Review Article

Therapies for Prevention and Treatment of Alzheimer’s Disease

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Alzheimer’s disease (AD) is the most common cause of dementia associated with a progressive neurodegenerative disorder, with a prevalence of 44 million people throughout the world in 2015, and this figure is estimated to double by 2050 [1]. Most people with AD (over 95%) have sporadic or late-onset AD (LOAD), a multifactorial disease in which environmental factors and genetic predisposition contribute to the pathology [2]. The other form of AD, familial or early-onset AD (EOAD), corresponds to less than 5% of the AD population and is due to mutations in any of the three following genes: (a) the amyloid precursor protein (APP) gene on chromosome 21, (b) presenilin 1 (PSEN-1) gene on chromosome 14, and (c) presenilin 2 (PSEN-2) gene on chromosome 1 [3–5]. The classification of AD is based on clinical criteria including medical history, physical examination, laboratory tests, neuroimaging, and neuropsychological evaluation [6].

1. Introduction

Alzheimer’s disease (AD) is an age-related, progressive, and irreversible neurodegenerative disorder characterized by cognitive and memory impairment, and it is the most common cause of dementia in older adults. The estimated prevalence of this disease in 2015 was 44 million people throughout the world and it is estimated that this figure will double by 2050 [1]. Most people with AD (over 95%) have sporadic or late-onset AD (LOAD), a multifactorial disease in which environmental factors and genetic predisposition contribute to the pathology [2]. The other form of AD, familial or early-onset AD (EOAD), corresponds to less than 5% of the AD population and is due to mutations in any of the three following genes: (a) the amyloid precursor protein (APP) gene on chromosome 21, (b) presenilin 1 (PSEN-1) gene on chromosome 14, and (c) presenilin 2 (PSEN-2) gene on chromosome 1 [3–5]. The classification of AD is based on clinical criteria including medical history, physical examination, laboratory tests, neuroimaging, and neuropsychological evaluation [6].

2. Pathogenesis and Clinical Features in AD

The neuropathological features of both forms of AD are characterized by the abnormal extracellular accumulation of amyloid-β peptide (Aβ) in amyloid plaques and tau protein aggregated in intracellular neurofibrillary tangles (NFTs). There are epidemiological, clinical, and experimental data that sustain several hypotheses of AD pathogenesis: (1) the amyloid cascade hypothesis proposes that the accumulation of Aβ as neuritic plaques, diffuse plaques, or oligomeric forms in the brain is the main pathogenic event [7]; Aβ plaques are composed primarily of Aβ peptides generated by the amyloidogenic pathway [1]. The amyloidogenic pathway produces amyloid peptides of 39–43 amino acids that are proteolytically derived from the sequential enzymatic action of β- and γ-secretases on amyloid precursor protein (APP) distributed in the neuron membrane [8, 9] while the nonamyloidogenic pathway produces nontoxic αAPP fragments that are generated by α-secretase action [5]; (2) the tau hypothesis suggests hyperphosphorylation of tau as the primary event [10]; (3)
Figure 1: The etiology of AD has been classified in different hypotheses.

the cholinergic hypothesis proposes that there is a reduction in the activity of choline acetyltransferase and acetylcholine levels in areas such as the cerebral cortex [11]; (4) the mitochondrial cascade hypothesis points to impairment of brain mitochondria as the first pathogenic event leading to neurodegeneration [6]; (5) the metabolic hypothesis holds that the disease is caused by changes in metabolic processes such as obesity, diabetes, and hypercholesterolemia [12]; finally, (6) the vascular hypothesis presents the reduction of cerebral blood flow as the main characteristic [13] (Figure 1). The clinical diagnosis of AD requires a neuropsychological evaluation according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V criteria) and of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA criteria).
Also, with the progression of the disease, laboratory tests such as oxidative stress products, Aβ levels, oxyesters including 24- and 27-hydroxycholesterol, and proinflammatory cytokines in blood and CSF [6, 7, 14], along with neuroimaging studies such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), should be performed [15]. The diagnosis is “probable AD” if cognitive impairment is shown in neuropsychological tests or “possible diagnosis of AD” if there are some positive results of biochemical and neuroimaging tests [2, 16]. It is important to note that, in most cases, but not always, impairment of cognitive domains in which the clinical diagnosis is AD correlates with the neuropathological features of postmortem brains with AD [2].

The disease is characterized by pathological changes, including hypometabolism [17], blood-brain barrier (BBB) disruption [13], oxidative stress, mitochondrial impairment [18], and neuroinflammation [19], which can be generated by several metabolic disorders considered strong risk factors for AD. The inflammatory response by activated microglia and astrocytes leading to the production of cytokines and reactive oxygen species (ROS) with associated neuronal damage is another important feature of AD pathogenesis [2].

2.1. Risk Factors for LOAD. To minimize the possibility of a future with a high percentage of people with AD, it is necessary to determine which are the factors that influence this disease. In recent years, a significant number of epidemiological studies related to the definition of risk factors for AD have been published. Risk factors for LOAD are classified as susceptibility genes and environmental factors [16]. LOAD has a strong genetic component, namely, apolipoprotein E (ApoE), the most widely studied genetic risk factor for AD. ApoE is produced by the liver, macrophages, and the central nervous system (CNS) [20]. In the CNS, it is produced by astrocytes and microglia; however, neuronal expression of ApoE can be induced in response to stress or neuronal damage under certain pathological conditions (stressors and injurious agents) [21].

The main metabolic and nongenetic risk factors include hypercholesterolemia [22, 23], obesity [24, 25], hyperhomocysteinemia [2], hypertension [26], and type 2 diabetes mellitus (T2DM) [27, 28].

2.1.1. Genetic Susceptibility to LOAD. Apolipoproteins are a family of proteins involved in lipid homeostasis, which bind and transport lipids through the lymphatic and circulatory systems [29]. It has been shown that ApoE has a strong relationship with the pathogenesis of LOAD [21]. ApoE is a glycoprotein of 299 amino acids and its structure varies depending on genetic polymorphisms [30]. The three major ApoE isoforms differ from each other by amino acid substitutions at positions 112 and 158 where the wild-type ε3 allele is Cys112 and Arg158, while the ApoE ε2 allele carries the Cys112 and Cys158 polymorphism, and the ApoE ε4 allele contains Arg112 and Arg158 [31]. A deficiency in ApoE can result in modifications in its structure and function [32], and an alteration of the function of ApoE results in an increase of plasma levels of cholesterol and triglycerides [29].

The ApoE ε4 allele is the most important genetic risk factor [29] and it was probably first identified as a risk factor for LOAD, by the initialization and acceleration of Aβ accumulation in the brain [33]. There are numerous studies that have replicated this association in different ethnic groups including African Americans [34], Latinos [35], Asians [36], and Caucasians [37, 38]. One study of the Chinese Han population showed that both the ApoE ε4 allele and the CYP17A rs743572 allele (a key regulatory enzyme in the steroidogenic pathway) increase the risk of LOAD [36]. Furthermore, a strong association has been reported between the ApoE ε4 allele and dementia due to AD pathology, but not with vascular dementia [39]; however, another study produced conflicting results showing that the ApoE ε4 allele has a strong relationship with vascular dementia through chronically degenerating white matter in the brain [40]. The mechanisms underlying the association between vascular risk factors and white matter damage are not fully understood.

Genome-wide association studies (GWAS) have identified polymorphisms in several genes that are associated with AD risk, including ABCA7 (which transports substrates across cell membranes), CLU (a stress-activated chaperone protein that functions in apoptosis, complement regulation, lipid transport, membrane protection, and cell–cell interactions), CRI, CD33 (involved in clathrin-independent receptor-mediated endocytosis), CD2AP (implicated in cytoskeletal reorganization and intracellular trafficking), EPHAI, BIN1 (involved in regulating endocytosis and trafficking, immune response, calcium homeostasis, and apotosis), PICALM (involved in clathrin assembly), and MS4A (associated with the inflammatory response) [41].

2.1.2. Metabolic and Nongenetic Risk Factors for LOAD

1) Hypercholesterolemia. High serum and plasma cholesterol levels have been suggested as risk factors for AD [42, 43]. In the adult brain, primary cholesterol synthesis occurs in astrocytes and in lesser proportion in neurons; cholesterol is transported into the brain by local high density lipoproteins (HDL) [22]. Low-density lipoprotein (LDL) levels are elevated in cardiovascular diseases and increased oxidation and nitration-related systemic modifications are observed in LDL (oxLDL) in hypercholesterolemia [44].

In an experimental cell-based study, cholesterol distribution within membrane is seen to have effects on APP metabolism, trafficking of APP, activities of β-, γ-, and α-secretases, and Aβ synthesis [45, 46]. The mechanism by which cholesterol deregulates Aβ metabolism has not yet been elucidated, but several studies suggest that changes in cholesterol levels alter the cell membrane [44] due to impairment of lipid rafts, which are membrane microdomains focused on protein trafficking [47], signal transduction [48], and neurotransmission [47, 49]. The γ-secretase cleavage of APP, the final step in Aβ peptide production, occurs in these cholesterol-rich lipid rafts [44].

In a recent study, it was suggested that inhibition of cholesterol biosynthesis, using AY9944, which blocks the final step of cholesterol biosynthesis, reduces γ-secretase activity
associated with the generation of Aβ peptides [50]. Moreover, low cholesterol levels increase α-secretase activity on APP [51], promoting neuroprotection by increasing levels of α-AUG fragments, which are involved in neurotrophic functions [52]. In another study, it was reported that plasma cholesterol levels in AD patients were elevated by about 10% compared to control subjects [53], though these levels have been linked to the burden of ApoE [54].

The brain is capable of metabolizing cholesterol excess to oxysterols, which are the product of cholesterol oxidation [23]. Several studies have reported some oxysterols including 6-cholesten-5α-hydroperoxide, 7-oxocholesterol (7-ketocholesterol), 7β-OHC (7β-hydroxycholesterol), 7-dehydrocholesterol, 27-OHC (27-hydroxycholesterol), and 25-OHC (25-hydroxycholesterol) [14, 44, 55]. The intermediates 24-OHC and 27-OHC are commonly found in the plasma of patients with AD, thus, these metabolites are very promising as biomarkers in AD patients [56].

(2) Hyperhomocysteinemia. Increased levels of homocysteine depend on several factors such as age, genetics, lifestyle, and sex [57]. The causes of this risk factor in the population are multiple and include both nongenetic and genetic mechanisms. Deficiency of vitamin B12, folate, and pyridoxine may be responsible for hyperhomocysteinemia in the general population [58]. Pharmacological data show that homocysteine stimulates lipid accumulation [57], inflammatory processes, and N-methyl-D-aspartate receptor (NMDA) activation [59]. NMDA receptors have been shown to mediate downstream effects of the Aβ peptide in AD models and the pharmacological inhibition of this receptor’s activity deletes the pathological effect of Aβ [60, 61].

(3) Hypertension. Several studies have linked hypertension to brain atrophy and the generation of NFTs; therefore, an association between hypertension and AD is conceivable [62]. However, this association is complex and differs with age. It has been shown that high blood pressure in middle age is associated with an increased risk of AD [63], while other studies found no association between hypertension in the elderly and dementia [26, 64].

(4) Obesity. Obesity is a precursor condition for numerous disorders, including hypercholesterolemia, cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus (T2DM) [17]. This is due to changes in lifestyle, for example, low levels of physical activity, an unbalanced diet, and overnutrition, leading to inflammatory and oxidative stress processes, altering the metabolic pathways necessary for homeostasis [24].

There are several studies linking obesity to increased cognitive decline and AD risk [12, 65, 66] and to central nervous system inflammation [67, 68] through an increase in proinflammatory cytokines [69]. Studies in both human and animal models suggest that particular dietary constituents may be important in modulating AD risk [70]. For example, a diet rich in fatty acids is associated with obesity and thus with a higher risk of AD [71, 72]. It was recently reported that a high-fat diet causes damage similar to that observed in Alzheimer’s pathology, such as potentiation of β-secretase processing of APP [73], cognitive impairment [74], and mitochondrial damage associated with insulin resistance [75].

Numerous studies have suggested that obesity in midlife is related to a greater risk of subsequent dementia [76, 77], while in a meta-analysis of longitudinal studies it was reported that obesity in late life is not always associated with AD [66]. In contrast, a recent cohort study reported that midlife obesity (measured as body mass index or BMI) reduces dementia risk [78]. The BMI is an obesity index and some studies have shown an association between BMI and AD, with a significant increase in risk for obese individuals [76]; however, adiposity may be a more important factor and predictor of AD risk than BMI [70].

Adiposity is defined as an increase in total body mass by adipose tissue alterations [79]. Notably, the effect of adiposity on AD incidence has been associated with the consequences of chronic hyperinsulinemia on the blood-brain barrier [80]; thus, it is known that midlife obesity is one of the main factors contributing to the development of type 2 diabetes [79]. It is known that adipose tissue produces regulatory molecules called adipokines, which have autocrine, paracrine, and exocrine effects [77]. Adipokine dysregulation has been correlated with AD, producing changes in proinflammatory adipokines such as an increase in TNF-α, interleukin 6 (IL-6), and leptin; a decrease in anti-inflammatory adipokines such as adiponectin; decreased brain derived neurotrophic factor (BDNF); and increased plasminogen activator inhibitor-1 (PAI-1) and angiotensin (AGT) [81, 82]. Adipokines are able to cross the BBB and activate their specific receptors in central nervous system regions such as the hippocampus [81]. The most important adipokines mentioned in the literature with regard to AD are leptin and adiponectin.

Leptin is a 16kDa adipocyte-derived hormone that is secreted in proportion to the adipose stores, with high circulating plasma levels in obesity [83] resulting in leptin resistance, which boosts tau phosphorylation, in turn increasing Alzheimer pathology [84]. In physiological conditions, leptin generates a reduction of body weight by suppressing appetite or increasing energy balance. Several studies have demonstrated that leptin has beneficial effects through the modulation of memory by regulating both long-term potentiation and synaptic plasticity [79]. In a study of peripheral blood adipokines in patients with AD, it was reported that low leptin levels increase AD risk [85]. However, other studies have reported that high leptin levels are associated with a high risk of dementia [86]. Existing data provide evidence that obesity may interfere with the neuroprotective effect of leptin on the brain, possibly by leptin resistance [87]. Leptin resistance is induced by several defects involving the leptin receptor, in BBB transport, cellular transduction, the induction of feedback inhibitors, and biological systems with changes in cellular networks [84]; overactive leptin receptor signaling results in its intense phosphorylation via the (Janus kinase) JAK-2/STAT-3 pathway, which improves suppression of cytokine signaling 3 (SOCS-3) expression [88]. SOCS-3 is a feedback inhibitor of leptin signaling and has been associated with leptin resistance in obesity. Interestingly, leptin signaling
downstream effectors such as adenosine monophosphatase-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) regulate the activity of glycogen synthase kinase 3β (GSK-3β) and BACE1, which are involved in tau phosphorylation and Aβ genesis [12, 89].

In addition to its effects on the AMPK pathway, leptin signaling results in the activation of the energy sensor sirtuin-1 (SIRT1), reducing the acetylation of the p65 subunit of NF-κB and leading to a reduction of tau phosphorylation and of Aβ1-40 production [89–91]. Moreover, it has been reported that AMPK and SIRT brain activity is inhibited by prolonged states of positive energy balance, as in obesity [92]. Leptin, as a trophic factor, activates different cascades and, for example, is critical in spine formation in hippocampal neurons; in culture, this is promoted through the phosphorylation of calcium/CaM-dependent kinase γ (CaMKI γ and β-pix), which are required for the trafficking of transient receptor potential-canonical (TrpCl/3) channels to the membrane [93]. Hence, leptin resistance and aging resulting in low levels of this protein are correlated with cognitive impairment and participation by other cytokines.

The adipokine adiponectin is a 30 kDa protein released by adipose tissue and the most abundant adipokine in plasma [94]. Unlike leptin, it is inversely correlated with fat mass; that is, circulating adiponectin levels decrease with increasing adiposity [83]. Adiponectin is a sensor of insulin and can induce body weight loss [95] and insulin resistance, with high levels of tumor necrosis factor (TNF) in plasma and adipose tissue [96]. Adiponectin has been found to modulate some brain functions such as memory and to produce a neuroprotective effect on hippocampal neurons [97, 98]. Furthermore, adiponectin levels are inversely associated with insulin resistance, obesity, type 2 diabetes, and AD. The mechanisms involving adiponectin in the brain are still unclear; however, many epidemiological studies have reported that, for both AD patients and T2DM patients, plasma adiponectin levels are significantly lower than those of healthy individuals [98], although a recent study did not produce the same results [99].

Adiponectin and TNF-α inhibit each other’s production in adipose tissue, and adiponectin does the same with IL-6, in addition to modulating inflammatory responses, inhibiting the NF-κB-induced pathway [81, 82]. An increase of NF-κB activity in inflammatory status promotes aspartyl protease β-site APP-cleaving enzyme (BACE1) synthesis, thus enhancing APP cleavage, and Aβ genesis where low adiponectin levels are associated with AD [82, 100].

The increase in proinflammatory adipokine TNF-α levels promotes neuroinflammation as well as inhibition of neuronal proliferation and differentiation [101]. The mechanism involved in these neurotoxic effects is as follows: increase in the production of other cytokines such as IL-6 and leptin, increase of AMPA receptor activity as well as secretases by the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (IkB) degradation pathway, and overactivation of NF-κB, which may stimulate APP production [81, 102].

The interleukin IL-6, also associated with AD, induces inflammation, inhibition of neurogenesis, and decrease of synaptic plasticity in the hippocampus by triggering neuroinflammation via STAT3, exerting cAMP response element-binding (CREB) protein downregulation by Akt inhibition or by the activation of transcription factors, which compete for a limited pool of coactivators such as STAT-1, c-Jun, and NF-κB, promoting hypocholinergic signaling [103–105].

A member of the neurotrophin family, BDNF, is expressed in adult neurons at high levels throughout the CNS [106] and a decrease thereof has been reported in obesity [107]. Low levels of BDNF have been related to many diseases such as AD because such levels induce a decrease in mitochondrial biogenesis, neuronal survival, and plasticity associated with a deficiency in the TrkB signaling receptor by different pathways: MAPK, a regulator of neuronal differentiation and maturation; PI3K, important in neuronal survival and synaptic protein formation; and PLCγ, which induces the release of intracellular Ca2+ related to synaptic plasticity [108]. Decreased BDNF also induces apoptosis in neurons by the inhibition of the antiapoptotic family Bcl-2 and the expression of the proapoptotic proteins Bax and Bad, promoting mitochondrial biogenesis [109].

The adipokines related to vascular health are PAI-1 and AGT, which are involved in cell migration and are related to learning and memory process. PAI-1 can be produced by adipocytes, microglia, and astrocytes; the increase of this adipokine in obesity is related to inflammation (an AD risk factor) and fibrinolysis. Moreover, PAI-1 has also been discussed as regards its possible neuroprotective effect associated with the MAPK/ERK pathway [81].

AGT is produced by the liver and white adipocyte tissue in order to increase blood pressure. Increased AGT has been reported in obesity and is considered a risk factor for AD because it increases blood pressure and inflammation [110].

(5) Type 2 Diabetes Mellitus (T2DM). Type 2 diabetes mellitus (T2DM) is another prevalent disease associated with obesity and aging, and it is considered an independent risk factor for AD [111]. T2DM and obesity are diseases that affect millions of people worldwide [28, 112]. T2DM is characterized by hyperglycemia resulting in production of increased hepatic glucose, impairment of insulin production by pancreatic β-cells, and insulin resistance [27]. Glucose is the only required source of energy for neurons and any disruption in glucose metabolism leads to compromised neuronal functions [113].

The proposed scenarios between diabetes and dementia are numerous; they include vascular lesions, inflammation, oxidative stress, elevated end products of glycolysis, insulin resistance, abnormal insulin receptor signaling, and degradation of insulin and its relation to Aβ protein deposits [114, 115]. Interestingly, both pathologies present amyloidogenesis that forms Aβ plaques [28]. High glucose levels and insulin resistance have a likely impact on oxidative stress pathways and neuroinflammatory signals in the brain, thereby connecting diabetes to neurodegeneration [112]. Furthermore, many researches sustain the hypothesis that AD responds to neuronal pathogenic energy imbalance produced by impairment in the function of glucose [116].

Insulin is a relevant molecule in the regulation of metabolism and energy expenditure. In the brain, insulin
is considered a paracrine/autocrine effector, binding to insulin receptors (IRs) and activating the IR substrate (IRS) in two canonical pathways, the phosphoinositide-3 kinase (PI3K)/Akt and the Ras/mitogen-activated kinase cascades [117]. Central insulin is considered to regulate structural and functional aspects of synapses, and neuron-specific insulin receptor knockout (NIRKO) in mice, producing defects in Akt–Foxo3, an insulin signal, develops insulin resistance and causes increased activation of GSK-3β and tau hyperphosphorylation [118, 119]. Insulin resistance impairs IR/PI3K/Akt/mTOR insulin signaling, promoting decreased GLUT4, AMPA, and NMDAR exportation to the membrane. Taken together, all these events result in glutamate neurotransmission and long-term potentiation (LTP) dysfunction and tau hyperphosphorylation [117]. It is also important to note that Aβ peptide can bind to the IR and also to ApoE; ApoE itself binds to the IR, and the different interactions between ApoE isoforms suggest that the ApoE ε4 genotype could lead to earlier impairment of brain insulin signaling [120].

3. Gastrointestinal Microbiota. Microbiota composition changes have been related as factor risk for several diseases such as obesity, atherosclerosis [121], and T2DM [122] in addition to gastrointestinal disease. More recently, microbiota has been involved with AD due to the possible infectious etiologies of neurogenerative diseases [123]. In this context, previous studies reported associations between Chlamydia pneumoniae [124] as well as herpes simplex virus infection and AD [125]. The possible mechanisms that link microbiota to AD include (1) interactions between the gut microbiota and the CNS in a “microbiota-gut-brain axis” [123], which modify immune response, enhancing response to cerebral Aβ [126], (2) microbiota that could promote prion-like behavior of amyloid proteins leading to neurodegeneration [127], and (3) microbiota changes during aging such as the increase in the proportion of Bacteroidetes to Firmicutes as well as the reduction of bifidobacterial counts [128], which decrease the synthesis of proinflammatory cytokines [129]. Finally, epidemiological links between oral bacteria and AD have been reported [121], due to the increase of TNF-α production [130]. Interestingly, oral and gut microbiota can be modified by diet.

3. Pharmacological Treatment

Alzheimer’s disease requires precise diagnosis, early if possible, and adequate etiological treatment, and, as an incurable age-related neurodegenerative disorder, its particular pathophysiology needs to be considered. The therapeutic options have focused on ameliorating the symptoms as well as reducing the rate of progression of damage, although this has not significantly reversed the disease, so prevention is a better solution for this public health problem [4, 131].

The toxic conformations of Aβ or tau in the brain are thought to spread the disease, and blocking the generation of these peptides may be part of useful treatments. Nevertheless, the current treatments of this disease are based on cholinesterase inhibitors and a glutamate antagonist, providing only symptomatic relief, while evidence for the complexity and multifinality of this dementia is recognized in basic and clinical studies [132]. Efforts in etiology-based treatment are currently underway in clinical trials, as well as complement preventive treatments such as physical activity, proper diet, cognitive stimulation, and the management of comorbidity [133].

3.1. Symptomatic Treatment

3.1.1. Acetylcholinesterase Inhibitors. It is well known that acetylcholine (ACh) plays a crucial role in mediating learning and memory [134]. Furthermore, direct interaction between Aβ and cholinergic systems has been proposed, with negative feedback to the production of the peptide; it has been suggested that the alteration in this negative feedback loop and abnormal accumulation of Aβ reduced cholinergic transmission effectiveness, focused on alpha-7 nicotinic acetylcholine receptors [135, 136].

On this basis, effective treatment for AD is achieved with cholinesterase inhibitors, which corresponds well to Davies and Maloney’s early cholinergic deficit hypothesis (1976) explaining AD pathophysiology. Tacrine, donepezil, rivastigmine, galantamine, xanthostigmine, para-aminobenzoic acid, coumarin, flavonoid, and pyrroloisoxazole analogs have been developed and studied for the treatment of AD. Rivastigmine, donepezil, and galantamine are the approved drugs that promote higher ACh levels and improve the brain’s cholinergic function by inhibiting the enzyme acetylcholinesterase which degrades the neurotransmitter [137–139]. In general, acetylcholinesterase inhibitors (except tacrine) are well tolerated and adverse effects are dose-related [4]. The acetylcholinesterase inhibitor ladostigil (TV3326) is in phase II clinical trials and it also produces antidepressant effects for the inhibition of monoamine oxidases A and B [140].

3.1.2. N-Methyl-D-aspartate Receptor (NMDA) Antagonist. Glutamate-mediated excitotoxicity is known to result in calcium overload and mitochondrial dysfunction, with increased nitric oxide generation, which can be detrimental to cells, forming high levels of oxidants and eliciting neuronal apoptosis. This overstimulation can be blocked by NMDA receptor antagonists such as memantine, which was approved in 2003 by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe AD, with a marginal beneficial effect on cognition in mild-to-moderate AD [4, 141, 142].

Memantine can protect neurons by attenuating tau phosphorylation through a decrease in glycogen synthase kinase 3β (GSK-3β) activity. This noncompetitive glutamatergic NMDA receptor antagonist can be administered alone or in combination with an acetylcholinesterase inhibitor [143], although there may be few significant favorable changes in the combination therapy [137].

3.1.3. Other Neurotransmitter Systems. Muscarinic and nicotinic ACh receptors are also considered targets for AD treatment, although selectivity of the agonists has been a problem outcome in clinical trials. EVP-6124 is currently in phase II trial [131].

Based on the cholinergic hypothesis and NMDA glutamate participation in AD, it is natural to consider the different
neurotransmitter networks, particularly of the hippocampus. Serotonin receptors are expressed in areas of the CNS involved in learning and memory. The inhibition of 5-HT$_4$ serotonin receptors was shown to promote acetylcholine release, and some compounds are in various stages of clinical research, considered as possible treatments for mild-to-moderate AD [140].

Histamine receptors, particularly H$_2$ receptors, are also present in large amounts in memory- and cognition-related structures in the brain. It seems that H$_3$ receptor antagonists may improve cholinergic neurotransmission. Phase I and II studies with H$_3$ antagonists are currently being conducted [139].

### 3.2. Etiology-Based Treatment

As indicated above, ApoE e4 is the major genetic risk factor for sporadic AD (the major risk factor is age), although, for disease-modifying treatment based on the amyloid cascade hypothesis, efforts are targeting secretase modulation and amyloid binders, as well as targeting kinases involved in the hyperphosphorylation of tau protein [131, 132, 140].

#### 3.2.1. Secretase Inhibitors

APP is first cleaved either by $\alpha$-secretase or by $\beta$-secretase enzymes, and the resulting fragments are processed by $\gamma$-secretase. The proposal of the “over-activation” of $\beta$- and $\gamma$-secretases, or age-related decreased $\alpha$-secretase processing, has led to the use of inhibitors for this amyloidogenic pathway [144].

Several metalloproteases have been studied with $\alpha$-secretase activity. The upregulation with gemfibrozil (PPAR- $\alpha$ agonist) of the $\alpha$-secretase “A disintegrin and metalloprotease” 10 (ADAM10) has been proposed as a good strategy for the prevention of $\beta$-secretase generation [145]; melatonin also stimulates the nonamyloidogenic processing of APP through positive transcriptional regulation of ADAM10 and ADAM17 [146] and stimulation with serotonin 5-HT$_4$ receptor agonists regulates $\alpha$-secretase activity [147]. Overexpression of matrix metalloproteinase 9 (MMP-9, another $\alpha$-secretase) also prevents cognitive deficits displayed by the transgenic AD mouse model harboring five familial AD-related mutations (5xFAD) [148].

The transmembrane aspartyl protease BACE1 has inhibitors proposed with a molecular docking-based approach for the inaccessible catalytic center that initially led to unsuccessful trials [131, 149, 150]. BACE1 plays an important role in the metabolism of myelination proteins; however, its inhibition displays less severe side effects than other ADAM proteases. Few compounds have reached clinical trials, the most promising being Merck Sharp & Dohme's MK-8931 (Verubec compound) and Eli Lilly/Astra-Zeneca's AZD3299 (LY3314814), in phase II/III trials NCT01739348 and NCT02245737, respectively [139, 140]. Flavonols and flavones, especially myricetin and quercetin, have exhibited very good cell-free BACE1 inhibitory effects [131].

$\gamma$-secretase is a transmembrane multisubunit protease complex, composed of presenilin 1, nicastrin, anterior pharynx defective-1 (APH-1), and presenilin 1 enhancer-2 (PEN-2), and it is involved in the proteolysis of many intramembranous signaling proteins. There have been many studies with $\gamma$-secretase inhibitors, which induced significant side effects, including gastrointestinal disorders and increased risk of skin cancer. One of its substrates is Notch protein, which regulates cell proliferation, differentiation, and growth; $\gamma$-secretase Notch-sparing inhibitors were designed, although results in clinical trials are not very promising [139]. It seems that $\alpha$-secretase activity is needed to prevent $\alpha$-$\beta$ peptide formation and its age-related downregulation may be compensated by dietary changes including several antioxidants that activate the promoter of the ADAM proteases involved; $\gamma$-secretase activity is also needed before $\beta$-secretase reaches APP in order to prevent $\alpha$-$\beta$, since evidence for genetic defects in $\gamma$-secretase (PSEN-1 and PSEN-2) as major risk factors for familial AD is conclusive. This may explain why the use of $\gamma$-secretase inhibitors has failed in early trials but modulators of this complex have better expectations.

The toxicity of $\gamma$-secretase inhibitors depends on other signaling pathways activated by other cleaved receptors, including Notch receptor [150]. It has been shown that a $\gamma$-secretase inhibitor, but not a $\gamma$-secretase modulator, induces defects in BDNF axonal trafficking and signaling [151]. These modulators have effects on the $\alpha$-$\beta$ cleaving site generator without affecting other cleaving sites of the complex [152, 153].

Hypercholesterolemia is considered a risk factor, as stated above, and also the participation of cholesterol in secretase activity has been discussed, but it is more important to recall that many acidic steroids are $\gamma$-secretase modulators that selectively decrease $\gamma$42; cholesterol, a cholesterol metabolite, is one of these endogenous modulators [154]; the regulation of these endogenous metabolites may be involved in obesity-induced AD (including other risk factors such as dyslipidemia and metabolic syndrome).

#### 3.2.2. Amyloid Binders

The deposition of $\alpha$-$\beta$ in AD is concentration-dependent; increased amyloidogenic processing of APP and inefficient removal of peptides may be involved in the pathology. There is reduced activity of $\alpha$-$\beta$-degrading enzymes, such as neprilysin, an insulin-degrading enzyme, as well as the ApoE determinant, which correlates well with the proposal of AD as a metabolic disorder [140].

Preventing the formation of $\alpha$-$\beta$ extracellular neuritic (senile) plaques is one of the targets for disease-modifying treatment in AD, although there is evidence of correlation with $\alpha$-$\beta$ biomarkers and cognitive deficits, previous to senile plaques. Inhibitors of $\alpha$-$\beta$ aggregation have reached clinical trials [140]. In addition, amyloid-$\beta$-directed immunotherapy includes several biological products involving probable sequestration of soluble monomeric $\alpha$-$\beta$ (solanezumab) or microglia-mediated clearance (bapineuzumab, crenezumab, gantenerumab, aducanumab, and BAN2401) currently in clinical trials [132]. However, active and passive immunization may involve side effects with neuroinflammation, which is considered in itself to explain the pathophysiology of AD, and anti-inflammatory agents for treatment of AD might be considered as well.

#### 3.2.3. Anti-$\alpha$-$\beta$ Aggregation Compounds

In recent decades, research has focused on developing therapies in which the $\alpha$-$\beta$ peptide formation or its aggregation is prevented. Among
the small molecule inhibitors of Aβ aggregation in clinical trials are tramprolate (phase III), cloquimol (phase II), scylloinositol (phase II), and epigallocatechin-3-gallate (phase II/III); although these drugs have achieved stabilization of the Aβ monomers, they have important side effects [155]. Also, synthetic β-sheet breaker peptides of the iAβ5p sequence such as azetidine-2-carboxylic acid, 3-phenyl azetidine-2-carboxylic acid, β-proline, and β-sulfonylproline modulate the cell damage caused by the Aβ exposure by preventing fibril formation and they have shown improved results with regard to spatial memory [156, 157]. Stemazole has been shown to protect SH-SY5Y cells from toxicity induced by Aβ in vitro, reducing Aβ aggregation [158]. Likewise, compounds such as curcumin, T718MA, and SK-PC-B70M protect neurons from Aβ-induced toxicity [156].

3.2.4. Tau Therapies. Prevention of aggregates of paired, helically twisted filaments of hyperphosphorylated tau in neurofibrillar tangles is one of the targets of this therapy. Immunotherapy has been developed; AADVac1 was the first vaccine in clinical trials, and AC1-35 (another liposomal-based vaccine) trials have begun [139].

Inhibitors of the phosphorylation of tau proteins such as tideglusib, an irreversible GSK-3β inhibitor, have been tested with no statistically significant benefits [139]; cyclin-dependent kinase 5 (CDK5), which is also involved in the hyperphosphorylation of tau proteins, has been considered as a possible drug target [140].

Several molecules have been shown to act as good inhibitors of tau aggregation and are in clinical trials. Among these drugs, methylene blue (MB) and its metabolites azure A and azure B are able to promote protein degradation and inhibit caspase-1 and caspase-3 activity [159]. Similarly, leucomethyleneimium with a suitable counterion (LMTX in phase III clinical trials) and methylthioninium chloride or MTC (phase II clinical trial) have been shown to reduce tau aggregation and reverse behavioral deficits in transgenic mouse models [160] and to slow the progression of the disease in patients with AD [10]. However, the exact mechanisms by which LMTX and MTC generate neuroprotective effects in vivo are not completely understood. Other promising inhibitors of tau aggregation are N-phenylamines, anthraquinones, phenylthiazolyl-hydrazides, rhodanines, benzothiazoles, and phenothiazines [161].

3.2.5. Other Therapies. As an age-related pathology, AD is correlated with other chronic-degenerative disorders, and coordinated therapies are needed. A type 2 diabetes hypothesis of AD has been developed, and intranasal insulin is included as a possible treatment for the disease, due to its ability to penetrate the brain-blood barrier [139].

Elevated low-density lipoprotein (LDL) concentration increases the risk of developing AD but the use of statins as a protective treatment is controversial [162, 163]. Dyslipidemia and obesity are considered causative factors in relation to other pathologies such as metabolic syndrome, which includes atherogenic dyslipidemia and central obesity, hyperglycemia and insulin resistance, hypertension, and a prothrombotic state and a proinflammatory state [164, 165]. Statins may prevent dementia due to their role in cholesterol reduction, although there is evidence that statins given in late life to people with a risk of vascular disease do not prevent cognitive decline or dementia [166]. There is a reduction in cholesterol levels in the diabetic brain, as well as in neuron-derived cholesterol content, which affects receptor signaling [167], so the use of statins in AD treatment should be with consideration to the early management of the disease.

In addition, drugs used in the treatment of type II diabetes mellitus may have a neuroprotective effect in AD. Amylin and glucagon-like peptide-1 receptor agonist are also under study as AD treatments [139].

Finally, the mitochondrial cascade hypothesis includes oxidative stress, a state of lost balance with overproduction of oxidative free radicals as well as reactive oxygen species (ROS) and reactive nitrogen species (RNS) [141, 168]. This imbalance also includes the participation of immune cells and NO signaling, and preventive treatment with antioxidants (see Nonpharmacological Treatments) and anti-inflammatory drugs is considered [169]. What is certain is that prevention is our best strategy for AD, with efforts to prevent obesity and chronic-degenerative disorders.

4. Nonpharmacological Treatments

Nonpharmacological treatments are important for the prevention of AD or as adjuvants in other treatments. AD prevention strategies can be divided into two groups, the first associated with lifestyle and the second with diet and chemical compounds.

4.1. Lifestyle. Lifestyle strategies include physical activity, mental challenges, energy restriction, and socialization as preventive factors in AD [170]. Physical activity such as aerobic exercise was associated with the reduction of AD deficits in a cohort study [171]. This was not consistent with studies that considered a small number of cases [172].

Exercise was reported to enhance hippocampal neurogenesis [173, 174] and learning in aging rodents [175]. The three mechanisms proposed in order to explain the exercise neuroprotective effect of exercise are (1) the release of neurotrophic factors such as BDNF and insulin-like growth factor (IGF-1), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF) [138, 176] from neurons in synaptic activity, which stimulates neurogenesis and synaptic neural plasticity through the stimulation of CREB transcription factor; (2) the reduction of free radicals in the hippocampus as well as the increase in superoxide dismutase and endothelial nitric oxide synthase [176]; (3) peripheral signals that help to support the demands of active neuronal networks such as BDNF release in addition to energy restriction on the brain [109, 177–179].

It has been proposed that mental challenges may protect against cognitive decline and probably against AD [180]. Computer courses and psychoducation have moderate beneficial effects [181]. Stimulation by cognitive activities has been associated with an increase in neuronal density, which provides brain reserve and plasticity [170].

The relation between caloric restriction and brain motivation is important since many years ago humans needed to
obtain their food by killing wild animals and often vigorous exercise was required [182]. In different AD mouse models treated with food and caloric restriction, a decrease in phosphorylated tau and amyloid-β was observed in the brain. The possible mechanism may be associated with SIRT1, a protein with nicotinamide adenine dinucleotide-dependent deacetylase or adenosine diphosphate-ribosyltransferase activity [183], because its increase was reported in p25 CK mice with characteristics similar to ADp. In addition, SIRT I stimulation by resveratrol induces neuronal death protection. SIRT1 levels also increase with NADp in vitro, and SIRT induces an increase of α-secretase and a decrease of β amyloid deposition in primary cultures in a mouse model of AD [184]. The relationship between hunger and neuroprotection was induced by ghrelin in a mouse model of AD; the results indicated improved cognition in the water maze test and a decrease in amyloid-β levels and inflammation [185].

Socialization is important to mental and physical human development and a lack thereof induces loneliness, which has been associated with various diseases such as depression, alcohol abuse, obesity, diabetes, hypertension, AD, and cancer [186].

### 4.2. Diet and Chemical Substances

Dietary supplements for prevention of AD were studied with vitamins such as B6, B12, folates, and E, C, and D vitamins. Vitamin B studies produced mixed results; on one hand, a two-year treatment with homocysteine and vitamin B in 271 patients indicated a significant difference compared to placebo in whole brain atrophy [187, 188], whereas other reports indicate different results [189, 190]. It has been proposed that folic acid has neuroprotective activity through an epigenetic mechanism that inhibits amyloid-β peptide accumulation. Studies with 2000 IU of vitamin E did not indicate a protective effect for AD with three years of treatment [191], nor with the combined treatment with vitamin C [192]. Additionally, vitamin D supplementation improves cognitive performance [193].

With regard to the intake of chemical substances, the results in alcohol studies indicate an association between the prevention of AD and low levels of red wine consumption [194] due to its polyphenols composition, whereas drinking alcohol frequently was associated with a risk of dementia [195]. Different molecules have been proposed for their neuroprotective effect, including glucosamine, omegas 3 and 6 which induce interleukins or prostaglandins for inflammatory responses [196], and antioxidants such as β-carotene and lycopene 6 [197].

Other studies of chemical substances related to possible protection against neuropsychiatric disorders such as AD were those related to the intake of plants and their secondary metabolites: flavonoids, alkaloids, or terpenoids [198, 199]. Flavonoids are considered safe [200] and their neuroprotection was confirmed in 90 people treated with flavanol [201]. Flavonoids also inhibit acetylcholinesterase and improve memory [202], in addition to inhibiting glutamate release [203].

Resveratrol is a polyphenol found in various plants, especially berries, peanuts, and red grapes, as well as in red wine [204]. This polyphenol has shown various biological activities such as antioxidant, anti-inflammatory, phytoestrogen, vasodilator, cardioprotective, and anticarcinogenic activities, while many studies have proposed resveratrol as a molecule with therapeutic potential in neurodegenerative diseases such as AD [205]. Neuroprotective functions of resveratrol in the pathogenesis of AD have been evaluated through different mechanisms of action. The neuroprotective effects of resveratrol have been associated with the modulation of transcription factors NF-κB, CAMP, p53, and cyclins, as well as an increase in BDNF among others related to mitochondrial biogenesis, oxidation of fatty acids, and suppression of proinflammatory molecules [206].

One mechanism by which resveratrol generates anti-inflammatory effects is by proinflammatory cytokine activity inhibition (IL-1β, IL-6, and TNF-α) and prostanoïd synthesis, principally prostaglandin E2 (PGE2) [207]. Furthermore, it has been shown that resveratrol has the ability to activate sirtuin, particularly SIRTI, leading to the protection of neurons from apoptotic processes and oxidative stress [208]; it has also been demonstrated that activation of SIRTI induced by resveratrol reduced NF-κB signaling pathway activation in glial cells exposed to Aβ [209]. Under normal cellular conditions, SIRTI is activated by AMPK, and then activated SIRTI is deacetylated to transcription factors such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α), which translocates to the nucleus and interacts with peroxisome proliferator-activated receptor (PPAR-γ) to enhance gene expression, which promotes cell survival and the proper functioning of mitochondria [206, 210].

Another flavonoid is luteolin which has been reported to exhibit significant action in AD prevention associated with its antioxidant, anti-inflammatory, and microglia-inhibiting effects along with improved spatial memory [211]. Luteolin also inhibits multiple transduction signals such as NF-κB, PKC, STAT3, and intracellular calcium [212, 213].

The Mediterranean diet may improve neuroprotection because it is based on low intake of saturated fatty acids, but high consumption of unsaturated fatty acids, as well as vegetables, legumes, fruits, fish, and olive oil, along with polyphenols such as oleanuropein aglycone (OLE), which interfere with amyloid aggregation, and reduced the LDL cholesterol levels. The monosaturated fatty acids have been reported with antioxidant and anti-inflammatory effects, as well as endothelial function improvement and less cognitive decline, whereas polysaturated fatty acids are important in neuronal membrane integrity and function; omega 3 was related to gene expression that might influence the inflammatory process, nerve membranes neuroplasticity, and synaptic transmission [214–218]. Another diet related to neuroprotection against neurodegenerative diseases is the Asiatic diet, because it includes high levels of green tea consumption, the antioxidant curcumin, and the dietary supplement *Gingko biloba*, considered to be a protector against memory decline, due to its antioxidant effect and the decrease of Aβ aggregation; it is necessary to increase the research in order to know its toxic effects [138]. On the other hand, the western diet is considered as a risk factor for AD because it is characterized by excessive consumption of sugar and animal
products, with a higher content of saturated fats, which negatively affect cognitive function, Aβ-deposition, and oxidative stress [218].

OLE is an important compound with neuroprotective effects because it interferes with amylin, tau, and Aβ peptide aggregation and toxicity in vitro, studied by behavioral, biological, biophysical, biochemical, and electrophysiological techniques. OLE also has pharmacological activities such as cardioprotective, antioxidant, anticancer, antimicrobial, and antiviral effects; this compound also prevents low-density lipoprotein oxidation and platelet aggregation, inhibiting eicosanoid production, and it produces an effect against metabolic syndrome: obesity and type 2 diabetes and hepatic steatosis induced by a high-fat diet in mice, probably associated with WNT expression downregulation of the inhibitor genes and toll-like receptor and of the proinflammatory cytokines. OLE also downregulates several transcription factors and their target genes involved in adipogenesis and upregulation genes such as β-catenin [214].

Another nonpharmacological treatment could be the intake of probiotics due to their reduction of the proinflammatory cytokines associated with gut microbiota changes during aging [128] (Figure 2). Probiotics administration in the elderly may improve gut health and boost anti-inflammatory activity [219], since the “microbiota-gut-brain axis” can decrease the neuroinflammatory process. Furthermore, the beneficial effects of probiotics in AD have been associated with their production of metabolites by fermentation, including short-chain fatty acids (SCFAs) such as propionic and butyric acids [220]. A recent study reported a neuroprotective effect of Clostridium butyricum which restored brain levels of butyrate in a mouse model of vascular dementia [221]. Probiotics increase intestinal barrier integrity by activating epithelial cells protecting against pathogens [222]. In addition, previous work showed downregulation of TNF-α levels and an increase in IL-10 production resulting from the administration of Lactobacillus rhamnosus [223]. It is important to note that the intake of probiotics, such as Lactobacillus plantarum, may also induce behavioral changes, through monoamine neurotransmitter augmentation [224].

AD is a multifactorial disease and the combination of two or more nonpharmacological treatments for prevention is important, in addition to pharmacological treatments. AD should be considered at early ages in order to avoid risk factors, and, for elderly individuals, increasing treatment to a combination of two or more nonpharmacological treatments strengthens prevention. In cases where dementia is present, it is important to improve treatments by adding lifestyle and dietary changes. AD research needs to be further developed in order to propose new molecules for therapy and prevention.

Competing Interests

The authors declare that they have no competing interests.

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References

[1] C. Van Cauwenberghe, C. Van Broeckhoven, and K. Sleegers, “The genetic landscape of Alzheimer disease: clinical implications and perspectives,” Genetics in Medicine, vol. 18, no. 5, pp. 421–430, 2015.

[2] S. Chakrabarti, V. K. Khemka, A. Banerjee, G. Chatterjee, A. Ganguly, and A. Biswas, “Metabolic risk factors of sporadic Alzheimer’s disease: implications in the pathology, pathogenesis and treatment,” Aging and Disease, vol. 6, no. 4, pp. 282–299, 2015.

[3] T. D. Bird, “Early-onset familial Alzheimer disease,” in Gene Reviews, R. Pagon, M. Adam, H. Ardinger et al., Eds., pp. 1–42, University of Washington, Seattle, Seattle, Wash, USA, 2012.
[4] L. W. Chu, “Alzheimer’s disease: early diagnosis and treatment,” Hong Kong Medical Journal, vol. 18, no. 3, pp. 228–237, 2012.
[5] X. Sun, W. Chen, and Y. Wang, “β-Amyloid: the key peptide in the pathogenesis of Alzheimer’s disease,” Frontiers in Pharmacology, vol. 6, pp. 1–9, 2015.
[6] C. Cervellati, P. L. Wood, A. Romani et al., “Oxidative challenge in Alzheimer’s disease: state of knowledge and future needs,” Journal of Investigative Medicine, vol. 64, no. 1, pp. 21–32, 2016.
[7] B. De Strooper and E. Karran, “The cellular phase of Alzheimer’s disease,” Cell, vol. 164, no. 4, pp. 603–615, 2016.
[8] C. Spuch, S. Ortolano, and C. Navarro, “LRP-1 and LRP-2 receptors function in the membrane neuron. Trafficking mechanisms and proteolytic processing in Alzheimer’s disease,” Frontiers in Physiology, vol. 3, article 269, pp. 1–14, 2012.
[9] S. H. Barage and K. D. Sonawane, “Amyloid cascade hypothesis: pathogenesis and therapeutic strategies in Alzheimer’s disease,” Neuroptides, vol. 52, pp. 1–18, 2015.
[10] G. Šimić, M. B. Leko, S. Wrage et al., “Tauprotein hyperphosphorylation and aggregation in Alzheimer’s disease and other tauopathies, and possible neuroprotective strategies,” Biomolecules, vol. 6, no. 6, pp. 1–28, 2016.
[11] A. Contestabile, “The history of the cholinergic hypothesis,” Behavioural Brain Research, vol. 221, no. 2, pp. 334–340, 2011.
[12] J. Folch, I. Patraca, N. Martínez et al., “The role of leptin in the sporadic form of Alzheimer’s disease. Interactions with the adipokines amylin, ghrelin and the pituitary hormone prolactin,” Life Sciences, vol. 140, pp. 19–28, 2015.
[13] L. Y. Di Marco, A. Venneri, E. Farkas, P. C. Evans, A. Marzo, and A. F. Frangi, “Vascular dysfunction in the pathogenesis of Alzheimer’s disease—a review of endothelium-mediated mechanisms and ensuing vicious circles,” Neurobiology of Disease, vol. 82, pp. 593–606, 2015.
[14] P. Gamba, G. Testa, S. Gargiulo, E. Staurenghi, G. Poli, and G. Leonardiuzzi, “Oxidized cholesterol as the driving force behind the development of Alzheimer’s disease,” Frontiers in Aging Neuroscience, vol. 7, article 189, 2015.
[15] L. Xu, X. Wu, R. Li et al., “Prediction of progressive mild cognitive impairment by multi-modal neuroimaging biomarkers,” Journal of Alzheimer’s Disease, vol. 51, no. 4, pp. 1045–1056, 2016.
[16] S. Ramírez-Díaz, G. Albert-Meza, J. Avila-Fuentes et al., Enfermedad de Alzheimer: Presente y Futuro, Planeación y Desarrollo, Monterrey, Mexico, 2011.
[17] A. Christensen and C. J. Pike, “Menopause, obesity and inflammation: interactive risk factors for Alzheimer’s disease,” Frontiers in Aging Neuroscience, vol. 7, article 130, pp. 1–14, 2015.
[18] Z. Chen and C. Zhong, “Oxidative stress in Alzheimer’s disease,” Neuroscienece Bulletin, vol. 30, no. 2, pp. 271–281, 2014.
[19] L. B. Haim, M.-A. Carrillo-de Sauvage, K. Ceyzériat, and C. Escartín, “Elusive roles for reactive astrocytes in neurodegenerative diseases,” Frontiers in Cellular Neuroscience, vol. 9, article 278, pp. 1–27, 2015.
[20] Y. Huang and R. W. Mahley, “Neurobiology of Disease Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer’s disease,” Neurobiology of Disease, vol. 72, pp. 3–12, 2014.
[21] V. Van-Giau, E. Bagyinszky, S. S.-A. An, and S. Y. Kim, “Role of apolipoprotein E in neurodegenerative diseases,” Neuropsychiatric Disease and Treatment, vol. 11, pp. 1723–1737, 2015.
[22] I. H. K. Dias, M. C. Polidori, and H. R. Griffiths, “Hypercholesterolaemia-induced oxidative stress at the blood–brain barrier,” Biochemical Society Transactions, vol. 42, no. 4, pp. 1001–1005, 2014.
[39] Y. L. Chai, H. K.-H. Yeo, J. Wang et al., “Apolipoprotein ε4 is associated with dementia and cognitive impairment predominantly due to Alzheimer’s disease and not with vascular cognitive impairment: a Singapore-based cohort,” *Journal of Alzheimer’s Disease*, vol. 51, no. 4, pp. 1111–1118, 2016.

[40] R. Wang, L. Fratiglioni, E. J. Laukka et al., “Effects of vascular risk factors and APOE ε4 on white matter integrity and cognitive decline,” *Neurology*, vol. 84, no. 11, pp. i128–i135, 2015.

[41] C. M. Karch and A. M. Goate, “Alzheimer’s disease risk genes and mechanisms of disease pathogenesis,” *Biological Psychiatry*, vol. 77, no. 1, pp. 43–51, 2015.

[42] J. R. P. Prasanthi, M. Schrag, B. Dasari et al., “Deferiprone reduces amyloid-β and tau phosphorylation levels but not reactive oxygen species generation in hippocampus of rabbits fed a cholesterol-enriched diet,” *Journal of Alzheimer’s Disease*, vol. 30, no. 1, pp. 167–182, 2012.

[43] S. Kosari, E. Badoor, J. C. D. Nguyen, A. S. Killcross, and T. A. Jenkins, “Effect of western and high fat diets on memory and cholinergic measures in the rat,” *Behavioural Brain Research*, vol. 235, no. 1, pp. 98–103, 2012.

[44] W. L. F. Lim, I. J. Martins, and R. N. Martins, “The involvement of lipids in Alzheimer’s disease,” *Journal of Genetics and Genomics*, vol. 41, no. 5, pp. 261–274, 2014.

[45] L. Puglielli, B. C. Ellis, A. J. Saunders, and D. M. Kovacs, “Ceramide stabilizes β-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid β-peptide biogenesis,” *The Journal of Biological Chemistry*, vol. 278, no. 22, pp. 19777–19783, 2003.

[46] C. Marquer, V. Devauges, J.-C. Cossec et al., “Local cholesterol increase triggers amyloid precursor protein-Bacel clustering in lipid rafts and rapid endocytosis,” *The FASEB Journal*, vol. 25, no. 4, pp. 1295–1305, 2011.

[47] L. K. Cuddy, W. Winick-Ng, and R. J. Rylett, “Regulation of the high-affinity choline transporter activity and trafficking by its association with cholesterol-rich lipid rafts,” *Journal of Neurochemistry*, vol. 128, no. 5, pp. 725–740, 2011.

[48] V. A. M. Villar, S. Cuevas, X. Zheng, and P. A. Jose, “Localization and signaling of GPCRs in lipid rafts,” *Methods in Cell Biology*, vol. 132, pp. 3–23, 2016.

[49] C. Ullrich, M. Pirchl, and C. Hummel, “Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits,” *Molecular and Cellular Neuroscience*, vol. 45, no. 4, pp. 408–417, 2010.

[50] Y. Kim, C. Kim, H. Y. Jang, I. Mook-Jung, and B. Kim, “Inhibition of cholesterol biosynthesis reduces γ-secretase activity and amyloid-β generation,” *Journal of Alzheimer’s Disease*, vol. 51, no. 4, pp. 1057–1068, 2016.

[51] E. Kojro, G. Gimpl, S. Lammich, W. März, and F. Fahrenholz, “Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the α-secretase ADAM 10,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 10, pp. 5815–5820, 2001.

[52] V. Vingtdeux and P. Marambaud, “Identification and biology of α-secretase,” *Journal of Neurochemistry*, vol. 120, no. 1, pp. 34–45, 2012.

[53] J. Popp, S. Meichsner, H. Kölsch et al., “Cerebral and extracerebral cholesterol metabolism and CSF markers of Alzheimer’s disease,” *Biochemical Pharmacology*, vol. 86, no. 1, pp. 37–42, 2013.

[54] J. Poirier, J. Miron, C. Picard et al., “Apolipoprotein E and lipid homeostasis in the etiology and treatment of sporadic Alzheimer’s disease,” *Neurobiology of Aging*, vol. 35, no. 2, pp. S3–S10, 2014.

[55] G. Marwarha and O. Ghribi, “Does the oxysterol 27-hydroxycholesterol underlie Alzheimer’s disease—Parkinson’s disease overlap?” *Experimental Gerontology*, vol. 68, pp. 13–18, 2015.

[56] V. Leoni and C. Caccia, “Oxysterols as biomarkers in neurodegenerative diseases,” *Chemistry and Physics of Lipids*, vol. 164, no. 6, pp. 515–524, 2011.

[57] M. Sharma, M. Tiwari, and R. K. Tiwari, “Hyperhomocysteinemia: impact on neurodegenerative diseases,” *Basic and Clinical Pharmacology and Toxicology*, vol. 117, no. 5, pp. 287–296, 2015.

[58] B. A. Maron and J. Loscalzo, “The treatment of hyperhomocysteinemia,” *Annual Review of Medicine*, vol. 60, pp. 39–54, 2009.

[59] R. Poddar and S. Paul, “Homocysteine-NMDA receptor-mediated activation of extracellular signal-regulated kinase leads to neuronal cell death,” *Journal of Neurochemistry*, vol. 110, no. 3, pp. 1095–1106, 2009.

[60] S. Li, M. Jin, T. Koegeleperger, N. E. Shepardson, G. M. Shankar, and D. J. Selkoe, “Soluble β oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors,” *Journal of Neuroscience*, vol. 31, no. 18, pp. 6627–6638, 2011.

[61] J. H. Birnbaum, J. Bali, L. Rajendran, R. M. Nitsch, and C. Tackenberg, “Calcium flux-independent NMDA receptor activity is required for Aβ oligomer-induced synaptic loss,” *Cell Death & Disease*, vol. 6, no. 6, Article ID e791, 2015.

[62] M. Wiesmann, C. Capone, V. Zerbi et al., “Hypertension impairs cerebral blood flow in a mouse model for Alzheimer’s disease,” *Current Alzheimer Research*, vol. 12, no. 10, pp. 914–922, 2015.

[63] E. Joas, K. Bäckman, D. Gustafson et al., “Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years,” *Hypertension*, vol. 59, no. 4, pp. 796–801, 2012.

[64] C. N. H. Abheiden, R. Van Doornik, A. M. Aukes, W. M. Van Der Flier, P. Scheltens, and C. J. M. De Groot, “Hypertensive disorders of pregnancy appear not to be associated with Alzheimer’s disease later in life,” *Dementia and Geriatric Cognitive Disorders Extra*, vol. 5, no. 3, pp. 375–385, 2015.

[65] Y. Lu, F. R. Day, S. Gustafsson et al., “New loci for body fat percentage reveal link between adiposity and cardiometabolic disease risk,” *Nature Communications*, vol. 7, Article ID 10495, 2016.

[66] E. Pedditizi, R. Peters, and N. Beckett, “The risk of over-weight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies,” *Age and Ageing*, vol. 45, no. 1, pp. 14–21, 2016.

[67] J. P. Thaler, C.-X. Yi, E. A. Schur et al., “Obesity is associated with hypothalamic injury in rodents and humans,” *The Journal of Clinical Investigation*, vol. 122, no. 1, pp. 153–162, 2012.

[68] D. J. Bonda, J. G. Stone, S. L. Torres et al., “Dysregulation of leptin signaling in Alzheimer disease: evidence for neuronal leptin resistance,” *Journal of Neurochemistry*, vol. 128, no. 1, pp. 162–172, 2014.

[69] A. Jayaraman, D. Lent-Schochet, and C. J. Pike, “Diet-induced obesity and low testosterone increase neuroinflammation and impair neural function,” *Journal of Neuroinflammation*, vol. 11, article 162, 2014.

[70] V. A. Moser and C. J. Pike, “Obesity and sex interact in the regulation of Alzheimer’s disease,” *Neuroscience & Biobehavioral Reviews*, 2015.
A. Eskilsson, E. Mirrasskhian, S. Dufour, M. Schwaninger, D. Engblom, and A. Blomqvist, “Immune-induced fever is mediated by IL-6 receptors on brain endothelial cells coupled to STAT3-dependent induction of brain endothelial prostaglandin synthesis,” *The Journal of Neuroscience*, vol. 34, no. 48, pp. 15957–15961, 2014.

L. Malmsten, S. Vijayaraghavan, O. Hovatta, A. Murutile, and T. Darreh-Short, “Fibriellar β-amyloid 1-42 alters cytokine secretion, cholinergic signalling and neuronal differentiatition,” *Journal of Cellular and Molecular Medicine*, vol. 18, no. 9, pp. 1874–1888, 2014.

L. M. Qin, R. Bouchard, and S. Pugazhenthii, “Regulation of cyclic AMP response element-binding protein during neuroglial interactions,” *Journal of Neurochemistry*, vol. 136, no. 5, pp. 918–930, 2016.

M. Rios, “BDNF and the central control of feeding: accidental bystander or essential player?” *Trends in Neurosciences*, vol. 36, no. 2, pp. 83–90, 2013.

J. C. Han, M. J. Muehlbauer, H. N. Cui, C. B. Newgard, and A. M. Haqq, “Lower brain-derived neurotrophic factor in patients with Prader-Willi syndrome compared to obese and lean control subjects,” *The Journal of Clinical Endocrinology & Metabolism*, vol. 95, no. 7, pp. 3532–3536, 2010.

F. Vanevski and B. Xu, “Molecular and neural bases underlying roles of BDNF in the control of body weight,” *Frontiers in Neuroscience*, vol. 7, article 37, pp. 1–9, 2013.

K. Marosi and M. P. Mattsson, “BDNF mediates adaptive brain and body responses to energetic challenges,” *Trends in Endocrinology and Metabolism*, vol. 25, no. 2, pp. 89–98, 2014.

A. Benigni, P. Cassis, and G. Remuzzi, “Angiotensin II revisited: new roles in inflammation, immunology and aging,” *EMBO Molecular Medicine*, vol. 2, no. 7, pp. 247–257, 2010.

K. Mittal and D. P. Katare, “Shared links between type 2 diabetes mellitus and Alzheimer’s disease: a review,” *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 2016.

S. Rosales-Corral, D.-X. Tan, L. Manchester, and R. J. Reiter, “Diabetes and alzheimer disease, two overlapping pathologies with the same background: oxidative stress,” *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 985845, 14 pages, 2015.

K. Talbot, H.-Y. Wang, H. Kazi et al., “Demonstrated brain insulin resistance in Alzheimer’s disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline,” *The Journal of Clinical Investigation*, vol. 122, no. 4, pp. 1316–1338, 2012.

T. Miyakawa, “Vascular pathology in Alzheimer’s disease,” *Psychogeriatrics*, vol. 10, no. 1, pp. 39–44, 2010.

D. Kapogiannis and M. P. Mattson, “Perturbed energy metabolism and neuronal circuit dysfunction in cognitive impairment,” *The Lancet Neurology*, vol. 10, no. 2, pp. 187–198, 2011.

R. O. Domínguez, M. A. Pagano, E. R. Marschhoff, S. E. González, M. G. Repetto, and J. A. Serra, “Alzheimer disease and cognitive impairment associated with diabetes mellitus type 2: associations and a hypothesis,” *Neurologia*, vol. 29, no. 9, pp. 567–572, 2014.

E. Calvo-Ochoa and C. Arias, “Cellular and metabolic alterations in the hippocampus caused by insulin signalling dysfunction and its association with cognitive impairment during aging and Alzheimer’s disease: studies in animal models,” *Diabetes/Metabolism Research and Reviews*, vol. 31, no. 1, pp. 1–13, 2015.

A. Kleinridders, W. Cai, L. Cappellucci et al., “Insulin resistance in brain alters dopamine turnover and causes behavioral disorders,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112, no. 11, pp. 3463–3468, 2015.

D. Nuzzo, P. Picone, S. Baldassano et al., “Insulin resistance as common molecular denominator linking obesity to Alzheimer’s disease,” *Current Alzheimer Research*, vol. 12, no. 8, pp. 723–735, 2015.

E. S. Chan, C. Chen, G. M. Cole, and B.-S. Wong, “Differential interaction of Apolipoprotein-E isoforms with insulin receptors modulates brain insulin signaling in mutant human amyloid precursor protein transgenic mice,” *Scientific Reports*, vol. 5, Article ID 13842, 2015.

D. K. Shoemark and S. J. Allen, “The microbiome and disease: reviewing the links between the oral microbiome, aging, and Alzheimer’s disease,” *Journal of Alzheimer’s Disease*, vol. 43, no. 3, pp. 725–738, 2015.

J. Qin, Y. Li, Z. Cai et al., “A metagenome-wide association study of gut microbiota in type-2 diabetes,” *Nature*, vol. 490, pp. 55–60, 2012.

F. Scheperjan, “Can microbiota research change our understanding of neurodegenerative diseases?”, *Neurodegenerative Disease Management*, vol. 6, no. 2, pp. 81–85, 2016.

P. Maheshwari and G. D. Eslick, “Bacterial infection and Alzheimer’s disease: a meta-analysis,” *Journal of Alzheimer’s Disease*, vol. 43, no. 3, pp. 957–966, 2015.

R. Mancuso, F. Baglio, M. Cabino et al., “Titers of herpes simplex virus type 1 antibodies positively correlate with grey matter volumes in Alzheimer’s disease,” *Journal of Alzheimer’s Disease*, vol. 38, no. 4, pp. 741–745, 2014.

R. P. Friedland, “Mechanisms of molecular mimicry involving the microbiota in neurodegeneration,” *Journal of Alzheimer’s Disease*, vol. 45, no. 2, pp. 349–362, 2015.

C. M. Lema Tomé, T. Tyson, N. L. Rey, S. Grathwohl, M. Britschi, and P. Brundin, “Inflammation and α-synuclein’s prion-like behavior in Parkinson’s disease—is there a link?”, *Molecular neurobiology*, vol. 47, no. 2, pp. 561–574, 2013.

G. Pérez-Martinez, C. Bäuerl, and M. C. Collado, “Understanding gut microbiota in elderly’s health will enable intervention through probiotics,” *Beneficial Microbes*, vol. 5, no. 3, pp. 235–246, 2014.

M. C. Collado, C. Bäuerl, and G. Pérez-Martinez, “Defining microbiota for developing new probiotics,” *Microbial Ecology in Health and Disease*, vol. 23, pp. 35–39, 2012.

A. R. Kamer, R. G. Craig, E. Pirraglia et al., “TNF-α and antibodies to periodontal bacteria discriminate between Alzheimer’s disease patients and normal subjects,” *Journal of Neuroimmunology*, vol. 216, no. 1-2, pp. 92–97, 2009.

A. Kumar, C. M. Nisha, C. Silakari et al., “Current and novel therapeutic molecules and targets in Alzheimer’s disease,” *Journal of the Formosan Medical Association*, vol. 115, no. 1, pp. 3–10, 2016.

P. Scheltens, K. Blennow, M. M. Breteler et al., “Alzheimer’s disease,” *The Lancet*, 2016.

L. Nelson and N. Tabet, “Slowing the progression of Alzheimer’s disease: what works?”, *Aging Research Reviews*, vol. 23, pp. 193–209, 2015.

D. Mitsushima, A. Sano, and T. Takahashi, “A cholinergic trigger drives learning-induced plasticity at hippocampal synapses,” *Nature Communications*, vol. 4, article 2760, 2013.
M. Chen, “The maze of APP processing in Alzheimer’s disease,” *Neuroscience*, vol. 307, pp. 26–36, 2015.

A. Garcia-Osta and C. M. Alberini, “Amyloid beta mediates memory formation,” *Learning and Memory*, vol. 16, no. 4, pp. 267–272, 2009.

P. Anand and B. Singh, “A review on cholesterolesterase inhibitors for Alzheimer’s disease,” *Archives of Pharmacal Research*, vol. 36, no. 4, pp. 375–399, 2013.

S. Andrieu, N. Coley, S. Lovestone, P. S. Aisen, and B. Vellas, “Prevention of sporadic Alzheimer’s disease: lessons learned from clinical trials and future directions,” *The Lancet Neurology*, vol. 14, no. 9, pp. 926–944, 2015.

J. Godyń, J. Jończyk, D. Panek, and B. Malawska, “Therapeutic strategies for Alzheimer’s disease in clinical trials,” *Pharmacological Reports*, vol. 68, no. 1, pp. 127–138, 2016.

J. Folch, D. Petrov, M. Ettcheto et al., “Current research therapeutic strategies for Alzheimer’s disease treatment,” *Neural Plasticity*, vol. 2016, Article ID 8501693, 15 pages, 2016.

H. Prentice, J. P. Modi, and J.-Y. Wu, “Mechanisms of neuronal protection against excitotoxicity, endoplasmic reticulum stress, and mitochondrial dysfunction in stroke and neurodegenerative diseases.” *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 964518, 7 pages, 2015.

X. Shi, X. Lin, R. Hu, N. Sun, J. Hao, and C. Gao, “Toxicological differences between NMDA receptor antagonists and cholineesterase inhibitors,” *American Journal of Alzheimer’s Disease and Other Dementias*, vol. 31, no. 5, pp. 405–412, 2016.

X. Wang, J. Blanchard, I. Grundke-Iqbal, and K. Iqbal, “Meman-tine attenuates Alzheimer’s disease-like pathology and cognitive impairment,” *PLoS ONE*, vol. 10, no. 12, Article ID e0145441, 2015.

M. Chen, “The maze of APP processing in Alzheimer’s disease: where did we go wrong in reasoning?” *Frontiers in Cellular Neurobiology*, vol. 9, article 186, pp. 1–10, 2015.

G. T. Corbett, F. J. Gonzalez, and K. Pahan, “Activation of peroxisome proliferator-activated receptor α stimulates ADAM10-mediated proteolysis of APP,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112, no. 27, pp. 8445–8450, 2015.

M. Shukla, H. H. Htoo, P. Wintchali et al., “Melatonin stim-u-lates the nonamyloidogenic processing of βAPP through the positive transcripational regulation of ADAM10 and ADAM17,” *Journal of Pinenal Research*, vol. 58, no. 2, pp. 151–165, 2015.

A. A. Pimenova, A. Thathiah, B. De Strooper, and L. Tseur, “Regulation of amyloid precursor protein processing by serotonin signaling,” *PLoS ONE*, vol. 9, no. 1, Article ID e87014, 2014.

A. Fragkouli, E. C. Tsilibrari, and A. K. Tzinia, “Neuroprotective role of MMP-9 overexpression in the brain of Alzheimer’s 5xFAD mice,” *Neurobiology of Disease*, vol. 70, pp. 179–189, 2014.

K. W. Menting and J. A. H. R. Claassen, “β-Secretase inhibitor; a promising novel therapeutic drug in Alzheimer’s disease,” *Frontiers in Aging Neuroscience*, vol. 6, article 165, 2014.

O. G. Tatarnikova, M. A. Orlov, and N. V. Bobkova, “Beta-amyloid and Tau-protein: structure, interaction, and prion-like properties,” *Biochemistry*, vol. 80, no. 13, pp. 1800–1819, 2015.

A. M. Weissmiller, O. Natera-Naranjo, S. M. Reyna et al., “A γ-secretase inhibitor, but not a γ-secretase modulator, induced defects in BDNF axonal trafficking and signaling: evidence for a role for APP,” *PLoS ONE*, vol. 10, no. 2, Article ID e0118379, 2015.

K. Takeo, N. Watanabe, T. Tomita, and T. Iwatsubo, “Contribution of the γ-secretase subunits to the formation of catalytic pore of presenilin 1 protein,” *The Journal of Biological Chemistry*, vol. 287, no. 31, pp. 25834–25843, 2012.

K. Takeo, S. Tanimura, T. Shinoda et al., “Allosteric regulation of γ-secretase activity by a phenylimidazole-type γ-secretase modulator,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 29, pp. 10544–10549, 2014.

J. I. Jung, A. R. Price, T. B. Ladd et al., “Cholesterenic acid, an endogenous cholesterol metabolite, is a potent γ-secretase modulator,” *Molecular Neurodegeneration*, vol. 10, article 29, 2015.

M. Awasthi, S. Singh, V. P. Pandey, and U. N. Dwivedi, “Alzheimer’s disease: an overview of amyloid beta dependent pathogenesis and its therapeutic implications along with in silico approaches emphasizing the role of natural products,” *Journal of the Neurological Sciences*, vol. 361, pp. 256–271, 2016.

J. Kalra and A. Khan, “Reducing Ap load and tau phosphorylation: emerging perspective for treating Alzheimer’s disease,” *European Journal of Pharmacology*, vol. 764, pp. 571–581, 2015.

A. Francioso, P. Punzi, A. Boiffi et al., “β-Sheet interfering molecules acting against β-amyloid aggregation and fibrillogene-sis,” *Bioorganic and Medicinal Chemistry*, vol. 23, no. 8, pp. 1671–1683, 2015.

M. Han, Y. Liu, Q. Tan et al., “Therapeutic efficacy of stemazol in a beta-amyloid injection rat model of Alzheimer’s disease,” *European Journal of Pharmacology*, vol. 657, no. 1–3, pp. 104–110, 2011.

C. Stack, S. Jainuddin, C. Elipenahli et al., “Methylene blue upregulates Nrf2/ARE genes and prevents tau-related neurotoxicity,” *Human Molecular Genetics*, vol. 23, no. 14, Article ID ddu080, pp. 3716–3732, 2014.

V. Melis, M. Magbagbeolu, J. E. Rickard et al., “Effects of oxidized and reduced forms of methylthioninium in two transgenic mouse tauopathy models,” *Behavioural Pharmacology*, vol. 26, no. 4, pp. 353–368, 2015.

B. Bulic, M. Pickhardt, E.-M. Mandelkow, and E. Mandelkow, “Tau protein and tau aggregation inhibitors,” *Neuropharmacology*, vol. 59, no. 4-5, pp. 276–289, 2010.

H. K. I. Dias, C. L. R. Brown, M. C. Polidori, G. Y. H. Lip, and H. R. Griffiths, “LDL-lipids from patients with hypercholesterolemia and Alzheimer’s disease are inflammatory to microvascular endothelial cells: mitigation by statin interven-tion,” *Clinical Science*, vol. 129, no. 12, pp. 1195–1206, 2016.

F. C. Lin, Y. S. Chuang, H. M. Hsieh et al., “Early statin use and the progression of Alzheimer disease: a total population-based case-control study,” *Medicine*, vol. 94, no. 47, Article ID e2143, 2015.

S. M. Grundy, “Metabolic syndrome update,” *Trends in Cardio-vascular Medicine*, vol. 26, no. 4, pp. 364–373, 2016.

K. Srikanthan, A. Feyh, H. Visweshwar, J. I. Shapiro, and K. Sodhi, “Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population,” *International Journal of Medical Sciences*, vol. 13, no. 1, pp. 25–38, 2016.

B. McGuinness, D. Craig, R. Bullock, and P. Passmore, “Statins for the prevention of dementia,” *The Cochrane Database of Systematic Reviews*, no. 2, Article ID CD003160, 2009.

K. Fukui, H. A. Ferris, and C. R. Kahn, “Effect of cholesterol reduction on receptor signaling in neurons,” *The Journal of Biological Chemistry*, vol. 290, no. 44, pp. 26383–26392, 2015.
V. Rani, G. Deep, R. K.Singh, K. Palle, and U. C. S. Yadav, “Oxidative stress and metabolic disorders: pathogenesis and therapeutic strategies,” *Life Sciences*, vol. 148, no. 11, pp. 183–193, 2016.

L. M. Waite, “Treatment for Alzheimer’s disease: has anything changed?” *Australian Prescriber*, vol. 38, no. 2, pp. 60–63, 2015.

M. K. Jedrzwiski, D. C. Ewbank, H. Wang, and J. Q. Trojanowski, “The impact of exercise, cognitive activities, and socialization on cognitive function: results from the national long-term care survey,” *American Journal of Alzheimer’s Disease & Other Dementias*, vol. 29, no. 4, pp. 372–378, 2014.

O. C. Okonkwo, S. A. Schultz, J. M. Oh et al., “Physical activity attenuates age-related biomarker alterations in preclinical AD,” *Neurology*, vol. 83, no. 19, pp. 1753–1760, 2014.

J. Verghese, R. B. Lipton, M. J. Katz et al., “Leisure activities and the risk of dementia in the elderly,” *The New England Journal of Medicine*, vol. 348, no. 25, pp. 2508–2516, 2003.

Y.-H. Sung, “Effects of treadmill exercise on hippocampal neurogenesis in an MPTP/probenecid-induced Parkinson’s disease mouse model,” *Journal of Physical Therapy Science*, vol. 27, no. 10, pp. 3203–3206, 2015.

M. S. Nokia, S. Lensu, J. P. Ahltainen et al., “Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained,” *The Journal of Physiology*, vol. 594, no. 7, pp. 1855–1873, 2016.

R. B. Speisman, A. Kumar, A. Rani, T. C. Foster, and B. K. Ormerod, “Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats,” *Brain, Behavior, and Immunity*, vol. 28, pp. 25–43, 2013.

T. Paillard, Y. Rolland, and P. S. de Barreto, “Protective effects of physical exercise in Alzheimer’s disease and Parkinson’s disease: a narrative review,” *Journal of Clinical Neurology*, vol. 11, no. 3, pp. 212–219, 2015.

P. Bekinschtein, C. A. Oomen, L. M. Saksida, and T. J. Bussey, “Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable?” *Seminars in Cell & Developmental Biology*, vol. 22, no. 5, pp. 536–542, 2011.

M. P. Mattson, “Lifelong brain health is a lifelong challenge. From evolutionary principles to empirical evidence,” *Aging Research Reviews*, vol. 20, pp. 37–45, 2015.

M. J. Schafer, M. J. Allred, S. H. Lee et al., “Reduction of β-amyloid and γ-secretase by calorie restriction in female Tg2576 mice,” *Neurobiology of Aging*, vol. 36, no. 3, pp. 1293–1302, 2015.

L. Fratiglioni, S. Paillard-Borg, and B. Winblad, “An active and socially integrated lifestyle in late life might protect against dementia,” *The Lancet Neurology*, vol. 3, no. 6, pp. 343–353, 2004.

J. A. Garcia-Casal, A. Loizou, E. Cspike, M. Franco-Martín, M. V. Perea-Bartolome, and M. Orrell, “Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis,” *Aging & Mental Health*, 2016.

T. Kishi and K. Sunagawa, “Exercise training plus calorie restriction causes synergistic protection against cognitive decline via up-regulation of BDNF in hippocampus of stroke-prone hypertensive rats,” in *Proceedings of the 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (EMBS ’12), pp. 6674–6676, San Diego, Calif, USA, August 2012.

Y. Kida and M. S. Goligorsky, “Sirtuins, cell senescence, and vascular aging,” *Canadian Journal of Cardiology*, vol. 32, no. 5, pp. 634–641, 2016.

I. Amigo and A. K. Kowaltowski, “Dietary restriction in cerebral bioenergetics and redox state,” *Redox Biology*, vol. 2, no. 1, pp. 296–304, 2014.

E. J. Dhurandhar, D. B. Allison, T. van Groen, and I. Kadish, “Hunger in the absence of caloric restriction improves cognition and attenuates alzheimer’s disease pathology in a mouse model,” *PLoS ONE*, vol. 8, no. 4, Article ID e60437, 2013.

R. Musttq, S. Shoib, T. Shah, and S. Mushtaq, “Relationship between loneliness, psychiatric disorders and physical health? A review on the psychological aspects of loneliness,” *Journal of Clinical and Diagnostic Research*, vol. 8, no. 9, pp. WE01–WE04, 2014.

C. A. de Jager, A. Oulhaj, R. Jacoby, H. Refsum, and A. D. Smith, “Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial,” *International Journal of Geriatric Psychiatry*, vol. 27, no. 6, pp. 592–600, 2012.

H. Kim, G. Kim, W. Jang, S. Y. Kim, and N. Chang, “Association between intake of B vitamins and cognitive function in elderly Koreans with cognitive impairment,” *Nutrition Journal*, vol. 13, no. 1, article 118, pp. 1–11, 2014.

Y. Sun, C.-J. Lu, K.-L. Chien, S.-T. Chen, and R.-C. Chen, “Efficacy of multivitamin supplementation containing vitamins b6 and b12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in Alzheimer’s disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese Patients,” *Clinical Therapeutics*, vol. 29, no. 10, pp. 2204–2214, 2007.

A. H. Ford, L. Flicker, H. Alfonso et al., “Vitamins B12, B6, and folic acid for cognition in older men,” *Neurology*, vol. 75, no. 17, pp. 1540–1547, 2010.

R. C. Petersen, R. G. Thomas, M. Grundman et al., “Vitamin E and donepezil for the treatment of mild cognitive impairment,” *The New England Journal of Medicine*, vol. 352, no. 23, pp. 2379–2388, 2005.

S. Arlt, T. Müller-Thomsen, U. Beisiegel, and A. Kontush, “Effect of one-year vitamin C- and E-supplementation on cerebrospinal fluid oxidation parameters and clinical course in Alzheimer’s disease,” *Neurochemical Research*, vol. 37, no. 12, pp. 2706–2714, 2012.

A. K. Gangwar, A. Rawat, S. Tiwari, S. C. Tiwari, J. Narayan, and S. Tiwari, “Role of Vitamin-D in the prevention and treatment of Alzheimer’s disease,” *Indian Journal of Physiology and Pharmacology*, vol. 59, no. 1, pp. 94–99, 2015.

J. L. Barranco-Quintana, M. F. Allam, A. S. Del Castillo, and R. F. Navajas, “Risk factors for Alzheimer’s disease,” *Revue Neurologique*, vol. 40, no. 10, pp. 613–618, 2005.

A. Giacosa, A. F. Adam-Blondon, S. Baer-Sinnott et al., “Alcohol and wine in relation to cancer and other diseases,” *European Journal of Cancer Prevention*, vol. 21, no. 1, pp. 103–108, 2012.

D. Cutuli, P. De Bartolo, P. Caporali et al., “α-3 polyunsaturated fatty acids supplementation enhances hippocampal functional-ity in aged mice,” *Frontiers in Aging Neuroscience*, vol. 6, article 220, pp. 1–17, 2014.

H. Nasri, A. Baradaran, H. Shirzad, and M. Rafeian-Kopaei, “New concepts in nutraceuticals as alternative for pharmaceuti-cals,” *International Journal of Preventive Medicine*, vol. 5, no. 12, pp. 1487–1499, 2014.
[198] F. I. Baptista, A. G. Henriques, A. M. S. Silva, J. Wiltfang, and O. A. B. da Cruz E Silva, “Flavonoids as therapeutic compounds targeting key proteins involved in Alzheimer’s disease,” ACS Chemical Neuroscience, vol. 5, no. 2, pp. 83–92, 2014.

[199] I. Solanki, P. Parihar, M. L. Mansuri, and M. S. Parihar, “Flavonoid-based therapies in the early management of neurodegenerative diseases,” Advances in Nutrition, vol. 6, no. 1, pp. 64–72, 2015.

[200] M. P. Corcoran, D. L. McKay, and J. B. Blumberg, “Flavonoid basics: chemistry, sources, mechanisms of action, and safety,” Journal of Nutrition in Gerontology and Geriatrics, vol. 31, no. 3, pp. 176–189, 2012.

[201] G. Desideri, C. Kwik-Uribe, D. Grassi et al., “Benefits in cognitive function, blood pressure, and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the Cocoa, Cognition, and Aging (CoCoA) study,” Hypertension, vol. 60, no. 3, pp. 794–801, 2012.

[202] H. B. Boudouda, A. Zaghib, A. Karioti et al., “Antibacterial, antioxidant, anti-cholinesterase potential and flavonol glycosides of Biscutella ranphalonia (Brassicaceae),” Pakistan Journal of Pharmaceutical Sciences, vol. 28, no. 1, pp. 153–158, 2015.

[203] T. Y. Lin, C. W. Lu, C. C. Chang, S. K. Huang, and S. J. Wang, “Luteolin inhibits the release of glutamate in rat cerebrocortical nerve terminals,” Journal of Agricultural and Food Chemistry, vol. 59, no. 15, pp. 8458–8466, 2011.

[204] J. A. Baur and D. A. Sinclair, “Therapeutic potential of resveratrol: the in vivo evidence,” Nature Reviews Drug Discovery, vol. 5, no. 6, pp. 493–506, 2006.

[205] T. Ma, M.-S. Tan, J.-T. Yu, and L. Tan, “Resveratrol as a therapeutic agent for Alzheimer’s disease,” BioMed Research International, vol. 2014, Article ID 350516, 13 pages, 2014.

[206] G. T. Diaz-Gerevini, G. Repossi, A. Dain, M. C. Tarres, U. N. Das, and A. R. Eynard, “Beneficial action of resveratrol: how and why?” Nutrition, vol. 32, no. 2, pp. 174–178, 2016.

[207] Y. A. Kim, G.-Y. Kim, K.-Y. Park, and Y. H. Choi, “Resveratrol inhibits nitric oxide and prostaglandin E, production by lipopolysaccharide-activated C6 microglia,” Journal of Medicinal Food, vol. 10, no. 2, pp. 218–224, 2007.

[208] S. Bastianetto, C. Ménard, and R. Quirion, “Neuroprotective action of resveratrol,” Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease, vol. 1852, no. 6, pp. 1195–1201, 2015.

[209] J. Chen, Y. Zhou, S. Mueller-Steiner et al., “SIRT1 protects against microglia-dependent amyloid-β toxicity through inhibiting NF-κB signaling,” The Journal of Biological Chemistry, vol. 280, no. 48, pp. 40364–40374, 2005.

[210] J. A. Godoy, J. A. Rios, J. M. Zolotzki, N. Braidy, and N. C. Inestrosa, “Signaling pathway cross talk in Alzheimer’s disease,” Cell Communication and Signaling, vol. 12, article 23, 2014.

[211] D. Y. Yoo, J. H. Choi, W. Kim et al., “Effects of luteolin on spatial memory, cell proliferation, and neuroblast differentiation in the hippocampal dentate gyrus in a scopolamine-induced amnesia model,” Neurological Research, vol. 35, no. 8, pp. 813–820, 2013.

[212] M. Zhu, D. Chen, D. Li et al., “Luteolin inhibits angiogenesis II-induced human umbilical vein endothelial cell proliferation and migration through downregulation of src and Akt phosphorylation,” Circulation Journal, vol. 77, no. 3, pp. 772–779, 2013.

[213] M. López-Lázaro, “Distribution and biological activities of the flavonoid luteolin,” Mini-Reviews in Medicinal Chemistry, vol. 9, no. 1, pp. 31–59, 2009.

[214] F. Casamenti, C. Grossi, S. Rigacci, D. Pantano, I. Luccarini, and M. Stefani, “Oleuropein aglycone: a possible drug against degenerative conditions. In vivo evidence of its effectiveness against Alzheimer’s disease,” Journal of Alzheimer’s Disease, vol. 45, no. 3, pp. 679–688, 2015.

[215] H. I. H. El-Sayyad, “Cholesterol overload impairing cerebellar function: the promise of natural products,” Nutrition, vol. 31, no. 5, pp. 621–630, 2015.

[216] A. Safournis, G. Tsivgoulis, T. N. Sergentanis, and T. Psaltopoulou, “Mediterranean diet and risk of dementia,” Current Alzheimer Research, vol. 12, no. 8, pp. 736–744, 2015.

[217] M. Baumgart, H. M. Snyder, M. C. Carrillo, S. Fazio, H. Kim, and H. Johns, “Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective,” Alzheimer’s and Dementia, vol. 11, no. 6, pp. 718–726, 2015.

[218] N. Hu, J.-T. Yu, L. Yan, Y.-L. Wang, L. Sun, and L. Tan, “Nutrition and the risk of Alzheimer’s disease,” BioMed Research International, vol. 2013, Article ID 524820, 12 pages, 2013.

[219] S. H. Duncan and H. J. Flint, “Probiotics and prebiotics and health in ageing populations,” Maturitas, vol. 75, no. 1, pp. 44–50, 2013.

[220] C.-S. Lin, C.-J. Chang, C.-C. Lu et al., “Impact of the gut microbiota, prebiotics, and probiotics on human health and disease,” Biomedical Journal, vol. 37, no. 5, pp. 259–268, 2014.

[221] J. Liu, J. Sun, F. Wang et al., “Neuroprotective effects of Clostridium butyricum against vascular dementia in mice via metabolic butyrate,” BioMed Research International, vol. 2015, Article ID 412946, 12 pages, 2015.

[222] D. Prescott, J. Lee, and D. J. Philpott, “An epithelial armamentarium to sense the microbiota,” Seminars in Immunology, vol. 25, no. 5, pp. 323–333, 2013.

[223] G. Divyashri, G. Krishna, Muralidhara, and S. G. Prapulla, “Probiotic attributes, antioxidant, anti-inflammatory and neuromodulatory effects of Enterococcus faecium CFR 3003: in vitro and in vivo evidence,” Journal of Medical Microbiology, vol. 64, no. 12, pp. 1527–1540, 2015.

[224] W.-H. Liu, H.-L. Chuang, Y.-T. Huang et al., “Alteration of behavior and monoamine levels attributable to Lactobacillus plantarum PS128 in germ-free mice,” Behavioural Brain Research, vol. 298, pp. 202–209, 2016.