Review Article

Antioxidant Therapies for Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease featuring progressive impairments in memory, cognition, and behavior and ultimately leads to death. The histopathological changes of Alzheimer's disease include neuronal and synaptic loss, formation of extracellular senile plaques and intracellular neurofibrillary tangles in brain. Multiple lines of evidence indicate that oxidative stress not only strongly participates in an early stage of Alzheimer's disease prior to cytopathology, but plays an important role in inducing and activating multiple cell signaling pathways that contribute to the lesion formations of toxic substances and then promotes the development of Alzheimer's disease. Many years of studies show that antioxidant therapies have enjoyed general success in preclinical studies. Therefore, this paper mainly focuses on the recent developments of common used antioxidant therapies for Alzheimer's disease and thus provides indications for future potential antioxidant therapeutic strategies of neurodegenerative diseases.

1. Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders that frequently cause dementia and affect the middle- to old-aged individuals, approximately one in four individuals over the age of 85. Dementia is characterized by a progressive cognitive decline leading to social or occupational disability. However, AD must be differentiated from other causes of dementia including vascular dementia, dementia with Lewy bodies, Parkinson's disease with dementia, frontotemporal dementia, and reversible dementias [1]. AD has multiple etiological factors including genetics, environmental factors, and general lifestyles [2], and its pathophysiological hallmarks include extracellular β-amyloid protein (Aβ) deposition in the forms of senile plaques and intracellular deposits of the microtubule-associated protein tau as neurofibrillary tangles (NFTs) in the AD brains. When the first case of a 51-year-old woman who presented with a relatively rapidly deteriorating memory along with psychiatric disturbances was diagnosed as AD by Alois Alzheimer in 1907, this disease was considered to be a relatively uncommon disorder with a variety of progressive and fatal neurological conditions including senile dementia and the early age at onset. Subsequent clinical and neuropathological studies identified senile plaques and NFTs as the most common causes of the disease in the elderly. Aβ is produced by sequential proteolytic processing of a larger Aβ protein precursor (APP) by β-secretase to generate a large secreted fragment sAβPP and a 99 aa cellular fragment CTFβ that includes Aβ, the transmembrane domain and the intracellular domain of APP [3]. AD is usually recognized as a syndrome, a common clinical-pathological entity with multiple causes. Specifically, the diagnosis of this disease is based not only on memory loss and impairment of at least one other cognitive domain, but also on a decline in global function, a deterioration in the ability to perform activities of daily living, and the appearance of disturbance in social or occupational function. What's more, characteristic idiopathic psychometric deficits upon clinical evaluation and further postmortem confirmations of the presence of the characteristic lesions mentioned above are quite necessary for its diagnosis.

Considerable variability in initial clinical presentation may be dependent on the brain regions affected. Over time, AD could be divided into two clinical phases depending on

the age of onset. A type of "presenile" dementia was usually defined for individuals younger than 65 years of age, whereas a similar dementia in the elderly, for example, in individuals over 65-year-old, was referred to as senile dementia of the Alzheimer type after the pioneering studies conducted by Roth et al. [4–6]. AD is now generally recognized as a single major cause of dementia with a prevalence that increases sharply after age 65. It has been reported that rare early-onset forms of AD are linked directly to highly penetrant autosomal dominant mutations in one of three different genes: amyloid precursor protein (APP) gene, presenilin (PS) 1 gene, or presenilin 2 gene. Early-onset forms of AD generally have extensive lesions including a tendency for white matter lesions and "cotton wool" plaques in some early onset cases associated with exon 9 presenilin-1 mutations [7]. Interestingly, in addition to classic AD pathology, Lewy body pathology has also been described in familial early onset cases [8]. However, late-onset AD (LOAD) which accounts for approximately 95% of all AD cases [9] likely results from the complex interplay of molecular, environmental, and genetic factors. It represents a significant and growing public health burden and is the third most costly medical conditions in the USA The causes of late-onset AD are not yet clarified, but aside from age, several other risk factors include family history of dementia, down syndrome, head trauma, being female, low education level, vascular disease, and environmental factors and genetic risk factors have been identified, therefore, high education, ingestion of estrogen, nonsteroidal anti-inflammatory drugs, and vitamin E may be protective for AD. AD pathology is found prematurely in down syndrome, which argues in favor of the amyloid cascade hypothesis, given that the β-amyloid protein precursor (AβPP) can be found on chromosome 21 and that down syndrome subjects have an extra copy of chromosome 21. Similar pathological presentations have been found in cases of down syndrome and most of these pathological features may also be present to a lesser extent in a large proportion of aged nondemented controls, lending support to the possibility that such individuals are in an extremely early preclinical stage of AD [10]. Previous studies have demonstrated that the most potent cause of late-onset AD is the $\varepsilon 4$ allele of the apolipoprotein (apo) E gene (APOE) on chromosome 19 [11]. The effect appears to be dose dependent. It has been reported that the presence of a single $\varepsilon 4$ allele increases the risk of AD by 2- to 4-fold while the double $\varepsilon 4$ allele increases the risk of AD by 4- to 8-fold. However, possessing the $\varepsilon 4$ allele is neither necessary nor sufficient for the development of AD. Therefore, though APOE genotyping may be useful for confirmation in some patients with dementia when a diagnosis of AD is unclear, it is not recommended by experts as a predictive test for AD in asymptomatic individuals, whereas APOE genotyping could be used in patients with a clinical diagnosis of AD and it may increase the specificity of the diagnosis.

2. Epidemiology

AD constitutes approximately 65% to 75% of all dementia cases. The prevalence of dementia in the United States in individuals aged 65 years or older is about 8%, incidence of AD increases with age, doubling every five to ten years from 1% to 2% at ages 65 to 70 years, to 30% and higher after the age of 85 years if those with milder forms of dementia or cognitive impairment are included. Rates of dementia are very much age dependent and increases exponentially with age. For persons between ages 65–69, 70–74, 75–79, 80–84, and 85 and older the incidence of AD has been estimated at 0.6%, 1.0%, 2.0%, 3.3%, and 8.4% [12]. Prevalence increases from 3% among individuals aged 65–74 to almost 50% among those 85 or older [13]. AD affects 25 million people worldwide and in the USA, prevalence was estimated at 5 million in 2007 and, by 2050, is projected to increase to 13 million [13]. Globally, the number of the elderly (aged 65 years and older) is projected to increase dramatically, more than doubling from 420 million in 2000 to 973 million in 2030 [1].

3. Pathophysiology

The exact mechanism of AD is still not clear. The most common and distinctive hallmark lesions present within the AD brains are the β-amyloid (Aβ-) containing senile plaques and the NFTs composed of hyperphosphorylated tau protein, which generate strong responses from the surrounding cellular environment and are responsible for much of the late-stage cognitive decline observed in AD patients. The neuritic plaque has been often highlighted as one of the major consensus criteria for the diagnosis of AD at autopsy. The other major hallmark NFTs are also occasionally called pretangles. Some studies have showed that the development of NFTs may protect against neuronal damage, since mutations in the Aβ precursor protein (APP) and the presence of NFT-containing neurons are associated with the reduced steady-state production of Aβ and reduced levels of oxidative stress. Alternative theories for the pathogenesis of AD suggest that such pathological formations of senile plaques and NFTs are primarily responsible for neurodegeneration. For example, when Aβ has aggregated sufficiently, this protein elicits a neuroinflammatory response via the activation of microglia and astrocytes [14, 15]. Following the initial neuroinflammatory response, the neurotoxic byproducts of inflammation cause additional oxidative damage to cells [16]. Similarly, the hyperphosphorylated tau fibrils create cytoskeletal stresses and promote neuronal dysfunction [17].

Neuronal and dendritic loss, neuropil threads, dystrophic neurites, granulovacuolar degeneration, Hirano bodies, and cerebrovascular amyloid are also typical of the AD brain. It is well recognized in recent years that [18] synapse loss is the most specific pathological feature of Alzheimer's disease, which is due at least in part to the recent studies to associate synapse loss with low-n soluble Aβ species. However, it should be pointed out that assessment of the synapse is not recommended in the diagnosis of AD at autopsy either by immunohistochemistry or electron microscopy [19].

The distinctive pathology between AD and aging is problematic, particularly in the elderly. Regarding the correlation between clinical diagnosis and pathological findings, it has

been reported that 76% of brains of cognitively intact elderly patients were interpreted as AD brains [20].

4. Oxidative Stress and Alzheimer's Disease

Accumulating evidence suggests that brain tissues in AD patients are exposed to oxidative stress during the development of the disease. Oxidative stress or damage such as protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation [21] is closely associated with the development of Alzheimer's disease. AD is characterized by neuronal and synaptic loss, formation, and accumulation of extracellular Aβ plaques produced from APP processing and intracellular NFTs composed of aggregated hyperphosphorylated tau proteins in brain, proliferation of astrocytes, and activation of microglial. Oxidative stress is generally characterized by an imbalance in production of reactive oxygen species (ROS) and antioxidative defense system which are responsible for the removal of ROS [22], both systems are considered to have major roles in the process of age-related neurodegeneration and cognitive decline. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($\bullet OH$), singlet oxygen ($^1O_2$), alkoxyl radicals ($RO\bullet$), peroxyl radicals ($ROO\cdot$), and peroxynitrites ($ONOO^-$), contribute to pathogenesis of numerous human degenerative diseases [23]. Certain antioxidants including glutathione, α-tocopherol (vitamin E), carotenoids, ascorbic acid, antioxidant enzymes such as catalase and glutathione peroxidases are able to detoxify H_2O_2 by converting it to O_2 and H_2O under physiological conditions [24]. However, when ROS levels exceed the removal capacity of antioxidant system under pathological conditions or by aging or metabolic demand, oxidative stress occurs and causes biological dysfunction [24]. For example, high levels of protein oxidation, lipid oxidation, advanced DNA oxidation and glycoxidation end products, carbohydrates, formation of toxic substances such as peroxides, alcohols, aldehydes, free carbonyls, ketones, cholestenone, and oxidative modifications in nuclear and mitochondrial DNA [25] are the main manifestations of oxidative stress or damage occurred during the course of Alzheimer's disease. Elevated levels of those oxidated formations mentioned above have been described not only in brain, but in cerebrospinal fluid (CSF), blood, and urine of AD patients [25, 26].

Age-related memory impairments correlate with a decrease in brain and plasma antioxidants defense mechanism. An important aspect of the antioxidant defense system is glutathione (GSH) which is responsible for the endogenous redox potential in cells [27]. Its most important function is to donate electrons to ROS so as to scavenge them. Intracellular glutathione concentration decreases with age mammalian brain regions including hippocampus [28, 29] which may lead to a situation that the rate of ROS production exceeds that of removal thus induces oxidative stress. Therefore, the imbalance among the radical detoxifying enzymes is a cause for oxidative stress in AD.

Many studies have provided evidence for the deleterious consequences of oxidative stress products on certain cellular targets in AD. Protein oxidation and the oxidation of nuclear and mitochondrial DNA have been observed in both AD patients and in elderly patients without AD, but the oxidation of nuclear and mitochondrial DNA appears to be present in the parietal cortex [30], whereas protein oxidation appears to be more marked in AD patients in the regions presenting the most severe histopathologic alterations [31]. In addition, increased lipid peroxidation in the temporal lobe where histopathologic alterations are very noticeable in the AD brains has been observed. The APOE genotype and those with the ε4 allele seem to be more susceptible to peroxidation than those without this allele [32].

As mentioned earlier, several studies have identified many end products of peroxidation including malondialdehyde [33], peroxynitrite [14, 34], carbonyls [35], advanced glycosylation end products (AGEs) [33], superoxide dismutase-1 [36], and heme oxygenase-1 [37] which is a cellular enzyme that is upregulated in the brain and in other tissues in response to an oxidative stimuli in the brains of AD patients, particularly in the NFTs.

5. Lipid Oxidation in AD

The lipoperoxidation phenomena also exert important influences on the pathogenesis of AD. Aβ causes lipoperoxidation of membranes and induces lipid peroxidation products. Lipids are modified by ROS and the correlations among lipid peroxides, antioxidant enzymes, senile plaques, and NFTs in AD brains are very strong. Markesbery showed that lipid peroxidation is a major cause of depletion of membrane phospholipids in AD [38]. Several breakdown products of oxidative stress have been observed in AD brains compared to age-matched controls [39], including acrolein, malondialdehyde, F2-isoprostanes, and 4-hydroxy-2,3-nonenal (HNE) which is the most highly reactive and the major neuronal and hippocampal cytotoxic lipid peroxidation product in high concentrations in AD patients and it contributes to impairments of the function of membrane proteins such as the neuronal glucose transporter GLUT 3, inhibition of neuronal glucose and glutamate transporters, inhibition of Na^+/K^+ ATPases, activation of kinases, and dysregulation of ionic transfers and calcium homeostasis, thus the increased calcium concentration could itself cause a cascade of intracellular events, resulting in increased ROS and cellular death that ultimately induce an apoptotic cascade mechanism, and lead to neurodegeneration in AD. Some other supporting evidence shows that the glutamate-dependent flux of calcium is associated with the production of free radicals by the mitochondria. It is also worth mentioning that elevated level of cerebrospinal fluid concentrations of F2-isoprostane which is produced by free radical-catalyzed peroxidation of arachidonic acid has been observed in AD patients [40]. This discovery is significant not only because it confirms that lipid peroxidation is elevated in AD, but because it provides indications of the possible use of the quantification of cerebrospinal fluid F2-isoprostane

concentrations as a biomarker for AD diagnosis. In addition, Busciglio and Yankner showed that in down syndrome, which involves a similar neurodegenerative component to that of AD, neuronal death occurs according to a process of apoptosis that is related to an increase in lipoperoxidation and can be stopped by catalase and free radical scavengers [41].

6. DNA Oxidation in AD

DNA bases are vulnerable to oxidative stress damage and it has been observed in AD brains that ROS induces calcium influx via glutamate receptors and triggers excitotoxic responses leading to cell death. DNA and RNA oxidation is marked by increased levels of 8-hydroxy-2-deoxyguanosine (8OHdG) and 8-hydroxyguanosine (8OHD) [42] which mostly localized in $A\beta$ plaques and NFTs. Increased levels of DNA strand breaks found in AD brains were first considered to be parts of apoptosis, but it is increasingly recognized that oxidative damage is responsible for DNA strand breaks, and this is consistent with the increased free carbonyls in the nuclei of neurons and glia in AD.

7. Glycoxidation in AD

Advanced glycation end products (AGEs), a diverse class of posttranslational modifications, are formed by a nonenzymatic reaction of a sugar ketone or aldehyde group with long-lived protein deposits and are also potent neurotoxins and proinflammatory molecules. Glycation of proteins starts as a nonenzymatic process with the spontaneous condensation of ketone or aldehyde groups of sugars with the free amino groups of a protein or aminoacid specifically lysine, arginine, and possibly histidine [43]. Accumulation of AGEs in the brain is a feature of aging and is also implicated in the pathophysiological development of AD. There is increasing evidence that the insolubility of $A\beta$ plaques is caused by extensive covalent protein cross-linking and AGEs can be cross-linked to long-lived proteins [44]. Extracellular AGEs accumulation is caused by an accelerated oxidation of glycated proteins, also called glycoxidation and has been demonstrated in senile plaques in different cortical areas in both primitive and classic plaques. Immunohistochemical studies demonstrate that AGEs colocalize to a very high degree with APOE [45]. Some studies have shown the presence of AGEs in association with two major proteins of AD, $A\beta$ and the microtubule-associated protein tau [33] which is the major component of the NFTs, and it has been shown to be subject to intracellular AGEs formation. Tau protein isolated from brains of AD patients can be glycated in the tubulin-binding region, giving rise to the formation of β-sheet fibrils [46], leading to its disability to bind to microtubules. Taken together, it can be concluded that AGEs are involved in the pathogenesis of AD, and free radicals are also involved in glycation processes and can promote the formation of $A\beta$ cross-linking. Additionally, it has been reported that AGEs and β-amyloid activate specific receptors such as the receptor for advanced glycation end products (RAGE) and the class A scavenger-receptor to foster ROS production and regulate gene transcriptions of various factors participated in inflammation through NFκB activation [47].

8. Mitochondrial Dysfunction in Alzheimer's Disease

Mitochondria has been shown to be the center of ROS production. In AD, alterations in mitochondrial function and damaged mitochondria in the course of aging and neurodegeneration have been observed [48]. Consistent defects in mitochondria in AD include defects of the electron transport chain which are major factors contributing to the production of free radicals and the deficiencies in several key enzymes responsible for oxidative metabolism including α-ketoglutarate dehydrogenase complex (KGDHC) and pyruvate dehydrogenase complex (PDHC), which are two important enzymes involved in the rate-limiting step of tricarboxylic acid cycle and cytochrome oxidase (COX) which is the terminal enzyme in the mitochondrial respiratory chain that is responsible for reducing molecular oxygen [49]. It has been reported that postmortem cytochrome-c oxidase activity was lower than normal in the cerebral cortex (frontal, parietal, temporal, and occipital) [50], in the dentate gyrus and the CA4, CA3, and CA1 zones of the hippocampus and in the platelets of AD brains. A decline in cytochrome-c oxidase activity rather than amounts of cytochrome-c oxidase is associated with decreased expression of messenger RNA (mRNA) molecules, which is lower in the midtemporal region of the brains of AD patients [51]. The functional abnormalities in mitochondria promote the production of ROS. In addition, it has been found that damaged mitochondrial DNA (mtDNA) presents in vulnerable neurons in AD brains [52], and formation of mitochondrial-derived lysosomes and lipofuscin is evident in almost all of AD neurons [53]. Quantitative morphometric measurements of the percentage of different types of mitochondria (normal, partially damaged, and completely damaged) indicate that neurons in AD brains show an obvious lower percentage of normal mitochondria and a significantly higher percentage of the completely damaged mitochondria compared to the aged-matched control group [54]. The cybrid technique is very promising for the study of neurodegenerative diseases [54]. Some studies from cybrid cell lines with mitochondria DNA from AD patients showed abnormal mitochondrial morphology, membrane potential, and ROS production, which demonstrated that mutant mitochondrial DNA in AD contributed to its pathology. Low vascular blood flow, $A\beta$ and β-amyloid protein precursor (AβPP) processing machinery have also been implicated in the development of AD and are associated with dysfunctional consequences for mitochondrial homeostasis [55]. AβPP is present in the mitochondrial import channel and potentially inhibits mitochondrial import [56], and it also impairs mitochondrial energy metabolism thus causes mitochondrial abnormalities. Furthermore, homocysteine is also a strong risk factor in the course of AD development and it inhibits several genes

encoding mitochondrial proteins and favors ROS production [57]. Apolipoprotein E4 (APOE4) is another factor that leads to mitochondrial dysfunction. Previous studies have shown that more APOE4 fragment in AD brains than in the age-matched controls, and it shows toxicity and impairs mitochondrial function and integrity [58].

The reason why mitochondrial defects exert an influence on the development of AD is that they can trigger two harmful events: the production of destructive free radicals and a reduction in energy resources. A reduction in the regional cerebral metabolic glucose concentration was observed in AD patients using positron emission tomography at rest. This was seen throughout the neocortex and was found to associate with the severity of dementia.

9. Therapeutic Strategies for Alzheimer's Disease

While no drug has been shown to completely protect neurons, there are two possible conceptual approaches to the treatment of AD. One approach is the treatment that prevents the onset of the disease by sequestering the primary progenitors or targets and reduces the secondary pathologies of the disease, slows disease progression or delay onset of disease, leads to the cessation or even the repair of neuronal damage after onset of disease, and eventually prevents the development of AD; another approach is the symptomatic treatment that treats the tertiary cognitive symptoms of the disease and protects from further cognitive decline. This approach reflects the current state of treatment and usually includes treating the cognitive impairment, decline in global function, deterioration in the ability to perform activities of daily living and behavioral disturbances. Notably, the appropriate treatment strategies depend on the severity of the disease and the specificity of each individual; however, currently available therapeutic agents are mainly targeted at specific symptoms of AD, agents such as cholinesterase/acetylcholinesterase inhibitors which are involved in the enhancement of cholinergic neurotransmission and inhibit the degradation of acetylcholine within the synapse are the major treatments for Alzheimer's disease. Other therapeutic agents and strategies including neurotrophins, antioxidants, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, blocking of excitotoxicity, the Aβ vaccine trials, immunotherapy, and secretase effectors have also been studied, but their use remains controversial. Therefore, preventive and disease-modifying treatment strategies still need further investigations for the eradication of AD from the general population.

Our knowledge of the pathophysiology and the history of AD has been increased greatly over the past decade, yet the definitive causes remain unclear and the cures have been elusive. Antioxidant therapy, as one of the promising therapeutic strategies for AD, has been studied for years. It has been reported that antioxidants such as lipoic acid (also called thioctic acid), vitamin E, vitamin C and β-carotene

may help break down intracellular and extracellular superoxide radicals and H_2O_2-cell-damaging compounds that are byproducts of normally functioning cells before these radicals damage cells or activate microglia through their action as intracellular second messengers [59, 60]. However, antioxidants may act as prooxidants under some defined circumstances. For example, vitamin E acts as a prooxidant in isolated lipoprotein suspensions such as parenteral nutrition solutions in clinical conditions [61]. The prooxidative activity of vitamin E at low concentrations of various oxidants has been widely documented in plasma lipoproteins [62–64]. Multiple lines of evidence suggest that the activity of vitamin E towards oxidation of plasma lipoproteins depends on oxidative conditions. Vitamin E consistently inhibits oxidation under strong oxidative conditions which is at high fluxes of free radicals as compared to the concentration of the vitamin [63], while under mild oxidative conditions, vitamin E behaves as a prooxidant and accelerates oxidation by a mechanism of tocopherol-mediated peroxidation [63]. In addition, in 2004, Kontush and Schekatolina reported that computer modeling of the influence of vitamin E on lipoprotein oxidation showed that the vitamin E developed antioxidative activity in CSF lipoproteins in the presence of physiologically relevant, low amounts of oxidants [65]. By contrast, under similar conditions, vitamin E behaved as a prooxidant in plasma lipoproteins, consistent with the model of tocopherol-mediated peroxidation established by Stocker in 1994 [62]. Vitamin A [66] and trace elements with antioxidant properties such as copper and selenium [67] may also become prooxidant both in vivo and in vitro under the right conditions. The prooxidant effects of selenium have been investigated in cultured vascular cells exposed to parenteral nutrition containing various forms and quantities of selenium [67]. In a recent study, Nakamura et al. [68] suggested that vitamin C may play an important role to prevent the prooxidant effect of vitamin E in LDL oxidation. Vitamin C combined with ferrous iron is a standard free radical generating system. The theory that the entire antioxidant systems normally form an important and complex network suggests that antioxidant intake from food is superior to vitamin supplements because high-dose supplementation with a single antioxidant vitamin in isolation could disrupt the balance of the network [69].

Therefore, taking considerations of the pathogenesis and oxidative damage-related mechanisms underlying AD, the network existing among the different antioxidants, and the relationship between prooxidant and antioxidant factors, this paper mainly focuses on the recent developments of common used antioxidants therapies for Alzheimer's disease and thus provides indications for future potential antioxidants therapeutic methods of neurodegenerative diseases. The chemical structure and potential function of the antioxidants are summarized in Table 1.

10. Antioxidant Therapies

10.1. Vitamins and Carotene. Vitamin E (α-tocopherol), vitamin C, and β-carotene are exogenous chain-breaking

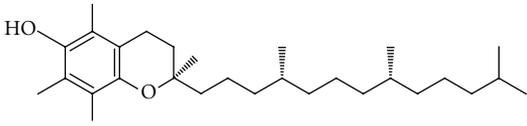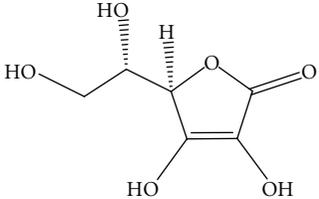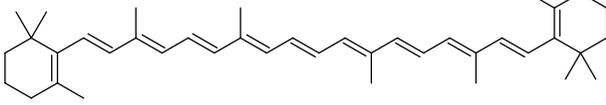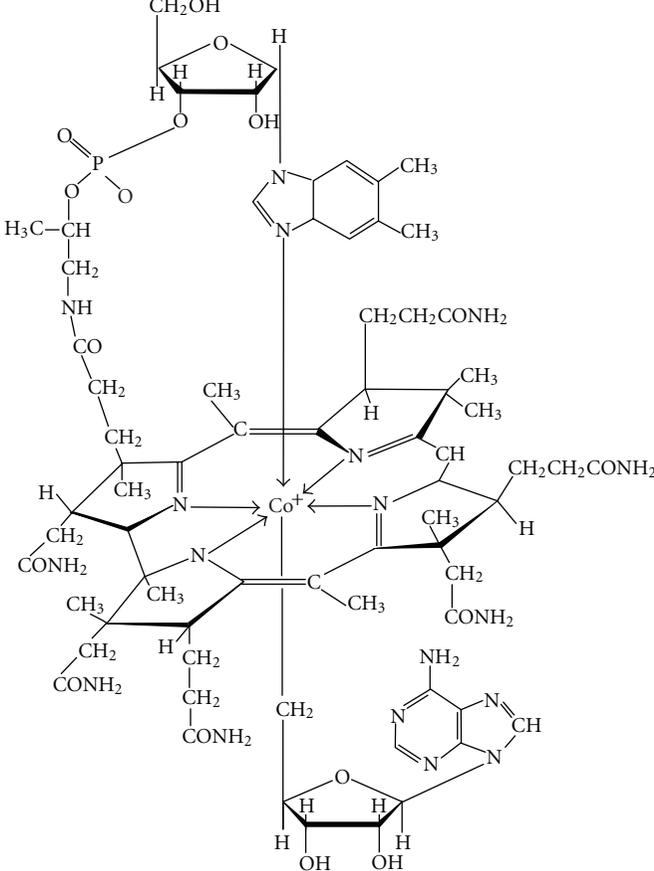TABLE 1: Chemical structure and potential function of the antioxidants.

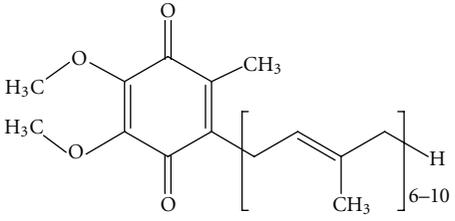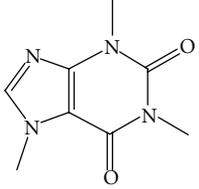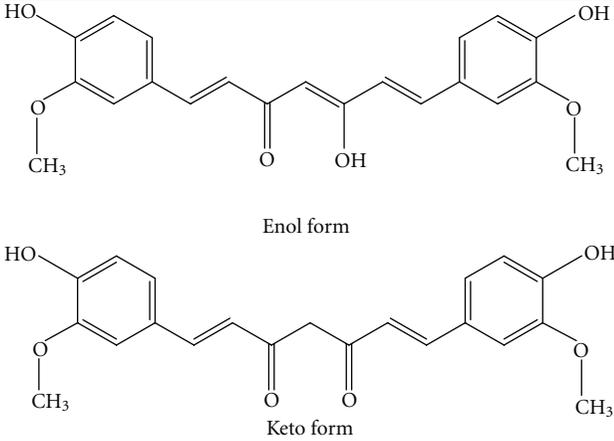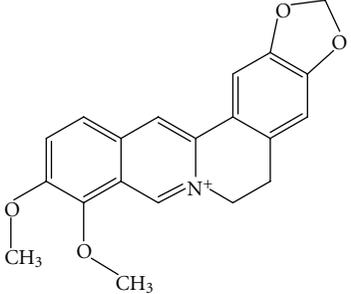| Antioxidant	Chemical structures	Potential functions
Vitamin E (α-tocopherol)		A powerful, lipid-soluble chain-breaking antioxidant found in lipid membranes, circulating lipoproteins and low-density lipoprotein (LDL) particles [70] and has been shown to decrease Free-radical-mediated damage caused by toxic chain reactions in neuronal cells and helps to inhibit dementia pathogenesis in mammalian cells.
Vitamin C		A water-soluble antioxidant, and an inhibitor of lipid peroxidation, acts as a major defense against free radicals in whole blood and plasma.
β-carotene		A lipid-soluble antioxidant which may reduce lipid peroxidation, improve antioxidant status [80], and quench singlet oxygen rapidly [81].
Vitamin B$_{12}$		An antioxidant that increases choline acetyltransferase activity in cholinergic neurons in cats [88] and improves cognitive functions in AD patients.
LA(α-lipoic acid)		A coenzyme of mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, can recycle other antioxidants such as vitamin C and E and glutathione and increase the production of acetylcholine or as a chelator of redox-active metals to combat the accumulation of lipid peroxidation products [94].
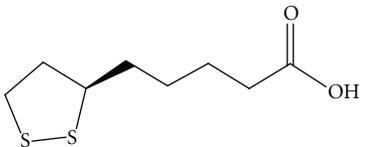
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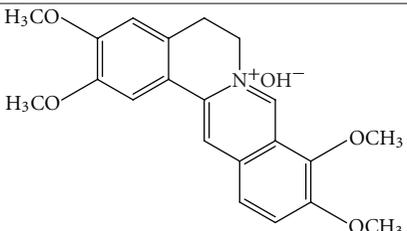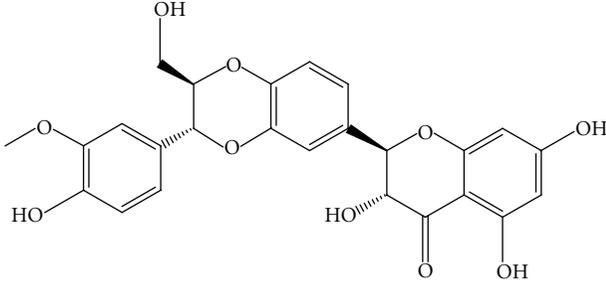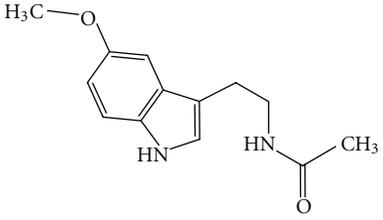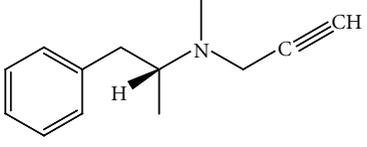| Antioxidant	Chemical structures	Potential functions
CoQ10 (ubiquinone)		A cofactor of the electron transport chain and it preserves mitochondrial membrane potential during oxidative stress and protects neuronal cells through attenuating Aβ overproduction and intracellular Aβ plaque deposits.
Selenium		A cofactor of glutathione peroxidase, and Se-glutathione peroxidase can also act as an antioxidant.
MitoQ		An antioxidant targeted to mitochondria and is produced by conjugation of the lipophilic triphenylphosphonium (TPP$^+$) cation to coenzyme Q [100].
Szeto Schiller (SS) peptide 31		A mitochondria-targeted antioxidants (MTAs) concentrate in the inner mitochondrial membrane and decrease mitochondrial toxicity [103], they can prevent the neurotoxin 1-methyl-4-phenylpyridium (MPP$^+$-) induced inhibition of oxygen consumption and ATP production and mitochondrial swelling [106].
Caffeine		An antioxidant that can inhibit amyloidosis and Aβ production and reduce brain Aβ levels in transgenic mouse models for early-onset familial AD.
Curcumin	 Enol form Keto form	An antioxidant that has antioxidant, antiinflammatory, and antiamyloid pathology activity in an Alzheimer transgenic mouse models, and it inhibits enzymes lipoxygenase and cyclooxygenase 2 that are responsible for the synthesis of the proinflammatory leukotrienes, prostaglandins, and thromboxanes [108].
Berberine		an antioxidant that exhibits anti-AD effects through both ChEs and Aβ pathways, and can also inhibit ROS and RNS [23].

TABLE 1: Continued.

Antioxidant	Chemical structures	Potential functions
Palmatine		An antioxidant that exhibits anti-AD effects through both ChEs and Aβ pathways and can also inhibit ROS and RNS [23].
Silibinin (silybin)		A flavonoid derived from the herb milk thistle (Silybum marianum), it prevents memory impairment and oxidative damage induced by Aβ in mice.
Ginkgo biloba		A natural plant that contains a variety of compounds such as flavonoids and terpenoids which have free radical scavenging ability, and it can reduce amyloid precursor protein [112] and inhibit Aβ aggregation in vitro.
Melatonin		A mammalian hormone synthesized mainly in the pineal gland, and it scavenges oxygen and nitrogen-based reactants generated in mitochondria by stimulating the expression and activity of glutathione peroxidase, superoxide dismutase, and NO synthetase [116], and it also contributes to the reduction of oxidative damage in cells [79].
Selegiline (L-deprenyl)		A selective monoamine oxidase-B inhibitor which can generate potent vasodilator nitric oxide particularly in cerebral blood vessels rapidly [127] and protect the vascular endothelium from the toxic effects of Aβ peptide and enhance the function of nigral neurons or enhance their survival by inhibiting oxidative deamination [73, 115].
Estrogen	Estradiol Estriol	An antioxidant which protects neurons from the toxicity of Aβ.
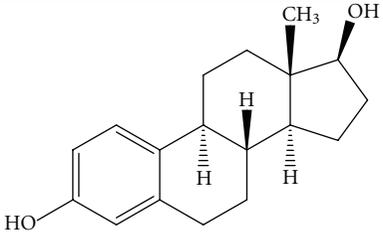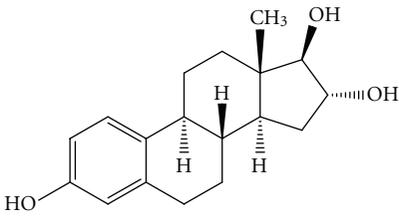
TABLE 1: Continued.

Antioxidant	Chemical structures	Potential functions
Estrogen	CH₃ O ... HO— ... Estrone	An antioxidant which protects neurons from the tacitly of Aβ.
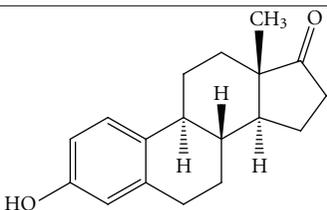
antioxidants, which decrease free-radical-mediated damage caused by toxic chain reactions in neuronal cells and help to inhibit dementia pathogenesis in mammalian cells. The most important lipid-phase antioxidant is α-tocopherol which is a powerful, lipid-soluble chain-breaking antioxidant found in lipid membranes, circulating lipoproteins and low-density lipoprotein (LDL) particles [70]. In experimental studies, vitamin E has been shown to attenuate toxic effects of β-amyloid and improve cognitive performance in rodents [71, 72]. In 1997, Sano et al. reported that in patients with moderately severe impairment from AD, treatment with α-tocopherol (2000 IU a day) reduces neuronal damage and slows the progression of AD [73], which indicates that the use of α-tocopherol may delay clinically important functional deterioration in AD patients. In 2004, Sung et al. reported that vitamin E suppresses brain lipid peroxidation and significantly reduces Aβ levels and senile plaque deposition in Tg2576 mice when it was administered early prior to the appearance of the pathology during the evolution of AD. However, if vitamin E supplementation was started at a later time point when amyloid plaques were already deposited, no significant effect is observed on the amyloidotic phenotype of these animals despite a reduction in brain oxidative stress [74]. In 2004, Nakashima et al. showed that treatment with α-tocopherol in transgenic (Tg) mice overexpressing human tau protein decreased carbonyls and 8-OHdG [75]. In 2007, Dias-Santagataet reported that administration of α-tocopherol significantly suppressed tau-induced neurotoxicity in Drosophila [76], and similar beneficial results were recently reported by others using transgenic mouse models of human tauopathies and AD [75], which underscored the therapeutic potential of vitamin E. In 2009, Pavlik et al. reported that patients whose regimens included vitamin E tended to survive longer than those taking no drug or a ChEI alone, and there was no evidence that treatment with high doses of vitamin E had an adverse effect on survival in an AD cohort followed-up for up to 15 years [77].

Vitamin C is a water-soluble antioxidant which is also a powerful inhibitor of lipid peroxidation and acts as a major defense against free radicals in whole blood and plasma. Bagi et al. have shown that chronic vitamin C treatment is able to decrease high levels of isoprostanes and oxidative stress in vivo, enhance NO bioavailability, restore the regulation of shear stress in arterioles, and normalize systemic blood pressure in methionine diet-induced hyperhomocysteinemia rats [78]. Besides, vitamin

C reduces α-tocopheroxyl radicals rapidly in membranes and LDL to regenerate α-tocopherol and possibly inhibits α-tocopheroxyl radical-mediated propagation [79]. Carotenoid is another lipid-soluble antioxidant which may reduce lipid peroxidation and improve antioxidant status [80]. The most known and studied carotenoid is the β-carotene which is a potent antioxidant able to quench singlet oxygen rapidly [81]. Vitamin C, vitamin E, and carotenoids have shown to synergistically interact against lipid peroxidation [79, 82]. However, it is not completely defined whether nutrient therapy is an effective treatment of Alzheimer disease. Lloret et al.'s findings indicate that vitamin E does not lower plasma oxidative stress for half of the AD patients [83] and some other study results have suggested that either through the diet or by supplements, consuming carotenes or vitamins C and E did not decrease the risk of developing AD, which indicates that antioxidant therapies have only enjoyed general success in preclinical studies in animal models but little benefit in human preventive studies or clinical trials [84]. In 2002, Morris et al. reported that higher intake of foods rich in vitamin E may modestly reduce long-term risk of dementia and AD after adjustment for age, education, sex, race, APOEε4, and length of followup, and this association was observed only among individuals without the APOEε4 allele [85], while dietary intakes of vitamin C, β-carotene, and flavonoids were not associated with dementia risk. Thus, future trials are still needed with a special consideration and focus on individual monitoring of therapeutic potential to avoid toxicity and assess biomarkers of efficacy [86].

In addition to vitamin E and vitamin C, vitamin B_{12} may also have some roles in the treatment of AD. In most studies the serum levels of vitamin B_{12} in AD patients were significantly lower than that of control group, which may partly contribute to degeneration of neurons [87]. Several studies indicated that vitamin B_{12} supplementation increased choline acetyltransferase activity in cholinergic neurons in cats [88] and improved cognitive functions in AD patients [89]. Therefore, the inclusion of vitamin B_{12} in multiple antioxidant therapeutic strategies may be useful.

11. Antioxidant Enzymes

Preventive antioxidants such as metal chelators, glutathione peroxidases, and SOD enzymes including a cytoplasmic antioxidant enzyme-copper-zinc superoxide dismutase

(CuZnSOD) [90] and a prosurvival mitochondrial antioxidant enzyme-MnSOD, repair enzymes such as lipases, proteases, and DNA repair enzymes [21] have also been shown to be essential for neural survival and neuronal protection against oxidative damages [91] and can be used to treat cognitive and behavioral symptoms of Alzheimer's disease [21]. Recent studies suggest that MnSOD plays a protective role during AD development, and MnSOD deficiency increases Aβ levels and accelerates the onset of behavioral alteration in APP transgenic mice [92].

12. Mitochondria-Targeted Antioxidants (MTAs)

Besides well-characterized antioxidants such as vitamin A, carotenoids, vitamin C, and vitamin E mentioned above, other antioxidants such as α-lipoic acid (LA), coenzyme Q10, NADH, Mito Q, Szeto Schiller (SS) peptide, and glutathione which is effective in catabolizing H_2O_2 and anions have some potential therapeutic value in the treatment of certain neurodegenerative diseases. Mitochondrial dysfunction is involved in the pathogenesis of many neurodegenerative diseases including Alzheimer's disease, so developing new therapeutic strategies targeting mitochondrial may shed a new light to AD treatment. It is known that oxidative stress induces mitochondrial fragmentation and altered mitochondrial distribution in vitro, and it also causes both structurally and functionally damage of mitochondria during pathogenesis of Alzheimer's disease [93]. Since overproduction of ROS by mitochondria is one of the major factors that contribute to the course of AD, many drugs targeting mitochondria tested or in development belong to metabolic antioxidants. Those antioxidants including R-α-lipoic acid (LA) and coenzyme Q10 (CoQ10) that can easily penetrate not only the cell, but the mitochondria, may provide the greatest protection.

LA(α-lipoic acid), also called thioctic acid, as a powerful antioxidant therapeutic and the coenzyme of mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, can recycle other antioxidants such as vitamins C and E and glutathione and increase the production of acetylcholine or as a chelator of redox-active metals to combat the accumulation of lipid peroxidation products [94]. In this respect, LA used in conjunction with acetyl carnitine protects neuronal cells via cell signaling mechanisms including some extracellular kinase signaling pathways which are dysregulated in AD [95]. It has been reported that chronic administration of the antioxidant LA decreased the expression of lipid peroxidation markers of oxidative modification but not β-amyloid load within the brains of both control and AD mice models, and LA treatment improved Morris water maze performance in the Tg2576 mouse model but was ineffective at altering cognition in the Y-maze test or in the wild-type group for both tests [96]. Therefore, taken together results obtained from previous studies, we conclude the action of LA may be targeting mitochondria, the most affected organelle responsible for AD development.

CoQ10 (ubiquinone) is a potent antioxidant and also an important cofactor of the electron transport chain where it accepts electrons from complex I and II. It preserves mitochondrial membrane potential during oxidative stress and protects neuronal cells through attenuating Aβ overproduction and intracellular Aβ plaque deposits. It is well known that mitochondrial dysfunction is associated with AD, and coenzyme Q10 and nicotinamide adenine dinucleotide (NADH) are needed for the generation of ATP by mitochondria, so it is essential to use these antioxidants for AD prevention. A study has shown that coenzyme Q10 (ubiquinol) scavenges peroxy radicals faster than α-tocopherol [97] and, like vitamin C, can regenerate vitamin E in a redox cycle [98]. However, it is weaker to improve clinical symptoms in patients with mitochondrial encephalomyopathies [98]. NADH administration (10 mg/day before meal) has been shown beneficial in a pilot study of 17 AD patients [99]. What's more, it has been suggested that selenium is a cofactor of glutathione peroxidase, and Se-glutathione peroxidase can also act as an antioxidant. Therefore, Selenium supplementation together with other antioxidants may also contribute to therapeutic strategies of AD.

Mito Q is another promising therapeutic antioxidant that has been successfully targeted to mitochondria, and it is produced by conjugation of the lipophilic triphenylphosphonium (TPP$^+$) cation to coenzyme Q [100]. With help of TPP$^+$, coenzyme Q penetrates into the membrane core and reaches the mitochondrial matrix where it is reduced to its active form (the antioxidant ubiquinol) by complex II to decrease lipid peroxidation, resulting in reduced oxidative damage [101]. It has been reported that Mito Q also exerts protective effects on cells by reducing free radicals, decreasing oxidative damage, and maintaining mitochondrial functions [102]. Some studies report that Szeto Schiller (SS) peptide 31, another kind of mitochondria-targeted antioxidants (MTAs) concentrates in the inner mitochondrial membrane and decreases mitochondrial toxicity [103]. Intracellular concentrations of [3H] SS-31 were 6-fold higher than extracellular concentrations [104]. In 2010, Manczak et al. reported that MitoQ and SS31 prevent Aβ toxicity in mitochondria on neurons from a Tg2576 mouse model and on mouse neuroblastoma (N2a) cells incubated with the Aβ peptide, which suggested that MitoQ and SS31 are warranted to act as potential drugs to treat AD patients [105]. Studies with isolated mitochondria showed that both SS31 and SS20 prevented the neurotoxin 1-methyl-4-phenylpyridium (MPP$^+$-) induced inhibition of oxygen consumption and ATP production and mitochondrial swelling [106]. These findings provide strong evidence that neuroprotective peptides such as SS-31 which target both mitochondrial dysfunction and oxidative damage are promising for the treatment of Alzheimer's disease [104].

13. Dietary Supplements

Various dietary supplements have been also shown to provide treatment of AD such as omega-3 polyunsaturated fatty acid (docosahexaenoic acid) [21], caffeine, and curry spice curcumin. Caffeine (500 mg or 5-6 cups of coffee a day) [106], epigallocatechin-gallate esters from green tea [106]

and red wine (Cabernet Sauvignon) have been shown to inhibit amyloidosis and Aβ production in both cell culture and animal models. Caffeine has antioxidant properties and has been demonstrated to reduce brain Aβ levels in transgenic mouse models for early-onset familial AD. In 2010, Prasanthi et al. reported that in the cholesterol-fed rabbit model system for late-onset sporadic AD, caffeine decreases cholesterol-enriched diet-induced increase in Aβ production and accumulation, reduces cholesterol-induced increase in phosphorylation of tau, attenuates cholesterol-induced increase in ROS and 8-Iso-PGF2α levels, reduces glutathione depletion, and also protects against cholesterol-induced ER stress [107]. In addition, there is substantial in-vitro data indicating that curry spice curcumin is a promising agent in the treatment or prevention of AD. It has antioxidant, antiinflammatory, and anti-amyloid pathology activity in an Alzheimer transgenic mouse models since it inhibits enzymes lipoxygenase and cyclooxygenase 2 that are responsible for the synthesis of the proinflammatory leukotrienes, prostaglandins, and thromboxanes [108]. It has also reported that curry spice curcumin reduces carbonyls and facilitates disaggregation of Aβ and reduction in AD-associated neuropathology in APP Tg2576 mice [109]. Nonetheless, important information regarding curcumin bioavailability, safety, and tolerability, particularly in the elderly is lacking. Various other factors including life-style factors such as calorie restriction [110], high activity in environmental enrichment and voluntary exercise have been shown to synergistically interact with antioxidants in attenuating AD neuropathophysiology.

14. Traditional Herbal Antioxidants

Some traditional herbal antioxidants also exhibit potential for AD treatment. Jung et al. reported that three major alkaloids in Coptidis Rhizoma-groenlandicine, berberine, and palmatine can potentially exhibit anti-AD effects through both ChEs and Aβ pathways and antioxidant capacities to inhibit ROS and RNS [23]. In addition, silibinin (silybin), a flavonoid derived from the herb milk thistle (Silybum marianum), has been also shown to have antioxidative properties. Silibinin prevents memory impairment and oxidative damage induced by Aβ in mice and may be a potential therapeutic agent for Alzheimer's disease [111]. Ginkgo biloba is a natural plant that contains a variety of compounds such as flavonoids and terpenoids which have free radical scavenging ability. Previous studies have shown that Ginkgo biloba can reduce amyloid precursor protein and inhibit Aβ aggregation in vitro. However, Stackman et al. have reported that Tg2576 mice treated with Ginkgo biloba showed cognitive improvement without any effects on Aβ levels or senile plaque [112]. In 2010, Garcia-Alloza et al. reported that there was no significant effect on senile plaque size after treatment with Ginkgo biloba, and it did not show any effects on Aβ levels measured postmortem by ELISA [113]. In addition, there have been several reports of serious side effects associated with commercially available ginkgo, including coma, bleeding, and seizures [114]. At present, there is still little evidence to support the use of Ginkgo biloba for the treatment of AD [115].

15. Other Antioxidants

15.1. Melatonin. Melatonin is a mammalian hormone synthesized mainly in the pineal gland, and it scavenges oxygen and nitrogen-based reactants generated in mitochondria by stimulating the expression and activity of glutathione peroxidase, superoxide dismutase, and NO synthetase [116], and it also contributes to the reduction of oxidative damage in cells [79]. Currently conduced studies have shown that antioxidant melatonin could inhibit Aβ-induced toxicity [117] and mitigate tau hyperphosphorylation [118–123]. In vivo, melatonin improved learning and memory deficits in an APP695 transgenic mouse model and in vitro, melatonin attenuated Aβ-induced apoptosis in AD cell models such as mouse microglial BV2 cells, rat astroglioma C6 cells and PC12 cells [124]. Besides, studies in transgenic AD mice and cultured cells have suggested that administration of melatonin inhibited the Aβ-induced mitochondria-related bax increase and it may also initiate the survival signal pathways. Another experiment demonstrated that melatonin inhibited the phosphorylation of NADPH oxidase via a PI3K/Akt-dependent signaling pathway in microglia exposed to Aβ_{1-42} [117]. Some studies also pointed that in APP Tg2576 mice models, melatonin decreased Aβ burden in young mice but showed no effects on F2-IsoPs or Aβ burden in older plaque-bearing mice [125, 126]. Taken together, the above evidence suggests that melatonin serves as a potential antioxidant therapeutic strategy for Alzheimer's disease but further clinical trials are still needed to determine the clinical value and efficacy of melatonin in the future.

15.2. Monoamine Oxidase-B Inhibitor. Selegiline (L-deprenyl) is a selective monoamine oxidase-B inhibitor with possible antioxidant properties and can be used in the treatment of neurodegenerative diseases. It can generate potent vasodilator nitric oxide particularly in cerebral blood vessels rapidly [127]. It may also protect the vascular endothelium from the toxic effects of Aβ peptide and enhance the function of nigral neurons or enhance their survival by inhibiting oxidative deamination [73, 115]. In 1997, Sano et al. reported that in patients with moderately severe impairment from AD, treatment with selegiline (10 mg a day) reduces neuronal damage and slows the progression AD [73]. These findings suggest that the use of selegiline may delay clinically important functional deterioration in patients with Alzheimer's disease. Though most of studies have shown that selegiline may bring improvements in cognition, behavior, and mood, little evidence shows a global benefit in cognition, functional ability, and behavior. In 2000, the authors of a meta-analysis of 15 clinical trials concluded that there was not enough evidence to recommend selegiline as a treatment for Alzheimer's disease.

15.3. Estrogen. Estrogen has been shown to act as an antioxidant to protect neurons from the toxicity of Aβ [115].

TABLE 2: Summary of the various antioxidants interventions in cells or animal models of AD and human trials studied for Alzheimer's disease.

Antioxidant intervention	Cells or animal models of AD	Human trials	Outcome	Reference
Vitamin E (α-tocopherol)	Aβ-induced AD rats model		Attenuated toxic effects of Aβ and improved cognitive performance.	[71]
		Treatment with α-tocopherol (2000 IU a day) in patients with moderately severe impairment from AD	Reduced neuronal damage and slowed progression of AD.	[73]
	APP Tg2576 mice		Suppressed brain lipid peroxidation, reduced Aβ levels and senile plaque deposition, and decreased F2-IsoPs levels.	[74]
	Transgenic mouse models of human tauopathies and AD		Suppressed tau-induced neurotoxicity, decreased carbonyls, and decreased 8OHdG.	[74, 75]
	Drosophila		Suppressed tau-induced neurotoxicity.	[76]
		AD patients whose regimens included vitamin E	Longer survival rate than those taking no drug or a ChEI alone.	[77]
Vitamin C	Methionine diet-induced hyperhomocysteinemia rats		Decreased oxidative stress in vivo, enhanced NO bioavailability, restored regulation of shear stress in arterioles, and normalized systemic blood pressure.	[78]
vitamin B$_{12}$	Cats		Increased choline acetyltransferase activity in cholinergic neurons.	[88]
		AD patients	Improved cognitive functions.	[89]
MnSOD	APP Tg2576 mice		Deficiency of MnSOD increases Aβ levels and accelerates the onset of behavioral alteration.	[92]
LA(α-lipoic acid)	APP Tg2576 mice		Decreased expression of lipid peroxidation markers of oxidative modification but not β-amyloid load within the brains; improved performance in Morris water maze but not effective at altering cognition in the Y-maze test.	[96]
MitoQ and Szeto Schiller (SS) peptide 31	APP Tg2576 mice and mouse neuroblastoma (N2a) cells incubated with the Aβ peptide		Prevented Aβ toxicity in mitochondria on neurons.	[105]
Caffeine	Cholesterol-fed rabbit model system for late onset sporadic AD		Decreased Aβ production and accumulation, reduced phosphorylation of tau, attenuated ROS and 8-Iso-PGF2α levels, and reduced glutathione depletion, and protection against cholesterol-induced ER stress.	[107]
Curcumin	APP Tg2576 mice		Reduced carbonyls and facilitated disaggregation of Aβ and reduction in AD associated neuropathology.	[109]
Silibinin	Aggregated A β_{25-35}-induced AD model mice		Prevented memory impairment and oxidative damage induced by Aβ.	[111]
Ginkgo biloba	APP Tg2576 mice		Improved cognitive functions but without any effects on Aβ levels or senile plaque.	[112]
		Postmortem brain ELISA measurement	No significant effects on senile plaque size or Aβ levels.	[113]

TABLE 2: Continued.

Antioxidant intervention	Cells or animal models of AD	Human trials	Outcome	Reference
Melatonin	APP695 transgenic mouse model		Improved learning and memory deficits.	[124]
	AD cell models such as mouse microglial BV2 cells, rat astroglioma C6 cells, and PC12 cells		Attenuated $A\beta$-induced apoptosis, inhibited $A\beta$-induced mitochondria-related bax increase.	[124]
	Microglia exposed to $A\beta_{1-42}$		Inhibited phosphorylation of NADPH oxidase via a PI3K/Akt-dependent signaling pathway.	[117]
	APP Tg2576 mice		Decreased $A\beta$ burden in young mice; no effects on F2-IsoPs or $A\beta$ burden in older plaque-bearing mice.	[125, 126]
Selegiline (L-deprenyl)		Treatment with selegiline (10 mg a day) in patients with moderately severe impairment from AD	Reduced neuronal damage and slowed progression of AD.	[73]

AD: Alzheimer's disease; 8OHdG: 8-hydroxy-2-deoxyguanosine; ChEI: cholinesterase inhibitors.

Although estrogen may have a neuroprotective effect [128], it does not appear to improve cognition or function in patients with Alzheimer's disease [129]. At present, there is no evidence that supports recommending the use of estrogen as an antioxidant to decrease the risk of AD or the progression of existing AD, therefore, further studies need to be conducted to determine if treatment with estrogen may prevent or delay the onset of AD or reduce its severity [115].

The various antioxidants interventions in cells or animal models of AD and human trials studied for Alzheimer's disease are summarized in Table 2.

16. Summary

Alzheimer's disease is recognized as a chronic neurodegenerative condition with a long asymptomatic period prior to recognizable clinical dementia. Multiple lines of evidence have shown strong implications that oxidative stress or damage plays essential roles in the pathogenesis of several neurodegenerative diseases such as AD through a number of mechanisms including oxidative damages caused by free radicals which may result in neuronal cell death. AD mice models show that increased oxidative damage is a relatively early event in the pathogenesis of AD that may be suppressed by antioxidants. Therefore, the development of approaches to prevent or reduce oxidative damages may provide therapeutic efficacy, and antioxidants have been identified as parts of these therapeutic strategies for Alzheimer's disease.

Metabolic antioxidants, mitochondria-directed antioxidants, and SS peptides have proved to be effective in AD mouse models and small clinical studies. It has also been shown that treatment with antioxidants vitamin E, vitamin C, selegiline, estrogen, Ginkgo biloba, and so forth may exert certain positive effects on the development of AD, but the efficacy of those antioxidants in clinical patients is still controversial and not so conclusive. Most antioxidant drugs show general success in animal models but less beneficial in human trials; clinical trials for AD prevention and treatment by antioxidants are still in their infancy. Therefore, further studies will be quite necessary to determine if antioxidants may decrease the risk or slow the progression of the disease for AD patients.

Acknowledgments

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