro-inflammation, oxidative stress, cell death modulation, and neuronal survival. The capacity of nutraceuticals to modify all of these processes reveals the potential to develop food-based strategies to aid brain development and enhance brain function, prevent and ameliorate neurodegeneration, and possibly reverse the cognitive impairment observed in Alzheimer's disease, the most predominant form of dementia in the elderly. The current review summarizes the experimental evidence of the neuroprotective capacity of nutraceuticals against Alzheimer's disease, describing their mechanisms of action and the *in vitro* and *in vivo* models applied to evaluate their neuroprotective potential.



1. INTRODUCTION

The effect of nutrition significantly impacts the aging process and the development of neurodegenerative diseases. For a long time, several compounds from food and medicinal herbs have been used to enhance mental performance including memory, motivation, concentration, and attention. Modifying these processes is considered an attractive approach for cognitive impairment management.[1]

Nutraceutical compounds in foods have been demonstrated to exert a pharmacological effect on brain metabolism.[2] These natural compounds can be obtained by consuming whole foods or as dietary supplements containing purified compounds.[3] Nutraceuticals have been used to improve brain health (Figure 1) because they directly influence cellular processes such as neurogenesis, synaptogenesis, synaptic transmission, neuro-inflammation, oxidative stress, cell death modulation, and neuronal survival.[4,5] Likewise, nutraceuticals also modulate complex brain functions such as neuro-regeneration, neuro-protection, neuroplasticity, memory, and cognition.[1,6,7] The capacity of nutraceuticals to modify all of these processes reveals the potential to develop food-based strategies, including the design of dietary supplements and foods added with nutraceuticals that exert neurological activity.

Moreover, cognitive decline associated with aging, which leads to the generation of neurological diseases such as Alzheimer's disease (AD), is of major concern in public health. Therefore, developing dietary supplements, foods, or beverages containing nutraceuticals that can prevent and ameliorate neurodegeneration and reverse cognitive impairment is of major relevance in the food industry and the public health sector.

The current review summarizes the experimental evidence of the neuroprotective capacity of nutraceuticals, considering their potential to mitigate the progression and symptomatology of AD, describing their mechanisms of action and the *in vitro* and *in vivo* models applied to evaluate their neuroprotective potential.

2. MATERIALS AND METHODS

All the information reviewed was collected from reliable scientific databases such as ScienceDirect, Scopus, PubMed, and Google Scholar using the keywords nutraceuticals, cognitive enhancement, neuroprotection, neuroplasticity, cognitive impairments, and Alzheimer's disease. Published articles from *in vitro* and *in vivo* research were used to explain the proposed mechanisms of action of the nutraceuticals. The figures were created with Biorender.com.

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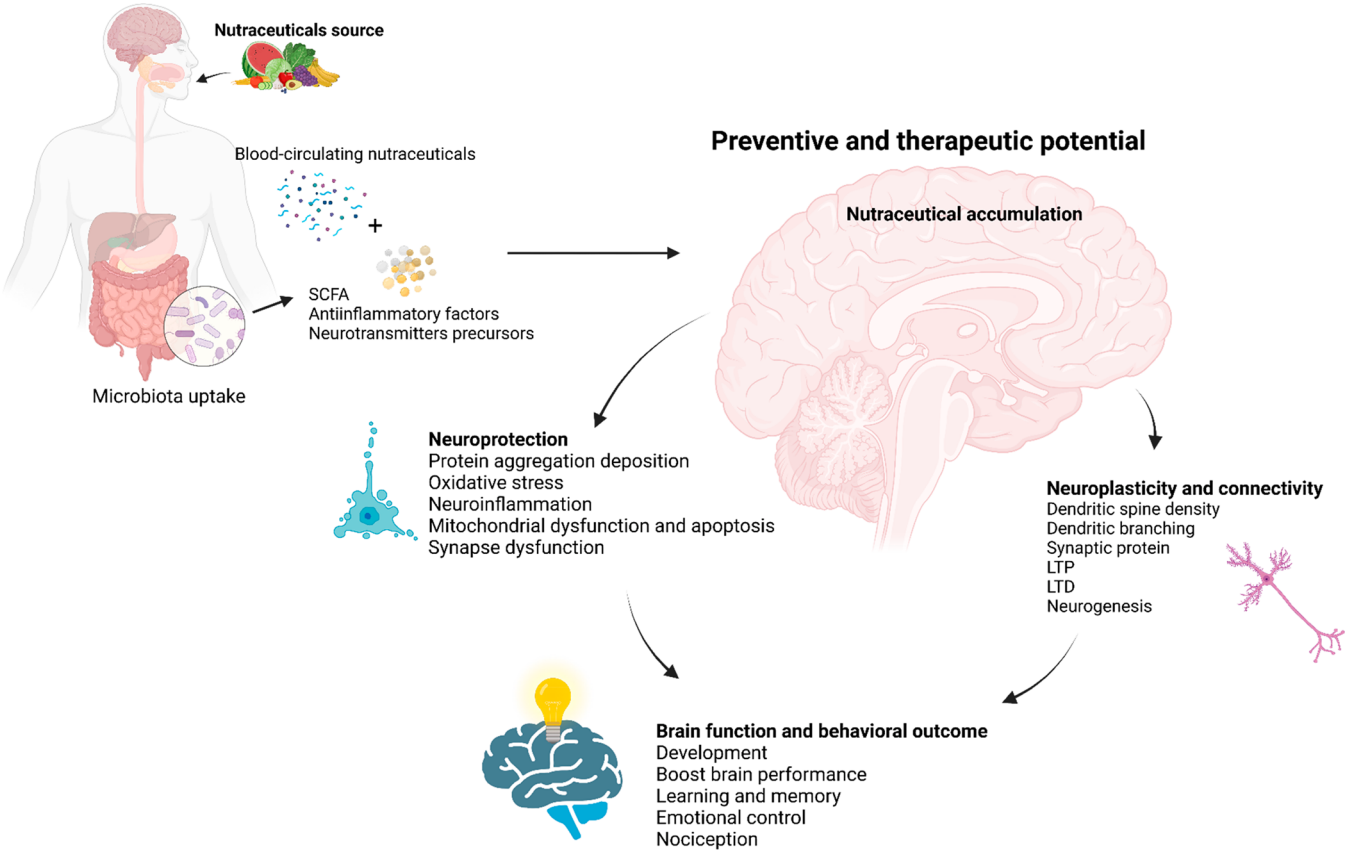

Figure 1. Schematic representation of nutraceutical-mediated preventive and therapeutic activity against neurological disorders. Nutraceuticals impact neuroplasticity, synaptic plasticity, and neuroprotective processes, modifying the morphology and function of neurons and glial cells, allowing optimal brain function and a tuned behavioral outcome.

3. ALZHEIMER'S DISEASE

Neurodegeneration is characterized by the irreversible damage and loss of neuronal cells during aging and is exacerbated in neuropathological conditions.[8] Aging is a complex and inevitable biological process involving neurodegeneration mechanisms that trigger changes in the brain architecture. Although these changes are part of a normal physiological process, they are also one of the main risk factors for developing chronic neurodegenerative diseases.[9] Therefore, the increase in life expectancy has favored the prevalence of neurodegenerative diseases such as AD, the leading cause of dementia worldwide in the population older than 60.[1]

AD is a multifactorial disease associated with various risk factors such as age, genetic factors, traumatic brain injuries, pre-existing diseases, infections, unhealthy lifestyles, and environmental factors.[10] Although the underlying origin of the pathological changes in AD remains unknown, these risk factors could compromise the integrity of the blood−brain barrier (BBB), decrease the cerebral blood flow, increase amyloid beta (Aβ) deposition, as well as cause neuroinflammation and oxidative stress, facilitating the production of Aβ or tau pathology, all of which could exacerbate the development of AD.[11]

Neuropathologically, AD is characterized by the accumulation of extracellular Aβ oligomers and the intracellular accumulation of neurofibrillary tangles of hyperphosphorylated tau protein affecting brain areas with high plastic capacities, such as the hippocampus and the cortex, and involved in higher functions such as learning and memory. These protein accumulations promote subsequent events such as glial activation, neurotransmitter deficits, increased neuroinflammation, and oxidative stress, resulting in the massive loss of neurons and synapses.[9,12]

The amyloid plaque formation begins with the sequential hydrolysis of the amyloid precursor protein (APP) by the β- and γ-secretases.[13] The β-site APP cleaving enzyme 1 (BACE1) is a transmembrane type I aspartyl protease that catalyzes the amyloidogenic cleavage at the APP β-site, leaving the membrane-associated 99 amino acids carboxyl-terminal fragment.[14] Then, the β-C-terminal fragment is cleaved by γ-secretase, a multimeric protein complex containing presenilin-1 (PSEN1) and -2 (PSEN2), nicastrin, Aph-1, and Pen-2.[15] This γ-secretase cleavage promotes the release of Aβ 37−43 peptides.

On the other hand, the neurofibrillary tangles are formed by the massive accumulation of insoluble paired helical filaments composed of the microtubule-associated protein tau.[16] The abnormal tau phosphorylation is an early molecular event leading to sequential structural changes in the tau protein, such as truncations.[17] Tau hyperphosphorylation, primarily at Ser-Pro or Thr-Pro motifs, involves proline-directed kinases such as MAPK, GSK3β, and CDK-5[18,19] and possibly other kinases such as CAMK, PKA, and PKC.[20] The subsequent tau hyperphosphorylation and aggregation correlate to axonal microtubule disassembly, affecting the axonal transport.[21]

The typical slowing down of learning and memory processes found in AD is generally attributed to a decrease in acetylcholine (Ach) levels in the synaptic cleft, leading to a

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loss of cholinergic transmission at the presynaptic level. The decrease in ACh levels can be due to a limited activity of the enzyme choline *O*-acetyltransferase, responsible for its synthesis, and on the other hand to the increased catalytic function of acetylcholinesterase (AchE), the enzyme responsible for its degradation. Additional Ach hydrolysis by butyrylcholinesterase also occurs but to a much lesser extent and with a lower affinity for ACh.[22] Inhibiting these enzymes represented an attractive therapeutic option to slow AD symptomatology.

The GABAergic system plays a central role in regulating, synchronizing, and preventing excess neuronal signaling in the hippocampus. AD animal models have revealed that early losses of GABAergic interneurons result in hippocampal hyperactivity. Although it is suggested that GABAergic dysfunction may be an early sign of AD pathology in animal models, there is no clear link between the modulation of GABA neurotransmission and the prevention of age-related cognitive impairment.[23] The function of GABA is not limited to signal transmission between neurons but also plays important roles in communications between neurons and microglia. Interestingly, GABA signaling seems to be essential for the activation of Aβ uptake by microglia, contributing to amyloid clearance.[24]

Moreover, the Aβ oligomers have been shown to impair synaptic plasticity by inhibiting LTP and enhancing LTD, the major forms of synaptic plasticity considered the neural basis of the learning and memory process.[25] The Aβ oligomers can cause neuritic dystrophy by activating Fyn tyrosine kinase and causing phosphorylation of NDMAR. Disturbing the NDMAR activity leads to synaptic loss and decreased spinal density, altering the availability of extracellular glutamate. Also, the Aβ aggregates elevate the intracellular Ca2+ level by increasing the membrane lipid peroxidation reaction and changing the membrane structure and function, suppressing LTP and promoting neuronal death.[26]

Oxidative stress is a crucial and early feature in the pathogenesis of AD due to aggravating the Aβ and hyperphosphorylated tau deposition, which directly initiates ROS formation via mitochondrial stress and NADPH oxidase activation. This activation and superoxide production are crucial in triggering oxidative stress and neurotoxicity. Nuclear factor erythroid-related factor 2 (NRF2) is a key factor in protecting against oxidative stress that regulates the expression of nearly 500 target genes that encode proteins acting as redox balancing factors, detoxifying enzymes, stress response proteins, and metabolic enzymes.[27]

Neuroinflammation is another important and inevitable pathological process implicated in AD. A widespread glial activation is an event associated with AD.[28] Activated microglia could excrete an excess of pro-inflammatory and neurotoxic factors with a pivotal role in neuroinflammation. In microglia, NRF2 modulates the production of cyclooxygenase 2 (COX2), nitric oxide synthase 2 (NOS2), IL-6, and tumor necrosis factor alpha (TNFα) and increases the levels of several anti-inflammatory markers. Senile animals and older adults have lower NRF2 protein and mRNA expression and diminished NRF2 activation than younger individuals, indicating that NRF2 functionality declines with age.[27]

The AD-induced brain structural changes, including a reduced gray matter volume, atrophy of the entorhinal cortex and hippocampus, elongation of the ventricles, synaptic degeneration, and increased permeability of the BBB, promote the AD symptoms such as memory impairment, behavioral changes, and other neuropsychiatric changes.[29,30] Indeed, clinical manifestations appear years before the clinical diagnosis of AD dementia.[31]

Although AD was first described in 1906, no disease-modifying preventive or therapeutic strategies exist.[32] Nowadays, disease-modifying treatments for AD are still under extensive research. Only symptomatic treatments are currently approved for mild to moderate AD forms. All these treatments try to counterbalance the neurotransmitter disturbance: 3 cholinesterase inhibitors and memantine. The AChE inhibitors were developed based on the cholinergic hypothesis, which suggests that the progressive loss of the cholinergic system is critically important for memory and learning.[33] These AChE inhibitors include donepezil, rivastigmine, and galantamine and are indicated for patients with mild to moderate AD, where the loss of cholinergic neurons is not severe as in end-stage AD. AchE inhibitors enhance central cholinergic neurotransmission by maintaining the Ach levels in the synaptic cleft, mitigating the decline in cognition at least during the first year of treatment. The only neuroprotective treatment strategy available for moderate to severe forms of AD is a low-to-moderate affinity noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine, which blocks the NMDA-mediated ion flux and ameliorates the dangerous elevated glutamate levels that lead to neuronal dysfunction.[33] Numerous efforts have been made to find effective disease-modifying therapy. Both Aβ and tau are prime targets for disease-modifying treatments. Many Aβ-directed therapies aim to lower the levels of parenchymal Aβ and amyloid deposits in the AD brain. For example, antiamyloid monoclonal antibodies are the first disease-modifying therapies for AD that achieve the slowing of clinical decline by intervening in the basic biological processes of the disease. Lecanemab (recently approved by FDA) is a humanized monoclonal antibody that binds with high affinity to an Aβ soluble protofibril that reduces amyloid markers in mild AD patients, resulting in a moderately lower decline in measures of cognition. However, its use was associated with adverse events.[34] Aducanumab is another monoclonal antibody against aggregated soluble and insoluble forms of Aβ and promotes the clearance of Aβ aggregates through the activation of microglial phagocytosis; however, there is no clear evidence that the Aβ clearance is correlated with less cognitive or functional decline.[35]

In addition, different prevention strategies have been proposed based on changing people's lifestyles, mainly diet. The diet changes involve using supplements, functional foods, natural extracts, and nutraceuticals to modify the inflammatory and neurodegeneration mechanisms of AD.[36] A food-based intervention is an attractive strategy for preventing and ameliorating AD.

4. PRECLINICAL MODELS TO EVALUATE THE NEUROLOGICAL ACTIVITIES OF NUTRACEUTICALS

It is generally agreed that the first step of the therapeutic compound discovery process consists of target identification and validation, almost obligatory identification of biochemical processes, and a macromolecule responsible within particular signaling pathways.[37] Thus, the basis for selecting promising nutraceuticals relies on scientific evidence from *in vitro* and *in vivo* studies.

Focusing on cognitive enhancement and neuroprotection evaluation, neuron culture has continued to propel basic

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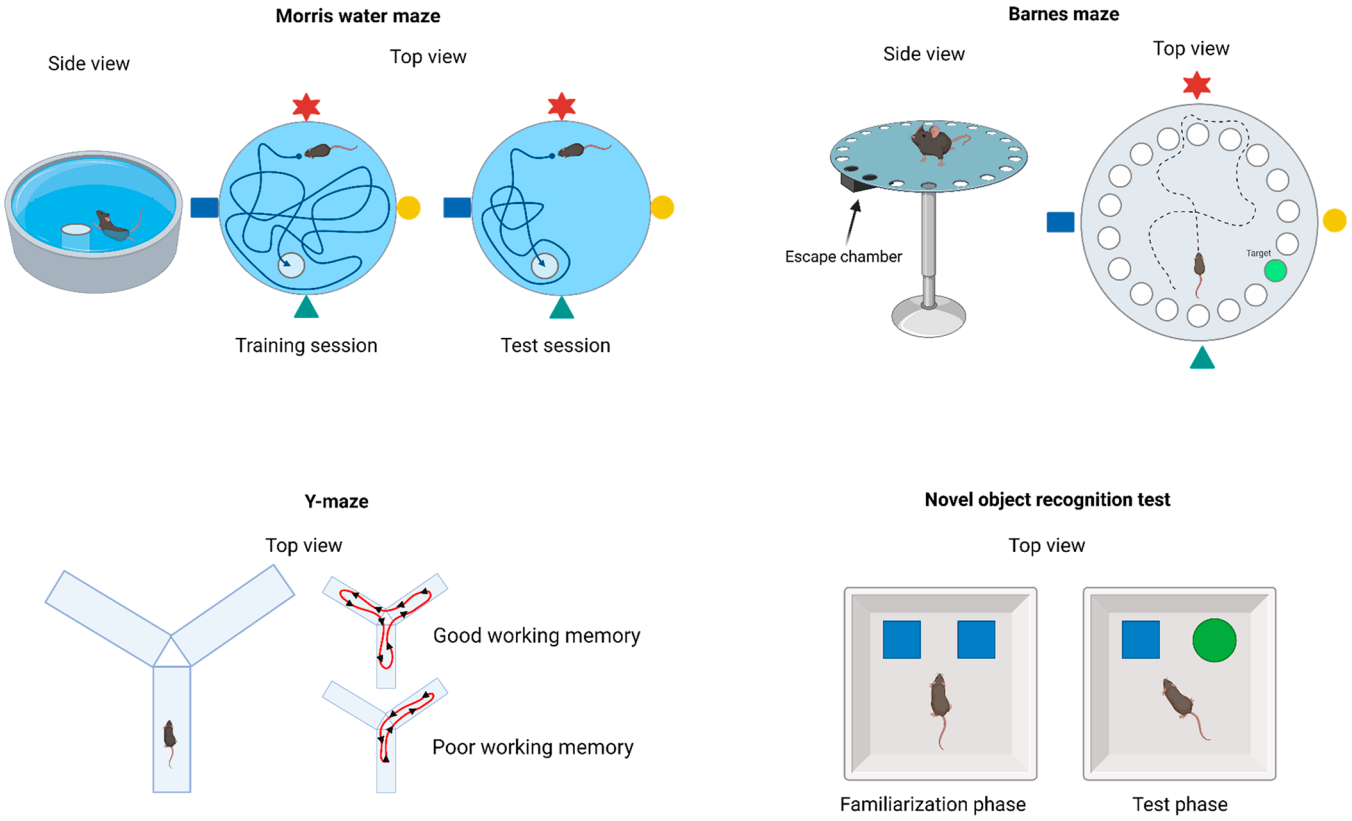

Figure 2. Behavioral tests for learning and memory assessment. All behavioral tests involve familiarization sessions to minimize the animal handling stress. The data generated in this kind of analysis provide an overview of the cognitive status.

neuroscience research for mechanistic determination. Although neuron culture cannot fully recapitulate brain function, the knowledge provided is invaluable.[38] For instance, the PC12 cells, a rat adrenal pheochromocytoma cell line, are commonly employed to study cell death and neurotoxic damage because they can be differentiated into sympathetic nerve-like cells under the induction of the nerve growth factor (NGF), growing cell protrusions, forming synapse-like structures, and synthesizing acetylcholine.[39] SH-SY5Y is a human neuroblastoma cell line and probably the most used in neuronal cell biology research, expressing typical immature neuronal markers such as nestin, doublecortin (DCX), and beta III tubulin. Using differentiation-inducing agents such as retinoic acid, the cells shift to a morphology resembling primary neurons, with smaller cell bodies, which are frequently polarized and present extended neurites and excitable membranes. Other cell models include primary neuronal culture or neurons derived from human-induced pluripotent stem cells. All these cell cultures are widely used to study autophagy, cell death, oxidative stress, mitochondrial dysfunction, disruption of neurotransmitter homeostasis, and alteration of neuritic length and synapsis.[40] These *in vitro* models allow the evaluation of molecular and cellular mechanisms of neuroplasticity phenomena underlying cognitive enhancement, such as functional plasticity, which include modification of the efficacy of synaptic transmissions, including long-term potentiation (LTP), dendritic spine maturation, and the activation of synapses. Structural plasticity, neurogenesis, changes in cell structure/neuroprotection, as well as mechanisms of axonal regeneration, dendrite branching, and synaptogenesis can be evaluated in these models.[41]

In parallel, rodent models have been workhorses in deepening our understanding of numerous pathophysiological mechanisms associated with disease progression. Current transgenic AD models provide critical mechanistic insights into pathological processes. The successfully mimicked neurodegeneration relies on familial AD mutations' overexpression.[42] For example, the triple-transgenic mouse model of AD (3xTg-AD) expresses three dementia-related transgenes, namely, APP_{SWE}, $PS1_{M146V}$, and tau_{P301L}, that promote both amyloid beta plaque and neurofibrillary tangle pathology as well as synaptic dysfunction, finally leading to learning and memory deficits. This pathology recapitulation makes it a valuable model for developing treatments and understanding the underlying mechanisms of AD.[43]

On the other hand, there are murine nontransgenic AD models induced with the infusion of several agents, including streptozotocin, amyloid beta peptides, colchicine, aluminum chloride, lipopolysaccharides, and D-galactose, among others,[44] to modeling pathological processes, such as oxidative stress, synaptic dysfunction, apoptosis, insulin resistance state, neuroinflammation, gut microbiota–brain axis alterations, lipid metabolism abnormalities, autophagy dysfunction, and metal ion disorders.[45]

In animal models, neuroplasticity can be measured in several ways including molecular and cellular analysis, microstructural analysis, behavioral tasks, and electrophysiological recordings. The molecular, cellular, and microstructural analysis can be performed in the same way as in the *in vitro* context. The cognitive capabilities of rodents, particularly memory and learning, can be assessed using several tests, including the Morris Water Maze (MWM), the Radial Arm Maze (RAM),

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Table 1. Summary of Neuroprotective and Neuroplasticity Effects of Nutraceuticals against Alzheimer's Disease

Compound	Natural source	Model	Outcomes	References
EGb761	*Ginkgo biloba*	Clinical healthy participants	Improvement of working memory and memory consolidation	57, 60−65
		Scopolamine-induced AD model	Improvement of MMSE score (improved cognitive capacity)	
		Aluminum-induced AD model	Dose-dependent inhibition of AChE activity	
		Aged mice	Improvement of learning and memory functions in passive avoidance tasks	
		Transgenic C. elegans	Promotion of neuronal excitability and LTP	
		Neuroblastoma N2a cell	Inhibition of the Aβ oligomerization and deposition	
			Inhibition of Aβ fibril formation	
Hericium erinaceus	H. erinaceus	Aβ25−35-induced AD model	Improvement of learning and memory functions in Y-maze and NOR test	68, 72−76
		Astrocytoma cells	Increase in mRNA and protein NGF levels	
		PC-12 cells	Promotion of NGF-dependent neurite outgrowth	
		APPswe/PS 1dE9 AD model	Increase proliferation of neuron progenitors and the number of newly born neurons in the hippocampus	
		Clinical MCI participants	Increase dendritic branching	
		Clinical MCI/AD participants	Reduction of the Aβ plaque burden	
			Amelioration of the astrocytes and microglia cells activation	
			Increase cognitive function score based on the Hasegawa Dementia Scale	
			Improvement of CASI and MMSE scores	
			Improvement of IADL score	
Caffeine	Coffee	Aβ25−35-induced AD model	Improvement of learning and memory functions in passive avoidance tasks	82, 83, 86, 89, 90
	Cocoa beans	PS1/APP transgenic mice	Antagonism of the A_{2A} receptor	
	Yerba matte	Hippocampal slices culture	Improvement of learning and memory functions in MWM	
	Tea leaves	Clinical AD participants	Increase expression of hippocampal BDNF and TrkB levels	
	Guarana	Clinical healthy participants	Induction of LTP in CA1 pyramidal neurons and increase of presynaptic Ca2+ evoking increased transmitter release	
	Berries		Inverse association between coffee intake and risk for AD development or MCI	
L-Theanine	Green tea	SH-SY5Y cell culture	Attenuation of apoptosis by decreasing the phosphorylation of JNK and expression of caspase-3	95, 97−100
	Camelia species	Aβ1−42-induced AD model	Improvement of learning and memory functions in MWM and passive avoidance task	
		APP/PS1 transgenic mice	Increase the synaptic transmission via the dopamine D1/5 receptor-PKA pathway	
		D-Galactose-induced brain damage	Amelioration of LTP impairment	
		Clinical healthy participants	Increase the release of dopamine and noradrenaline levels	
		Clinical MCI participants	Improvement of memory in a fear conditioning paradigm	
			Improvement of Ach levels and downregulation of AchE	
			Downregulation of TNF-α, IL1β, and IL-6	
			Upregulation of PGC-1α and BDNF expression	
			Modulation of mental alertness by increasing activity in the alpha frequency band	
			Improvement of attention and working memory in Cognitrax	
Curcumin	*Curcuma longa*	Aβ-1−42 induced AD model	Improvement of learning and memory functions in MWM, Y-maze, and open-field test	107−113, 115
		Aged rat	Upregulation of BDNF and phospho-ERK expression in the hippocampus	
		5XFAD transgenic AD mice	Improvement of learning and memory functions in NOR	
		In vitro cell-free	Upregulation of synaptophysin	
		Primary cortical neuronal culture	Improvement of learning and memory functions in MWM	
		SH-SY5Y cell culture	Increase the social recognition index in the social recognition test	
			Increase the hippocampal neurogenesis	
			Upregulation of Wnt2, NeuroD1, Nnat, Tiam1, and Unc5d expression	
			Reduction of the Aβ plaque burden	
			Prevention of dystrophic neurites in CA3	
			Promotion of disassembly of preformed Aβ aggregates	
			Inhibition of Aβ oligomers	
			Inhibition of apoptosis by downregulation of caspase-3 and upregulation of phospho-Akt	
			Inhibition of reactive oxygen species levels	

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Table 1. continued

Compound	Natural source	Model	Outcomes	References
			Downregulation of BACE-1, PS1 and GSK-3β expression	
PUFAS	Salmon	Fat-1 transgenic mice	Increase the spine density in CA1 pyramidal neurons	123−137
	Mackerel	Embryonic stem cell culture	Upregulation of F-actin, GAP43, GluR1, PSD95, and synapsin-1 expression	
	Halibut	Primary hippocampal culture	Promotion of neuron differentiation and neuritic branching complexity	
	Sardines	SH-S5Y5 cell culture	Increase neuronal survival	
	Tuna	Aged rat	Inhibition of Aβ fibril formation	
		Healthy Wistar rat	Improvement of learning and memory functions in the RAM	
		Aβ1−42-induced AD model	Increase the DHA content and the DHA/arachidonic acid ratio in the cortex	
		Aβ1−42-induced AD model	Induction of LTP in CA1 pyramidal neurons	
		CHO cell culture	Promotion of neuritic branching complexity	
		SAMP8 transgenic mice	Upregulation of synaptophysin and PSD95 expression in CA3	
		Clinical AD participants	Upregulation of BDNF/TrkB/CREB signaling pathway	
		Tg2576 transgenic AD model	Reduction of intercellular Aβ1−42 concentration	
		3xTg-AD model	Downregulation of APP, PS1, and BACE1 protein expression	
		Primary neuron/glia cells coculture	Reduction of soluble/insoluble Aβ40 and soluble Aβ42 levels	
		Neuro 2A cell culture	Improvement of learning and memory functions in MWM	
			Improvement of MMSE score (improved cognitive capacity)	
			Reduction of insoluble Aβ peptides levels in the cortex	
			Decrease Aβ plaques in the hippocampus and parietal cortex	
			Inhibition of steady-state levels of PSEN1 by either the α- or β-secretase.	
			Reduction of intraneuronal Aβ accumulation in the hippocampus and amygdala	
			Reduction of tau accumulation and the levels of tau phosphorylation	
			Downregulation of soluble Aβ peptides secretion	
			Promotion of APP processing via the nonamyloidogenic pathway	
			Inhibition of apoptosis by Bcl-xl, Bcl-2, and Bfl-1A upregulation, Bax and Bik downregulation	
			Increase the PS levels in the cell membrane leading to faster translocation and phosphorylation of Akt and inhibiting the caspase-3 activity	
Chlorogenic acid	Coffee	APP/PS1 AD transgenic mice	Increase of neuron density in CA1	142, 143,
	Berries	SH-SY5Y cell culture	Inhibition of pyknosis and demyelination in the hippocampus	145−149
	Cocoa	Clinical MCI participant	Upregulation of the lysosomal activity via the mTOR/TFEB pathway	
	Tea	Scopolamine-induced AD model	Inhibition of Aβ1−42 β-sheet formation, inhibiting the Aβ aggregation into oligomers and fibrils	
	Apples	*In vitro* cell-free	Improvement of cognitive and attention/executive functions	
	Carrots	Primary neuron culture	Improvement of learning and memory functions in passive avoidance task, Y-maze, and MWM	
		PC-12 cell culture	Inhibition of AchE activity in the hippocampus and frontal cortex	
			Inhibition of apoptosis by downregulating Bax, C-caspase-3, and Cyto C expression and upregulating Bcl-xL and Bcl-2	
			Inhibition of apoptosis by upregulating the Akt/GSK-3β signaling pathway	
Luteolin	Celery	Endothelial cells/astrocytes coculture	Increase of neuroprotection against Aβ-mediated toxicity	151, 153−155
	Parsley	Streptozotocin-induced AD model	Amelioration of BBB permeability	
	Broccoli	Tg2576 transgenic AD model	Downregulation of TNF-α, IL-1β, IL-6, IL-8, and COX-2 by downregulating p38/MAPK activation, IKK phosphorylation levels, and inhibiting NF-κB p65 nuclear translocation	
	Onion	N2a cells	Inhibition of cell loss in CA1	
	Carrots		Improvement of learning and memory functions in Morris water maze	
	Peppers		Inhibition of Aβ deposition, GSK-3β activation, tau hyperphosphorylation	
	Cabbages		Inhibition of generation of Aβ peptides	
	Apple		Downregulation of PS1-mediated γ-secretase APP processing activity	
	Chrysanthemum			
Quercetin	Apples	Primary neuron culture	Inhibition of BACE-1 enzyme activity	161, 163−166
	Grapes	*In vitro* cell-free	Decrease of Aβ1−40 and Aβ1−42 levels	

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Table 1. continued

Compound	Natural source	Model	Outcomes	References
	Garlic	3xTg-AD model	Inhibition of the AChE and butyrylcholinesterase activities	
	Asparagus	APPswe/PS 1dE9 transgenic AD	Inhibition of Aβ oligomer deposition	
	Onions	Aβ1−42-induced AD model	Reduction of the paired helical filament of tau hyperphosphorylated	
	Tomatoes		Improvement of learning a memory function in an elevated plus maze test	
	Berries		Downregulation of BACE-1-mediated APP processing activity	
	Capers		Restoration of mitochondrial dysfunction via increasing AMPK activity, mitochondrial membrane potential, mitochondrial ATP levels, and decreasing ROS production	
	Red leaf lettuce		Increase of intracellular Aβ clearance	
			Upregulation of NGF, BDNF, CREB, and EGR-1 expression	
			Promotion of neurogenesis in DG	
			Improvement of learning and memory functions in MWM	
Resveratrol	Grapes	Neural stem cells culture	Inhibition of inflammation by downregulating TNF-α, IL-1β, IKKα, IKKβ, iNOS, and COX-2	172−178
	Peanuts	RAW 264.7 cell culture	Inhibition of oxidative stress by upregulating SOD-1, NRF2, Gpx1, Cat, GSH, and HO-1	
	Blueberries	*In vitro* cell-free	Amelioration of inflammation via TLR4/NF-κB/STAT signaling cascade by inhibiting the IκB phosphorylation, activation of STAT1 and STAT3, and TNF-α and IL-6 secretion	
	Bilberry	SAMP8 mice	Inhibition of the β-sheet fibril formation	
	Cranberry	Ibotenic acid-induced AD model	Upregulation of ADAM10 by SIRT1, promoting the nonamyloidogenic processing of APP	
	Purple grape	D-Galactose-induced AD model	Inhibition of Aβ peptide deposition	
			Downregulation of tau hyperphosphorylation at serine 396	
			Amelioration of NR2A/NR2B levels by overexpression of SIRT1	
			Improvement of learning and memory functions in open field tests	
			Amelioration of oxidative stress	
			Inhibition of Aβ peptides secretion	
			Downregulation of NF-κB and RAGEs expression in the hippocampus	
Rosmarinic acid	Rosemary	PC-12 cell culture	Promotion of cell differentiation and cholinergic function partially dependent on the ERK1/2 signaling function	180−182
	Lamiaceae family	Tg2576 transgenic AD model	Promotion of neuroprotection against Aβ25−35-induced neurotoxicity via Akt/GSK-3β/Fyn and Nrf2 activation	184,185
		Aβ1−42-induced AD model	Upregulation of phase-II enzymes such as HO-1, NQO1, GCLc, and TrxR	
			Inactivation of GSK-3β via serine 9 phosphorylation	
			Upregulation of the dopaminergic synapse pathway	
			Downregulation of NMDAR and AMPA activity	
			Increase hippocampal neurogenesis	
			Upregulation of synaptic markers synaptophysin, synapsin II and III	
			Inhibition of Aβ plaque deposition	
Probiotics/ postbiotics	SCFA	BV2 cell culture	Suppression of the M1 phenotype by inhibiting COX-2 and NF-κB p65 phosphorylation	190−194
	S. thermophilus	*In vitro* cell-free	Interfere with initial Aβ1−40 and Aβ1−42 peptide assembly	
	B. longum	Scopolamine-induced AD model	Inhibition of BACE1 enzyme	
	B. breve	3xTg-AD model	Promotion of the hippocampal expression of p-CREB and BDNF	
	B. infantis	APP/PS1 transgenic AD model	Upregulation of SIRT1 expression	
	L. acidophilus		Increase the activity of GST, GPx, SOD, and CAT via SIRT1 upregulation	
	L. plantarum		Improvement of learning and memory functions in MWM	
	L. paracasei		Inhibition of Aβ peptide deposition	
	L. delbrueckii			
	L. brevis			
	C. butyricum			
Alpha-linoic acid	Red meat	3xTg-AD mice	Activation of the insulin receptor substrate and increase brain glucose intake	195, 197
	Carrots	PC12 cell culture	Activation of the PI3K/Akt signaling pathway	
	Beets		Induction of LTP in CA1 pyramidal neurons	
	Spinach		Inhibition of Aβ25−35-induced apoptosis	
	Broccoli		Downregulation of Bax and caspase-3, upregulation of Bcl-2	
	Potatoes		Downregulation of NF-κB activity	
Vitamin B12	Meat	Clinical AD participants	Improvement of the Montreal Cognitive Assessment test, naming scores, orientation scores, and Alzheimer's Disease Assessment Scale-Cognitive score of attention	200−203
	Dairy	Clinical AD participants	No improvement in MMSE score	
	Eggs	Clinical AD participants	Attenuation of atrophy of the bilateral hippocampus and parahippocampal gyrus, retrosplenial precuneus, lingual and fusiform gyrus, and cerebellum	
	Fish	Scopolamine-induced AD model	Inhibition of neuroinflammation	
			Inhibition of apoptosis	
			Attenuation of overexpression of caspase-3 and cyclooxygenase-2	

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Table 1. continued

Compound	Natural source	Model	Outcomes	References
			Increase of PSD-95, neurexin 1, and neuroligin proteins levels	
Vitamin B3	Meat	5XFAD transgenic AD mice	Inhibition of Aβ plaque deposition	206−209
	Dairy	Aβ1−42-induced AD rat model	Attenuation of neuronal dystrophy and neuronal loss	
	Grains	Primary hippocampal culture	Improvement of learning and memory functions in Y-maze	
		3xTgAD mouse model	Downregulation of APP, NF-κB, and PSEN1 expression, upregulation of SIRT-1	
			Inhibition of ROS generation	
			Induction of LTP in hippocampal neurons	
			Improvement of learning and memory functions in MWM	
			Inhibition of microglia Iba-1 expression	
			Increase of microglia Aβ uptake	
			No changes in brain cytokine concentration	
			Increase of hippocampal neurogenesis	
			Attenuation of neuroinflammation	
			Improvement of motor function	

the Y-maze, the Barnes Maze, and the Novel Object Recognition (NOR) test (Figure 2). MWM is a widely used test to assess and determine cognitive deficits in rodents used as models for neurological diseases.[46] This test uses a circular pool virtually divided into quadrants with spatial cues to locate a submerged escape platform. Spatial learning and reference memory are determined generally by the preference for the platform area, the swimming time, and the distance toward the escape platform.[46] RAM is another popular behavioral test of spatial and associative learning that exploits rodents' natural tendency to explore, learn, and remember different spatial locations of food reinforcement. The procedure for RAM testing involves an initial adaptation to the maze environment. A "win-shift" acquisition protocol is then followed. Animals are trained to recognize that only one of the arms will contain food. The animal is reinforced ("win") for entry into the arm of the maze, and then, it must "shift" to another arm. The test concludes when the animal enters all arms or a time limit elapses. Both working and reference memory can be measured on the basis of the amount of time it takes for an animal to find the arm, leading to food, and the number of times it traverses an arm it has previously visited. Exploring a previously visited arm indicates that the animal did not remember previously choosing that spatial path.[47]

The Y-maze is used to assess short-term memory. Y-maze spontaneous alternation is a behavioral test based on the animals' natural curiosity for exploration. The animals typically tend to explore a new arm of the maze rather than return to one that was previously visited. Testing is carried out in a Y-shaped maze with three identical arms at a 120° angle from each other. After the introduction to the center of the maze, the animal is given free access to all three arms. If the animal chooses a different arm than the one from which it arrived, this choice is called an alternation. This is considered the correct response, whereas returning to the previous arm is considered to be an error. A high percentage is taken as a good working memory, indicating that the mouse has recalled which arms it has already visited.[48]

The Barnes maze is another important tool for spatial learning and memory assessment. It consists of a circular table with holes and visual cues around the circumference. Most of these holes lead to an open drop to the floor, but a single hole leads to an escape chamber where the animal can hide. A rodent is naturally motivated to avoid open spaces and bright lights and therefore attempts to find the drop box. In training trials, the animal is led to an escape chamber. In subsequent trials, the animal is placed in the center of the apparatus and must find an escape chamber on its own. Rodents typically remember which hole contains the escape chamber and quickly proceed in a direct path toward the hole. Researchers can measure the amount of time to find the correct hole, the number of incorrect holes explored, and the length of the exploratory path.[47]

The NOR test is also widely used to evaluate memory disorders and provide information on attention, memory, and anxiety, exploiting the novelty preference of rodents. The most common version of this test consisted of three phases: the habituation phase, in which the animals were familiarized with the exploration space; the familiarization phase is when the animals are in the presence of two identical objects; and finally, in the test phase, the animals are placed back in the exploration space but one of the objects is exchanged for another with a similar size and shape. The fundamental note is that object recognition is distinguished by more time spent interacting with the novel object.[49] The data generated in this kind of analysis provide an overview of cognitive status.

In summary, preclinical studies have led to a better understanding of the mechanistic activity of a compound of interest with a translational approach.

5. NEUROPROTECTIVE POTENTIAL OF NUTRACEUTICALS AGAINST ALZHEIMER'S DISEASE

There has been considerable interest in phytochemicals, herbal extracts, and bioactive ingredients as disease-modifying and neuroprotective agents.[50] Historically, a trace path links herbalism, ethnopharmacology, phytotherapy, and alternative medicine to nutraceuticals.[51] The use of medicinal herbs for brain data was from ancient Greece. Homer's Odyssey tells how Odysseus recovered the memories of his crew using an antidote that may be *Galanthus nivalis*, the original source of the current AchE inhibitor galantamine.[52] Due to the heterogeneous nature of traditional herbal products, their use imposes challenges to qualify control and quality assurance and demonstrate their safety and effectiveness.[53] For this reason,

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scientists isolated and evaluated some compounds rather than evaluating the whole herbal preparation. For example, in the early 1990s, EGb761 became one of the most popular supplements for enhancing memory. However, no conclusive data support its efficacy in the treatment of dementia. One of the first reports of the use of nutraceuticals to enhance cognition capacity was done by Joseph et al., reporting that a diet supplemented with extracts from antioxidant-rich foods such as blueberry, spinach, or strawberry can reverse neuronal aging and provide protection against the aged-related cognitive dysfunctions.[8] Nowadays, modern drug development is strongly focused on the idea that a drug should possess just one site of action, with little or no additional effects that might compromise its selectivity. However, in the modern context of the molecular and cellular neuroscience of neurodegenerative conditions, multiple mechanisms are involved, e.g., oxidative stress, excitotoxicity, protein aggregation, disturbed proteostasis, inflammation, and altered cerebral blood flow. Therefore, efforts are needed to improve the bioavailability and the *in vivo* transport across the BBB and biochemical stability via drug delivery approaches to optimal efficacy in the brain.[51]

In the past years, studies have demonstrated the role of nutraceuticals in reducing cognitive deficits and preventing and protecting against neuronal damage, pathological changes, and symptomatology during the transition of the different stages of AD.[54] Modulation cellular processes such as neurogenesis, synaptogenesis, synaptic transmission, neuro-inflammation, oxidative stress, cell death modulation, and neuronal survival with nutraceuticals can be integrated into neuroprotective strategies for AD patients, mainly preserving and restoring the brain's normal function.[55] This section focuses on some nutraceuticals with solid evidence for neuroprotection and amelioration of neurodegeneration and cognitive dysfunction in AD (Table 1).

5.1. *Ginkgo biloba*. *Ginkgo biloba* is a gymnosperm that is well-known for its medical application. Specifically, the standardized EGb761 leaf extract has been used to treat memory impairment and dementia, including AD, for more than 40 years.[56,57] Studies have demonstrated that components of EGb761, including ginkgolide A, ginkgolide B, and bilobalide, as well as flavonoids, quickly reach the CNS after oral administration.[58]

Despite the few detailed molecular reports, EGb is claimed to have antidementia effects. A meta-analysis evaluating 2561 patients with dementia and cognitive impairment showed that consuming 240 mg of EG daily for 22−26 weeks slowed the patients' cognitive decline, function, and behavior.[59] In a clinical evaluation, healthy participants were given 120 mg of *Ginkgo biloba* for 30 days. After the 30-day treatment, neuropsychological tests to assess cognitive variables revealed memory process improvements, mainly working memory and memory consolidation.[60] A 20-year follow-up prospective study using the population-based cohort study "Paquid" showed that nondemented participants using EGb had a lower decline of the mini-mental state evaluation (MMSE) score than subjects who did not. At the end of the evaluation period, the MMSE score of people who used EGb remained above the threshold of 24, meaning a roughly normal cognitive function.[57]

Preclinical studies suggested that EGb-induced cognitive enhancement is mediated by central cholinergic system modulation, synaptic plasticity, the inhibition of Aβ aggregation, and antioxidant capacity. Inhibiting AChE, the metabolizing enzyme of the ACh neurotransmitter, is considered to be a promising strategy for cognitive enhancement in AD patients. In this context, EGb exhibited a dose-dependent inhibitory effect on AChE activity in a scopolamine AD-like model. The *in vitro* evaluation determined an IC50 with 268.33 μg of EGb. In the *in vivo* evaluation, a significant decrease in AChE activity was achieved at 30 and 60 mg/kg daily for 7 days. In the passive avoidance task, 30 and 60 mg/kg of EGb exhibited a significant increase in the transfer latency time and no transfer response.[61] In an aluminum-induced AD-like rat model, the treatment of 200 mg/kg of EGb for 28 days improved learning and memory functions in the passive avoidance test, manifested by a more extended latency period to enter the dark chamber. In addition, the EGb markedly reduced the AChE activity.[62]

Regarding synaptic plasticity, the acute and chronic administration of 300 mg/kg of EGb increased neuronal excitability and LTP in aged mice, as demonstrated by the population spike threshold reduction and increased post-tetanic potentiation/early LTP. The authors suggested that the interaction between EGb and the glutamatergic system could be responsible for the pre- and postsynaptic responses observed.[63]

Aβ oligomers promote synaptic dysfunction, an early event that leads to the neurodegeneration observed in AD.[64] Wu et al.[64] reported that treatment with 100 μg/mL of EGb 761 for 36 h inhibits the Aβ oligomerization and deposits in *Caenorhabditis elegans*. Moreover, EGb treatment alleviates the Aβ-induced paralysis of *C. elegans*. Transgenic *C. elegans* paralysis correlates positively with Aβ oligomer density.[64] In the same way, the inhibition of Aβ oligomerization by EGb 761 was demonstrated in a neuroblastoma N2a cell line stably expressing Swedish mutant APP695 and exon-9 deletion mutant PSEN1 (sweΔ9). In this study, the 100 μg/mL EGb761 treatment inhibited Aβ fibril formation by 82 ± 6%.[65]

Although these results denote the cognitive enhancement and antiamyloidogenic and antidementia properties of *Ginkgo biloba*, the molecular mechanism remains unclear.

5.2. *Hericium erinaceus*. *Hericium erinaceus*, also known as the Lion's mane or Monkey's head mushroom, is a mushroom belonging to the family Hericiaceae that has been used as a medicine or food in China and Japan without harmful effects. Recently, the chemical constituents of *H. erinaceus* have been investigated for their interesting bioactivities, especially their potential to prevent neurodegenerative diseases.[66] Some *H. erinaceus* compounds, such as erinacines, are cyathin diterpenoids that cross the BBB, suggesting a greater opportunity for targeting the CNS.[67] Erinacines are capable of stimulating the NGF synthesis and promote NGF-induced neurite outgrowth in nerve cells *in vitro* and *in vivo*.[68,69] NGF is a neurotrophic factor that plays a critical protective role in developing and surviving sympathetic, sensory, and forebrain cholinergic neurons.[70] NGF is essential for forming post-synaptic and presynaptic specializations on dendrites.[71]

Studies have demonstrated that *H. erinaceus* ameliorated Aβ-induced cognitive decline in mice and people with mild cognitive impairment. An Aβ25−35-induced AD mice model diet containing 5% dried *H. erinaceus* for 23 days (food intake average 5.4 g/day) prevented the cognitive impairment, resulting in a significant increase in the alternation behavior and the discrimination index in the Y-maze and NOR test.[72] These effects could be partially mediated by promoting NGF activity as this research group previously reported in

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astrocytoma cells and AD mice models. Exposing the astrocytoma cell culture 100 μg/mL of *H. erinaceus* increased the mRNA-NGF levels. The authors demonstrated the physiological effects of *H. erinaceus* on the promotion of neurite outgrowth via NGF. PC-12 cells cultered with the conditioned medium of the astrocytoma cells exposed to 250 μg/mL of extract of *H. erinaceus* increased the morphological differentiated PC-12 cell density.[68] In the APPswe/PS 1dE9 AD mice, the treatment of 300 mg/kg/day of *H. erinaceus* for 30 days increased the levels of NGF and the NGF−precursor ratio in the hippocampus, promoting the proliferation of neuron progenitors and the number of newly born neurons in the DG. Similarly, the 30-day gavage administration of 30 mg/kg/day of erinacine A in the same AD model decreased the Aβ production and accumulation, reduced the Aβ plaque burden, inhibited the reactive glia and activation of microglia, and increased hippocampal neurogenesis. The erinacine A treatment also enhanced the dendritic branching complexity associated with recovering the cognitive decline observed in this model.[73] The cognitive improvement was also reported after 81 days of *H. erinaceus* administration in the APP/PS1 AD mice model.[74]

In a clinical trial, administering four 250 mg tablets containing 96% of *H. erinaceus* dry powder three times a day for 16 weeks increased the cognitive function of people over 50 years old diagnosed with mild cognitive impairment.[75] In another clinical study conducted by Li et al., the 49 weeks of administration of three 350 mg tablets per day of *H. erinaceus* in patients diagnosed with mild AD significantly improved the cognitive abilities screening instrument (CASI) and MMSE score. Moreover, a significant instrumental activities of daily living (IADL) score difference was also reported. CASI and MMSE higher scores represent better cognition, while higher IADL scores represent a lower level of dependence. Interestingly, the blood-based AD markers baseline showed a trend toward improving superoxide dismutase (SOD), apolipoprotein E (APOE4), and alpha 1-antichymotrypsin (α-ACT) levels.[76] Although further biochemical and molecular studies are necessary to evaluate the mechanistic activity of *H. erinaceus*, the data denote the possible effects of delaying other AD neurodegenerative processes.

5.3. Caffeine. Caffeine is a trimethyl-xanthine found in various plants' seeds, nuts, and leaves, such as coffee, cocoa beans, yerba matte and tea leaves, and guarana berries.[77] Caffeine is the most widely consumed psychoactive alkaloid capable of crossing the BBB and influences cerebral functions such as objective and perceived cognitive performance and increases alertness and wakefulness and performance of memory tasks; therefore, caffeine has been used to promote arousal, attention, energy, and elevated mood.[78] The neuromodulation processes of caffeine to modify synaptic activity include the inhibition of phosphodiesterase, mobilizing intracellular calcium, adenosine receptor antagonism, and modulation of GABA receptors.[79] Other effects include modification of the blood flow to the brain. Generally, positive behavioral changes are related to caffeine ingestion.[80]

Preclinical studies showed that caffeine could protect and reverse AD-like cognitive impairment in transgenic AD mice.[81] Dall'Igna et al. tested a dose of caffeine of 30 mg/kg for 4 days in an Aβ25−35-induced AD mice model. This caffeine administration ameliorated the poor performance in the inhibitory avoidance and spontaneous alternation tasks. The authors suggest a cognitive improvement mediated by the A_{2A} receptor antagonism.[82] In addition, Han et al. demonstrated that 0.75 and 1.5 mg/day of caffeine increased the memory capability of PS1/APP AD mice. The caffeine significantly decreased the escape latency in the MWM in a dose-dependent manner. The Western blotting analysis demonstrated that caffeine increased the expression of the hippocampal brain-derived neurotrophic factor (BDNF) and TrkB.[83] BDNF is a neurotrophin essential in neuronal plasticity, including hippocampal neurogenesis and learning and memory processes. The levels of BDNF, and its primary receptor TrkB, have been reported to decrease in AD.[84]

LTP is a critical process in the context of synaptic plasticity. It involves the persistent strengthening of synapses, leading to a long-lasting increase in the level of signal transmission between neurons. This process is relevant to encoding, storing, consolidating, and retrieving in a subset of memory processes.[85] Martín and Buo reported that applying 10 mM caffeine induces the LTP in an NMDA receptor-independent form in Schaffer collateral-CA1 pyramidal neurons in rat hippocampal slices. LTP could increase the presynaptic Ca^{2+}, evoking the increased transmitter release.[86]

Longitudinal clinical studies investigated caffeine consumption and its impact on cognitive impairment. Although there is no consensus on the results, some studies demonstrated a improved cognition after long-term caffeine consumption, reducing age-related cognitive impairment and creating a lower incidence of AD.[87,88] Maia and de Mendonça reported an inverse association between coffee intake and the risk for AD development. This case-control study included 54 patients with probable AD according to the National Institute of Neurologic and Communicative Disorders and Stroke criteria and the Alzheimer's Disease and Related Disorders Association. The daily caffeine intake was calculated for 20 years preceding the diagnosis of AD. Interestingly, participants with AD had an average daily caffeine intake of 73.9 ± 97.9 mg, whereas the controls had an average of 198.7 ± 135.7 mg.[89] A 3-year follow-up study performed by Solfrizzi et al. including 1445 cognitively normal subjects found that constant coffee consumption habits are associated with a reduced risk of the incidence of mild cognitive impairment.[90] All of these studies demonstrated that caffeine protects against cognitive decline and the risk of developing AD.

5.4. L-Theanine. L-Theanine is a unique nonprotein amino acid and a natural homologue of glutamate found in various *Camellia* species, especially *Camellia sinensis*, the well-known green tea.[91] Regarding the metabolism of L-theanine, it is reported that 200 mg of L-theanine orally administered increased the plasma concentration of theanine in a dose-dependent manner at 0.5 and 2 h after intake.[92] Moreover, L-theanine can cross the BBB, probably by the leucine-preferring transport, and accumulates in the brain parenchyma within a time window of 0.5 up to 5 h.[93,94] As a natural glutamate antagonist with a higher binding capacity for the AMPA/kainite and NMDA receptors, L-theanine inhibits the glutamate reuptake in the synaptic cleft, attenuating the glutamate toxicity.[95,96] Although the underlying therapeutic mechanisms are unclear, L-theanine treatment can benefit patients with cognitive impairment. For example, in transgenic SH-SY5Y cell culture expressing the APP Swedish mutation, the treatment with 0.5 mM of L-theanine attenuated L-glutamate-induced apoptosis by decreasing the phosphorylation of JNK and expression of caspase-3.[95]

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The oral administration of 2 and 4 mg/kg of L-theanine significantly prevented the memory impairment in a dose-dependent manner in an Aβ1−42-induced AD mice model, decreasing the escape latency and step-through latency in the MWM and step-through passive avoidance test.[97] L-Theanine facilitates hippocampal synaptic transmission via the dopamine D1/5 receptor-PKA pathway. The oral administration of 0.4 mg/mL of L-theanine can restore hippocampal LTP impairment and improve memory in APP/PS1 AD mice. Interestingly, L-theanine also elevates the hippocampal release of dopamine and noradrenaline levels.[98] Rats fed with 200 and 400 mg/kg of L-theanine significantly improved the level of ACh and decreased the AChE levels in a dose-dependent manner. Given that ACh, serotonin, and dopamine have been shown to improve cognitive processes, such as attention, learning, and memory, the potential therapeutic use of L-theanine may be mediated by manipulating these neurotransmitters. In this study, L-theanine also inhibited the expression of proinflammatory factors such as TNF-α, IL1β, and IL-6, in the rat brain. Also, it enhanced the expression of PGC-1α and BDNF, promoting resistance to neuron damage.[99]

In a randomized placebo-controlled study conducted in Japanese subjects aged 50−69 years with an MMSE-Japanese version score ≥24, it was demonstrated that 50 min after a single dose of 100.6 mg of L-theanine the attention and working memory were improved, as shown by the reduction in the reaction time to attention tasks (Stroop test, Cognitrax) and the increase in the number of correct answers with a lower number of omission errors in working memory tasks (four-part continuous performance test, Cognitrax).[100] All of these data suggest that L-theanine can be integrated into strategies that might improve cognitive dysfunction under pathological conditions.

5.5. Curcumin. Curcumin is a low molecular polyphenol and the most active compound of *Curcuma longa*.[101] Beneficial properties of curcumin include anti-inflammatory, antioxidant, chemopreventive, and chemotherapeutic properties. Although studies indicated that curcumin crosses the BBB, the main drawback is low bioavailability due to poor solubility, low absorption in plasma and tissues, rapid metabolism, and rapid excretion. Therefore, new formulations must be developed to overcome this issue.[102]

Curcumin consumption in old age has been associated with better cognitive function, and preclinical studies have reported beneficial effects on the experimental models of AD.[103] Yang et al. indicated a favorable curcumin stoichiometry for inhibiting oligomer and fibril Aβ formation. ELISA and ultrastructural analysis revealed that Aβ monomers form fewer oligomers in the presence of curcumin and aid the promotion of the disassembly of preformed Aβ aggregates in a dose-dependent manner.[104] Although the mechanism implicated in the inhibition of polymerization and destabilization of Aβ remains unclear, a possible explanation is that curcumin binds to the ends of extending Aβ fibrils and increases the depolymerization rate by destabilizing the conformation of the Aβ peptide recently incorporated into the fibril ends.[105] Interestingly, a structure and activity relationship analysis suggested that the 4-hydroxyl group on the benzene ring of curcumin is crucial for its anti-Aβ aggregation, including the specific binding to Aβ fibrils and the destabilization of the β-sheet-rich conformation of Aβ molecules of fibrils.[106]

In cultured cortical neurons exposed to Aβ peptides, treatment with 10 μM of curcumin inhibits apoptosis by downregulating activated caspase-3 and upregulating phospho-Akt[107] as well as by decreasing the intracellular ROS levels in neurons.[108]

Modulating the APP processing is another possible way to reduce the Aβ levels. The BACE and presenilin-dependent γ-secretase cleavage mediate APP sequential proteolysis. In line with this, APPswe-transfected SH-SY5Y neuroblastoma cells treated with 20 μM curcumin significantly downregulated the mRNA and protein levels of PSEN1 and GSK-3β.[109] In primary cortical cell culture, 3−30 μM of curcumin suppresses the Aβ1−42-induced upregulation of BACE-1 in a dose-dependent manner and prevents structural changes toward β-sheet-rich secondary structure.[110]

A seven day treatment of 50, 100, and 200 mg/kg/day of curcumin improves cognitive functions in a dose-dependent manner in an Aβ-1−42-induced AD rat model. This cognitive improvement is probably mediated by promoting BDNF and phospho-ERK expression in the hippocampus.[111] In a similar AD rat model, the 10-day intraperitoneal administration of 50 mg/kg/day of curcumin and 2.5 mg/kg/day of nano-encapsulated curcumin increased the spontaneous alternation behavior and the object recognition index. The Western blotting analysis showed that curcumin attenuated the BDNF and synaptophysin reduction following the Aβ-1−42 injection.[112]

In aged rats, the administration of 480 mg/kg of curcumin for 6 and 12 weeks significantly increased the social recognition index in the social recognition test. Regarding spatial learning and memory abilities, the MWM showed that the 12-week curcumin treatment promoted a longer stay in the target quadrant. Interestingly, an enhanced neurogenesis in the dentate gyrus is also reported, which in turn is associated with better MWM performance. The transcriptomic analysis demonstrated that curcumin induced the expression of several genes, including *Wnt2*, *NeuroD1*, *Nnat*, *Tiam1*, and *UncSd*, that are involved in the proliferation and differentiation of neural stem cells, neuron maturation, and dendritic arborization.[113]

The specific mechanisms by which curcumin affects neuronal excitability and ameliorates synaptic transmission in AD models remain unclear. Spectral analysis of multielectrode array recordings of spontaneous neuronal activity reported that curcumin attenuated the initial synaptic dysfunction of organotypic hippocampal slice cultures exposed to Aβ-1−42. The electrophysiological recordings showed that 10 μM of curcumin for 24−48 h could minimize the progressively decreased local field potential power at a lower rate than cultures with only Aβ-1−42.[114] These results demonstrate that curcumin can reverse the Aβ-1−42-induced synaptically propagated neuronal activity attenuation.

Using a curcumin aerosol formulation (5 mg/mL) to increase the BBB permeability, McClure et al. reported a reduced Aβ plaque burden and a longer distance between Aβ plaques in 5XFAD mice brains after 4.5 months of preventive treatment. In the CA3 region, treated mice did not display dystrophic neurites, a neurite population with less dense distribution with the apex at 4−5 μm, representing abnormal and swollen neurites associated with AD. In contrast, the untreated group exhibited significant dystrophic neurites 10-fold larger than the normal counterpart, exclusively near the Aβ plaque. This effect on synaptic function is associated with treated animals' improved overall cognitive function.[115]

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In contrast, clinical trials on AD patients showed no such promising results. There is no significant difference in clinical measures nor cognitive measures between the curcumin and placebo group even after 12 months of treatment.[116] The failed attempt to demonstrate the therapeutic effect of curcumin lies in its poor bioavailability. Only serum Aβ1−40 tended to rise after curcumin intake, possibly reflecting the curcumin's ability to disaggregate the Aβ deposits and release the peptides for circulation and disposal.[84]

Although the available clinical studies do not confirm the protective effect of curcumin for AD treatment, most of the preclinical research indicates that curcumin has both preventive and therapeutic effects on cognition and suggests that curcumin might be one of the most promising compounds for developing AD therapies. However, new formulations and delivery strategies to improve the bioavailability should be considered.

5.6. Polyunsaturated Fatty Acids. Polyunsaturated fatty acids (PUFAs) are fatty acids that contain more than one saturation state in their backbone and must be obtained from the diet. For example, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be found in fish such as salmon, mackerel, halibut, sardines, tuna, and herring.[117]

In the brain, PUFAs are mainly supplied by the blood, regulating the structure and function of neurons, glial cells, and endothelial cells.[118] According to some studies, the PUFAs' brain transportation includes blood plasma absorption and attachment to HDL, LDL, and VLDL lipoproteins for further tissue incorporation. Other mechanisms may include protein-dependent facilitated transport mechanisms such as the fatty acid translocase FAT/CD36, the fatty acid transport proteins, and the fatty acid-binding proteins (FABPs).[119,120] The most abundant PUFAs in the brain are the omega-3 (ω-3) and omega-6 (ω-6) families, and they have an essential role during brain development, especially in neuroplasticity modifications.[119] Neuroplasticity modulation by ω-3 and ω-6 PUFAs is probably mediated by modifying the fluidity of neuronal membranes, affecting the properties of membrane-bound enzymes, receptors, and transporters.[121] For instance, ω-3 and ω-6 PUFAs can bind to the ligand domain of nuclear receptors such as the retinoid X receptor, which plays critical roles in neurogenesis, neuron differentiation, and neuroplasticity.[122]

Preclinical and epidemiological studies suggested that a DHA and EPA enriched diet may prevent AD. DHA can increase neurite length and the ramification complexity as a neurotrophic factor. Examination of dendritic spine density in the hippocampus of the Fat-1 mouse model, a transgenic model particularly enriched with endogenous DHA, revealed a higher spine density in CA1 pyramidal neurons than in wild-type counterparts and the increased expression of dendritic spine-related genes *F-actin*, *GAP43*, *GluR1*, *PSD95*, and *synapsin-1*. *In vitro* assays corroborated these findings; 5 μM DHA promoted the differentiation of embryonic stem cells into neurons, increasing in 2.85-fold the neurite branching, supporting the role for DHA in promoting neuron maturation.[123]

In hippocampal cultures exposed to Aβ1−42, the treatment with 5 and 25 μM DHA significantly increased neuronal survival by 47 and 88% after 8 h.[124] The 20 μM DHA treatment inhibited the *in vitro* Aβ1−42 fibrillation by acting during the nucleus formation of oligomers and their elongation into mature fibrils. Interestingly, this anti Aβ fibrillation property significantly decreased the oligomer-induced toxicity in neuronal cells.[125] A DHA-enriched diet reduced the Aβ burden in a Tg2576 AD mouse model. Animals fed DHA-enriched diets (0.6% DHA) for 103 ± 5 days reduced the insoluble Aβ levels in the cortex, including the reduction of Aβ1−42 and Aβ1−40 levels by 53.6% and 47.5%, respectively, which in turn decreases the total plaque by 40%, mainly in the hippocampus, perirhinal, and parietal cortex.[126] Green et al. suggested that Aβ reduction can be attributed to a decrease in steady-state levels of PSEN1 and not to altered APP processing by either the α- or β-secretase. In this study, after 9 months of DHA supplementation (2.3 g of DHA/kg) in 3xTg-AD mice, there was reduced intraneuronal Aβ accumulation in the hippocampus and amygdala. DHA dietary supplementation significantly reduced the PSEN1 levels, while the levels of APP, ADAM10, and BACE-2 remained unaltered. The 9 months of DHA supplementation also reduced the somatodendritic accumulation of tau and the levels of tau phosphorylation, which can be correlated with the phospho-JNK reduction reported.[127]

The NPD1, a DHA-derived 10,17*S*-docosatriene, promotes neuron survival via apoptosis inhibition and promotes neuroprotection programs in a primary coculture of neurons and glia exposed to Aβ1−42. The 50 nM DHA treatment downregulates the secretion of soluble Aβ peptides, while there was a time-dependent increase of NPD1 levels. Interestingly, sAPPα, a 612 amino acid fragment derived from α-secretase-mediated cleavage of APP in the nonamyloidogenic pathway, promotes the NPD1 biosynthesis 2.3- to 5-fold. When 50 mM NPD1 is added to Aβ1−42-exposed cultures, there is significant neuron and glia protection against apoptosis and cell shrinkage, including an overall morphology restoration resembling the control cells. The DHA and NPD1 treatments promote the upregulation of antiapoptotic genes Bcl-xl, Bcl-2, and Bfl-1A and downregulation of proapoptotic genes Bax and Bik.[128]

In the Neuro 2A cell culture, 25 μM DHA affected the phosphatidylserine (PS) accumulation. This PS increase promoted the faster translocation and phosphorylation of Akt without alteration of PI3K activation. Akt inhibits caspase-3 activity, indicating that translocation of Akt is essential for the PS-mediated survival signaling via the PI3K/Akt pathway.[129]

In aged rats, the oral administration of 300 mg/kg of DHA improves the performance of the RAM tasks, decreasing the number of reference memory and working memory errors. In contrast, the same treatment decreased only the reference memory errors in young rats. In both young and aged rats, the treatment increased the DHA content and DHA/arachidonic acid ratio in the hippocampus and cortex, indicating a direct relation with the enhanced hippocampus-dependent learning processes.[130,131]

On the other hand, the oral administration of EPA at 1.0 mg/g/day for 8 weeks promotes LTP in rat CA1.[132] Che et al. reported that the gavage administration of 150 mg/kg/day of EPA for 26 days increased the dendritic spine density and the expression of synaptophysin and PSD95 in CA3 of Aβ1−42-induced AD rats. The neuroplasticity improvement is attributed to increased BDNF/TrkB/CREB signaling activation.[133]

Che et al. showed that CHO cells transfected with APP751 and PSEN1 mutation reduced the extracellular Aβ1−40 and intercellular Aβ1−42 concentration by decreasing APP,

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PSEN1, and BACE1 protein expression after treatment with 20 μg/mL of EPA. In the SAMP8 mice, an accelerated aging model displaying age-related learning and memory disorders, a diet containing 1% of EPA promoted the reduction of soluble/insoluble Aβ1−40 and soluble Aβ1−42 levels, as well as APP and BACE1 RNA and protein levels in the hippocampus, which is directly associated with the spatial learning and memory function improvement reported in MWM.[134]

A meta-analysis reported that adults with mild memory complaints improved their episodic memory in response to DHA supplementation of >1 g/day, alone or combined with EPA.[135] In the OmegAD clinical trial enrolling 204 AD patients with an MMSE score ≥15, a daily intake of 1.7 g of DHA and 0.6 g of EPA for six months conferred a slower cognition decline, mainly the memory component in those with very mild dysfunction.[136] In the Framingham Heart Study, the participants were followed up with for 9.1 years until they developed all-cause dementia and AD. In this study, the association between the DHA intake of 0.18 g/d, the rising DHA levels in plasma, and the lower risk of developing all-cause dementia (47%) and AD (39%) are reported.[137]

Despite the promising findings of preclinical and epidemiological studies, no concrete effect of EPA or DHA on AD has been observed in clinical studies. Nevertheless, the results of these studies have generated much excitement to explore the potential benefits of omega PUFA supplementation in preventing cognitive decline in the at-risk elderly population.

5.7. Chlorogenic Acid. Chlorogenic acid is among the most available phenolic acid compounds in foods such as coffee, berries, cocoa, tea, apples, and others.[138] Chlorogenic acid is a set of *trans*-cinnamic esters and quinic acids, including coumaroyl-, feruloyl-, caffeoyl-, and dicaffeoyl-quinic acids.[139] Chlorogenic acid and its metabolites are BBB permeable and can be widely distributed in the brain.[140]

A wide range of preclinical studies support that chlorogenic acid exhibits anti-inflammatory, antioxidant, and potent neurotrophic activity, which may contribute to reducing the risk of neurodegeneration.[141] For example, a clinical trial demonstrated that consuming 1107.2 mg of chlorogenic acid daily for 12 weeks improves attention, executive functions, and other cognitive functions in people with mild cognitive impairment.[142]

On the other hand, the oral gavage of 40 mg/kg/day of chlorogenic acid for 180 days ameliorates the cognitive deficits of transgenic APP/PS1 AD mice. Microstructural analysis of the CA1 region revealed a higher cell density, absent of pyknosis and demyelination features in the hippocampus. The same research demonstrated a lysosomal activity enhancement via the mTOR/TFEB pathway, inhibiting excessive autophagy and attenuating the massive loss of CA1 neurons. This chlorogenic-acid-induced neuroprotection was also observed in the SH-SY5Y cell culture exposed to Aβ25−35.[143] Chlorogenic acid also prevents Aβ1−42 β-sheet formation, inhibiting Aβ aggregation. This property is mediated by the caffeoyl group, which might form covalent bonds with Aβ1−42 residues, interfering with forming Aβ oligomers and destabilizing Aβ42 aggregates.[144]

AChE and butyrylcholinesterase are key enzymes linked to AD that highly impact cholinergic neuronal function; increasing the concentrations of ACh and butylcholine in the synaptic cleft represents the primary treatment modality against AD cognitive impairment.[145] In this sense, Oboh et al. demonstrated the *in vitro* inhibition of both enzymes in a dose-dependent manner.[146] In a scopolamine-induced cognitive impairment mice model, 6−9 mg/kg of chlorogenic acid administration ameliorated the learning and memory deficits, as showed by the Y-maze, passive avoidance, and MWM tests. *Ex vivo* AChE activity assay showed an IC_{50} on enzyme activity at 97 μg/mL and reduced MDA levels in the hippocampus and frontal cortex by 71.94% and 47.65%.[147] Docking analysis supported the chlorogenic binding affinity to AChE and butyrylcholinesterase.[148]

Chlorogenic acid at 50 μM alleviated the neuron apoptosis by upregulating the expression of antiapoptotic proteins Bcl-xL and Bcl-2 and downregulating the levels of the proapoptotic factors Bax, C-caspase-3 and Cyto C in primary hippocampal neurons exposed to Aβ-25−35. This treatment also downregulated p-eIF2α, ATF4, and CHOP levels, suggesting an antiapoptotic effect mediated by inhibiting the endoplasmic reticulum stress state.[149] In aluminum-induced apoptosis in PC12 cells, the antiapoptotic effect of 10 μM chlorogenic acid is mediated by upregulating the Akt/GSK-3β signaling pathway, attenuating the accumulation of ROS and Aβ1−42.[150]

In summary, these findings provide a therapeutic direction for chlorogenic acid for AD, delaying the occurrence and progression of the disease and benefiting patients.

5.8. Luteolin. Luteolin is a flavonoid widely distributed in vegetables and fruits, such as celery, parsley, broccoli, onion leaves, carrots, peppers, cabbages, apple skins, and chrysanthemum flowers. It has been shown that this flavone possesses a variety of therapeutic activities, including antioxidant, anti-inflammatory, and anticancer.[151] Luteolin is BBB permeable and can be detected in brain tissues after oral intake. The access to the brain probably is through an adenosine triphosphate-binding cassette transporter.[152,153]

In an *in vitro* BBB model exposed to Aβ1−40 fibrils, the treatment of 3−30 μM luteolin increased the cell viability of the coculture in a concentration-dependent manner. The 10 and 30 μM treatments also protected the BBB function and ameliorated the BBB permeability, preserving the trans-endothelial electrical resistance value and reducing the flux of fluorescein. Moreover, the luteolin treatment reduced the proinflammatory cytokine levels, including TNF-α, IL-1β, IL-6, IL-8, and COX-2. The Western blotting analysis suggested that the mechanism of this inflammatory regulation involves the suppression of p38/MAPK activation, downregulation of IKK phosphorylation levels, and inhibition of NF-κB p65 nuclear translocation.[154]

Examination of CA1 of streptozotocin-induced AD rats demonstrated that 20 mg/kg of luteolin completely abolished the reduced thickness of the CA1 layer. This neuroprotective effect is associated with improved spatial learning and memory impairment in MWM.[155] In a Tg2576 AD mice model with traumatic brain injury, the intraperitoneal administration of 20 mg/kg/day of luteolin for 15 days significantly decreased the Aβ deposition, GSK-3β activation, tau hyperphosphorylation, and proinflammatory cytokines in the brain.[152]

The effects of luteolin in APP proteolysis were determined in mutant APP transgenic N2a cells. Luteolin diminished the Aβ peptide generation in >70% and >85% at 20 and 40 μM, respectively. Also, luteolin treatment lowered γ-secretase cleavage activity in a concentration-dependent manner. According to the authors, luteolin modulates the γ-secretase activity by the repression of GSK-3α/β phosphorylation-mediated inactivation, which in turn alters the PSEN1-

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mediated γ-secretase APP processing. This data suggests that luteolin exerts its antiamyloidogenic effects by downregulating γ-secretase activity via PSEN1 interference.[156] A proper mechanistic understanding of the therapeutic potential of luteolin is crucial for developing interventions aimed at preventing or ameliorating neurodegeneration.

5.9. Quercetin. Quercetin is a ubiquitous flavonoid present in numerous plants, fruits, and vegetables including apples, grapes, garlic, asparagus, onions, tomatoes, berries, capers, and red leaf lettuce.[157] Although its antioxidant capacity represents the most well-accepted pharmacological role, it is undoubtedly responsible for the modulation of several other effects, including neuroprotection.[158] The quercetin potential therapeutic approaches are limited because of its bioavailability, low aqueous solubility, and rapid gastrointestinal digestion.[159] However, some studies suggest that quercetin can partially penetrate through the BBB and accumulate in the brain.[160,161]

AD neuroprotection conferred by quercetin treatment has been observed in several preclinical studies. Shimmyo et al. reported a direct inhibition of the BACE-1 enzyme activity in a concentration-dependent manner. The treatment with 20 μM quercetin significantly decreased Aβ1−40 and Aβ1−42 levels in the primary neuron culture.[162] Quercetin possesses a structural requirement containing hydrophobic moieties essentials to fibril inhibition through hydrophobic interaction with the aromatic amino acids of β-sheet structures.[163] However, further studies are required to corroborate this effect.

Khan et al. showed an *in vitro* cell-free inhibition of the AChE and butyrylcholinesterase activities after quercetin exposition, preventing the degradation of acetylcholine.[164] The administration of 25 mg/kg of quercetin intraperitoneally every 48 h for three months increased the cell density in the hippocampal subiculum of a 3xTg-AD model, attenuating the extracellular βA deposition, the neurofibrillary tangles, astrogliosis, and microgliosis in the hippocampus and the amygdala. Additionally, quercetin reversed the learning and memory impairment.[165]

The amelioration of the cognitive impairment in the APPswe/PSEN1dE9 transgenic AD mouse treated with 20 and 40 mg/kg/day of quercetin for 16 weeks seems to be mediated by restoring the mitochondrial dysfunction via increasing the AMPK activity, mitochondrial membrane potential, and mitochondrial ATP levels, decreasing ROS production, and reducing Aβ plaque density. Activation of the AMPK cascade decreases the Aβ deposition through regulating APP processing and distribution and promoting the Aβ clearance.[166] The oral gavage of 40 mg/kg/day of quercetin for one month promoted the proliferation of progenitor cells in the dentate gyrus by upregulation of *BDNF*, *NGF*, *cAMP response element-binding protein* (*CREB*), and *early growth response protein 1* (*EGR-1*) genes in Aβ1−42-induced AD rats. This effect on neuroplasticity is associated with improved spatial learning and memory.[167]

Although quercetin showed neuroprotective efficacy in several preclinical studies, its low BBB penetrability limits its effectiveness in combating neurodegenerative disorders. Thus, developing strategies to enhance its bioavailability is necessary.

5.10. Resveratrol. Resveratrol is a polyphenol found in several plants such as grapes, peanuts, blueberries, bilberry, cranberry, and purple grape. The primary source of resveratrol is the fresh grape skin.[168]

Although resveratrol has a low bioavailability and poor aqueous solubility, some studies suggest that a chronic administration can increase its bioavailability and reach the brain at therapeutic concentrations.[169−171]

Resveratrol may protect against AD neuropathology and cognitive deterioration.[172] In a neural stem cells culture, 10 μM resveratrol normalizes the Aβ-induced inflammation, abrogating the secretion of TNF-α and IL-1β, as well as the mRNA transcripts of IKKα, IKKβ, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). In addition, the resveratrol ameliorated the oxidative stress state by upregulating SOD-1, NRF2, Gpx1, Catalase, GSH, and HO-1.[173] The 50 μM resveratrol treatment also prevented the Aβ-mediated proinflammatory effect on RAW 264.7 macrophages via the TLR4/NF-κB/STAT signaling pathway, inhibiting the IκB phosphorylation, activation of STAT1 and STAT3, and TNF-α and IL-6 secretion.[174]

On the other hand, 100 μM of resveratrol might inhibit around 90% of the β-sheet fibril formation and disaggregate preformed Aβ 1−42 fibrils.[175] The effect on Aβ clearance is probably mediated by SIRT1 expression. SIRT1 can regulate the Aβ metabolism by modulating APP processing; the loss of SIRT1 is closely related to the exacerbated production of Aβ.[176] Resveratrol also induces the overexpression of ADAM10 through SIRT1 activation, promoting the APP nonamyloidogenic processing and reducing the presence of Aβ deposits in a SAMP8 mice model. In the same study, the resveratrol 1 g/kg supplementation downregulates the tau hyperphosphorylation at serine 396 (a reliable marker of AD severity), dropping the CDK5 protein levels and p25/p35 ratio, indicating an inactivation of this kinase in the cortex.[177]

In an AD rat model induced with ibotenic acid, intraperitoneal administration of 20 mg/kg of resveratrol ameliorated the deleterious effects of the ibotenic acid. It is suggested that overexpression of SIRT1 normalizes the expression of NR2A/NR2B levels, mitigating acetylcholine receptor gene expression and acetylcholinesterase activity, reducing oxidative stress and significantly reducing the morphological changes in the hippocampus, thereby improving spatial memory.[178]

In an AD model induced by ovariectomy and chronic D-galactose administration, the treatment with 40 and 80 mg/kg of resveratrol decreased insoluble Aβ1−42 and NF-κB levels in the hippocampus. Also, this treatment appears to protect BBB integrity by reducing the expression of advanced glycation end products (RAGE), matrix metalloprotein-9 (MMP-9), and promoting the expression of Claudin-5. These results suggest that resveratrol helps protect against Aβ1−42-mediated neuroinflammation and prevents BBB impairment.[179]

5.11. Rosmarinic Acid. Rosmarinic acid is an ester of caffeic acid and is detectable mostly in plants of the Lamiaceae family, particularly the rosemary *Rosmarinus officinalis*. Rosmarinic acid has a variety of biological activities such as antioxidant, anti-inflammatory, antiapoptotic, and neuroprotective.[180] However, it has a low BBB penetration, limiting brain accumulation.[181] Therefore, different approaches must be considered to increase the availability to achieve higher concentrations in the brain with significant beneficial effects.

Although rosmarinic acid exhibits a low availability, its neuroprotective properties are notorious. For example, rosmarinic acid displayed a neurotrophic effect in PC12 cells. This effect is mediated partially by the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway.[182] Rosmarinic acid also protects PC12 cells against Aβ25−35-induced neurotoxicity, probably via Akt/GSK-3β/Fyn and the NRF2

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activation, a master regulator of the endogenous antioxidant response.[183] Mechanistically, rosmarinic acid enhances the nuclear translocation of NRF2 in a Fyn dephosphorylation-dependent manner. As a result, transcripts and protein levels of phase-II enzymes, such as HO-1, NQO1, GCLc, and TrxR, can be upregulated. Fyn is an important substrate of GSK-3β signaling, a pathway that plays an essential role in cellular growth, development, inflammation, and apoptosis processes.

Interestingly, 10 μM of rosmarinic acid promoted the activation of Akt, which increased serine 9 phosphorylation of GSK-3β, maintaining an inactive state.[183] This event prevents tau protein's fibrilization and β-sheet assembly, as observed by atomic force microscopy and molecular docking analysis. The molecular docking study revealed that rosmarinic acid could bind to the fibril-forming hexapeptide motif of tau ^{306}VQIVYK^{311}, destabilizing the β-sheet structure and inhibiting the subsequent tau aggregation.[184]

In Tg2576 AD mice fed a diet containing 0.5% rosmarinic acid for 10 months, there was an upregulation of genes of the dopaminergic synapse pathway, such as synthesis enzyme DOPA decarboxylase (Ddc) and dopamine receptor D2 (Drd2). In contrast, NMDAR activity, including downstream glutamatergic synapse-related genes AMPA2, 3, and 4 (alpha 2, 3, and 4) (Gria2, Gria3, and Gria4) and NMDA2B (epsilon 2) (Grin2b) was decreased.[181] This is very interesting because glutamate excitotoxicity, mediated by excessive NMDAR activity, is one of the neurodegenerative processes underlying AD. In an acute Aβ1−42-induced AD mouse, the 16 mg/kg rosmarinic acid administration for 15 days improved the hippocampal neurogenesis, increasing the Ki67/NeuN/DCX positive cell density. The treatment also enhanced the expression of synaptic markers synaptophysin, synapsin II, and III.[185] These findings were further confirmed in the same mouse model. The same rosmarinic acid treatment (16 mg/kg) for 15 days promoted a substantial reduction in Aβ plaques and increased cell density of DCX+/Ki67+ cells, indicating promotion of the hippocampal neurogenesis.[186]

The findings suggest that rosmarinic acid may be a promising candidate for treating AD.

5.12. Probiotics/Postbiotics. Probiotics are "*live microorganisms that confer a health benefit to the host when administered in adequate amounts*". Most probiotics are generally recognized as safe and considered nutraceuticals that promote intestinal health and modulate the host immune system.[187]

The composition of the gut microflora, which in turn produces signaling molecules such as short-chain fatty acids (SCFAs), biogenic amines (such as serotonin, histamine, and dopamine), hormones (such as ghrelin and leptin), and other amino-acid-derived metabolites such as GABA and tryptophan, can regulate the CNS functions and directly influence cognition.[188] Indeed, aging strongly impacts gut microbiota composition, favoring the development of pro-inflammatory bacteria. Many studies have shown that AD patients exhibit a significant decrease in *Firmicutes*, accompanied by higher *Proteobacteria*, *Gammaproteobacteria*, and *Enterobacteria* abundances. It has been suggested that gut dysbiosis is a common basis for a broad spectrum of age-related pathologies, including the early stages of AD pathogenesis, because these bacteria can alter key molecules involved in synaptic plasticity such as NMDA and serotonin receptors, BDNF, and CREB.[188] Also, the low-grade inflammatory state enhances immuno-senescence, oxidative stress, cytokine secretion, and neuroinflammation.[189] Given that the gut microflora is connected to the brain through the afferent enteric nervous/autonomic nervous system and the vagus nerve, the paracrine effects of probiotic organisms could trigger neuroprotective activities.[190]

Evidence suggests that probiotics can exert an anti-AD effect by increasing the expression of CREB and BDNF. CREB is a cellular transcription factor that is highly associated with learning and long-term memory. BDNF, regulated by CREB, displays important roles in synaptic plasticity and, consequently, in memory by enhancing the proliferation of neural precursor cells and the generation of newborn neurons and supporting the survival of neurons.[187] For instance, the oral administration of 1×10^{10} CFU of *Lactobacillus pentosus* var. plantarum C29 increases the hippocampal expression of p-CREB and BDNF in a scopolamine-induced AD model. The increment of these factors is associated with improving Y-maze and MWM performance.[190]

In a 3xTg-AD mouse model, a 16-week supply of 200bn bacteria/kg/day of a probiotic formulation with *Streptococcus thermophilus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subs bulgaricus, and *L. brevis* significantly recovered the decrease in SIRT1 levels. p53 is one of the targets of SIRT1 and, upon deacetylation, represses the p53-dependent apoptosis. SIRT1 specifically decreases the acetylated-p53 levels. SIRT1 is directly involved in oxidative stress regulation, and in this case, the probiotic formulation increased the activity of the antioxidant enzymes GST, GPx, SOD, and CAT, mediated probably by SIRT1 upregulation, restoring basal levels of the carbonyls, 3-NT, and 4-HNE levels. This data demonstrated that probiotic formulation could preserve the brain redox homeostasis in AD.[191]

Another underlying probiotic neuroprotective mechanism might be the production of SCFA, which can reach the brain, downregulate the pro-inflammatory cytokine production, and modulate the microglia M1 phenotype.[192] The supplementation with 200 μL of *Clostridium butyricum* (1×10^9 CFU mL^{-1}) ameliorated the cognitive deficits and the Aβ deposition in an APP/PS1 AD mouse model. Moreover, *C. butyricum* treatment suppressed the microglial M1 phenotype and the production of IL-1β and TNF-α. The *in vitro* assays in Aβ-induced BV2 cells showed that butyrate could suppress the M1 phenotype by inhibiting COX-2 and NF-κB p65 phosphorylation.[193]

Short-chain fatty acids also interfere with Aβ aggregation. Ho et al., with photoinduced cross-linking of unmodified protein analysis, revealed that valeric acid, butyric acid, and propionic acid interfere with initial Aβ1−40 and Aβ1−42 peptide assembly.[194] Despite promising results showing the influence of gut microbiota in neurological and psychiatric pathologies, the mechanisms of action and the effects of probiotics remain largely unknown, and several gaps must be clarified.

5.13. Alpha-lipoic Acid. On the other hand, alpha-lipoic acid, also known as 1,2-dithiolane-3-pentanoic acid or thioctic acid, is a naturally occurring dithiol compound synthesized *de novo* in the mitochondria and absorbed from the diet, such as red meat, carrots, beets, spinach, broccoli, and potatoes. The alpha-lipoic acid and its reduced form, dihydrolipoic acid, readily cross the BBB and exhibit antioxidant, anti-inflammatory, and antidiabetic activities.[195] Studies have found that alpha-lipoic acid-treated AD patients showed a slowed global cognitive decline, while the underlying mechanism remains

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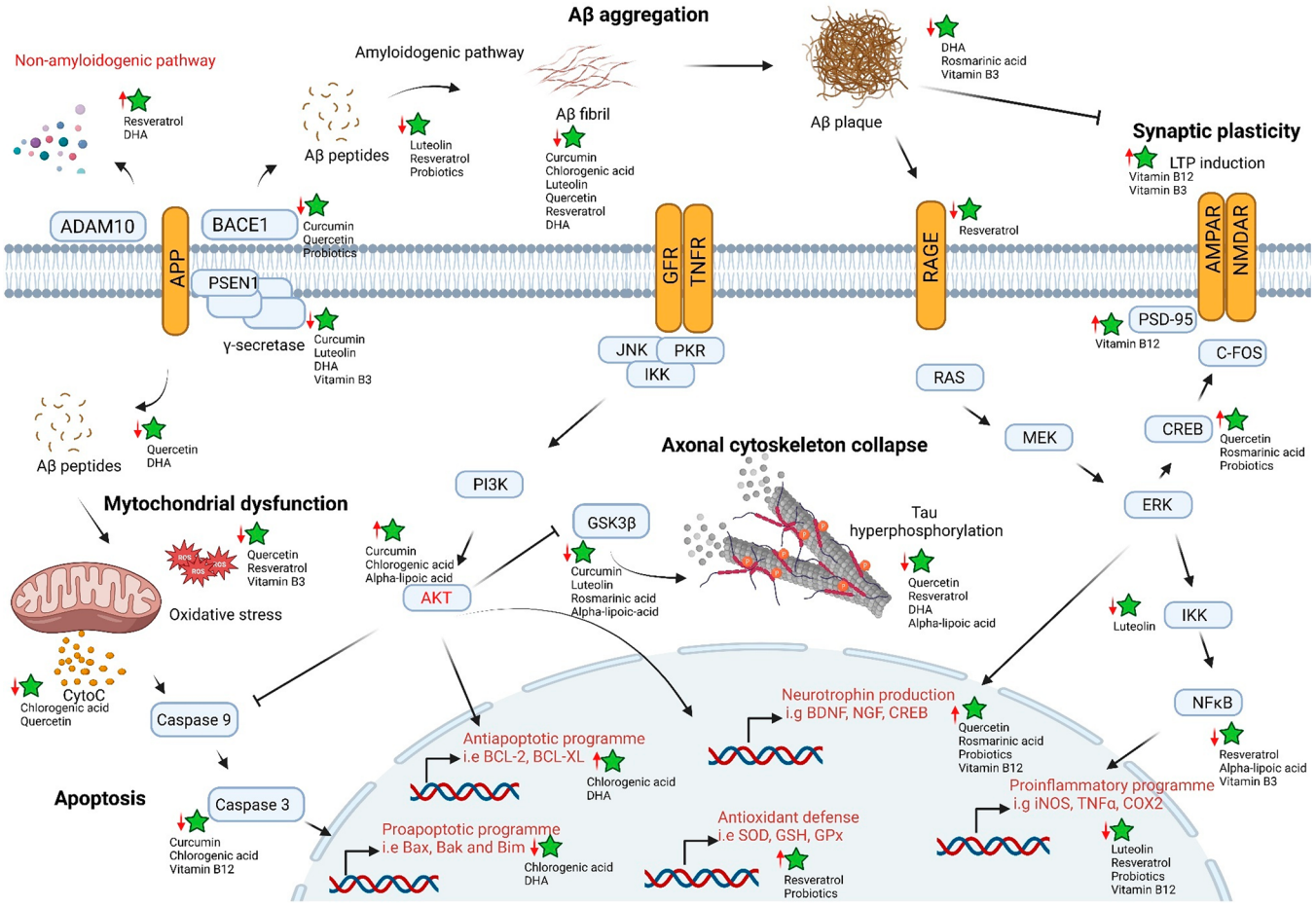

Figure 3. Nutraceutical-mediated signaling pathways underlying some neuroprotective processes. The brain accumulation of nutraceuticals leads to the activation of pathways such as the PI3K/Akt signaling pathway, which induces the expression of antiapoptotic genes and downregulates the proapoptotic program. The PI3K/Akt signaling pathway also promotes neurotrophin production (growth factors) and other elements essential in neuronal differentiation, maturation, and survival. On the other hand, the PI3K/Akt signaling pathway modulates the tau hyperphosphorylation ratio, modulating the axon stability and transport. Most nutraceuticals significantly affect the Aβ peptide aggregation, inhibiting the activation of proinflammatory processes and apoptosis and demonstrating their multimodal neuroprotective potential. Up arrows: denote upregulation of activity and expression. Down arrows: denote downregulation of activity and expression. ADAM10 = A disintegrin and metalloproteinase domain-containing protein 10. APP = Amyloid precursor protein. Aβ = Amyloid beta. BACE1 = Beta secretase 1. PSEN1 = Presenilin 1. GFR = Growth factor receptor. TNFR = Tumor necrosis factor receptor. RAGE = Receptor for advanced glycation end products. LTP = Long-term potentiation. GSK-3β = glycogen synthase kinase 3 beta. COX-2 = Prostaglandin-endoperoxide synthase 2. TNFα = Tumor necrosis factor-alpha. iNOS = Inducible nitric oxide synthase. SOD = superoxide dismutase. GSH = Glutathione. GPx = Glutathione peroxidase. BDNF = Brain-derived neurotrophic factor. NGF = Nerve Growth Factor.

largely unknown.[196] For instance, 3xTg-AD mice fed 0.23% (w/v) alpha-lipoic acid in drinking water for 4 weeks showed an increased brain glucose uptake, activated the insulin receptor substrate, and enhanced the activation of the PI3K/Akt signaling pathway. An important downstream target of activated Akt is GSK-3β, phosphorylated (and inactivated) at Ser9, which is widely associated with hyperphosphorylation of the protein tau. The alpha-lipoic acid feeding increased the LTP electrophysiology in old 3xTg-AD mice.[197] An *in vitro* assay showed that 100 μM alpha-lipoic acid rescued the PC-12 cell viability inhibition and repressed the Aβ25−35-induced apoptosis. After the apha-lipoic acid intervention, the levels of Bax and caspase-3 were significantly lower, and the expression of Bcl-2 was higher. In addition, alpha-lipoic acid reduced NF-κB activity. Interestingly, alpha-lipoic acid can reactivate the Wnt pathway; the expression levels of Frizzled2, p-GSK-3β, and total β-catenin were significantly increased, while the expression levels of total GSK-3β and p-β-catenin were significantly decreased. This data demonstrates that alpha-lipoic acid rescued Aβ25−35-induced cytotoxicity through the Wnt-β-catenin pathway.[195]

5.14. Vitamin B12. Vitamin B12 is a water-soluble vitamin that humans obtain from animal-sourced foods such as meat, dairy, eggs, and fish.[198] It acts as a cofactor in DNA synthesis. Particularly in the CNS, it has a key role in myelin and neurotransmitters synthesis and membrane phospholipids, essential for maintaining the integrity of the nervous system.[199] In a randomized, single-blinded, placebo-controlled trial in patients diagnosed clinically with probable AD, the daily supplementation with folic acid (1.2 mg/day) and vitamin B12 (50 μg/day) for six months had a beneficial effect on the Montreal Cognitive Assessment test, naming scores, orientation scores, and Alzheimer's Disease Assessment Scale-Cognitive score of attention.[200] In contrast, in another randomized, double-blind controlled clinical trial in patients with moderate AD (Mini-Mental State Examination scores

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between 14 and 26), the daily high-dose supplementation of 5 mg/day of folate, 25 mg/day of vitamin B6, and 1 mg/day of vitamin B12 during 18 months had no beneficial effect on the primary cognitive measure.[201] In another clinical trial conducted by Douaud et al. on patients with MCI, the daily high-dose B-vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, and vitamin B12 0.5 mg) over 2 years slowed shrinkage of posterior brain regions, including the bilateral hippocampus and parahippocampal gyrus, retrosplenial precuneus, lingual and fusiform gyrus, as well as the cerebellum.[202]

In a scopolamine-induced AD rat model, the intraperitoneal administration of 2 mg/kg of vitamin B12 reduced the scopolamine-induced hippocampal neuroinflammation and apoptosis, attenuating the overexpression of caspase-3 and cyclooxygenase-2 and increasing the nPSD-95, neurexin 1, and neuroligin protein levels.[203]

5.15. Vitamin B3. Vitamin B3, also known as nicotinic acid and nicotinamide and collectively as niacin, is a water-soluble vitamin and an essential precursor for the endogenous formation of nicotinamide adenine dinucleotide. Although niacin can be produced in the liver from tryptophan through the kynurenine pathway, the main source of this vitamin is dietary foods, particularly meat, grains, and milk-based products.[204] Interestingly, dietary niacin may protect against AD and age-related cognitive decline, as suggested by a prospective population-based study, Chicago Health and Aging Project (CHAP), where authors found that a higher food intake of niacin was associated with a slower annual rate of cognitive decline.[205] In another study, the daily oral administration of 100 mg/kg of FDA-approved niacin in 5xFAD mice for 30 days reduced plaque burden and neuronal dystrophy, attenuated neuronal loss, and saved working memory deficits, demonstrating a robust therapeutic effect of niacin. The authors suggested that the neuroprotective activity of niacin is probably mediated by the activation of the HCAR2 in microglia, which leads to microglia proliferation, lower Iba-1 expression, and an enhanced Aβ uptake but not overall changes in brain cytokine concentration.[206] The nicotinamide mononucleotide also counteracts the amyloid toxicity by reducing the expression of APP, NF-κB, and PSEN1, accompanied by the upregulation of Sirt1 and the attenuation of ROS generation and by improving neuron survival and LTP both in organotypic hippocampal slice cultures, and an Aβ1−42-induced AD rat model also prevented the Aβ1−42 oligomer-induced impairment of spatial learning and memory.[207,208] Moreover, a 12 mM treatment of vitamin B3 for six months reduced the DNA damage, neuroinflammation, and cell death of hippocampal neurons, increasing the adult hippocampal neurogenesis and improving the learning, memory, and motor function in a 3xTgAD mouse model.[209]

These studies underlined the protective effects of vitamin B3 against Aβ-induced neurotoxicity.

In summary, all these findings revealed that nutraceuticals modulate signaling pathways and mechanisms underlying some neuroprotective processes (Figure 3) and could rescue the AD-like alterations characterized by accumulated amyloid plaques, neuroinflammation, impaired learning and memory, and neurogenesis, reiterating their potential as promising agents for food-based strategies for AD prevention and cognitive decline management.

6. PHARMACOLOGICAL CONSIDERATIONS TO EVALUATE THE NEUROPROTECTIVE POTENTIAL OF NUTRACEUTICALS

A nutritional approach to preventing or delaying AD progression or other neurodegenerative processes represents a safe option, is highly cost-effective and easily administrated, and can be a socially acceptable intervention. In line with this, nutraceuticals have gained popularity due to their potential to boost intelligence, concentration, and memory among cognitive functions.[210]

However, the incomplete evidence of its effectiveness and the social consequences of long-term intake must be considered since, despite its natural origin and system tolerability, some complications can occur, mainly at higher concentrations.[211] There is a misconception regarding the categorization of herbal medicinal products as "safe" because they are derived from a "natural" source; the truth is that "safety" and "natural" are not synonymous.[212] Examples of this misconception are the controversial cardiovascular effects of high caffeine intake[213] and the contraindicated use of Ginkgo extracts in patients with hypertension or patients on anticoagulant therapy due to the caffeine capacity to modulate the blood flow and Ginkgo properties to inhibit platelet-activating factor and alter bleeding time.[212] Consequences of the inadequate knowledge of their mode of action, potential adverse reactions, contraindications, and interactions with existing pharmaceutical drugs or comorbidities will result in a low or nonbioactivity with health safety concerns.[212]

Thus, before nutraceutical-based products become routinely consumed to prevent or manage age-related cognitive decline, some issues, including safety doses, standardization of active constituents, and evaluation of combinations for the best response, must be addressed. Several nutraceutical compounds have not been evaluated similarly or with the same rigor to demonstrate the ascribed potentiating effect. Indeed, little evidence of the mechanism of action of some compounds is only based on *in vitro* assays, without the *in vivo* evaluation to determine compounds' pharmacokinetic and toxicologic concerns and obviously to corroborate the *in vitro* results. To achieve a scientific understanding of the underlying mechanism of a drug or compound, it is recommended that *in vitro* studies be conducted early in the development process to determine the criteria for an *in vivo* study with a translational approach.[214] The key objectives of the *in vivo* testing broadly include (I) providing concrete evidence that the predicted *in vitro* effects of the compound can be achieved by a determined administration route; (II) establishing the safety and effective starting doses and concentration regimens for clinical trials; and (III) determining suitability for human administration based on acceptable risk assessment.[215]

Regarding clinical research, to avoid discrepancies between trials, future research should focus on experiments with more diverse human groups in terms of demography, age, health, gender, or weight. Defining the patient population with any needed stratification strategies and diagnostics validated before initiating the study is essential.[216] Test duration is also a key parameter to consider because, as mentioned above, the action mechanism of nutraceuticals depends on time and accumulation in the target organ. Furthermore, advanced neuroimaging assessment should be frequently used in these studies to confirm or refute the potential beneficial effects.[210]

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On the other hand, bioavailability is important to evaluate the potential benefits of nutraceuticals with neuroprotective potential.[217] Understanding the metabolic fate of compounds could increase the credibility of their proposed neurological benefits.[143] The presence of the BBB represents a considerable challenge for brain targeting for many therapeutic compounds because this severely restricts the therapy of many CNS diseases, including AD.[218] Therefore, establishing a neurologic nutraceutical effect is challenging due to the BBB pass because they must reach an optimum brain concentration to stimulate a determined mechanism.[219] In this context, the nutraceutical must be capable of passing the BBB in either the intact form or their metabolites and accumulating in the brain parenchyma.

Some examples of novel formulations that have been applied to improve bioavailability include nanoparticulate systems, including nanoencapsulation, liposomal encapsulation, micellization, and complexation with phospholipids.[220] The best strategies for brain delivery are liposomes and micelles.[221] Liposomes are the drug-delivery system of choice for systemic delivery. Their lipid bilayer comprises phosphatidylcholine, sphingomyelin, or glycerophospholipids, which can accommodate hydrophobic compounds while in the aqueous core.[222] Moreover, the bilayer conjugation/decoration antibodies, transferrin, insulin, and targeting glucose transporters, among other cell-penetrating peptides, are strategies used to improve drug bioavailability and tissue penetration with outstanding results.[223]

Micelles are formed by dispersing low molecular weight amphiphiles in an aqueous environment to aggregates and form stable spheroidal nanostructures with a hydrophobic core and hydrophilic surface,[224] which can increase the encapsulation of hydrophobic compounds by 1000-fold.[225] Similarly to liposomes, micelles can be conjugated with particular targeting ligands to improve brain delivery.

The intranasal administration represents a very attractive approach because this route of transportation encompasses the ability for the compound delivery directly into the brain, exploiting the olfactory as well as trigeminal nerve pathway, bypassing BBB, improving site-specific delivery. and avoiding systemic side effects.[226] However, some key factors that will determine the efficacy of delivery are the delivery to the olfactory area as opposed to the respiratory region, the dose volume, the retention time at the nasal mucosal surface, penetration of nasal epithelia, and a reduction of compound metabolism in the nasal cavity.[227] In this context, using nanoparticles, penetration enhancers, and matrices like chitosan will improve the delivery to the brain via the nose-to-brain route.

7. CONCLUSIONS

The population and the medical community are considering the incorporation of nutraceuticals into functional foods or their use as supplements with nonpharmacological approaches in the prevention and management of several illnesses, including age-related conditions and chronic neurodegenerative diseases. Nutraceuticals are apt for preventing and treating such disorders because of their nontoxic, non-habit-forming, and efficient bioactivities for promoting neurological well-being. The experimental data described herein show various nutraceuticals' beneficial effects, particularly in AD, highlighting their neuroprotective, neuroplasticity, and immunomodulant activity. However, many high-quality studies are still needed to evaluate the therapeutic potential of these nutraceuticals. For example, determining the therapeutic compound concentration in the target zone is essential, particularly considering the bioavailability after ingestion and other dietary factors, such as formulation and composition of the overall long-term diet. Furthermore, knowledge of the 3D structures of molecules and their targets is now playing a major role in all stages of drug discovery. Integrating computational and experimental strategies has been of great value in identifying and developing novel promising compounds and exploring the ligand conformations adopted within the binding sites of macromolecular targets. With these analyses, the doses and the effectiveness of the compounds can be optimized. Also, it is important to consider that synergistic mechanisms between food components are responsible for neuroprotective effects, as shown by certain nutrients and nutraceuticals. Clarifying the safety, tolerability, and mechanism of action of these compounds on a large scale of subjects would help us to choose better nutraceuticals to prevent and manage neurodegenerative pathologies.

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