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# Alzheimer's Disease Pathology and Oxidative Stress: Possible Therapeutic Options

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## Abstract

Alzheimer's disease (AD) is one of the most common causes for the development of Dementia in the elderly. In past two decades there has been abundant research in pathogenesis of AD and possible prevention and treatment. Research evidences have suggested the major role of oxidative stress in the pathogenesis of AD. Sources of this stress are disruption of homeostasis of metals, mitochondrial dysfunction, genetic mutations, β Amyloid accumulation, hyperphosphorylation of tau and inflammation. Oxidative damage found in AD occurs as a result of advanced glycation end products, nitration, lipid peroxidation adduction products, carbonyl modified neurofilament protein and free carbonyls. All the products, discussed above have been considered as blood biomarkers for early diagnosis of AD. Various antioxidant therapies have been identified and studied for prevention and possible treatment of AD, based on role of oxidative stress in pathogenesis of AD. In this review we briefly discuss about the sources of oxidative stress and pathogenesis of AD, along with various newer and older antioxidant therapeutic options.

**Keywords:** Alzheimer's disease; Oxidative stress; Blood biomarkers; Antioxidant therapies

## Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease which causes dementia in the elderly, characterized by the gradual deterioration of the memory and other cognitive functions and it passes through various stages and finally results in complete incapacity and death of the patient within 3 to 9 years [1]. Increasing age is a major risk factor for sporadic forms of AD. Population of the elderly is increasing worldwide and therefore the prevalence of AD. AD has become one of the leading causes of disability and death among the elderly [2-5]. There has been abundant research in AD disease in the past few decades, but the exact cause and pathogenesis of AD are not completely understood, and right now, we do not have effective treatment options for the disease. Etiology of the AD is multifactorial and quite a mysterious phenomenon. Research in the genetics and molecular biology has explained some of the underlying mechanisms for the pathologies **found in the AD. Research in the genetics has identified the genes involved in the AD.**

| Gene | Chromosome | AD category | Age of onset |
|---|---|---|---|
| **Presenilin I** | 14 | Early onset familial AD | 25-60 years |
| **APP** | 21 | Early onset familial AD | 40-64 years |
| **Presenilin II** | 1 | Early onset familial AD | 45-84 years |
| **APOE e4** | 19 | Early to late onset familial and sporadic AD | >50 years |

**Table1:** Genes involved in Alzheimer's disease [6-9]

Apart from these, α2-macrogobulin gene located on chromosome 12 [10] and other unidentified genes also determine the susceptibility in late onset forms and sporadic cases.

Amyloid hypothesis is another causative mechanism in AD. Principle hallmark of the AD neuropathology are: Senile plaques (typically composed of amyloid protein) and neurofibrillary tangle (mainly composed of tau protein). Both of these are the result of amyloidogenesis and specifically, formation and deposition of a long β-Amyloid peptide (Aβ) of 42 or 43 amino acids (Aβ42). Various mutations have also been described on the APP (Amyloid precursor protein); PS I (Presenilin-I) or PS II (Presenilin-II) genes all causes increase production of this long β-Amyloid peptide [11]. In addition to this, cytokines, transforming growth factor β1, interleukin1 and various complement factors are also involved in the process of amyloidogenesis [12,13].

Amyloid hypothesis explains the neuropathology to some extent but it does not explain the relation between amyloidogenesis and development of neurofibrillary tangle. There is a question about how this neurodegeneration and neuronal death occur? It seems that free radicals probably responsible for these processes. The free radical hypothesis of aging was proposed years ago, says that age related accumulation of the reactive oxygen species (ROS) results in damage to major components of the cell: nucleus, mitochondrial DNA, membranes, and cytoplasmic proteins. Most neurodegenerative diseases including AD are the result of imbalance between free radical generation and free radical scavengers [14-16]. The human Brain consumes large amount of oxygen compared other organs, like it weighs only 2% of the body weight but consumes about 20% oxygen supplied by the respiratory system [17]. This high energy consumption of the brain suggests that it is more susceptible to oxidative stress. Because neuron is the basic functional unit of the brain, it has higher metabolic rate, and therefore more vulnerable to oxidative damage

[18]. Other reasons for their vulnerability are; low content of glutathione, a natural antioxidant [19] and high amount of polyunsaturated fatty acids in their membranes [20]. Age is the key risk factor for the AD because free radical injury to the neurons can gradually accumulate over the years [21]. Such general findings suggest that free radical injury is associated with many age related pathologies including AD and other neurodegenerative diseases [22].

## Oxidative damage and sources of oxidative stress in AD

Under normal physiological conditions, there is balance between free radicals and antioxidants, which is disturbed in pathological conditions. Oxidative damage occurs when the reactive oxygen species are in excess of cellular antioxidant defences. Oxidative damage found in AD occurs as a result of advanced glycation end products [23-26], nitration [27,28], lipid peroxidation adduction products [29,30], carbonyl modified neurofilament protein and free carbonyls [31,32].

Research in molecular biology has suggested that mitochondrial dysfunction [33-36], metal accumulation [33,37,38], hyperphosphorylated Tau [39,40], inflammation[41,42], β-Amyloid (Aβ) accumulation [33,35,36] are responsible for the oxidative stress and damage. Oxidative stress occurs because the components of the antioxidant system like superoxide dismutase (SOD) in mitochondria and cytosol, glutathione peroxidase, and catalase are deficient or destroyed. As a result the clearance of the free radicals reduces and oxidative stress arises [43-45]. Apart from this oxidative stress also contributes to Aβ accumulation and tau hyperphosphorylation, which suggests that it plays an important role in pathogenesis of AD [33,36,46] and it can be biomarker and possible treatment target for AD [46-48].

### Lipid oxidation

Neurons are very rich in phospholipids, and are very important for the process of neurotransmission, neuronal interactions and cognition. These phospholipids have high proportions of PUFA, especially docosahexaenoic acid and arachidonic acid. It has been found that when free radical production increases, PUFA content of the brain gradually decreases [49,50]. In addition, the products of lipid peroxidation are very unstable and automatically converted into malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), ketones, epoxides, and hydrocarbons in the presence of iron [49]. Many studies have confirmed that patients with AD and mild cognitive impairment have increased levels of MDA and 4-HNE in their brains [51-53]. Isoprostanes (F2-IsoPs) are produced from arachidonic acid via esterification. Levels of F2-IsoPs and F4-IsoPs have been found to be increased in cerebrospinal fluid (CSF) in patients with AD and mild cognitive impairment (MCI) [54-57].

### Protein oxidation

As a result of oxidative damage proteins are converted to protein carbonyls, levels of which are high in brains of AD patients [53]. Tyrosine is converted to 3-nitrotyrosine and dityrosine after reaction with reactive oxygen and nitrogen species. The level of 3-nitrotyrosine residue in the CSF is negatively correlated with mental status examination score [58,59]. One study has shown that levels of total protein nitration in the inferior parietal lobule and in the hippocampus in the patients with MCI are much higher than those in healthy control subjects, which shows that protein nitration starts early in the AD pathology.

### Nucleic acid oxidation

8-hydroxydeoxyguanosine (8-OHdG) is formed due to DNA oxidation. The level of 8-OHdG in mitochondrial DNA in the parietal cortex of the AD patients is increased significantly as compared to the controls [60]. The level of 8-OHG is found to be increased a decade before the appearance of neurofibrillary tangles (NFTs) and Aβ plaques in the brain of AD patients. DNA oxidation can also be measured by DNA strand breakage. One study has reported that the level of DNA strand breakage in cerebral cortex of AD patients is twice as compared controls [61].

All the products, discussed above have been considered as blood biomarkers for early diagnosis of AD [49]. It requires further research to establish their efficacy as early biomarkers.

## The Role of Metals in AD

From the beginning, transition metals like copper, iron, aluminum, zinc etc. are the target for the research in AD pathology. These metals play critical role in the production of the free radicals. Areas of brain (hippocampus, amygdala etc.) involved in the AD pathology have shown abnormal levels of these metals [62]. Oxidative stress is produced when these metals interact with Aβ.

Iron is involved in Fenton's and Haber-Weiss's type of reactions and result in the formation of the free hydroxyl radical. On interaction between iron and Aβ, there is reduction of Fe3+ to Fe2+ and generation of H2O2, which further produces free hydroxyl radicals [63]. Accumulation of iron, ferritin and transferrin is seen in neuritic plaques in AD [64,65]. One study has shown that distribution pattern of iron in the brain of AD patients matches the distribution of senile plaques and NFTs [66]. Another study has shown that level of iron binding protein p97 is increased in blood serum and CSF in AD patients [67]. Author has suggested that level of p97 can be used as marker of the disease, can be useful in identifying the AD patients and also for assessing the effect of the therapeutic approaches.

The presence of transition metals in amyloid deposits in AD patients indicates direct interaction between these metals and Aβ [68-70]. Copper and zinc both can bind to the Aβ monomer via three histidine residues and one tyrosine residue, producing conformational change in the peptide which promotes its aggregation [71,72]. Copper is involved in free hydroxyl radical formation similar to iron. When copper interacts with the Aβ, cuproenzyme like complex is formed [71]. In this process, the electron is transferred from Aβ to Cu2+, Cu2+ is converted to Cu+ forming Aβ radical [73]. During this process copper donates two electrons to the oxygen, generating H2O2 [73,74], and setting up conditions to further produce hydroxyl radical (Fenton type reaction) [75]. These data also suggest that ROS generated from the interaction between transition metals and Aβ are important contributors to the oxidative stress in Aβ-mediated neurotoxicity and AD pathogenesis. Another fact that suggest the possible role of copper in neurodegeneration is that copper is essential for the activity of many enzymes like, cytochrome-c oxidase and superoxide dismutase [76].

Aluminum has been suggested to be involved in AD pathology because of, high level of aluminum concentration in brains of AD patients, reports of aluminum toxicity and an association between aluminum concentration in water and the prevalence of AD [77]. Recently some studies have questioned the possible role of aluminum because aluminum content is not elevated in the brain regions of AD

patients that are selectively vulnerable to the neuropathologic changes associated with the disease [78].

The linkage between aberrant metal homeostasis and AD pathology has made researchers think about AD treatment targeting Aβ-metal interaction and probably it can emerge as a promising therapeutic option. Some metal chelating compounds have been tested for their possible efficacy as a treatment option [79]. One such compound is clioquinol, which is Cu/Zn chelator and orally bioavailable, it blocks Aβ induced production H2O2 and Cu/Zn induced aggregation of Aβ peptide and can significantly reduce the Aβ deposition in the brains of transgenic mice [80,81]. One randomized, placebo controlled, double blind, clinical trial has been done using clioquinol in patients with moderately severe AD. Results showed that clioquinol treatment lowered plasma Aβ42 levels and slowed cognitive impairment in more severely affected patients during 36 week period [82].

## Mitochondria Dysfunction and Oxidative Stress

Mitochondria are very essential organelles that are responsible for a variety of cellular functions like ATP synthesis, calcium homeostasis, cell survival and death. Mitochondrial electron transport chain is a major site for ROS production in the cell and mitochondria are highly vulnerable to oxidative stress [83,84]. Many studies have demonstrated the role of mitochondria dysfunction in AD pathogenesis. Hippocampal neurons have shown many mitochondrial and metabolic abnormalities in AD patients compared to age matched controls [85-87].

Studies have shown that oxidative phosphorylation is at lower level in AD, and this can be explained by both, energy deficits and the production of free radicals. Mitochondrial electron transport chain that results in the production of ATP by via reduction of oxygen to water is a complex enzymatic system which consists of 5 distinct phases [35]:

Complex 1 (NADH dehydrogenase)

Complex 2 (succinate dehydrogenase)

Complex 3 (ubiquinol-cytochrome-c oxidase)

Complex 4 (cytochrome-c oxidase)

Complex 5 (ATP synthase)

Research evidences have confirmed mitochondrial dysfunction in aging and neurodegenerative diseases such as AD, Huntington disease, and Parkinson disease, and particularly dysfunction in cytochrome-c oxidase in complex 4 in AD [88]. One study showed that postmortem cytochrome-c oxidase activity was around 25-30% lower than normal in cerebral cortex and platelets of AD patients [87]. Symonian and hyman have demonstrated lower than normal cytochrome-c oxidase activity in dentate gyrus and the $CA_4$, $CA_3$ and CA zones of hippocampus [89]. Another study has shown lower than normal levels of mRNA concentrations in subunit 1 and 3 of cytochrome-c oxidase [90]. In fact amounts of cytochrome-c oxidase are normal in brains of AD patients; it is the enzyme activity that is affected [91].

Studies have shown that Aβ may disrupt mitochondria function and contribute energy deficits and neuronal death seen in AD. The interaction between Aβ and mitochondria is also responsible for the free radicals production. Aβ was located in mitochondria in brains of AD patients, in transgenic mice and in neuroblastoma cells expressing human mutant APP [92,93]. In isolated mitochondria, Aβ can cause oxidative injury to the mitochondrial membrane, disrupt protein mobility and lipid polarity and inhibit the enzymes of mitochondria electron transport chain, leading to increased mitochondrial membrane permeability and cytochrome c release [94,95]. SODs are enzymes that provide protection against superoxide and other free radicals. The activity of one such enzyme manganese SOD (MnSOD) is decreased which further increases the levels of ROS and compromises the mitochondria function, and contributes to the loss of mitochondrial membrane potential and finally caspase activation and apoptosis [96].

Uncoupling proteins (UCPs) are mitochondrial anion carrier proteins which are a part of cellular protective mechanisms against oxidative damage to mitochondria. They are located on the inner mitochondrial membrane [97]. Upon activation by ROS and other products of lipid peroxidation, these proteins decrease the proton motive force, reduce the mitochondrial membrane potential and ATP production, eventually causing mitochondria uncoupling and decrease ROS production from mitochondria [98]. Therefore UCPs are considered as a protective mechanism against oxidative stress. In AD brains the expression of UCP2, 4 and 5 is significantly decreased and this protective mechanism becomes dysfunctional [99]. Evidences suggest that there is a relation between Aβ accumulation and expression and activation of UCPs. Upregulation of UCP2 and UCP4 protein levels in response to exposure to the superoxide is dysfunctional in SH-SY5Y neuroblastoma cells expressing APP mutant, mechanisms are unclear but it suggests that Aβ accumulation may lead to irreversible cellular modifications that render the cells vulnerable to the oxidative stress. Aβ accumulation is also linked to the loss of calcium homeostasis in cells by mitochondria [100].

Researchers have discovered mutations in cytochrome-c oxidase genes that segregate with late onset AD [101]. It has given considerable support to the link between mitochondrial function and cytochrome-c oxidase. Cytochrome-c oxidase is produced by effect of both mitochondrial and nuclear genes but mostly by two mitochondrial genes, CO1 and CO2 encoding for the subunit I and II respectively. CO3 is the gene encoding for the subunit III. One study has described DNA polymorphisms in CO1 and CO2 but not in CO3, that aggregate in AD [101]. However, further research concluded that these polymorphisms are not present in the mitochondrial genome but are rather nuclear pseudogenes [102,103].

## Aβ Induced Toxicity and Oxidative Stress

Aβ is produced from the APP by proteolytic cleavage by two membrane bound proteases beta-secretase and gamma-secretase. Beta-secretase is also known as beta site APP cleaving enzyme 1 (BACE) and gamma-secretase is a multiprotein complex consisting of presenilin (PS), nicastrin (NCT), anterior pharynx defective 1 (APH1), and presenilin enhancer protein 2 (PEN-2) [1,104,105]. Beta-secretase and gamma-secretase cleaves APP at different sites and finally Aβ peptides of varying length are generated [1,104,106]. Among them, 42-amino acid form of Aβ is more toxic because of is faster self-aggregation into oligomers [1,106,107]. Research evidences suggest that soluble Aβ oligomers are the most neurotoxic and their level correlate with severity of cognitive decline in AD [106,107]. Alpha-secretase is a third protease that prevents the formation of toxic Aβ peptides. Dysfunctional activity of these three proteases, results in Aβ accumulation, which stimulates diverse cell signaling pathways, and lastly resulting in synaptic degeneration, neuronal loss, and cognitive decline [104,106-111].

Studies have implicated oxidative stress in Aβ induced neurotoxicity [112]. Levels of hydrogen peroxide and lipid peroxides could be increased with Aβ treatment within cell cultures in in vitro experiments [113]. Mutant forms of APP and PS-I can result in increased hydrogen peroxide and nitric oxide production as well as oxidative alterations of proteins and lipids, which were correlated with the age associated Aβ accumulation, this confirms that Aβ promotes oxidative stress [92,114-116]. Excessive activation of N-methyl D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors through NMDA agonists results in tremendous influx of Na+ and Ca++ and secondary influx of H2O, eventually causes acute cellular edema and narcotic cell death. The persistent elevation of Ca2+ causes disruption of the mitochondria, release of cytochrome C and activation of caspases, finally producing programmed cell death (apoptosis) [117]. In Hippocampal neuronal cell lines, the production of ROS by Aβ oligomers required the activation of NMDA receptors and subsequent increase in Ca++ influx. All these findings suggest possible role of soluble Aβ oligomers as a proximal neurotoxins and the involvement of oxidative stress in the synaptic impairment and neuronal loss induced by soluble Aβ oligomers [118]. Consistently, the natural antioxidants like, gingko biloba, curcumin, and green tea catechins have shown to exert neuroprotective functions by attenuating Aβ induced ROS generation and neuronal apoptosis [119-122].

Apart from mediating Aβ induced cytotoxicity, studies have shown that oxidative stress promotes the production of Aβ. Various studies in transgenic mice models overexpressing mutant APP, have shown that defects in antioxidant system caused elevated oxidative stress and significantly increased Aβ deposition, while dietary antioxidants lowered the elevated oxidized proteins and decreased Aβ levels and Aβ plaque burden in brain [123-125]. Based on these findings, overexpression of the MnSOD decreased oxidative stress and increased antioxidant defense capability in brains associated with reduction in Aβ plaque burden and restoration of some memory deficits [126]. Similarly, deletion of cytoplasmic Cu/Zn SOD was found to increase Aβ oligomerization suggesting the possible role of oxidative stress in Aβ oligomerization [127]. These all findings suggest that oxidative stress is important for Aβ oligomerization/deposition and plaque formation.

Many studies have focused on how oxidative stress increases Aβ production and revealed that oxidative stress decreases the activity of alpha-secretase while promoting the activities of beta-secretase and gamma-secretase, enzymes critical for generation of Aβ from APP [128-132]. Studies have demonstrated that oxidative stress activates major cell signaling c-Jun N-terminal kinase (JNK) pathway which causes induction of BACE and PS1expression and activation of gamma-secretase. As a result, more amount of Aβ is produced and its clearance is decreased leading to Aβ deposition, plaque formation and eventually neurotoxicity [133,134]. The activation of JNK pathway [135-137] and increased BACE and PS1 activity [138-140] both have been detected in AD brains; thus, it is possible that elevated levels of oxidative stress in AD brains may initiate the activation of ROS sensitive cell signaling pathway including JNK, which induces the expression of BACE and PS1, ultimately enhancing the production of Aβ and the deterioration of cognitive function.

Studies have shown that neuronal oxidative damage was more in AD subjects with lesser amounts of Aβ deposition or in AD subjects with shorter disease duration [141,142]. In addition to this, there was an inverse relationship between the oxidative damage to nucleic acids and the amounts of intraneuronal Aβ42 in the hippocampus and subiculum of AD brains [143]. These strange observations have led to the hypothesis that Aβ may be playing a protective role against oxidative stress [144]. Evidences suggest that lower nanomolar levels of Aβ can be neurotrophic or neuroprotective [145,146]. Aβ, in normal physiological concentrations was shown to inhibit autooxidation of lipoproteins in CSF and plasma [147] and to increase hippocampal long term potentiation [148], whereas the higher nanomolar levels of Aβ caused the toxic effects. From all these findings, we can conclude that low levels of Aβ may have potential role in normal function of the cells, while the abnormal production, accumulation and aggregation of specific forms of Aβ, which can be increased by oxidative stress, may impair the neuronal activity and exacerbate neuronal oxidative insults, contributing to the pathological development of AD [146-149].

## Hyperphosphorylated Tau

Hyperphosphorylated Tau is the major component of the NFTs, and is significantly correlated with neurodegeneration and cognitive decline in AD [104]. Surprisingly, neurons with NFTs showed significantly lower levels of 8-OHG despite obvious oxidative damage. This suggests that tau phosphorylation and NFT formation may have a protective role for neurons from oxidative stress [150]. However, research evidences suggest that tau is associated with oxidative stress in AD. In a Drosophila model of human tauopathy, reduction in gene dosage of thioredoxin reductase or mitochondrial SOD2 promotes tau induced neurodegenerative histopathological abnormalities and neuronal apoptosis [40]. While, treatment with the antioxidants like vitamin E and C decrease the level of ROS and tau induced neuronal death [39,151]. The link between tau pathology and oxidative stress has been demonstrated in transgenic mice models P301S and P301L. Studies have shown that reduced activity of NADH-ubiquinone oxidoreductase with mitochondrial dysfunction impairs mitochondrial oxidative phosphorylation and ATP synthesis [152-154]. Accordingly, Coenzyme Q10 (CoQ10) which is a key component of electron transport chain significantly reduces lipid peroxidation and increases complex 1 activity, consequently improves survival and behavioral deficits in P301S mice [155]. In addition to this, the convergence of Aβ and tau pathologies on mitochondria dysfunction was demonstrated in triple transgenic mouse model (PR5/APP/PS2) (tripleAD), which has both Aβ and tau histopathologic features of the disease in the brain of the mouse [156]. When Proteomics analysis of the tripleAD brain samples was done, it has demonstrated deregulation of 24 proteins, in which one third were mitochondrial proteins related to complex 1 and 4 of electron transport chain [157]. Interestingly, deregulation of mitochondrial complex 4 was shown to be Aβ dependent, while deregulation of complex I was tau dependent [157]. The effects of both Aβ and tau on mitochondrial function were found to be synergistic and age associated, which results in reduction of mitochondrial oxidative phosphorylation and ATP synthesis, eventually leading to the synaptic loss, and neuronal death [157].

## Apolipoprotein E and Oxidative Stress

Apolipoprotein E (ApoE) gene is polymorphic and it has three isoforms: Apo ε2, Apo ε3 and Apo ε4. The ε4 allele has been linked to both late onset family forms and sporadic forms of AD, whereas ε2 allele was found to offer protection. In central nervous system, ApoE is produced mainly by astrocytes and take part in transport of cholesterol to neurons through ApoE receptors, and is a crucial cholesterol carrier

in brain and has possible role in neuroplasticity-related phenomena because it requires changes in membrane lipids. One researcher has found that ApoE has beneficial effect for neuronal protection but it is isoforms dependent, like Apo ε4 isoform is less effective than Apo ε2 and Apo ε3 [158]. There is possibility that Apo ε4 may not be toxic but it simply has less protective effects than ε2 and ε3. Some researchers showed that ApoE has protective role against free radicals and has significant antioxidant property but it is also isoforms dependent like, effect is clearly perceptible with isoform ε2 but less so with ε3 and even less so with ε4 [159]. However, another study showed that ApoE is sensitive to free radical attack in isoform dependent manner. The isoform ε4 is more sensitive to free radical attack than isoform ε3 and ε3 is more sensitive than isoform ε2. An antioxidant like gingko biloba extract EGb 761, protects ApoE from oxidation in a similar isoform dependent manner, the Apo ε4 being maximally protected [160]. Further research has showed relation between lipid peroxidation in AD and ApoE genotype. They showed that the level of lipid peroxidation in AD is isoform dependent and were higher with Apo ε4 allele. The concentration of ApoE in brains of AD patients is inversely proportional to the level of lipid peroxidation, which confirms the hypothesis that ApoE has beneficial effect against lipid peroxidation and the effect is more pronounced with ε4 allele. Research finding showed that EGb 716 effectively decreases the level of lipid peroxidation in the brains of AD patients [161].

## Inflammation

Inflammation also takes part in the production of free radicals. Deposition of Aβ initiates inflammatory cascade which attracts and activates microglia and astrocytes, leading to their aggregation around Aβ deposits, and release of pro-inflammatory mediators such as cytokines, chemokines, ROS, and complement proteins that may result in neuronal damage [162-164]. Microglia also has scavenger receptors by which it interacts with Aβ, causes ROS secretion and cell immobilization [165].

## Antioxidant Therapeutics

The role of oxidative stress in AD pathology is very promising in development of future therapeutic strategies for prevention and possible treatment of AD. Various antioxidant therapies identified and studied on the basis of role of antioxidants in decreasing the ROS production and exerting neuroprotective effects on neurons in AD patients [166,167]. Most abundantly researched and studied are vitamins and carotene. Vitamin E (α-tocopherol), vitamin C (L-ascorbic acid), and β-carotene (Endogenous antioxidant compounds and also found in the diet) are chain breaking antioxidants which decrease free radical mediated damage in neuronal cells and help to inhibit dementia pathogenesis in mammalian cells. Vitamin B2 is an antioxidant and has been shown to increase choline acetyltransferase activity in cholinergic neurons cats and improves cognitive functions in AD patients [168].

Here, we are not mentioning each and every antioxidant therapeutic option because in last two decades there has been abundant research and studies for protective role of antioxidants in AD. We just mentioning the categories of the antioxidant therapies based on their target actions and the recent research in the same field. The possible categories are mentioned below:

Delanty and Dichter have made review of antioxidant therapies in neurological disorders and categorize various available antioxidants depending on whether compounds are endogenous or exogenous and their underlying mechanism of action [169].

Endogenous enzymes, eg, superoxide dismutase, catalase, glutathione peroxidase

Endogenous antioxidant compounds (also found in the diet), eg, α-tocopherol, ascorbic acid

Other endogenous antioxidant substances, eg, uric acid, glutathione, melatonin

Endogenous antioxidant cofactors, eg, selenium, coenzyme Q10

Precursors and derivatives of endogenous antioxidant compounds and enzymes, eg, acetyl cysteine, polyethylene glycol superoxide dismutase

Metal chelators, eg, deferoxamine

Naturally occurring plant substances, eg, flavonoids (in gingko biloba and black tea), lycopene in (tomatoes), guilingji (a Chinese herbal medicine)

Synthetic free radical compounds, eg, 21-aminosteroids, pyrrolopyrimidines, ebselen

Compounds with other primary beneficial therapeutic effects, but that may also have free radical scavenging activity, eg, selegiline, probucol, carvedilol, aspirin, magnesium, statins [169]

Feng and Wang have described the various Antioxidant strategies for the AD [170]:

Antioxidant therapies: vitamin E (α-tocopherol), vitamin C, β-carotene, vitamin B2

Antioxidant Enzymes: superoxide dismutase (MnSOD-Mitochondrial, Cu/Zn SOD-cytoplasmic), catalase, glutathione peroxidase

Mitochondrial targeted Antioxidants: vitamin A, carotenoids, vitamin C, and vitamin E and others (α-lipoic acid (LA), coenzymeQ10, NADH, Mito Q, Szeto Schiller (SS) peptide, and glutathione)

Dietary supplements: omega-3 polyunsaturated fatty acid (docosahexaenoic acid), caffeine, and curry spice curcumin

Traditional Herbal Antioxidants: three major alkaloids in CoptidisRhizoma-groenlandicine, berberine, and palmatine, silibinin (silybin), a flavonoid derived from the herb milk thistle (Silybummarianum), Ginkgo biloba, ginsenosides isolated from Panax spp. ginseng herb [171]

Other Antioxidants: Melatonin, Monoamine Oxidase-B Inhibitor (Selegiline), and Oestrogen

Melatonin is endogenous hormone synthesized in pineal gland. It stimulates the expression and activity of glutathione peroxidase, SOD, and NO synthetase, by this it scavenges ROS and RNS generated in mitochondria, eventually contributes to the reduction of oxidative damage in cells [172,173]. Selegiline is a selective monoamine oxidase-B inhibitor with possible antioxidant properties [174]. One study reported that in patients with moderate to severe AD, treatment with selegiline reduces neuronal damage and slows the progression of AD [175]. Estrogen has been shown to have role in neuronal protection against oxidative damage and neuroprotective effects [176], but it does

not produce any beneficial effects on cognition and functioning in AD [170,177].

Tritrpenoids, are polycyclic compound derived from the linear hydrocarbon squalene. They are widely distributed in edible and medicinal plants [178]. Xanthoceraside, a triterpene derived from the husk of xanthocerassorbifolia Bunge, is used by Chinese as a traditional remedy for rheumatism. One researcher has reported that xanthoceraside ameliorates the oxidative stress and inflammatory responses induced by Aβ25-35, attenuates memory impairments and is a potential candidate for an AD treatment [179]. Another triterpenoid, 2-Cyano-3, 12-Dioxooleana-1, 9-Dien-28-Oic acid-Methylamide (CDDO-MA) is studied in Tg19959 mice, after 3 months of administration, it significantly improved spatial memory retention, reduced plaque burden, Aβ42 levels, microgliosis and oxidative stress in Tg19959 mice [180].

The Rhinacanthusnasutus is an herb found in Thailand and South East Asia, belongs to Acanthaceae family [181]. Extracts from the leaf and root contain varying amounts of phenolic and flavonoid compounds, triterpenoid-lupeol, and the sterols stigmasterols and β-sitosterol. The ethanol extracts of leaf and root have high free radical scavenging effects. It protects HT-22 cells (mouse hippocampal cell lines) against glutamate and Aβ toxicity. This protection is combination of effects of various compounds, resulting from more than one mechanism, including free radical scavenging, inhibition of caspase and growth factor production [182].Puerarin, a major isoflavone glycoside from Kudzu root (Puerarialobata) has been reported to exhibit estrogen like and antioxidant properties. Pretreatment of primary hippocampal neurons with peurarin significantly reduced Aβ25-35-induced oxidative stress possibly through scavenging of ROS, inhibiting lipid peroxidation and interrupting the glycogen synthase kinase-3β (GSK-3β) signaling [183].

Many antioxidants have been identified and studied for the possible therapeutic role in AD, but none has given consistent beneficial results, therefore their efficacy in prevention and possible treatment of AD is always a question. Recently, many dietary and herbal antioxidants and other antioxidants targeting the mitochondria have shown promising results but it requires further research and confirmation of the efficacy.

## Conclusion

Growing evidence suggests that oxidative stress plays a major role in the pathogenesis of AD. This production of the free radicals has been linked to the disruption of the metal ion homeostasis, mitochondrial dysfunction, genetic mutations, increased Aβ42 production and aggregation, decreased clearance of Aβ, inflammatory mediators, and tau hyperphosphorylation, in a manner of vicious pathophysiological cycle. Combination of all these processes results into oxidation of lipids, proteins and nucleic acids, and their products have been considered as blood biomarkers for early diagnosis of AD, but their efficacy as early biomarkers is still a question. Regardless a primary or secondary event, oxidative stress is important factor contributing to the pathogenesis of AD. Free radical scavenging or prevention of their formation may delay the onset or slow down the progression of AD through various mechanisms, including reduction of oxidative stress mediated neurotoxicity, inhibition of Aβ production and aggregation, restoration of mitochondria function and metal homeostasis, reduction in tau phosphorylation and polymerization. Accordingly, research evidences suggest that various antioxidant therapies play role in free radical scavenging and reduce oxidative stress, therefore they are possible therapeutic options and research targets. Some studies also have shown that metal chelators have some role in reduction in oxidative stress arising due to metal dyshomeostasis, but further research is required for confirmation of their therapeutic role.

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