Review Article

The Role of Oxidative Stress-Induced Epigenetic Alterations in Amyloid-β Production in Alzheimer's Disease

Li Zuo,[1,2] Benjamin T. Hemmelgarn,[1] Chia-Chen Chuang,[1] and Thomas M. Best[3]

[1]*Radiologic Sciences and Respiratory Therapy Division, School of Health and Rehabilitation Sciences,*
 The Ohio State University College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
[2]*Molecular Physiology and Rehabilitation Research Laboratory, School of Health and Rehabilitation Sciences,*
 The Ohio State University College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA
[3]*Division of Sports Medicine, Department of Family Medicine, Sports Health & Performance Institute,*
 The Ohio State University Wexner Medical Center, Columbus, OH 43210, USA

Correspondence should be addressed to Li Zuo; zuo.4@osu.edu

An increasing number of studies have proposed a strong correlation between reactive oxygen species (ROS)-induced oxidative stress (OS) and the pathogenesis of Alzheimer's disease (AD). With over five million people diagnosed in the United States alone, AD is the most common type of dementia worldwide. AD includes progressive neurodegeneration, followed by memory loss and reduced cognitive ability. Characterized by the formation of amyloid-beta (Aβ) plaques as a hallmark, the connection between ROS and AD is compelling. Analyzing the ROS response of essential proteins in the amyloidogenic pathway, such as amyloid-beta precursor protein (APP) and beta-secretase (BACE1), along with influential signaling programs of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Jun N-terminal kinase (JNK), has helped visualize the path between OS and Aβ overproduction. In this review, attention will be paid to significant advances in the area of OS, epigenetics, and their influence on Aβ plaque assembly. Additionally, we aim to discuss available treatment options for AD that include antioxidant supplements, Asian traditional medicines, metal-protein-attenuating compounds, and histone modifying inhibitors.

1. Introduction

Alzheimer's disease (AD) is the most prevalent type of dementia with over five million people affected in the United States and 35 million worldwide [1]. The existence of amyloid-β (Aβ) plaques and tau neurofibrillary tangles (NFTs), leading to synaptic loss, is the major hallmark of AD pathogenesis [2–5]. Aβ, a 36–43 amino acid peptide that has been shown to clump together, forms amyloid aggregates that act in a prion fashion [6]. Zinc (Zn), Copper (Cu), and Iron (Fe) ions have also been implicated in the protein aggregation process, with Cu and Zn spatially correlated with amyloid plaques [7]. These plaques are often found in aging neurons, together with NFTs that are formed from hyperphosphorylated tau proteins. With time, this buildup of plaques and tangles can trigger the neurodegeneration associated with AD, resulting in cognitive deterioration with impaired speech, vision,

behavior, and eventually death [8, 9]. Although individual facets of AD pathogenesis are understood, the mechanism of neurodegeneration is complex due to the fact that AD develops differently in each patient [10–12]. One possible vehicle for deposition and accumulation of Aβ in AD is oxidative stress (OS), mediated by the production of reactive oxygen species (ROS) (Figure 1) [3, 13–15].

Particularly in biological systems, ROS are a category of important free radicals such as superoxide and hydroxyl radicals produced as a byproduct of oxidative phosphorylation in the mitochondria's electron transport chain (ETC), with smaller amounts originating from cellular membrane, endoplasmic reticulum (ER), and peroxisomes [16–20]. Interestingly, Aβ can form complexes with Cu and generate hydrogen peroxide via the reduction of Cu^{2+} [21]. The body can be exposed to ROS directly from exogenous sources, such as tobacco smoke and radiation [22–24]. ROS can also act
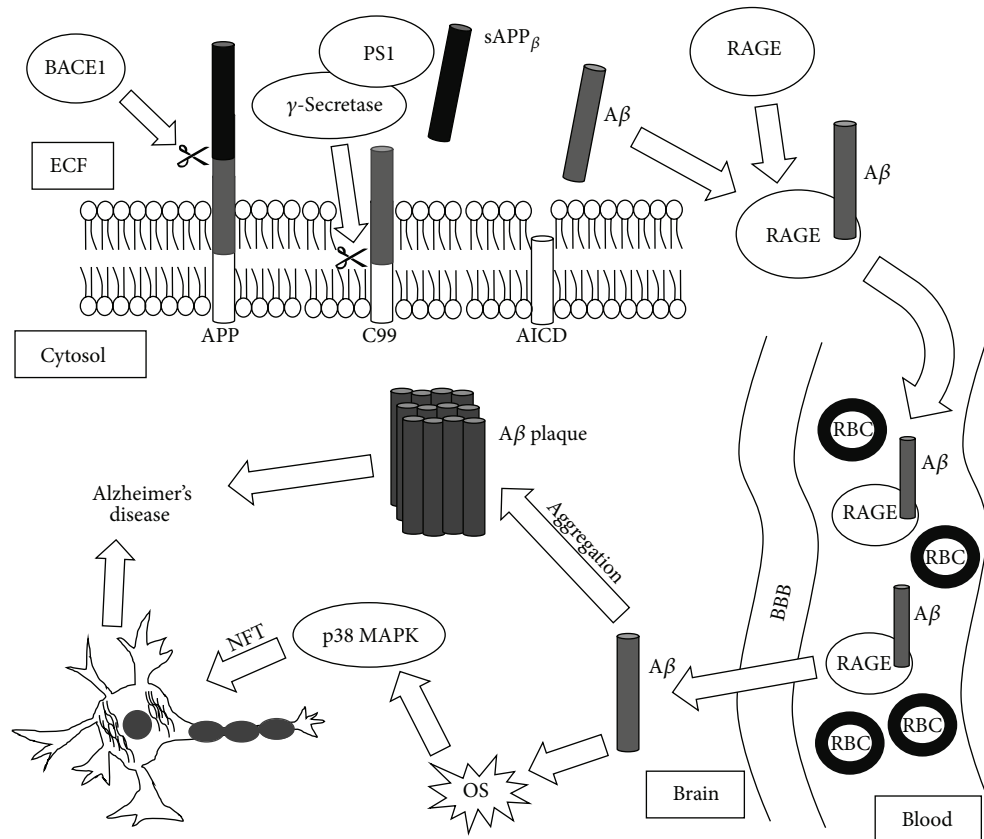
FIGURE 1: The role of amyloidogenesis in Alzheimer's disease. Amyloid-β originates as amyloid-beta precursor protein in the plasma membrane, which is cleaved sequentially by beta-site APP cleaving enzyme 1 and gamma-secretase. Following interaction between receptors for advanced glycation end products, which leads to its uptake in the brain, amyloid-β can form insoluble plaques and induce neurofibrillary tangles in neurons, the hallmarks of Alzheimer's disease. Aβ, amyloid-β; AICD, amyloid intracellular domain; APP, amyloid-beta precursor protein; BACE1, beta-site APP cleaving enzyme 1; BBB, blood-brain barrier; C99, residual 99 amino acids from C-terminal of APP; ECF, extra cellular fluid; p38 MAPK, p38 mitogen-activated protein kinase; OS, oxidative stress; PS1, presenilin 1; NFT, neurofibrillary tangle; RAGE, receptor for advanced glycation end products; RBC, red blood cell.

as necessary signaling molecules [25–27]. However, if their concentration increases markedly or the body cannot remove the excess species efficiently, these molecules can cause cellular damage. ROS oxidize essential cellular components such as DNA, proteins, and lipids, leading to disruption in cell homeostasis [28, 29].

In the process of aging and neurodegenerative diseases, the decline of normal antioxidant defense mechanisms increases the brain's vulnerability to oxidative damage known as OS [30]. ROS have the ability to modify crucial molecules in the cell, including proteins shown to be involved in neurodegenerative diseases [31]. Misregulation of ROS, due to either mitochondrial dysfunction, age, or both, has been implicated in numerous neurodegenerative diseases. By connecting ROS production to Aβ plaque formation, a more complete map of amyloidogenesis can allow researchers to focus their efforts on viable treatment options for AD.

2. Importance of ROS in Neurology

2.1. Natural Formation and Function of ROS. OS can be indicated by cell damage and impairment of cell signaling

as a direct or indirect result of the accumulation of ROS in the cell. In some biological contexts, ROS provide essential molecular services. For example, neutrophils generate superoxide via NADPH oxidase in order to sequester or eliminate pathogens [32]. In many cases, superoxide forms from oxidative phosphorylation that occurs in the respiratory chain of mitochondria, especially in the sites of NADH dehydrogenase (complex I) and cytochrome bc1 (complex III) [13, 17]. The ETC transfers electrons from a series of protein complexes that act as electron donors and acceptors, with diatomic oxygen acting as the ultimate electron acceptor. Leakage in the ETC does occasionally occur, and premature redox reactions between oxygen and complexes I and III produce superoxide radicals [33]. Complexes I and III are also susceptible to malfunction during the process of aging, which can lead to additional OS [34]. ROS can be generated from pathological conditions such as hyperglycemia and hypoxic insults [3, 35, 36]. Aging is associated with increased OS due to long-term exposure of ROS and insufficient defense mechanisms in the brain [31, 34, 37]. The accumulation of such ROS eventually leads to significant cell damage [34, 38–41].
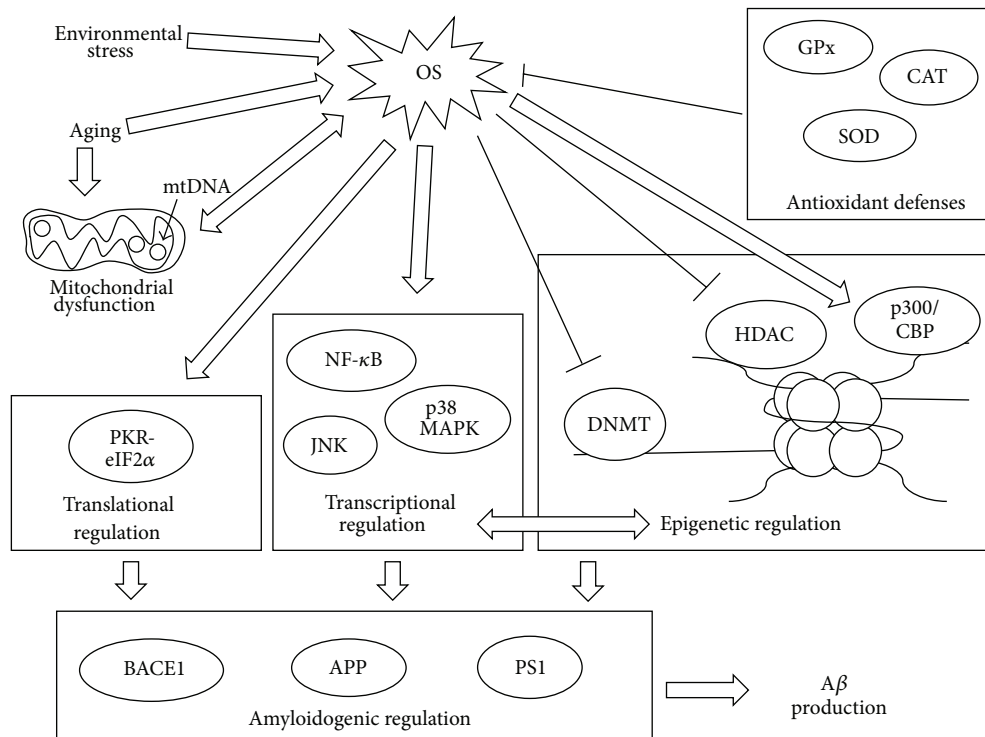
FIGURE 2: The role of oxidative stress in the multiple domains of amyloid-β production regulation. Oxidative stress, caused from reactive oxygen species production, creates an environment which is epigenetically, transcriptionally, and translationally favorable for amyloid-β production. Aβ, amyloid-β; APP, amyloid-beta precursor protein; BACE1, beta-site APP cleaving enzyme 1; CAT, catalase; DNMT, DNA methyltransferase; eIF2α, eukaryotic translation initiation factor-2alpha; GPx, glutathione peroxidase; HAT, histone acetyltransferase; HDAC, histone deacetylase complex; JNK, c-Jun N-terminal kinase; p38 MAPK, p38 mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OS, oxidative stress; PKR, double-stranded RNA dependent protein kinase; PS1, presenilin 1; SOD, superoxide dismutase.

2.2. Inorganic-Related Pathoetiology. Exposure to environmental factors such as pollutants, chemicals, and radiation can disrupt the balance between prooxidant and antioxidant levels, thereby inducing OS [5, 42]. Elevated ROS are due to activated phagocytes in chronic inflammation under stress, whereas the declining antioxidant levels are associated with mutated antioxidant enzymes or toxins [42]. Poisoning in herbicides, such as paraquat, can indirectly influence neurotransmitter metabolism by altering redox cycling [42] and has been linked to Parkinson's disease [43]. Nutritional factors also play crucial roles in AD development: excess Fe deposits can increase the formation of ROS while Zn can contribute to Aβ peptide aggregation [5, 44]. Recent studies show a detection of higher Fe concentration in AD patient brains, particularly in the area of the hippocampus and the parietal cortex. Fe-induced ROS can damage the cell membrane via lipid peroxidation and the subsequent neurotoxicity leads to potential cell death [5, 45]. Though present in high concentrations in Aβ aggregates, Fe has not been copurified with Aβ. On the other hand, Cu and Zn copurify with Aβ in human *postmortem* brains [46]. In a study by Chen et al., Zn addition was exclusively found to encourage protofibril formation. This process occurred without nucleation of Aβ oligomers [47]. Additionally, Cu has been found to form enzymatic complexes with Aβ that mirror

the antioxidant superoxide dismutase (SOD). These Aβ·Cu^{2+} complexes have long been understood to directly generate hydrogen peroxide via Cu^{2+} reduction [48]. More recently, Mayes et al. demonstrated how Aβ fibrils, when bound to Cu^{2+}, could convert hydrogen peroxide into hydroxyl radicals [49]. Although further investigation on the mechanism is necessary, environmental and nutritional-derived OS proposes a novel approach to therapeutic strategies in neurodegenerative diseases (Figure 2) [5].

2.3. Endogenous Antioxidant Defense Mechanisms. ROS molecules are natural byproducts of normal cellular biochemistry. In order to maintain homeostasis, the body has evolved several endogenous antioxidant molecules and enzymes to mitigate ROS-induced cytotoxicity [41]. Some of the better-studied antioxidant enzymes include SOD, catalase (CAT), and glutathione peroxidase (GPx) (Figure 2). Humans possess three types of SOD. SOD1 and SOD3, which contain Zn and Cu as cofactors, are located in the cytoplasm and extracellular space, respectively. SOD2 is located in the mitochondria and binds to manganese as a cofactor [50]. These metalloproteins can facilitate the dismutation of superoxide into oxygen and hydrogen peroxide [29, 50]. Peroxide, still a ROS molecule, is further processed by the antioxidant CAT. CAT is a nearly universal enzyme for

organisms exposed to oxygen and catalyzes the decomposition of hydrogen peroxide into water and oxygen [51]. The selenium containing GPx restores oxidized membrane lipids [52], while also reducing hydrogen peroxide to water [53]. With the coordination of these antioxidants, a healthy cell can effectively control the potential dangers of ROS.

2.4. Dysfunction due to ROS Production and Neurodegeneration. While these antioxidants can help protect an organism from oxidative damage, they themselves can also be oxidized by ROS. Choi et al. examined the oxidative modifications that SOD1 could undergo in AD brains [54]. SOD1 was found to be oxidized and carbonylated in the brain, and its activity was markedly reduced in patients with AD. The downregulation of intracellular SOD is found to contribute to the acceleration of Aβ oligomerization and initiate early onset of cognitive impairment [55]. SOD1 was also observed in protein aggregates, implicating its role in AD pathogenesis [54]. Casado et al. and Ansari and Scheff both demonstrated reduced levels of SOD, CAT, and GPx in AD patient blood samples and human *postmortem* frontal cortex samples, respectively [56, 57]. Additionally, glutathione (GSH) redox cycling is reported to be essential in the brain's detoxification of ROS [41]. As the most abundant antioxidant, GSH acts in the first response to OS [58]. Reduced antioxidant capacity is a hallmark of AD, and the ensuing OS can lead to neurodegeneration. This oxidative imbalance illuminates the potential brain damage and cellular dysfunctions arising from OS [3, 41, 59]. If the level of ROS exceeds the protection of endogenous antioxidant pathways in persistence, cell death is likely and is almost universally implicated in neurodegeneration [38].

Le Bras et al. examined how increased ROS could activate cell-death machinery [60]. ROS are able to promote mitochondrial membrane permeability, releasing calcium (Ca^{2+}). ROS can also discharge amplification factors of mitochondria-induced apoptosis, activate caspases, and induce DNA damage. By initiating these hallmarks of mitochondria-induced apoptosis, ROS have the capacity to trigger neuronal death. Furthermore, mitochondrial DNA (mtDNA) is another target of oxidation by ROS (Figure 2) [61]. Liu et al. showed how large sections of mtDNA were mutated in patients with neurodegenerative diseases and how mutations could make mitochondria more vulnerable to apoptosis [61]. In addition, Patten et al. determined how ROS affected apoptosis through other means. For example, ROS have been shown to stabilize p53 and activate c-Jun N-terminal kinase (JNK) [62]. Activation of these central elements in mitochondria-induced apoptosis can lead to eventual neurodegeneration.

2.5. Aging and Oxidative Stress. Many neurodegenerative diseases are associated with old age [63], and most symptoms appear in people over age 60 [64]. Recent research has suggested that the elderly are more prone to OS (Figure 2) [65, 66]. Complex I deficiencies are more prevalent in aging patients, suggesting that a less efficient ETC can create higher concentrations of ROS than in younger people [67]. Hamilton and Holscher used an AD mouse model to show that neurogenesis was markedly reduced in aging mice,

together with increased Aβ plaque formation as a result of OS [65]. Additionally, mitochondria can be viewed as dynamic organelles, which are constantly undergoing a process of fusion and fission [68]. Conley et al. and Hauptmann et al. have demonstrated how mitochondrial dysfunction is more common with age [69, 70]. If the mitochondrial fission-fusion homeostasis is disrupted, accelerated ROS production will ensue (Figure 2) [71]. The resulting increase in ROS is detrimental for the cell due to superoxide and hydrogen peroxide's reactivity with essential molecules, including DNA and lipids [72]. Mitochondria accumulate membrane damage as they age, which can assist increased ROS production. Hauptmann et al. observed that mitochondrial dysfunction could begin as early as three months in an AD mouse model [70]. This is critical since mitochondrial dysfunction is generally viewed as one of the first steps of AD pathogenesis [37].

3. Neuropathological Characteristics of Alzheimer's Disease

3.1. Amyloidogenic Pathway. One of the major pathological indications of AD is the formation of extracellular plaques loaded with Aβ peptide [4, 73, 74]. Understanding the process in which Aβ is formed is likely of the utmost importance in the search for an effective AD treatment. The amyloid-beta precursor protein (APP) is an integral membrane protein whose normal function is not yet fully understood. By altering APP levels in transgenic mice, it was suggested that APP is important in synapse plasticity [75, 76]. APP is processed in two distinct mechanisms: the amyloidogenic, or plaque forming, and the nonamyloidogenic. In the nonamyloidogenic route, APP is processed by an α-secretase and then γ-secretase to yield an APP intracellular domain and soluble N-terminal fragment called p3 [77]. The majority of APP enters the nonamyloidogenic pathway, and other factors, such as mutations, environmental stimuli, and aging, are likely to influence this pattern; however, the mechanism remains unclear [4].

The sequential enzymatic breakdown of APP by the beta-site APP cleaving enzyme 1 (BACE1) and the γ-secretase complex with presenilin 1 (PS1) highlights the amyloidogenic pathway [2, 4, 5, 37, 78–80]. Other products formed from these actions include a truncated type of sAPP (sAPP$_\beta$) and the residual 99 amino acids of APP (C99) from the cleavage of APP by BACE1. The remaining amyloid intracellular domain (AICD) is formed due to the liberation of Aβ cleaved from C99 by γ-secretase, leaving AICD in the plasma membrane (Figure 1) [81]. Though Aβ has observed beneficial characteristics, such as its function as an antimicrobial peptide [82], it is highly associated with formation of bulky plaques that ultimately result in neuronal degradation. Soluble Aβ oligomers are recognized as the most neurotoxic form of Aβ [41, 55, 83]. Its ability to bind to preexisting Aβ aggregates or lipid membranes (e.g., gangliosides) and potential to alter other cytoskeletal proteins can lead to synaptotoxicity within neurons [84]. Additionally, the activity of BACE1 is markedly higher in old age, linking age with Aβ plaque production [85]. The receptor for advanced glycation end products (RAGE)

is an important Aβ receptor and the binding of Aβ to RAGE facilitates transportation across the blood-brain barrier (BBB) [86], thereby aiding in accumulation of Aβ protein within the brain (Figure 1). Cho et al. described how RAGE could stimulate BACE1 expression through RAGE's ability to generate an intracellular Ca^{2+} response that activates nuclear factor of activated T-cells 1 (NFAT1), a BACE1 activator. BACE1 then cleaves APP to form Aβ, which completes the feedback loop by acting as a RAGE activator [87].

3.2. Connection between Aβ-Induced OS and Tau Neurofibrillary Tangles (NFTs).
Another pathophysiological characteristic of AD is the formation of intracellular NFTs consisting of an abnormal accumulation of hyperphosphorylated tau protein [4, 73]. Normally, tau serves to assemble and stabilize microtubule structures and is essential for the transportation of vesicles containing neurotransmitters within the neuronal axons. The excess phosphorylated tau aggregates and forms insoluble helical filaments that limit the transportation of neurotransmitters. As a result, NFTs interfere with communication between neurons and eventually lead to cognition impairment. Like Aβ oligomers, tau aggregates are cytotoxic [4].

Aβ-induced OS alters cellular signaling pathways and initiates a phosphorylation response. An increase in activation of JNK and p38 mitogen-activated protein kinase (MAPK) is noticeable in AD *postmortem* brains, suggesting a possible linkage between dysregulation of MAPK signaling pathway and AD pathogenesis [88]. Giraldo et al. demonstrated that p38 MAPK polypeptide is involved in tau hyperphosphorylation. The p38 MAPK and other kinases can be activated in response to Aβ accumulation. Activated p38 MAPK polypeptide phosphorylates tau protein, producing a hyperphosphorylated tau response. This study illustrates a positive correlation between tau aggregation and activated p38. Therefore, the activation of p38 is an indicator for tau hyperphosphorylation, further supporting the pathological association between Aβ and tau in AD (Figure 1) [88].

3.3. Aβ Formation Leads to Apoptosis in Neurons.
Aβ has been associated with neurodegeneration and is found at elevated levels in AD brains [89]. The increase in Aβ causes neurodegeneration by activating apoptotic death signals such as caspase pathways in neurons [90–93]. Ferreiro et al. stated that Aβ was involved in depleting Ca^{2+} amounts in the ER [90], resulting in a high level of cytosolic Ca^{2+} that causes the mitochondrial membrane to lose its chemical potential, inducing mitochondrial apoptotic events. They demonstrated that lower levels of GSH, in response to increased Ca^{2+} release, result in ROS accumulation [91]. Aβ has also been shown to increase the activity of calcineurin (CaN), a protein phosphatase that catalyzes dephosphorylation of Bcl-2-associated death promoter (BAD). As a proapoptotic protein, BAD triggers cytochrome c release after translocating to the mitochondria [92]. In addition, Aβ proteins associate with the caspase cascade, leading to proteolysis of caspase targets and eventual apoptosis [93].

3.4. Neurodegeneration Results in Decreased Cognitive Ability, Dementia, and Memory Loss.
Aβ has been referred to as an initiator in the mitochondrial, ER, and caspase-responsive apoptotic pathways, which collectively lead to neurodegeneration [90–93]. Neuronal atrophy is an essential characteristic of AD, as well as memory deficits, a loss of cognitive ability, and dementia [8, 94]. A study of 764 participants attempted to map Aβ in the brain. Posterior cortical regions, associated with memory retrieval in younger participants, show Aβ deposits in the elderly with AD [95]. Aging mice expressing an AD-linked APP variant formed Aβ plaques, resulting in memory loss [96]. The isolated Aβ protein induced memory deficits when injected into young rats [96]. Similarly, Aβ dimers extracted from the cerebral cortex of AD patients were found to affect learned behavior memory when administered to normal rats. The Aβ dimers were concluded to be the smallest toxic species for synapse structure [97]. Therefore, Aβ has been reliably shown to induce AD effects in a variety of experimental settings.

4. The Role of ROS in Alzheimer's Disease

4.1. Epigenetic Alteration of Aβ (Methylation and Acetylation).
ROS activity has long been understood to affect DNA transcription through its oxidation of DNA and related proteins [98, 99]. Epigenetics refers to the changes in gene expression through chemical processes, such as histone modification and DNA methylation, without the disruption of DNA sequence. Acting as an anchor for DNA, histones contain N-terminal tails that can be methylated, sumoylated, phosphorylated, and ubiquitinated, as well as other posttranslational modifications. Histone acetylation and deacetylation are the most well-studied mechanisms, with histone acetyltransferases (HATs) and histone deacetylases (HDACs) attaching or removing acetyl groups to the histone tails, respectively. Acetylation neutralizes the positive charge associated with the histone tail, limiting the attraction among the negative phosphate groups of DNA. Relaxed DNA offers easier access for gene transcription [100]. DNA methyltransferases (DNMTs) are closely tied to the process of histone acetylation, modifying DNA structure by transferring methyl groups to cytosine-guanine (CpG) dinucleotides. Generally, methylated CpG sequences can induce histone modifications that repress the transcriptional complex's ability to access DNA [100]. Oxidation of the guanine residue in CpG dinucleotides can also affect the epigenetic regulatory complexes in a similar manner, placing emphasis on OS in the regulation of CpG sites [101]. These sites are particularly important in AD, as the promoter regions of APP and BACE1 contain 65 and 36 CpG sites, respectively [3]. The presence of these sites adds significance to the idea that the essential genes of amyloidosis are potentially regulated in an epigenetic manner. Additionally, epigenetics can be influenced by environmental stimuli; however, it can also change naturally during growth and development [102].

Recently, explorations of epigenetic regulation mechanisms present a novel insight into OS and its relation to AD [3, 103]. Several studies have revealed the epigenetic control of Aβ production in the progression of AD [104,

105]. Chromatin remodeling has also been reported to assist in the upregulation of BACE1 and Aβ production [106, 107]. Sung et al. and Chouliaras et al. have shown that not only is there global decrease of DNA methylation in the hippocampus of *postmortem* AD patients, but also APP-related mutations cause an epigenetic shift in an AD model cell line [102, 103]. Clearly, epigenetic mechanisms are meaningful in Aβ plaque formation. Gu et al. studied what possible agents could provoke this epigenetic shift in AD patients [3]. When neuroblastoma cells were treated with hydrogen peroxide, there was a significant increase in histone acetylation together with a decrease in DNA methylation. This histone hyperacetylation and DNA hypomethylation resulted in increased APP and BACE1 transcription, possibly by a gain of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity [3]. This study shows how OS can cause Aβ plaque formation through means of epigenetic mechanisms and offers promise for treatment approaches directed at this pathway. Cytosine in a CpG site of DNA undergoes frequent methylation and regulates gene expression during development, differentiation, pathogenesis, and aging [3, 102]. Besides DNA methylation, DNA hydroxymethylation describes a different biological role in the epigenetic modification of AD. 5-Hydroxymethylcytidine (5-hmC) and 5-methylcytidine (5-mC) levels are significantly decreased in AD brains [103]. The linkage between epigenetic dysregulation and AD is evidently supported by previous studies with correlation to OS [3, 103]. The modified transcriptional expression of AD-related genes (APP, BACE1, and PS1) enhances Aβ production and contributes to AD pathogenesis and development [3, 108]. Furthermore, epigenetic mechanisms associated with OS, especially altered methylation or CpG oxidation, exacerbate the progression of oxidative DNA damage (Figure 2) [3].

4.2. Activation of Stress-Related Signal Pathway Increases BACE1 and APP Transcription. Due to the neuropathological nature of AD, many studies have investigated how the Aβ formation pathway can be manipulated. Using the potent DNMT inhibitor S-adenosylhomocysteine (SAH), Lin et al. were able to hypomethylate PS1 and APP promoters, accompanied by increased expression of PS1 and APP. As a result, Aβ protein production is increased [109]. Guo et al. showed that JNK and p38 MAPK, stress-related MAPKs, are activated with addition of anisomycin and induce intracellular Aβ production in neuroblastoma cells [110]. APP and BACE1 were found to be upregulated as a result of demethylation of their promoters. Simultaneously, transcription of HAT p300/CREB-binding protein (CBP) was increased, while transcription of DNMTs and HDACs was downregulated [110]. This study confirmed that Aβ overproduction could occur during times of cellular stress through a hypomethylation/hyperacetylation-dependent pathway. Increasingly, evidence suggests the contribution of epigenetic dysregulation to AD pathogenesis [25, 102]. The epigenetic modification in AD-related genes is a result of activation of JNK and p38 MAPK pathways [3, 111]. In the presence of anisomycin, the reduction of DNMT activity induces an overexpression of APP, BACE1, and PS1

[102, 112]. In addition, Gu et al. have identified hydrogen peroxide as an activator for the distinct MAPK cascades. DNA methylation is markedly reduced in APP and BACE1 promoters after treatments with hydrogen peroxide [3]. The finding further suggests the role of OS in modulating DNA methylation and histone acetylation in specific AD-related genes (Figure 2) [3, 25].

4.3. Translational Regulation of Aβ. In a separate investigation, the addition of hydrogen peroxide in human neuroblastoma cells resulted in enhanced expression of BACE1, supporting the observation that OS can heighten BACE1 levels [111]. JNK is believed to be responsible for this increase in BACE1 mRNA, while JNK signaling is correlated with tau-induced toxicity [38]. Moreover, eukaryotic translation initiation factor-2alpha (eIF2α) was found to translationally regulate initiation of BACE1 protein synthesis [111]. The eIF2α undergoes phosphorylation upon its activation, and elevated levels of phosphorylated eIF2α have been reported in AD brains [113]. Phosphorylated eIF2α generally stops protein translation in response to cellular stress; however certain stress response genes, such as BACE1, are activated by eIF2α [111]. Double-stranded RNA dependent protein kinase (PKR) responds to cellular hardship in a proapoptotic manner by activating other stress signaling cascades including eIF2α [114]. Therefore, PKR-eIF2α expands BACE1 protein expression via translational regulation in response to OS (Figure 2) [111]. Suppression of aberrant eIF2α phosphorylation ameliorated AD symptoms in a mouse AD model [113].

5. Treatment

5.1. Antioxidant Supplements. Promising strategies for AD treatment fall on those that can decrease Aβ oligomer and phosphorylated tau levels, promote neuroprotection, and alleviate OS [112, 115]. With the view that ROS are the instigators in Aβ production, it is understandable that much research has focused on the clinical opportunity of antioxidants in alleviating AD symptoms. Gubandru et al. measured the effects of several antioxidant supplements on certain OS markers such as advanced glycation end products (AGEs), protein carbonyls (CRBNLs), and malondialdehyde (MDA) [73]. Although the sample size was small (21 AD patients and 10 controls), results demonstrated how the antioxidant supplement Rivastigmine decreases AGEs in AD patients, while Donepezil restores GSH and total antioxidant capacity (TAC). Therefore, antioxidant supplements offer potential strategies to ameliorate AD in dementia patients [73].

JNK and NF-κB are well-known activators of the amyloidogenic pathway and are responsive to OS [116, 117]. As a free radical scavenger, molecular hydrogen (H$_2$) can specifically reduce hydroxyl radicals. To that end, Wang et al. demonstrated how the reducing agent hydrogen-rich saline could decrease neural inflammation and OS induced by Aβ [118]. Specifically, mice were injected with Aβ and then treated with hydrogen-rich saline for 10 days. OS markers, including the levels of 8-hydroxydeoxyguanosine (8-OHdG), JNK, and NF-κB, were all reduced in the hydrogen-rich saline administered group. Therefore, hydrogen-rich saline

inversely regulates the activation of JNK [118]. This study suggests that hydrogen-rich saline can be used to relieve the symptoms of neuroinflammation [119] and OS in AD patients by attenuation of JNK and NF-κB-induced OS response [118].

Rutin is a naturally occurring glycoside that acts as both an anti-inflammatory and an antioxidant agent. Wang et al. previously demonstrated rutin's ability to inhibit Aβ plaque formation and relieve OS [120]. In another study directly aimed at rutin's role in protecting against AD, mice treated with rutin displayed favorable levels of antioxidant markers, such as increased SOD and GPx activity, reduced memory deficits, and fewer Aβ oligomers [41]. Inflammatory cytokines interleukin- (IL-) 1β and IL-6 were also found to be at lower levels in treated murine brains. In addition, rutin supplementation enhances the activity of SOD, GPx, and CAT [121]. Due to its demonstrated antioxidant and anti-inflammatory properties, rutin shows great potential as a future treatment for AD patients.

Resveratrol, normally found in grapes and red wine, is a phytoalexin that is produced by plant species as a defense mechanism against fungal attack. Its neuroprotective/antioxidant properties have been shown useful in AD treatment [94]. For example, resveratrol can protect astrocytes, the human brain's most plentiful cell, against ROS damage. Astrocytes are important sources of GSH, a major antioxidant in the body, and a decline in GSH levels occurs in aged brains due to the increased vulnerability against OS [122]. Resveratrol provides a shield for astrocytes, which in turn modulates GSH levels and reinforces its antioxidant activity [122]. In addition, resveratrol hinders cellular apoptosis through influencing intracellular signaling pathways and antioxidant mechanisms, such as reducing NF-κB activation and scavenging ROS intermediates. Particularly, resveratrol activates sirtuin protein, a NAD-dependent HDAC, and ultimately improves mitochondrial bioenergetic efficiency through a pathway mediated by sirtuin-1 (SIRT1) and inhibits the formation of Aβ fibrils [94, 123]. Thus, resveratrol's potential to protect neurons from Aβ- and OS-induced toxicity displays promising therapeutic applications during AD progression.

Vitamin E includes a group of antioxidant molecules called tocopherols and tocotrienols [124]. Given its free radical scavenging activity and biological significance in treating other diseases, Vitamin E as a therapy for AD has attracted much attention. Interestingly, a study examining the effect of Vitamins A, C, and E for OS concluded that not only could Vitamin E restore antioxidant activity, but it was found to be more effective than Vitamin A and C, in the rat brain [125]. However, in a more recent study there was no significant difference recorded between patients taking Vitamin E (800 IU/day) over those taking a placebo [126]. A review of the effect of Vitamin E in AD treatment highlights the conflicting results of many studies [127]. Mecocci and Polidori concluded that various obstacles, such as the permeability of the BBB, the delicate antioxidant/free radical equilibrium, and vascular factors of AD pathogenesis, could be responsible for reduced Vitamin E efficacy [128]. Focusing on improving Vitamin E uptake in the brain and optimizing a treatment plan should lead to more realistic results for

Vitamin E supplementation. These challenges make Vitamin E and other antioxidants difficult but worthy potential AD treatment candidates [41, 120, 122, 128].

5.2. Traditional Medicine. Traditional Chinese and Ayurvedic medicine has led to various potential candidates for AD treatment. Su He Xiang Wan (SHXW) is a combination of herbs used in traditional Chinese medicine for clinical problems including stroke, infantile convulsions, and seizures [129, 130]. Jeon et al. studied the effect of SHXW when inhaled by mice injected with Aβ into the hippocampus [130]. SHXW mice showed reduced memory impairment and suppressed Aβ-induced JNK and p38 activations. In SH-SY5Y cells, repression of Aβ-induced apoptosis was observed, and upregulation of Heme oxygenase (HO-1) and nuclear factor-like 2 (Nrf2) indicated mitigated ROS formation [130]. Together, these findings suggest the promise of SHXW to treat AD patients. Clinical studies remain to be conducted to determine the potential efficacy of SHXW.

The Chinese native *Ginkgo biloba* tree has a long history of practice in Chinese traditional medicine [131]. Investigation of its potential role in western medicine has yielded mixed results. A study was performed on 395 subjects with dementia who were treated with 240 mg/day of EGb 761, an extract from *Ginkgo biloba* leaves. Patients that were treated with EGb 761 scored higher on the Short Syndrome Test (SKT), a measure of cognitive ability [132]. A second study showed similar results on the SKT, as well as improved secondary efficacy variables such as caregiver distress scores, Alzheimer's Disease Activities of Daily Living International Scale, and Verbal Fluency Test [133]. However, a separate long-term study testing the effectiveness of EGb 761 in the prevention of AD showed no significant difference between EGb 761 and the matched placebo in terms of AD diagnosis [134], which requires further investigation.

In India, the spice turmeric is a major constituent in curry powders and has been used for digestive ailments [135]. Curcumin, a molecule found in turmeric, has antioxidant activity [136]. Lim et al. observed the effect of low (160 ppm) and high (5000 ppm) dose curcumin on Alzheimer-like pathology in mice. Both high and low concentrations led to a reduced amount of oxidized proteins, as indicated by western blot analysis of carbonylation levels in murine brains. In addition, low dose curcumin lowered soluble and insoluble Aβ by up to 50%. However, APP expression remained unchanged [136]. Yang et al. demonstrated that curcumin can cross the BBB to bind to Aβ and hinder aggregation of Aβ, reducing Aβ levels in mice with previously established Aβ deposits [137].

5.3. Metal Ion Chelators. As mentioned earlier, Fe, Cu, and Zn have been implicated in various aspects of AD, including Fe-induced cognitive damage [45], Cu- and Zn-mediated amyloid aggregation [138], and Cu-mediated ROS generation [48, 49]. Investigations into the possibility of metal-protein-attenuating compounds (MPACs) that abate proteins from interacting with ions have yielded promising results. Iodochlorhydroxyquin, commonly known as clioquinol, is an MPAC that was the focus of a pilot phase 2 clinical trial carried out by Ritchie et al. Over 9 months, 36 patients

participated in a double-blinded, placebo-controlled study that showed a reduction in plasma Aβ42 levels, with no changes in Cu levels. Although the myelo-optic neuropathy associated with chronic use of clioquinol caused its withdrawal in 1970, clioquinol appears to be safe to use with no adverse effects that were reported in this study [139]. Separately, Lannfelt et al. examined the efficacy of PBT2. A successor to clioquinol, PBT2 is a second-generation 8-OH quinolone MPAC that also demonstrated beneficial effects in targeting Aβ oligomers. Aβ42 levels were lowered dose-dependently of PBT2, and no severe adverse effects were reported [140]. Further research into the efficacy and safety of MPACs could hold much potential in the search for effective AD treatment.

5.4. HDAC Inhibitors. Epigenetically, AD genomes have been found to be globally DNA-hypomethylated and histone-hyperacetylated [141]. This epigenetic profile is beneficial for BACE1 expression and Aβ production, thus leading to AD formation. If these epigenetic changes could be reversed, possibly Aβ aggregation could be suppressed. To test this idea, Sung et al. developed two novel HDAC inhibitors (HDACIs) to determine Aβ levels in response to histone deacetylation [108]. Overall, Aβ40 and Aβ42 levels, two common sizes of the Aβ protein, were lower with exposure to HDACIs *in vitro*. β- and γ-Secretase component transcription was suppressed and transcription of Aβ degrading enzymes, such as matrix metalloproteinase-2 (Mmp2), was increased. Additionally, aged AD mice showed improved learning capabilities and reduced memory deficits when exposed to HDACIs [142]. Addition of curcumin, a p300 inhibitor, reduced the expression of BACE1 via histone H3 acetylation inhibition in an Alzheimer cell line [143], further promoting the idea of epigenetics as an initial step in Aβ production. Thus, these inhibitors can be potentially used as alternative treatment options for AD in clinical settings.

6. Conclusions

The features of AD pathogenesis are interrelated with OS. Although it remains unclear whether OS is a direct cause or a result of AD pathology, evidence demonstrates that Aβ plaques, NFTs, and mitochondrial dysfunction all contribute to and are influenced by the imbalance of the oxidative state in the brain. Overproduction of Aβ protein is increased through upregulation of both APP and BACE1, as well as involvement of transcriptional and translational coordinators. The activation of stress-induced MAPK (e.g., p38 MAPK) signaling pathways further contributes to the hallmarks of AD. Therapies that include a diet with high levels of antioxidants could both guard against deleterious epigenetic changes and alleviate the devastating clinical manifestations of AD. Additionally, compounds derived from traditional Chinese and Ayurvedic medicine could potentially be candidates for clinical trials given their success in the laboratory. MPACs that target the impact of metal ions in OS and protein aggregation, as well as inhibitors of the HAT/HDAC enzymes, restore global epigenetic expression that is altered by OS.

Inhibition of this event reduces apoptosis and neurodegeneration observed in histone-altered cells. Studies that continue to elucidate the exact mechanism of OS-induced Aβ production and the effectiveness of antioxidants and small molecule inhibitors will be paramount to the treatment of AD. With increasing understanding of AD pathogenesis, the findings provide promising prospects guiding future clinical investigations and discovery of novel treatment approaches.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

References

[1] D. J. Selkoe, "Preventing alzheimer's disease," *Science*, vol. 337, no. 6101, pp. 1488–1492, 2012.

[2] D. A. Butterfield, "The 2013 SFRBM discovery award: selected discoveries from the butterfield laboratory of oxidative stress and its sequela in brain in cognitive disorders exemplified by Alzheimer disease and chemotherapy induced cognitive impairment," *Free Radical Biology and Medicine*, vol. 74, pp. 157–174, 2014.

[3] X. Gu, J. Sun, S. Li, X. Wu, and L. Li, "Oxidative stress induces DNA demethylation and histone acetylation in SH-SY5Y cells: potential epigenetic mechanisms in gene transcription in Aβ production," *Neurobiology of Aging*, vol. 34, no. 4, pp. 1069–1079, 2013.

[4] H. W. Querfurth and F. M. LaFerla, "Alzheimer's disease," *The New England Journal of Medicine*, vol. 362, no. 4, pp. 329–344, 2010.

[5] M. Nizzari, S. Thellung, A. Corsaro et al., "Neurodegeneration in Alzheimer disease: role of amyloid precursor protein and presenilin 1 intracellular signaling," *Journal of Toxicology*, vol. 2012, Article ID 187297, 13 pages, 2012.

[6] J. Stöhr, J. C. Watts, Z. L. Mensinger et al., "Purified and synthetic Alzheimer's amyloid beta (Aβ) prions," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, no. 27, pp. 11025–11030, 2012.

[7] L. M. Miller, Q. Wang, T. P. Telivala, R. J. Smith, A. Lanzirotti, and J. Miklossy, "Synchrotron-based infrared and X-ray imaging shows focalized accumulation of Cu and Zn co-localized with β-amyloid deposits in Alzheimer's disease," *Journal of Structural Biology*, vol. 155, no. 1, pp. 30–37, 2006.

[8] J. Hardy and D. J. Selkoe, "The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics," *Science*, vol. 297, no. 5580, pp. 353–356, 2002.

[9] M. Meyer-Luehmann, T. L. Spires-Jones, C. Prada et al., "Rapid appearance and local toxicity of amyloid-β plaques in a mouse model of Alzheimer's disease," *Nature*, vol. 451, no. 7179, pp. 720–724, 2008.

[10] P. T. Francis, A. M. Palmer, M. Snape, and G. K. Wilcock, "The cholinergic hypothesis of Alzheimer's disease: a review

of progress," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 66, no. 2, pp. 137–147, 1999.

[11] M. Gatz, C. A. Reynolds, L. Fratiglioni et al., "Role of genes and environments for explaining Alzheimer disease," *Archives of General Psychiatry*, vol. 63, no. 2, pp. 168–174, 2006.

[12] J. Hardy and D. Allsop, "Amyloid deposition as the central event in the aetiology of Alzheimer's disease," *Trends in Pharmacological Sciences*, vol. 12, no. 10, pp. 383–388, 1991.

[13] V. Adam-Vizi, "Production of reactive oxygen species in brain mitochondria: contribution by electron transport chain and non-electron transport chain sources," *Antioxidants and Redox Signaling*, vol. 7, no. 9-10, pp. 1140–1149, 2005.

[14] D. J. Bonda, X. Wang, G. Perry et al., "Oxidative stress in Alzheimer disease: a possibility for prevention," *Neuropharmacology*, vol. 59, no. 4-5, pp. 290–294, 2010.

[15] E. Mariani, M. C. Polidori, A. Cherubini, and P. Mecocci, "Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview," *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, vol. 827, no. 1, pp. 65–75, 2005.

[16] A. Federico, E. Cardaioli, P. Da Pozzo, P. Formichi, G. N. Gallus, and E. Radi, "Mitochondria, oxidative stress and neurodegeneration," *Journal of the Neurological Sciences*, vol. 322, no. 1-2, pp. 254–262, 2012.

[17] M. P. Murphy, "How mitochondria produce reactive oxygen species," *Biochemical Journal*, vol. 417, no. 1, pp. 1–13, 2009.

[18] C. X. C. Santos, L. Y. Tanaka, J. Wosniak, and F. R. M. Laurindo, "Mechanisms and implications of reactive oxygen species generation during the unfolded protein response: roles of endoplasmic reticulum oxidoreductases, mitochondrial electron transport, and NADPH oxidase," *Antioxidants & Redox Signaling*, vol. 11, no. 10, pp. 2409–2427, 2009.

[19] M. H. Yana, X. Wang, and X. Zhu, "Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease," *Free Radical Biology and Medicine*, vol. 62, pp. 90–101, 2013.

[20] F. J. Corpas, J. B. Barroso, and L. A. del Río, "Peroxisomes as a source of reactive oxygen species and nitric oxide signal molecules in plant cells," *Trends in Plant Science*, vol. 6, no. 4, pp. 145–150, 2001.

[21] C. Opazo, X. Huang, R. A. Cherny et al., "Metalloenzyme-like activity of Alzheimer's disease β-amyloid: Cu-dependent catalytic conversion of dopamine, cholesterol, and biological reducing agents to neurotoxic H_2O_2," *The Journal of Biological Chemistry*, vol. 277, no. 43, pp. 40302–40308, 2002.

[22] A. Valavanidis, T. Vlachogianni, and K. Fiotakis, "Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles," *International Journal of Environmental Research and Public Health*, vol. 6, no. 2, pp. 445–462, 2009.

[23] P. A. Riley, "Free radicals in biology: oxidative stress and the effects of ionizing radiation," *International Journal of Radiation Biology*, vol. 65, no. 1, pp. 27–33, 1994.

[24] T. Yamamori, H. Yasui, M. Yamazumi et al., "Ionizing radiation induces mitochondrial reactive oxygen species production accompanied by upregulation of mitochondrial electron transport chain function and mitochondrial content under control of the cell cycle checkpoint," *Free Radical Biology and Medicine*, vol. 53, no. 2, pp. 260–270, 2012.

[25] B. C. Dickinson and C. J. Chang, "Chemistry and biology of reactive oxygen species in signaling or stress responses," *Nature Chemical Biology*, vol. 7, no. 8, pp. 504–511, 2011.

[26] T. Finkel, "Signal transduction by reactive oxygen species," *The Journal of Cell Biology*, vol. 194, no. 1, pp. 7–15, 2011.

[27] P. D. Ray, B.-W. Huang, and Y. Tsuji, "Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling," *Cellular Signalling*, vol. 24, no. 5, pp. 981–990, 2012.

[28] K. Brieger, S. Schiavone, F. J. Miller Jr., and K.-H. Krause, "Reactive oxygen species: from health to disease," *Swiss Medical Weekly*, vol. 142, Article ID w13659, 2012.

[29] B. Halliwell, "Oxidative stress and neurodegeneration: where are we now?" *Journal of Neurochemistry*, vol. 97, no. 6, pp. 1634–1658, 2006.

[30] R. Buffenstein, Y. H. Edrey, T. Yang, and J. Mele, "The oxidative stress theory of aging: embattled or invincible? Insights from non-traditional model organisms," *Age*, vol. 30, no. 2-3, pp. 99–109, 2008.

[31] L. Zuo and M. S. Motherwell, "The impact of reactive oxygen species and genetic mitochondrial mutations in Parkinson's disease," *Gene*, vol. 532, no. 1, pp. 18–23, 2013.

[32] Q. Remijsen, T. V. Berghe, E. Wirawan et al., "Neutrophil extracellular trap cell death requires both autophagy and superoxide generation," *Cell Research*, vol. 21, no. 2, pp. 290–304, 2011.

[33] S. Dröse and U. Brandt, "Molecular mechanisms of superoxide production by the mitochondrial respiratory chain," *Advances in Experimental Medicine and Biology*, vol. 748, pp. 145–169, 2012.

[34] K. Leuner, T. Schütt, C. Kurz et al., "Mitochondrion-derived reactive oxygen species lead to enhanced amyloid beta formation," *Antioxidants & Redox Signaling*, vol. 16, no. 12, pp. 1421–1433, 2012.

[35] Q. Chen, E. J. Vazquez, S. Moghaddas, C. L. Hoppel, and E. J. Lesnefsky, "Production of reactive oxygen species by mitochondria: central role of complex III," *The Journal of Biological Chemistry*, vol. 278, no. 38, pp. 36027–36031, 2003.

[36] L. Zuo and T. L. Clanton, "Reactive oxygen species formation in the transition to hypoxia in skeletal muscle," *American Journal of Physiology—Cell Physiology*, vol. 289, no. 1, pp. C207–C216, 2005.

[37] K. Leuner, W. E. Müller, and A. S. Reichert, "From mitochondrial dysfunction to amyloid beta formation: novel insights into the pathogenesis of Alzheimer's disease," *Molecular Neurobiology*, vol. 46, no. 1, pp. 186–193, 2012.

[38] D. Dias-Santagata, T. A. Fulga, A. Duttaroy, and M. B. Feany, "Oxidative stress mediates tau-induced neurodegeneration in *Drosophila*," *Journal of Clinical Investigation*, vol. 117, no. 1, pp. 236–245, 2007.

[39] R. González-Domínguez, T. García-Barrera, and J. L. Gómez-Ariza, "Metabolomic study of lipids in serum for biomarker discovery in Alzheimer's disease using direct infusion mass spectrometry," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 98C, pp. 321–326, 2014.

[40] P. Mao and P. H. Reddy, "Aging and amyloid beta-induced oxidative DNA damage and mitochondrial dysfunction in Alzheimer's disease: implications for early intervention and therapeutics," *Biochimica et Biophysica Acta: Molecular Basis of Disease*, vol. 1812, no. 11, pp. 1359–1370, 2011.

[41] P.-X. Xu, S.-W. Wang, X.-L. Yu et al., "Rutin improves spatial memory in Alzheimer's disease transgenic mice by reducing $A\beta$ oligomer level and attenuating oxidative stress and neuroinflammation," *Behavioural Brain Research*, vol. 264, pp. 173–180, 2014.

[42] G. S. B. Aseervatham, T. Sivasudha, R. Jeyadevi, and D. A. Ananth, "Environmental factors and unhealthy lifestyle influence oxidative stress in humans—an overview," *Environmental Science and Pollution Research International*, vol. 20, no. 7, pp. 4356–4369, 2013.

[43] F. Kamel, "Epidemiology. Paths from pesticides to Parkinson's," *Science*, vol. 341, no. 6147, pp. 722–723, 2013.

[44] J. R. Walton, "Evidence for participation of aluminum in neurofibrillary tangle formation and growth in Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 22, no. 1, pp. 65–72, 2010.

[45] Y. Qin, W. Zhu, C. Zhan et al., "Investigation on positive correlation of increased brain iron deposition with cognitive impairment in Alzheimer disease by using quantitative MR R2$\prime$ mapping," *Journal of Huazhong University of Science and Technology: Medical Science*, vol. 31, no. 4, pp. 578–585, 2011.

[46] A. S. Pithadia and M. H. Lim, "Metal-associated amyloid-β species in Alzheimer's disease," *Current Opinion in Chemical Biology*, vol. 16, no. 1-2, pp. 67–73, 2012.

[47] W.-T. Chen, Y.-H. Liao, H.-M. Yu, I. H. Cheng, and Y.-R. Chen, "Distinct effects of Zn^{2+}, Cu^{2+}, Fe^{3+}, and Al^{3+} on amyloid-β stability, oligomerization, and aggregation: Amyloid-β destabilization promotes annular protofibril formation," *The Journal of Biological Chemistry*, vol. 286, no. 11, pp. 9646–9656, 2011.

[48] X. Huang, C. S. Atwood, M. A. Hartshorn et al., "The Aβ peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction," *Biochemistry*, vol. 38, no. 24, pp. 7609–7616, 1999.

[49] J. Mayes, C. Tinker-Mill, O. Kolosov, H. Zhang, B. J. Tabner, and D. Allsop, "β-Amyloid fibrils in alzheimer disease are not inert when bound to copper ions but can degrade hydrogen peroxide and generate reactive oxygen species," *The Journal of Biological Chemistry*, vol. 289, no. 17, pp. 12052–12062, 2014.

[50] V. Afonso, R. Champy, D. Mitrovic, P. Collin, and A. Lomri, "Reactive oxygen species and superoxide dismutases: role in joint diseases," *Joint Bone Spine*, vol. 74, no. 4, pp. 324–329, 2007.

[51] P. Chelikani, I. Fita, and P. C. Loewen, "Diversity of structures and properties among catalases," *Cellular and Molecular Life Sciences*, vol. 61, no. 2, pp. 192–208, 2004.

[52] Q. Ran, H. Liang, Y. Ikeno et al., "Reduction in glutathione peroxidase 4 increases life span through increased sensitivity to apoptosis," *Journals of Gerontology—Series A Biological Sciences and Medical Sciences*, vol. 62, no. 9, pp. 932–942, 2007.

[53] R. Prabhakar, T. Vreven, K. Morokuma, and D. G. Musaev, "Elucidation of the mechanism of selenoprotein glutathione peroxidase (GPx)-catalyzed hydrogen peroxide reduction by two glutathione molecules: a density functional study," *Biochemistry*, vol. 44, no. 35, pp. 11864–11871, 2005.

[54] J. Choi, H. D. Rees, S. T. Weintraub, A. I. Levey, L.-S. Chin, and L. Li, "Oxidative modifications and aggregation of Cu,Zn-superoxide dismutase associated with alzheimer and Parkinson diseases," *The Journal of Biological Chemistry*, vol. 280, no. 12, pp. 11648–11655, 2005.

[55] K. Murakami, N. Murata, Y. Noda et al., "SOD1 (copper/zinc superoxide dismutase) deficiency drives amyloid β protein oligomerization and memory loss in mouse model of Alzheimer disease," *The Journal of Biological Chemistry*, vol. 286, no. 52, pp. 44557–44568, 2011.

[56] Á. Casado, M. E. López-Fernández, M. C. Casado, and R. De La Torre, "Lipid peroxidation and antioxidant enzyme activities in vascular and alzheimer dementias," *Neurochemical Research*, vol. 33, no. 3, pp. 450–458, 2008.

[57] M. A. Ansari and S. W. Scheff, "Oxidative stress in the progression of alzheimer disease in the frontal cortex," *Journal of Neuropathology and Experimental Neurology*, vol. 69, no. 2, pp. 155–167, 2010.

[58] B. P. Yu, "Cellular defenses against damage from reactive oxygen species," *Physiological Reviews*, vol. 74, no. 1, pp. 139–162, 1994.

[59] A. Nunomura, G. Perry, G. Aliev et al., "Oxidative damage is the earliest event in Alzheimer disease," *Journal of Neuropathology and Experimental Neurology*, vol. 60, no. 8, pp. 759–767, 2001.

[60] M. Le Bras, M.-V. Clément, S. Pervaiz, and C. Brenner, "Reactive oxygen species and the mitochondrial signaling pathway of cell death," *Histology and Histopathology*, vol. 20, no. 1, pp. 205–220, 2005.

[61] C. Y. Liu, C. F. Lee, and Y. H. Wei, "Role of reactive oxygen species-elicited apoptosis in the pathophysiology of mitochondrial and neurodegenerative diseases associated with mitochondrial DNA mutations," *Journal of the Formosan Medical Association*, vol. 108, no. 8, pp. 599–611, 2009.

[62] D. A. Patten, M. Germain, M. A. Kelly, and R. S. Slack, "Reactive oxygen species: stuck in the middle of neurodegeneration," *Journal of Alzheimer's Disease*, vol. 20, no. 1, pp. S357–S367, 2010.

[63] M. T. Lin and M. F. Beal, "Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases," *Nature*, vol. 443, no. 7113, pp. 787–795, 2006.

[64] M. Martinez-Vicente and A. M. Cuervo, "Autophagy and neurodegeneration: when the cleaning crew goes on strike," *Lancet Neurology*, vol. 6, no. 4, pp. 352–361, 2007.

[65] A. Hamilton and C. Holscher, "The effect of ageing on neurogenesis and oxidative stress in the $APP_{swe}/PS1_{deltaE9}$ mouse model of Alzheimer's disease," *Brain Research*, vol. 1449, pp. 83–93, 2012.

[66] G. Barja, "Free radicals and aging," *Trends in Neurosciences*, vol. 27, no. 10, pp. 595–600, 2004.

[67] E. R. Stadtman, "Protein oxidation in aging and age-related diseases," *Annals of the New York Academy of Sciences*, vol. 928, pp. 22–38, 2001.

[68] K. Itoh, K. Nakamura, M. Iijima, and H. Sesaki, "Mitochondrial dynamics in neurodegeneration," *Trends in Cell Biology*, vol. 23, no. 2, pp. 64–71, 2013.

[69] K. E. Conley, D. J. Marcinek, and J. Villarin, "Mitochondrial dysfunction and age," *Current Opinion in Clinical Nutrition & Metabolic Care*, vol. 10, no. 6, pp. 688–692, 2007.

[70] S. Hauptmann, I. Scherping, S. Dröse et al., "Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice," *Neurobiology of Aging*, vol. 30, no. 10, pp. 1574–1586, 2009.

[71] P. H. Reddy, T. P. Reddy, M. Manczak, M. J. Calkins, U. Shirendeb, and P. Mao, "Dynamin-related protein 1 and mitochondrial fragmentation in neurodegenerative diseases," *Brain Research Reviews*, vol. 67, no. 1-2, pp. 103–118, 2011.

[72] J. K. Andersen, "Oxidative stress in neurodegeneration: cause or consequence?" *Nature Medicine*, vol. 10, pp. S18–S25, 2004.

[73] M. Gubandru, D. Margina, C. Tsitsimpikou et al., "Alzheimer's disease treated patients showed different patterns for oxidative stress and inflammation markers," *Food and Chemical Toxicology*, vol. 61, pp. 209–214, 2013.

[74] S. Soriano, D. C. Lu, S. Chandra, C. U. Pietrzik, and E. H. Koo, "The amyloidogenic pathway of amyloid precursor protein (APP) is independent of its cleavage by caspases," *The Journal of Biological Chemistry*, vol. 276, no. 31, pp. 29045–29050, 2001.

[75] S. Matsuyama, R. Teraoka, H. Mori, and T. Tomiyama, "Inverse correlation between amyloid precursor protein and synaptic plasticity in transgenic mice," *NeuroReport*, vol. 18, no. 10, pp. 1083–1087, 2007.

[76] C. Priller, T. Bauer, G. Mitteregger, B. Krebs, H. A. Kretzschmar, and J. Herms, "Synapse formation and function is modulated by the amyloid precursor protein," *The Journal of Neuroscience*, vol. 26, no. 27, pp. 7212–7221, 2006.

[77] E. Kojro and F. Fahrenholz, "The non-amyloidogenic pathway: structure and function of alpha-secretases.," *Sub-cellular biochemistry*, vol. 38, pp. 105–127, 2005.

[78] C. A. H. Petersen, N. Alikhani, H. Behbahani et al., "The amyloid β-peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 35, pp. 13145–13150, 2008.

[79] W. T. Kimberly, M. J. LaVoie, B. L. Ostaszewski, W. Ye, M. S. Wolfe, and D. J. Selkoe, "γ-Secretase is a membrane protein complex comprised of presenilin, nicastrin, Aph-1, and Pen-2," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 11, pp. 6382–6387, 2003.

[80] R. Vassar, B. D. Bennett, S. Babu-Khan et al., "β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE," *Science*, vol. 286, no. 5440, pp. 735–741, 1999.

[81] F. M. LaFerla, K. N. Green, and S. Oddo, "Intracellular amyloid-β in Alzheimer's disease," *Nature Reviews Neuroscience*, vol. 8, no. 7, pp. 499–509, 2007.

[82] S. J. Soscia, J. E. Kirby, K. J. Washicosky et al., "The Alzheimer's disease-associated amyloid β-protein is an antimicrobial peptide," *PLoS ONE*, vol. 5, no. 3, Article ID e9505, 2010.

[83] S. Moghbelinejad, M. Nassiri-Asl, T. Naserpour Farivar et al., "Rutin activates the MAPK pathway and BDNF gene expression on beta-amyloid induced neurotoxicity in rats," *Toxicology Letters*, vol. 224, no. 1, pp. 108–113, 2014.

[84] S. Hong, B. L. Ostaszewski, T. Yang et al., "Soluble Aβ oligomers are rapidly sequestered from brain ISF in vivo and bind GM1 ganglioside on cellular membranes," *Neuron*, vol. 82, no. 2, pp. 308–319, 2014.

[85] H. Fukumoto, D. L. Rosene, M. B. Moss, S. Raju, B. T. Hyman, and M. C. Irizarry, "β-secretase activity increases with aging in human, monkey, and mouse brain," *The American Journal of Pathology*, vol. 164, no. 2, pp. 719–725, 2004.

[86] R. Deane, S. D. Yan, R. K. Submamaryan et al., "RAGE mediates amyloid-β peptide transport across the blood-brain barrier and accumulation in brain," *Nature Medicine*, vol. 9, no. 7, pp. 907–913, 2003.

[87] H. J. Cho, S. M. Son, S. M. Jin et al., "RAGE regulates BACE1 and Aβ generation via NFAT1 activation in Alzheimer's disease animal model," *The FASEB Journal*, vol. 23, no. 8, pp. 2639–2649, 2009.

[88] E. Giraldo, A. Lloret, T. Fuchsberger, and J. Viña, "Aβ and tau toxicities in Alzheimer's are linked via oxidative stress-induced p38 activation: protective role of vitamin E," *Redox Biology*, vol. 2, pp. 873–877, 2014.

[89] J. Ghiso and B. Frangione, "Amyloidosis and Alzheimer's disease," *Advanced Drug Delivery Reviews*, vol. 54, no. 12, pp. 1539–1551, 2002.

[90] E. Ferreiro, R. Resende, R. Costa, C. R. Oliveira, and C. M. F. Pereira, "An endoplasmic-reticulum-specific apoptotic pathway is involved in prion and amyloid-beta peptides neurotoxicity," *Neurobiology of Disease*, vol. 23, no. 3, pp. 669–678, 2006.

[91] E. Ferreiro, C. R. Oliveira, and C. M. F. Pereira, "The release of calcium from the endoplasmic reticulum induced by amyloid-beta and prion peptides activates the mitochondrial apoptotic pathway," *Neurobiology of Disease*, vol. 30, no. 3, pp. 331–342, 2008.

[92] P. Agostinho, J. P. Lopes, Z. Velez, and C. R. Oliveira, "Over-activation of calcineurin induced by amyloid-beta and prion proteins," *Neurochemistry International*, vol. 52, no. 6, pp. 1226–1233, 2008.

[93] A. Awasthi, Y. Matsunaga, and T. Yamada, "Amyloid-beta causes apoptosis of neuronal cells via caspase cascade, which can be prevented by amyloid-beta-derived short peptides," *Experimental Neurology*, vol. 196, no. 2, pp. 282–289, 2005.

[94] T. S. Anekonda, "Resveratrol—a boon for treating Alzheimer's disease?" *Brain Research Reviews*, vol. 52, no. 2, pp. 316–326, 2006.

[95] R. L. Buckner, A. Z. Snyder, B. J. Shannon et al., "Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory," *Journal of Neuroscience*, vol. 25, no. 34, pp. 7709–7717, 2005.

[96] S. Lesné, T. K. Ming, L. Kotilinek et al., "A specific amyloid-β protein assembly in the brain impairs memory," *Nature*, vol. 440, no. 7082, pp. 352–357, 2006.

[97] G. M. Shankar, S. Li, T. H. Mehta et al., "Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory," *Nature Medicine*, vol. 14, no. 8, pp. 837–842, 2008.

[98] R. Ghosh and D. L. Mitchell, "Effect of oxidative DNA damage in promoter elements on transcription factor binding," *Nucleic Acids Research*, vol. 27, no. 15, pp. 3213–3218, 1999.

[99] A. J. Parsian, M. C. Funk, T. Y. Tao, and C. R. Hunt, "The effect of DNA damage on the formation of protein/DNA complexes," *Mutation Research: Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 501, no. 1-2, pp. 105–113, 2002.

[100] A. P. Bird and A. P. Wolffe, "Methylation-induced repression—belts, braces, and chromatin," *Cell*, vol. 99, no. 5, pp. 451–454, 1999.

[101] N. H. Zawia, D. K. Lahiri, and F. Cardozo-Pelaez, "Epigenetics, oxidative stress, and Alzheimer disease," *Free Radical Biology and Medicine*, vol. 46, no. 9, pp. 1241–1249, 2009.

[102] H. Y. Sung, E. N. Choi, S. Ahn Jo, S. Oh, and J.-H. Ahn, "Amyloid protein-mediated differential DNA methylation status regulates gene expression in Alzheimer's disease model cell line," *Biochemical and Biophysical Research Communications*, vol. 414, no. 4, pp. 700–705, 2011.

[103] L. Chouliaras, D. Mastroeni, E. Delvaux et al., "Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients," *Neurobiology of Aging*, vol. 34, no. 9, pp. 2091–2099, 2013.

[104] S. Scarpa, R. A. Cavallaro, F. D'Anselmi, and A. Fuso, "Gene silencing through methylation: an epigenetic intervention on Alzheimer disease," *Journal of Alzheimer's Disease*, vol. 9, no. 4, pp. 407–414, 2006.

[105] S.-C. Wang, B. Oeize, and A. Schumacher, "Age-specific epigenetic drift in late-onset Alzheimer's disease," *PLoS ONE*, vol. 3, no. 7, Article ID e2698, 2008.

[106] C. U. Lithner, C. Hernandez, J. D. Sweatt, and A. Nordberg, "Epigenetic effects of Aβ and the implication on the pathophysiology in Alzheimer's disease," *Alzheimer's & Dementia*, vol. 7, no. 4, supplement, p. S508, 2011.

[107] S. C. F. Marques, R. Lemos, E. Ferreiro et al., "Epigenetic regulation of BACE1 in Alzheimer's disease patients and in transgenic mice," *Neuroscience*, vol. 220, pp. 256–266, 2012.

[108] Y. M. Sung, T. Lee, H. Yoon et al., "Mercaptoacetamide-based class II HDAC inhibitor lowers Aβ levels and improves learning and memory in a mouse model of Alzheimer's disease," *Experimental Neurology*, vol. 239, no. 1, pp. 192–201, 2013.

[109] H.-C. Lin, H.-M. Hsieh, Y.-H. Chen, and M.-L. Hu, "S-Adenosylhomocysteine increases β-amyloid formation in BV-2 microglial cells by increased expressions of β-amyloid precursor protein and presenilin 1 and by hypomethylation of these gene promoters," *NeuroToxicology*, vol. 30, no. 4, pp. 622–627, 2009.

[110] X. Guo, X. Wu, L. Ren, G. Liu, and L. Li, "Epigenetic mechanisms of amyloid-β production in anisomycin-treated SH-SY5Y cells," *Neuroscience*, vol. 194, pp. 272–281, 2011.

[111] F. Mouton-Liger, C. Paquet, J. Dumurgier et al., "Oxidative stress increases BACE1 protein levels through activation of the PKR-eIF2α pathway," *Biochimica et Biophysica Acta*, vol. 1822, no. 6, pp. 885–896, 2012.

[112] M. W. Dysken, P. D. Guarino, J. E. Vertrees et al., "Vitamin e and memantine in Alzheimer's disease: clinical trial methods and baseline data," *Alzheimer's and Dementia*, vol. 10, no. 1, pp. 36–44, 2014.

[113] T. Ma, M. A. Trinh, A. J. Wexler et al., "Suppression of eIF2α kinases alleviates Alzheimer's disease-related plasticity and memory deficits," *Nature Neuroscience*, vol. 16, no. 9, pp. 1299–1305, 2013.

[114] M. Morel, J. Couturier, C. Lafay-Chebassier, M. Paccalin, and G. Page, "PKR, the double stranded RNA-dependent protein kinase as a critical target in Alzheimer's disease," *Journal of Cellular and Molecular Medicine*, vol. 13, no. 8 A, pp. 1476–1488, 2009.

[115] D. Xue, M. Zhao, Y.-J. Wang et al., "A multifunctional peptide rescues memory deficits in Alzheimer's disease transgenic mice by inhibiting Aβ42-induced cytotoxicity and increasing microglial phagocytosis," *Neurobiology of Disease*, vol. 46, no. 3, pp. 701–709, 2012.

[116] E. K. Kim and E.-J. Choi, "Pathological roles of MAPK signaling pathways in human diseases," *Biochimica et Biophysica Acta—Molecular Basis of Disease*, vol. 1802, no. 4, pp. 396–405, 2010.

[117] J. G. Scandalios, "Oxidative stress: molecular perception and transduction of signals triggering antioxidant gene defenses," *Brazilian Journal of Medical and Biological Research*, vol. 38, no. 7, pp. 995–1014, 2005.

[118] C. Wang, J. Li, Q. Liu et al., "Hydrogen-rich saline reduces oxidative stress and inflammation by inhibit of JNK and NF-κB activation in a rat model of amyloid-beta-induced Alzheimer's disease," *Neuroscience Letters*, vol. 491, no. 2, pp. 127–132, 2011.

[119] J. Li, C. Wang, J. H. Zhang, J.-M. Cai, Y.-P. Cao, and X.-J. Sun, "Hydrogen-rich saline improves memory function in a rat model of amyloid-beta-induced Alzheimer's disease by reduction of oxidative stress," *Brain Research*, vol. 1328, pp. 152–161, 2010.

[120] S.-W. Wang, Y.-J. Wang, Y.-J. Su et al., "Rutin inhibits β-amyloid aggregation and cytotoxicity, attenuates oxidative stress, and decreases the production of nitric oxide and proinflammatory cytokines," *NeuroToxicology*, vol. 33, no. 3, pp. 482–490, 2012.

[121] K. Jiménez-Aliaga, P. Bermejo-Bescós, J. Benedí, and S. Martín-Aragón, "Quercetin and rutin exhibit antiamyloidogenic and fibril-disaggregating effects in vitro and potent antioxidant activity in APPswe cells," *Life Sciences*, vol. 89, no. 25-26, pp. 939–945, 2011.

[122] B. Bellaver, D. G. Souza, D. O. Souza, and A. Quincozes-Santos, "Resveratrol increases antioxidant defenses and decreases proinflammatory cytokines in hippocampal astrocyte cultures from newborn, adult and aged Wistar rats," *Toxicology in Vitro*, vol. 28, no. 4, pp. 479–484, 2014.

[123] A. Granzotto and P. Zatta, "Resveratrol and Alzheimer's disease: message in a bottle on red wine and cognition," *Frontiers in Aging Neuroscience*, vol. 6, article 95, 2014.

[124] R. B.-F. Brigelius-Flohé and M. G. Traber, "Vitamin E: function and metabolism," *FASEB Journal*, vol. 13, no. 10, pp. 1145–1155, 1999.

[125] S. M. K. R. Zaidi and N. Banu, "Antioxidant potential of vitamins A, E and C in modulating oxidative stress in rat brain," *Clinica Chimica Acta*, vol. 340, no. 1-2, pp. 229–233, 2004.

[126] A. Lloret, M.-C. Badía, N. J. Mora, F. V. Pallardó, M.-D. Alonso, and J. Viña, "Vitamin e paradox in alzheimer's disease: it does not prevent loss of cognition and may even be detrimental," *Journal of Alzheimer's Disease*, vol. 17, no. 1, pp. 143–149, 2009.

[127] N. Farina, M. G. E. K. N. Isaac, A. R. Clark, J. Rusted, and N. Tabet, "Vitamin E for Alzheimer's dementia and mild cognitive impairment," *The Cochrane Database of Systematic Reviews*, vol. 11, Article ID CD002854, 2012.

[128] P. Mecocci and M. C. Polidori, "Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease," *Biochimica et Biophysica Acta—Molecular Basis of Disease*, vol. 1822, no. 5, pp. 631–638, 2012.

[129] S. Jeon, S. Bose, J. Hur et al., "A modified formulation of Chinese traditional medicine improves memory impairment and reduces Aβ level in the Tg-APPswe/PS1dE9 mouse model of Alzheimer's disease," *Journal of Ethnopharmacology*, vol. 137, no. 1, pp. 783–789, 2011.

[130] S. Jeon, J. Hur, H. J. Jeong, B.-S. Koo, and S. C. Pak, "SuHeXiang Wan essential oil alleviates amyloid beta induced memory impairment through inhibition of Tau protein phosphorylation in mice," *The American Journal of Chinese Medicine*, vol. 39, no. 5, pp. 917–932, 2011.

[131] T. Yoshikawa, Y. Naito, and M. Kondo, "Ginkgo biloba leaf extract: review of biological actions and clinical applications," *Antioxidants and Redox Signaling*, vol. 1, no. 4, pp. 469–480, 1999.

[132] O. Napryeyenko, G. Sonnik, and I. Tartakovsky, "Efficacy and tolerability of Ginkgo biloba extract EGb 761 by type of dementia: analyses of a randomised controlled trial," *Journal of the Neurological Sciences*, vol. 283, no. 1-2, pp. 224–229, 2009.

[133] H. Herrschaft, A. Nacu, S. Likhachev, I. Sholomov, R. Hoerr, and S. Schlaefke, "Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg," *Journal of Psychiatric Research*, vol. 46, no. 6, pp. 716–723, 2012.

[134] B. Vellas, N. Coley, P.-J. Ousset et al., "Long-term use of standardised ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial," *The Lancet Neurology*, vol. 11, no. 10, pp. 851–859, 2012.

[135] H. Hatcher, R. Planalp, J. Cho, F. M. Torti, and S. V. Torti, "Curcumin: from ancient medicine to current clinical trials," *Cellular and Molecular Life Sciences*, vol. 65, no. 11, pp. 1631–1652, 2008.

[136] G. P. Lim, T. Chu, F. Yang, W. Beech, S. A. Frautschy, and G. M. Cole, "The curry spice curcumin reduces oxidative damage

and amyloid pathology in an Alzheimer transgenic mouse," *The Journal of Neuroscience*, vol. 21, no. 21, pp. 8370–8377, 2001.

[137] F. Yang, G. P. Lim, A. N. Begum et al., "Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo," *The Journal of Biological Chemistry*, vol. 280, no. 7, pp. 5892–5901, 2005.

[138] V. Tõugu, A. Karafin, K. Zovo et al., "Zn(II)- and Cu(II)-induced non-fibrillar aggregates of amyloid-β (1–42) peptide are transformed to amyloid fibrils, both spontaneously and under the influence of metal chelators," *Journal of Neurochemistry*, vol. 110, no. 6, pp. 1784–1795, 2009.

[139] C. W. Ritchie, A. I. Bush, A. Mackinnon et al., "Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in alzheimer disease: a pilot phase 2 clinical trial," *Archives of Neurology*, vol. 60, no. 12, pp. 1685–1691, 2003.

[140] L. Lannfelt, K. Blennow, H. Zetterberg et al., "Safety, efficacy, and biomarker findings of PBT2 in targeting Aβ as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial," *The Lancet Neurology*, vol. 7, no. 9, pp. 779–786, 2008.

[141] J. Gräff and I. M. Mansuy, "Epigenetic dysregulation in cognitive disorders," *European Journal of Neuroscience*, vol. 30, no. 1, pp. 1–8, 2009.

[142] J. Gräff and L.-H. Tsai, "The potential of HDAC inhibitors as cognitive enhancers," *Annual Review of Pharmacology and Toxicology*, vol. 53, pp. 311–330, 2013.

[143] X. Lu, Y. Deng, D. Yu et al., "Histone acetyltransferase p300 mediates histone acetylation of PS1 and BACE1 in a cellular model of Alzheimer's disease," *PLoS ONE*, vol. 9, no. 7, Article ID e103067, 2014.