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Oxidant/Antioxidant Imbalance and the Risk of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia characterized by progressive loss of memory and other cognitive functions among older people. Senile plaques and neurofibrillary tangles are the most hallmarks lesions in the brain of AD in addition to neurons loss. Accumulating evidence has shown that oxidative stress–induced damage may play an important role in the initiation and progression of AD pathogenesis. Redox impairment occurs when there is an imbalance between the production and quenching of free radicals from oxygen species. These reactive oxygen species augment the formation and aggregation of amyloid-β and tau protein hyperphosphorylation and vice versa. Currently, there is no available treatments can modify the disease. However, wide varieties of antioxidants show promise to delay or prevent the symptoms of AD and may help in treating the disease. In this review, the role of oxidative stress in AD pathogenesis and the common used antioxidant therapies for AD will summarize.

Keywords: Alzheimer's disease, antioxidants, oxidative stress.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of dementia characterized by progressive loss of memory and other cognitive functions among older people, AD is placing a considerable emotional and financial burden on patients, their families, caregivers and society, as more people live long enough to become affected. AD begins slowly. It first affects the brain regions of CA1 region of the hippocampus, prefrontal cortex and pyramidal cells in lamina II of the entorhinal cortex that control memory, thought and language. Over time, symptoms get worse. Patients may not recognize family members or have trouble writing, reading or even speaking. AD typically begins after age 60 with death occurring on average a decade or so passes after diagnosis [1].

Pathology

Histopathology of post-mortem brains obtained from AD clinically characterized patients provided the first clues to the mechanisms of disease and potential interventions. It led to the description of the disease a century ago by Alois Alzheimer [1], and the identification of the AD hallmark lesions. The histopathological changes include extracellular deposits of amyloid-β (Aβ) forming senile plaques and intracellular neurofibrillary tangles (NFT) formed by accumulation of abnormal hyperphosphorylated filaments of tau in pyramidal neurons. Besides these features, a large body of evidence indicates prominent activation of inflammatory processes and the innate immune response activation. Classic senile plaques are spherical structures consisting of a central core of Aβ fibrous protein that is surrounded by degenerating or dystrophic nerve endings. The Aβ protein contains a 40 or 42 amino acid peptide of Aβ that is derived from proteolytic processing of a larger amyloid precursor protein (APP) molecule via two pathways: the α pathway and the β pathway. APP is degraded by α -secretase to produce a non-amyloidogentic molecules, whereas the sequential enzymatic actions of beta-site APP-cleaving enzyme 1 (BACE-1), a β-secretase, generated small APPβ (sAPPβ) in the extracullar space. sAPPβ is subsequently degraded by γ -secretase, a protein complex contains presenilin 1 at its catalytic core, to release Aβ and APP intracellular C-terminal domain (AICD) [2]. It is believed that the most toxic Aβ40–42 peptides are resulted by the abnormal processing of the APP molecule [3]. However, the produced Aβ is degraded by many enzymes includes, but not limited to, insulin-degrading enzyme (IDE) and neprilysin (NEP). NEP and IDE are reduced in AD [4]. The imbalance between Aβ production and clearance causes Aβ to accumulate in the extracellular space. Aβ1–42 readily forms insoluble clumps and initiates a cascade of events leading to apoptosis and neuronal dysfunction or death. This process called the amyloid hypothesis (Fig. **1**).

On the other hand, NFT is a phosphorylated tau protein (p Tau) and found in the intracellular space of the neurons and are composed of paired helical filaments and straight filaments of hyperphosphorylated microtubule-associated protein (MAP), tau protein. The intracellular deposition of NFT causes destroying the normal cytoskeletal architecture with subsequent neuronal cell death. This process called the tau hypothesis.

The most consistent neurochemical change associated with AD has been the well-documented decline in cholinergic activity that has inspired many attempts to treat AD with cholinergic drugs based on cholinergic hypothesis. However, additional alerts in Ca^{2+} homeostasis, catecholamine

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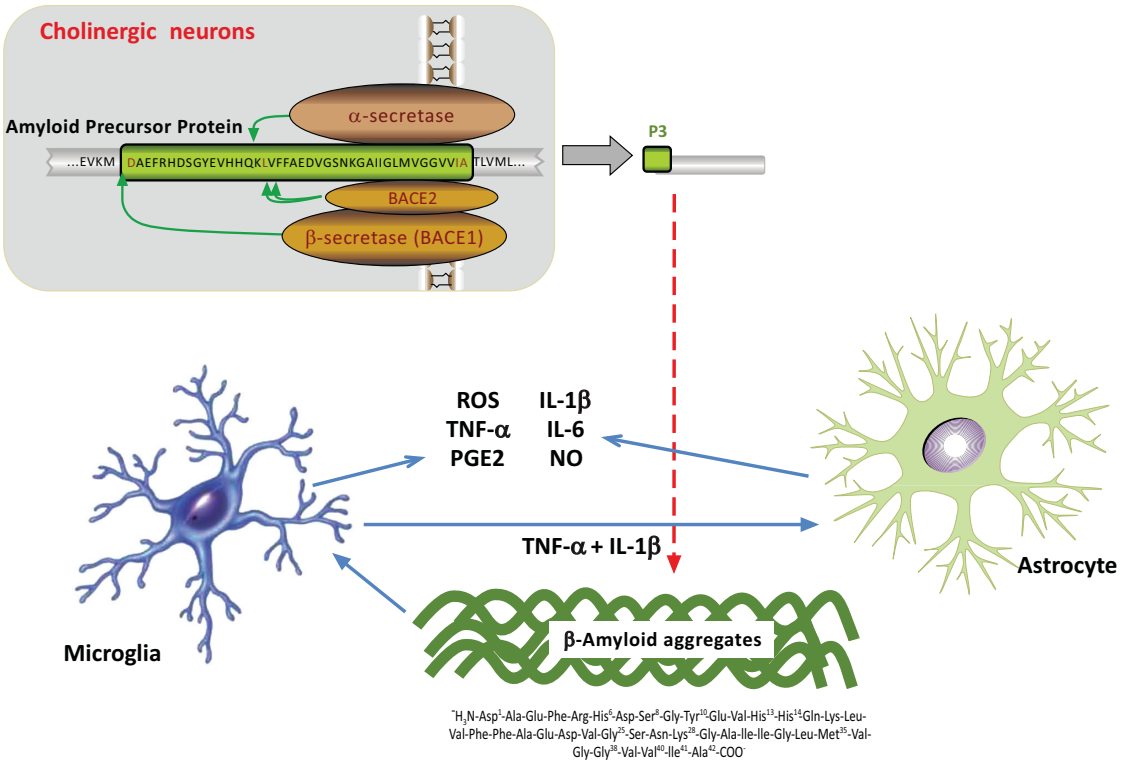


Fig. (1). Amyloid hypothesis. During AD development, amyloid precursor protein is cleavage to produce β amyloid peptide that aggregates and accumulates to form amyloid-β plaques. This plaques cause neurotoxicity or microglia activation, which in turn microglia release ROS and many pro-inflammatory cytokines such as NO, PGE_2, IL-1, IL-6, and TNF-α that accelerate cholinergic neuron damage. These pro-inflammatory cytokines subsequently activate astrocytes that also produce more cytokines to amplify the inflammatory signals and result in neuroinflammation and neurodegeneration.

(norepinephrine), serotonin, glutamate and neuropeptides [corticotrophin-releasing factors (CRF) and somatostatin (SRIF)] have also been described [5].

Genetics

Mutations in any one of a number of different single-gene on chromosomes 1, 14, and 21 can cause familial Alzheimer's disease (FAD) of early-onset Alzheimer's. Mutations of APP gene on chromosome 21 cause the formation of abnormal APP. A mutation of presenilin 1 (PS-1) gene on chromosome 14 causes abnormal PS-1 to be made, and a mutation of presenilin 2 (PS-2) gene on chromosome 1 leads to abnormal PS-2. However, the genetic causes of late-onset Alzheimer's, which develops after age 65, are not yet completely understood [6], but they likely include a combination of age, genetic, environmental, and lifestyle factors that influence a person's risk for developing the disease. A gene called Apolipoprotein E (ApoE) found on chromosome 19 appears to be a risk factor for the late-onset form of Alzheimer's. ApoE comes in several different alleles, or forms. The three forms of ApoE are ApoE ε2, ApoE ε3, and ApoE ε4 [7]. While inheritance of ApoE ε4 increases the risk AD development, ApoE ε2 substantially protects against it.

Epidemiology

AD is a multifactorial disease and no specific environmental exposure has been found to be consistently associated with AD onset. Furthermore, the strong association between AD and increasing age may partially reflect the cumulative effect of different factors including genetic susceptibility, depression, traumatic head injuries, exposure to toxins and electromagnetic fields and vascular factors including midlife high blood pressure, cerebral and cardiovascular disease, smoking, obesity and diabetes as increasing disease risk factors, while anti-inflammatory medications and low to moderate alcohol consumption seem to reduce the disease risk. In addition, education and occupational history status are highly correlated (e.g., low education versus high education and unskilled versus skilled worker) with either a higher prevalence [8] or incidence of AD [9]. Low cognitive activities, poor social network or social disengagement have been shown to increase the risk of dementia in the elderly [10]. In supporting of these factors, the high level of complex mental activities, more frequently participating in mentally stimulating and physically activities are correlated with a reduced the AD risk [11].

CURRENT ANTI-ALZHEIMER'S TREATMENT

Currently, no drug treatments are available that can slow or stop Alzheimer's disease progression. However, scientists around the world are studying dozens of treatment strategies that may have the potential to delay or prevent the symptoms of AD [12].

There are two main types of medication can help for a time with memory symptoms and other cognitive changes that associated with Alzheimer's disease; cholinesterase in-

hibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists. The two types of drugs are worked in different ways. Cholinesterase inhibitors include rivastigmine, donepezil and galantamine to treat mild to moderate Alzheimer's, whereas; the NMDA receptor antagonist is memantine to treat moderate to severe Alzheimer's.

Cholinesterase inhibitors help by preventing acetylcholinesterase from breaking down acetylcholine at the nerve ending. Increased concentration of acetylcholine leads to improve the communication between the nerve cells that use acetylcholine as a neurotransmitter, which may in turn temporarily improve or stabilize the symptoms of Alzheimer's disease [13-14]. This class of medications may be used for three years, possibly longer.

The action of NMDA receptor antagonist is quite different from, and more complex than, that of cholinesterase inhibitors. It is thought to work by blocking glutamate. Glutamate, the major excitatory neurotransmitter in CNS, is released in excessive amounts and this causes the neurons to be damaged further. Memantine can protect neurons by blocking these effects of excess glutamate [15].

OXIDATIVE STRESS AND AD

Oxidative stress (OS) reflects the imbalance between the production and quenching of free radicals from oxygen species in the biological system. The disturbances in the normal redox status of cell can cause an increment in reactive oxygen species (ROS). These ROS play a key role in many chronic diseases including cancer, mitochondrial diseases [16], neurodegenerative diseases [17, 18]. Accumulating evidence has shown that the presence of extensive OS is a characteristic of AD brains in addition to the established pathology of senile plaques and NFT [19]. The interventions between OS and other key events in AD, which amplify the complexity of this issue was summarized in Fig. (**2**).

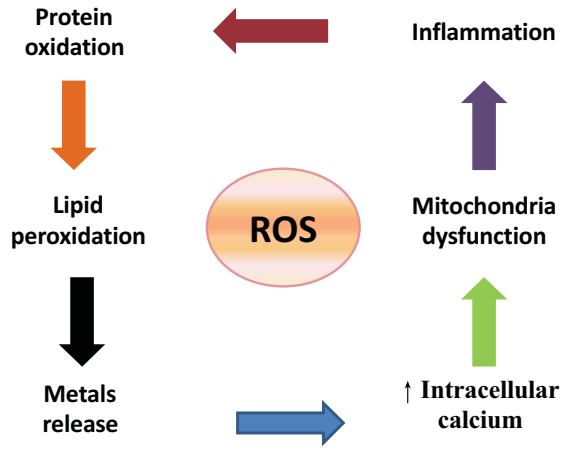


Fig. (2). Interventions between oxidative stress and the other key factors in AD.

Nucleic Acids Oxidation

Excess ROS or free radicals can oxidize nucleic acid which 8-hydroxyguanosine and 8-hydroxydeoxyguanosine (8-OHdG) are formed as markers of DNA, RNA and mitochondrial DNA (mtDNA) oxidative damage. Nucleic acids damage is thought to play a key step in neuronal loss associated with aging and many neurodegeneration diseases [20]. mtDNA is highly susceptible to oxidative stress because of its vicinity to ROS generation, the absence of histones and has limited repairing mechanisms. mtDNA damage could potentially cause bioenergetic and nerve dysfunctions. Interestingly, mtDNA damage is observed before Aβ deposition and neuronal degeneration [21]. Indeed, DNA oxidative damage is a feature of AD and considered as an early event in AD progression [20, 22].

Proteins Oxidation

It has been demonstrated that the levels of 3-nitrotyrosine and protein carbonyls, which are resulted from protein oxidation are elevated in brains of patients who suffered from AD [23]. Proteins oxidation causes advanced glycation end products (AGEs) that can be a factor in the development or even worsening of many diseases. AGEs chemically are posttranslation modified proteins that are formed when adding nonenzymatically monosaccharides to the amino group of the protein. This protein undergoes further modification via oxidation, condensation, and dehydration to produce the AGEs. This reaction, which is catalyzed by transition metals such as iron to form enediol radical, which produces free radicals by reducing molecular oxygen. AGEs may speed up oxidative damage via either direct radical production by chemical oxidation and degradation of AGEs, indirect oxidative stress via AGE-receptor (RAGE) binding and activation of signaling pathways such as upregulation of the transcription factor nuclear factor-κB (NF-κB), or by interacting with microglia in an acute phase reaction that results in a respiratory burst and potentiate free radical production that leads to deficits in learning and memory [24]. AGEs colocalized with the senile plaques of AD-affected brains [25]. Moreover, the senile plaques contain 3 times more AGEs than that of the age-matched brains control. AGE modified Aβ to form Aβ-AGEs and accelerates the aggregation and accumulation of nonfibrillar soluble Aβ *in vitro*, which suggests that this process may also occur *in vivo* and creates vicious cycles or positive feedback loops [26-27]. Interestingly, Aβ is considered as a ligand of RAGE this in turn mediates Aβ-induced oxidative damage. In addition to the accumulation of free radical damage, alterations in the antioxidant enzymes activity or expression such as superoxide dismutase (SOD) and catalase have been observed in both CNS and peripheral tissues of AD patients [28]. Moreover, the increased oxidative damage to lipids and proteins and the decline of glutathione and radical detoxifying enzymes activity are more localized to the synapses and correlate with the severity of the disease, suggesting that oxidative stress could be involved in AD-related synaptic loss [29].

Lipid Peroxidation

CNS is a major target for lipid peroxidation. In the brain, low concentrations of the endogenous antioxidant component glutathione and the antioxidant enzyme catalase, a high metabolic rate (consumes about 20–30% of inspired oxygen), and a high proportion of polyunsaturated fatty acids (PUFAs) make this organ an ideal target for oxidative damage [30]. As a result of PUFAs attacked by free radical,

malondialdehyde (MDA) and 4-hydroxy-2,3-nonenal (HNE) are formed beside to acrolein as a reactive substance. In AD brains elevated MDA, HNE and acrolein has been identified. Moreover, lipid peroxidation markers noted in patients with mild cognitive impairment, suggesting that lipid peroxidation is an early event in AD progression. Furthermore, MDA is also found in different brain regions and cerebrospinal fluid (CSF) of AD patients [31]. Lipid peroxidation reacts with macromolecules causing impairment of the function of membrane proteins such as the neuronal glucose transporter (GLUT 3), reduction of glucose metabolism by inhibiting enolase, inhibition of glutamate transporters, inhibition of Na^+/K^+ ATPases, inhibition of antioxidant enzymes as SOD 1 and hemeoxygenase 1, activation of kinases, and dysregulation of ionic transfers and calcium homeostasis [32]. Disruption of Ca^{2+} homeostasis, due to increase in intracellular Ca^{2+}, could cause a cascade of intracellular events as ROS generation and cellular death by apoptosis, and it also worth noting that AD shows Ca^{2+}-dependent cell death [33].

Metals Homeostasis Disturbance

As mention above and recent evidences suggest that disruption of metal homeostasis may also contribute to oxidative damage [34-35]. During aging metals such zinc, iron and copper accumulate in the brain which act as antioxidants. Metal dependent enzymatic processes are important for brain metabolism and metal dyshomehostasis is linked to AD progression. Zinc, iron and copper are able to interact with secretase that promoting APP cleavage, senile plaque formation, facilitating Aβ aggregation and hyperphosphorylation of tau protein [35, 34]. Furthermore, copper, zinc and iron bind to Aβ triggering signaling cascades that amplify oxidative damage [34]. In addition, synaptic zinc has been associated with increasing plaque burden in brain of AD mouse models [36]. There is evidence that disruption of zinc homeostasis may play an important role in microtubule and tau pathology [37]. Regarding this fact, divalent metal ion chelators such as clioquinol and desferrioxamine have had some success in altering the progression of AD [38-39] by facilitating solubilization of Aβ plaques. However, zinc might at low concentration actually protects the neurons by blocking Aβ channels or compete with Cu for Aβ binding [2] and partially prevents the cognition loss.

Mitochondrial Dysfunction

Mitochondrial dysfunction appears to play a prominent role in the early events of AD progression [40]. Regarding this fact, a decreased in oxidative phoshorylation genes expression of mitochondria was noted in the neocortex of AD brain and this decreased was correlated with the severity of dementia [32]. There are evidences that both phosphorylated tau protein and Aβ deactivated complexes I and IV, respectively. Indeed, AD markers are alerted mitochondrial oxidative phosphorylation (OXPHOS) system. Furthermore, loss of mitochondrial integrity plays an important role in synaptic dysfunction [41]. Moreover, deposition of Aβ leads to more mitochondrial damage [42] by interacting with Aβ-binding alcohol dehydrogenase the mitochondrial protein (ABAD, a neuronal mitochondrial enzyme exacerbates Aβ-mediated mitochondrial and neuronal dysfunction). The formed complex prevents the binding of NAD^+ to ABAD, thereby changing mitochondrial membrane permeability and reducing the activity of respiratory enzymes causing ROS generation. Also, mitochondrial mobility has also been altered in AD causing a mitochondrial reduction in neurites [43]. Aβ plaques induce a reduction in motile mitochondria [44-45]. In addition, Aβ significantly alerted mitochondrial fission and fusion by changing the expression of almost proteins that regulate this process.

Moreover, in spite of the growing number of data concerning the central role of mitochondria in apoptosis signaling. A reduction in mitochondrial membrane potential induce mitochondrial permeability transition pore (mtPTP) as an early universal event of apoptosis. The liberation of mitochondrial cytochrome *c* and apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space into the cytoplasm are also the most key events in activating the cascade of reactions that leading to cell death. Such alterations in mitochondrial structure have been noted as a causative mechanism in AD pathogenesis [46].

CAN MICROBIOME BE LINKED TO AD?

Nowadays, accumulating evidences are linked between microbiome and homeostatic status of CNS. For example, gastrointestinal (GI) tract contains gram-positive organisms are capable to metabolize glutamate to GABA crosses blood brain barrier [47], GI microbiome can significantly alert BDNF expression and reduce its level in hippocampus and cortex [48], GI microbiome can generate β-**N**-methylamino-L-alanine (BMAA), neurotoxin induced NMDA activation, glutathione depletion, oxidative stress and intra-neuronal protein misfolding [49], some bacteria and fungus can produce amyloids against human defenses, those amyloids can aggregate into oligomers promote amyloid fibril formation [50], lastly, some types of bacteria can produce phenol soluble modulins (PSMs; some peptides), those PSMs activate strongly formyl-peptide receptor 2 (FPR2) of neutrophil [51]. Interestingly, FPR2 can bind to a wide variety of amyloid-like ligands [52].

CAN ANTIOXIDANTS BE CONSIDERED AS A THERAPEUTIC TARGET IN AD?

Antioxidants are molecules that inhibit the oxidation of other molecules. Antioxidants are widely used and have been investigated for the prevention of many diseases. In the recent years, many natural compounds with antioxidant properties have been investigated as adjuvant therapies for AD and other neurodegenerative diseases. It has been reported that antioxidants such as vitamin E or α-tocopherol, β -carotene, vitamin C, lipoic acid and *N*-acetylcysteine and others may offer protection against extracellular and intracellular ROS and H_2O_2-cell-damaging compounds that are generated as byproducts of normal cell functioning before these radicals damage cells or activate microglia through their action as intracellular second messengers [53].

As accumulating evidences have concerned oxidative stress in AD initiation and progression, the possibility of using natural antioxidants for prevention and treatment of AD has attracted considerable attention. Furthermore, antioxidant therapy is considered a promising low risk therapeutic strategy for AD. This review will mainly focus on the

recent development of common used antioxidant therapy for AD and thus will provide indication for the future potential antioxidant therapeutic methods for AD patients. The potential functions of the different antioxidants are summarized in (Table **1**).

Table 1. The potential functions of some antioxidants in Alzheimer's disease.

Antioxidant	Potential functions
Melatonin	Enhance the rest-activity rhythm and improved sleep quality [54]. Prevent Aβ fibrillogenesis and aggregation [55].
Estrogens	Enhance the uptake of aggregated Aβ into microglia [56]. Reduce Aβ production [57].
Selenium	Stimulate mitochondrial biogenesis signaling and enhance mitochondrial functional performance [58]. Reduce tau level [59].
Polyphenols	Ellagic acid and punicalagin: Potent β-secretace inhibitors [60]. Curcumin: Inhibit cytokines that initial amyloid production [60]. Epigallocatechin-3-gallate: Reduce Aβ production and plaque deposition in brains [61].
Vitamins	Vitamin E: Improve cognitive performance [62-64] and suppress tau-induced neurotoxicity [65]. β-Carotene: Increase choline acetyltransferase activity [66]. Vitamin B12: Enhance neurochemistry [67]. 1,25Dihydroxy-vitamin D3: Increase the phagocytic clearance of amyloid plaques [68].
Docosahexaenoic acid	Maintain integrity and neuronal function. Limit the production and accumulation of neurotoxic Aβ from its APP v [69-70]
CoQ_{10}	Improve brain bioenergetics [71]. Attenuate Aβ overproduction and intracellular Aβ deposition in the cortex [72].

ROLE OF MELATONIN IN AD

Melatonin appears as unique for several reasons. Melatonin is an ubiquitously compound synthesized in the pineal gland and other body organs and tissues [73] suggesting that melatonin involves in a number of not yet defined activities at the cellular level and acts as a hormone. The majority of melatonin directly released from the pineal gland via the pineal recess to the cerebrospinal fluid (CSF) [74], moreover, melatonin production decreases with the aging, a fact which has been suggested to a the major predisposing factor in age-associated degenerative diseases [75, 76].

Melatonin (Fig. **3**) and other structurally related indolic compounds proved to be more potent than classical antioxidants [77-78]. Melatonin can directly detoxify both reactive oxygen and nitrogen species or indirectly by regulating the enzymatic activity that promotes the overall antioxidative defense systems [73]. In addition, metabolites formed from the interaction between melatonin and free radicals, including N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), are also efficient free radical scavengers. Moreover, melatonin exerts anti-excitatory effects, this effect is supported by observations showing that melatonin keep neurons away from Aβ toxicity via GABA receptor activation. This sedating effects of melatonin and its related compounds display particular chronobiological activity that make them capable of correcting the circadian rhythm disorders seen in AD patients [75]. In this regard, 10 patients have mild cognitive impairment (MCI) treated with melatonin (6 mg/day for 10 days) exhibited significantly better rest-activity rhythm with improved sleep quality, the patients also have ability to remember previously learned items along with a significant reduction in depressed mood [54].

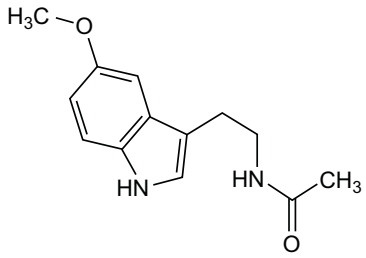


Fig. (3). Chemical structure of melatonin ($C_{13}H_{16}N_2O_2$).

The anti-fibrillogenic activity of melatonin and its metabolites were observed not only **in vitro** but also **in vivo** [79, 75]. Evidence derived from transgenic mouse model indicates that melatonin administrated at early phase regulates APP and Aβ metabolism with little anti-amyloid at the late phase [80]. The possible mechanism beyond this action is the ability of melatonin to inhibit glycogen synthase kinase-3 (GSK-3) and up-regulate the c-Jun N-terminal kinase resulted in matrix metalloproteinases activation that degrades Aβ. It has been demonstrated that melatonin directly interacts with Aβ and prevents its aggregation [55]. Melatonin could promote the conversion of β -sheets into random coils and inhibit progressive β-sheet and/or amyloid fibrils by disrupting the imidazole-carboxylate salt bridges. Melatonin may not only reduce Aβ neurotoxicity, but also facilitate the clearance of Aβ peptide by increasing the proteolytic degradation via increased insulin-degrading enzyme (IDE) activity [80].

Oral administration of melatonin attenuated Aβ-induced proinflammatory cytokines, by inhibiting NF-κB binding to DNA and suppressing inducible nitric oxide synthase (iNOS) gene expression in brain of rat [81]. As a consequence, melatonin and its metabolites may improve the clinical course of AD.

Besides melatonin traditional role as an antioxidant and free radical scavenger, melatonin maintains mitochondrial homeostasis and inhibits mitochondrial cell death pathways by lowering electron leakage, inhibiting the opening of mtPTP, thus maintaining the mitochondrial respiratory electron flux. In addition, administration of melatonin inhibited the Aβ-induced mitochondria-related factor up-regulation as Bax and suppressed caspase-3 activity and melatonin may

also initiate the survival signal pathways. Taken together, the above mentioned evidences suggest that melatonin serves as a potential antioxidant therapeutic strategy for AD [32].

ROLE OF ESTROGEN IN AD

The antioxidant property of estrogens is attributed to the novel redox cycling of catechol estrogens [82]. Estrogens are one of the best-studied classes of molecules for their potential role in neuroprotection. Furthermore, estrogenic prevention and a disease-modifying therapy against AD are well studied. Estrogens are powerful neuroprotective agents against oxidative stress and excitatory neurotoxicity. These activities are attributed to the capability of estrogens to maintain proper mitochondrial functions and suppress mitochondrial apoptosis-related proteins. The ability of estrogens to protect neurons from a number of toxic insults, including Aβ peptide have been extensively assessed [83]. Estrogens significantly regulate Aβ processing and deposition.

Data from *ex vivo* experiment showed that each of the three major circulating estrogens; E2, estrone and estriol (Fig. **4**) can reduce Aβ fibrillation. Also, estrogen enhances the uptake of Aβ into human cortical microglia [56] and prevents Aβ aggregation while concomitantly increases soluble APPα [84], accelerates APP trafficking in the trans-Golgi network [57] and reduces the expression of BACE-1 [83], thereby reduces the production of Aβ. Moreover, 17β-estradiol and the selective estrogen receptor modulators such as raloxifene and tamoxifen in human neuroblast long-term cell cultures showed neuroprotective effects by increasing resistance against Aβ-induced toxicity [85]. Furthermore, data form *in vivo* study conducted with transgenic mouse containing the human Swedish APP mutation showed that E2 reduced Aβ [86]. Further, in transgenic mouse with double mutations in APP and PS-1 genes, E2 treatment showed a significant reduction in brain Aβ [87]. However, Green *et al.* [88] showed that E2 has no effect on Aβ in PDAPP transgenic mouse. Interestingly, in one clinical trial, estrogen treatment improved memory function in women with AD by its ability to maintain and sustain neuronal viability [89]. However, estrogen is ineffective in reversing AD process.

ROLE OF SELENIUM IN AD

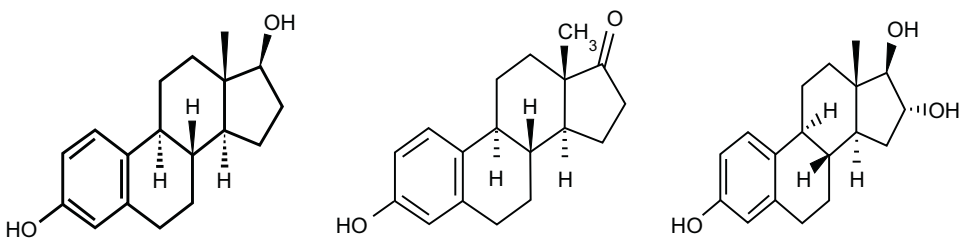
Selenium (Se), a vital trace element that is abundant in the brain, mainly exerts its antioxidative effect through selenoproteins, such as glutathione peroxidase, thioredoxin reductase, selenoprotein P, selenoprotein R, and selenoprotein M [90]. There has been heightened interest in the role of Se in health and neurologic disorders including AD [91-92]. It has been reported that the level of Se declines with age [93] and Se deficiency might increase the risk of AD [94]. AD patients demonstrated significantly lower Se levels in plasma, erythrocytes, and nails when compared with the control group [95]. Se intake may slow down the onset of cognitive decline associated with AD [59].

Connections have been observed between Se and risk factors of AD. Relations have been shown between Se and ApoE and presenilin 2, both genetic risk factors for AD [96]. Several autopsy studies using human postmortem brain tissue samples from AD patients and healthy control patients investigated whether AD is associated with altered levels of Se [92]. Supplementation of sodium selenite significantly stimulated mitochondrial biogenesis signaling and enhanced mitochondrial functional performance in murine hippocampal neuronal cells [58]. Sodium selenite also prevented cognitive deficits and oxidative damage in a rat model of AD [97]. Furthermore, sodium selenate was reported to mitigate tau pathology, neurodegeneration and functional deficits through the activation of protein phosphatase 2A in AD mice, significantly boosting phosphatase activity [98]. Meanwhile, organo-selenium decreased amyloid burden and prevented RNA and DNA oxidative damage in APP/PS1 mice [99]. Although the effect of selenium on AD has been investigated in a number of studies, moreover, selenomethionine (Se-Met) treatment reduced the levels of tau. Se-Met treatment also reduced the phosphorylation of tau at the site Ser404 [59].

ROLE OF METAL ION CHELATION IN AD

Interactions between metal ions and Aβ are one of the currently accepted hypotheses "metal hypothesis of AD". Further, abnormal metal ion homeostasis is connected with the AD neuropathogenesis. Based on this fact, prevention of metal-Aβ interactions and restoration of metal ion homeostasis in the brain via metal chelation therapy has been proposed in order to reduce metal-Aβ species neurotoxicity [100].

To date, strategy of metal chelator has been used as agent for metal ion chelation therapy in AD. Desferrioxamine B (Desferal®; a drug used to treat Fe overload) was the first compound used to treat metal overload in the CNS and to dissolve amyloid aggregates. Desferrioxamine B significantly improved the behavioral and cognitive declines of AD patients [101]. Clioquinol [CQ, a classic metal chelator for Cu (II) and Zn(II)] also used to prevent Aβ plaques forma-



17β-Estradiol Estrone Estriol

Fig. (4). Estrogens chemical structures. 17β-Estradiol ($C_{18}H_{24}O_2$), estrone ($C_{18}H_{22}O_2$) and estriol ($C_{18}H_{24}O_3$).

tion. However, the use of these synthetic metal chelators also led to various disadvantages: (i) its hydrophilic and charged characters disable the blood brain barrier crossing (ii) it is rapidly degraded and caused miss location of metal ions *in vivo*, (iii) it cause significant side effects such as anemia due to its strong affinity for Fe(III), and (iv) some of metal chelators as CQ may cause neurotoxicity and mutagenicity.

Hence, the search for new metal chelators without side effects continues to grow. Natural metal chelators such as *Linum usitatissimum*, *Punica granatum*, and garlic extract are effective in preventing heavy metals-associated toxicities [102-103]. Hence, the use of natural compounds or their active components have proven to be a promising approach for safer metal chelation.

ROLE OF POLYPHENOLS IN AD

Polyphenols are secondary metabolites of plant that constitute one of the most common and widespread groups of substances in plants and apparently act as defense (against herbivores, microbes, viruses or competing plants) and signal compounds, as well as protecting the plant from ultraviolet radiation and oxidants and may contribute to flavor, color and oxidative stability in plants. The term "phenolic" or "polyphenol" can be precisely defined chemically as a substance which possesses an aromatic ring bearing one (monophenol) or more (polyphenol) hydroxyl substituents, including functional derivatives (esters, methyl ethers, glycosides, etc.). The main classes under polyphenols are phenolic acids, flavonoids, stilbenes and lignans. Pomegranates, apples, grapes, green tea and many other plant sources are the subject of increasing scientific interest because of their antioxidant and anti-inflammatory properties with possible health benefits. Many of polyphenols received intensive studies for their potential disease prevention or treatment effects and are worthy of consideration for AD.

Punica granatum (pomegranate) has the potential to suppress the AD pathogenic cascade at multiple sites. Pomegranate juice decreased amyloid load and improved behavior in APPsw (double Swedish APP mutation; Tg2576) transgenic mouse model of AD [61]. Ellagic acid, punicalagin and punicalin (Fig. **5**) of pomegranate were found to be powerful β -secretace inhibitors [60]. Also, pomegranate shows a direct radical scavenging activity with lipid peroxidation inhibiting property, particularly metal catalyzed peroxidation [103]. Pomegranate is also known as a good inhibitor of gene expression of inflammatory cytokines such as IL-6, IL-8, vascular endothelial growth factor (VEGF) and prostaglandin E2 (PGE2), COX-2, and iNOS by influence of inhibition of JUN and NF-κB-mediated gene transcription [104-105]. All of these inflammatory cytokines have been implicated in Aβ toxicity, indicating the multi-target inter-

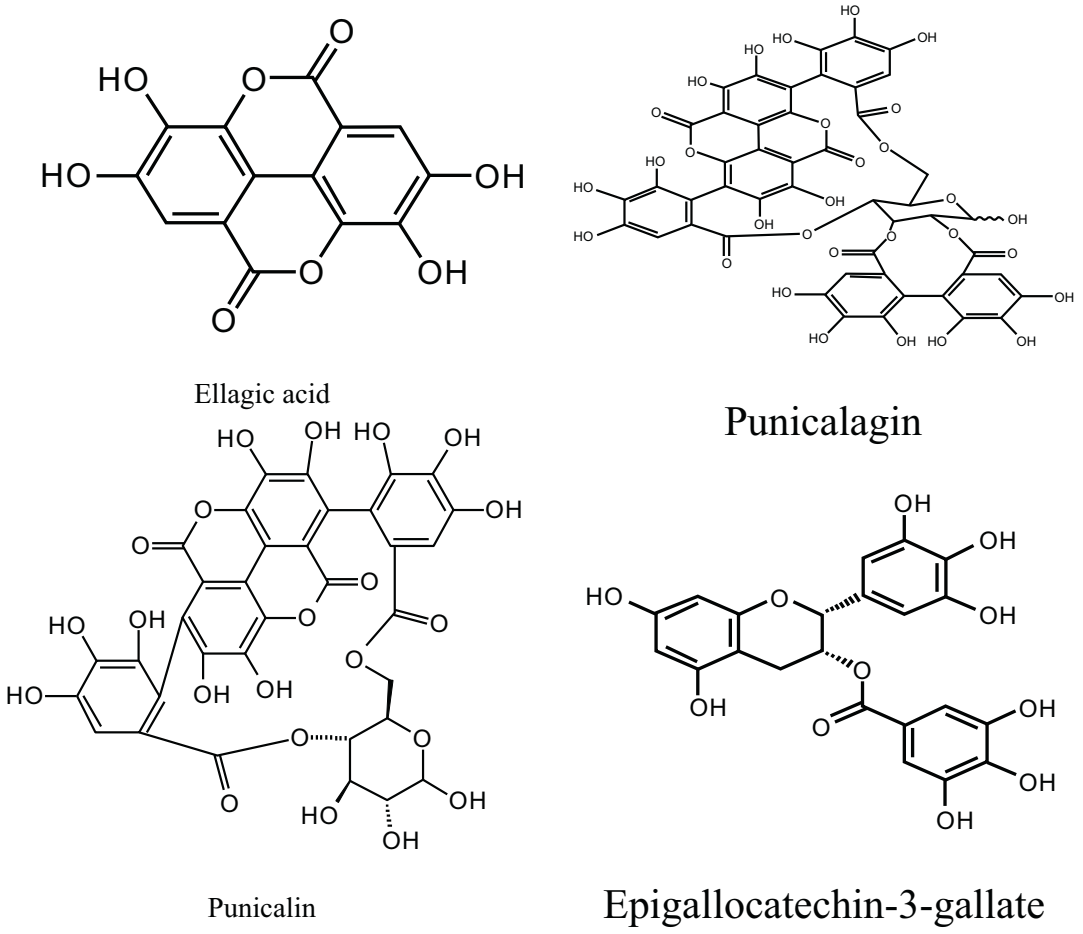


Fig. (5). Chemical structures of Ellagic acid ($C_{14}H_6O_8$), punicalagin ($C_{48}H_{28}O_{30}$), punicalin ($C_{34}H_{22}O_{22}$) and epigallocatechin-3-gallate ($C_{22}H_{18}O_{11}$).

vention of pomegranate in AD. In addition, pomegranate polyphenols attenuate disruption of mitochondrial membrane [106]. Furthermore, pomegranate has other proven anti-amyloid activities. Pomegranate decreased soluble Aβ levels and Aβ deposition by inhibiting BACE1 [60]. Ellagic acid, a phenol found abundantly in pomegranate inhibits Aβ plaques formation and Aβ toxicity *in vitro* [107]. Another polyphenol found in pomegranate, epigallocatechin-3-gallate (EGCG; Fig. **5**), reduces Aβ formation and Aβ plaques deposition in the brain of transgenic mouse containing the human Swedish APP mutation [61]. This anti-amyloid activity of pomegranate remains effective in aged mice, even after amyloid deposition continues over time. Interestingly, pomegranate was shown to decrease Aβ plaques load and improve memory impairment in behavioral performance testes in AD transgenic mice [108] even in response to acute Aβ brain injection [109].

ROLE OF TRADITIONAL HERBS IN AD

Aged garlic extract (AGE) has demonstrated beneficial effects in AD models [110]. AGE and its active ingredients S-Allyl-L-Cysteine (SAC; Fig. **6**) treatments not only decreased Aβ plaques loads in the brains of APP transgenic mice, but also ameliorated tau pathology by inhibiting GSK-3β and increased levels of synaptic protein markers as synaptosomal-associated protein 25 (SNAP-25) [111]. Previous research has demonstrated that AGE protects the cellular structures from Aβ-mediated neurotoxicity [112]. Interestingly, SAC was shown to have Aβ disaggregation property *in vitro* by activating peroxisome proliferators-activated receptors-α(PPAR-α) in microglia and macrophages that involved in Aβ clearance [113]. In APP transgenic mice, four months of AGE and SAC treatments significantly reduced both Aβ load and Aβ plaques numbers in the brain versus non-treated controls [114]. In addition, AGE treatment resulted in a significant reduction in the intracellular APP level. Moreover, SAC treatment can prevent Aβ-mediated neurodegeneration in hippocampus by preventing endoplasmic reticulum (ER) stress and improve memory deficits [115]. Mechanistically, SAC prevents Aβ-induced neuroinflammation and toxicity by inhibiting NF-κB activation and also reverses ROS-mediated decline in cholinergic function of the neurons by increasing in levels of neuronal acetylcholine transferase activity [110].

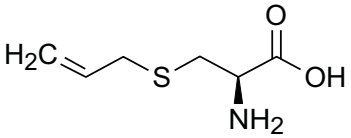


Fig. (6). Chemical structure of S-Allyl-L-Cysteine ($C_6H_{11}NO_2S$).

Silymarin is a mixture of four flavonolignane diastereomers; silibinin (or silybin), isosilybin, silydianin and silychristin, the major ingredients of the milk thistle extract (*Silybum marianum*). Silymarin showed anti-amyloid property *in vivo* and significantly reduced the Aβ plaque burden associated with microglial activation, Aβ plaques formation and disturbed behavior in APP transgenic mice. However, this anti-amyloid property of Silymarin is not attributed to β-secretase inhibition. Silymarin might act also to enhance neuronal cell viability by activating protein kinase B and inhibiting caspase-3 as well as attenuate Aβ neurotoxicity in AD model mice [116]. In addition, silibinin (Fig. **7**) prevents memory impairment and oxidative damage induced by Aβ in mice [117].

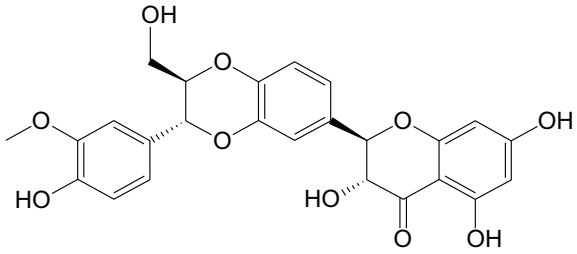


Fig. (7). Chemical structure of silibinin ($C_{25}H_{22}O_{10}$).

ROLE OF VITAMINS IN AD

α-Tocopherol (vitamin E), L-ascorbic acid (vitamin C), β-carotene (a precursor form of vitamin A) and vitamin D are organic compound with antioxidant properties, which decrease free-radical-mediated damage in neuronal cells and help to inhibit dementia and cognitive impairment [32]. Therefore, it has been postulated that vitamins could be used as important therapeutic strategies.

There are two groups of vitamin E with different ten forms; five as tocotrienols and five as tocopherols and identified by α-, β-, γ-, δ- and ε-. The most biologically active form of vitamin E is α-tocopherol (Fig. **8**). The work of Sano *et al.* [118] gave impetus to the idea of vitamin E as the treatment of AD. At the present days, the same group has reported that vitamin E benefits in patients with mild to moderate AD were seen by slowing functional decline [119]. Vitamin E lowered the oxidation of blood glutathione and the peroxidation of plasma lipids that cause an improvement in AD. *In vivo* studies, vitamin E has been shown to prevent the toxic effects of Aβ and improve cognitive performance [62-64]. In the Chicago Health and Aging Project, higher intakes of vitamin E from natural sources were associated with decline in Alzheimer's disease incidence [120]. Similarly, in the Rotterdam study, high vitamin E intake was associated with reduced the incidence of dementia [63]. Furthermore, Dias-Santagataet *et al.* [121] reported that α-tocopherol administration significantly prevented tau-induced neurotoxicity in Drosophila, and similar beneficial outcomes were recently reported by other researchers using tau pathology in transgenic mouse model [65], which underscored the therapeutic value of vitamin E. However, vitamin E should come from foods, rather than supplements, where, vitamin E from supplements has not been shown to reduce AD risk [122]. Mechanistically, the potential effect of vitamin E in AD is remain elusive, however, vitamin E may exert this potential by preventing Aβ-induced ROS, protecting against oxidation-mediated decline in neurotransmission-associated protein, inhibiting inflammatory cytokines those participated in neuroinflammation and activating PP2A.

Vitamin B12 (Fig. **9**) is essential for the health of the brain and nervous system and for blood cell formation [123]. However, vitamin B12 is lowered in elderly adults especially in males. Moore *et al.* [124] showed that low serum levels of vitamin B12 are allied with neurodegenera-

tive disease and cognitive impairment and that vitamin B12 therapy does not improve cognition in patients without pre-existing deficiency. Vitamin B12 supplementation increased the activity of choline acetyltransferase in cholinergic neurons in cats [66] and improved cognitive performance in AD patients possibly by its ability to reduce homocysteine levels [125]. Hyperhomocysteinemia was implicated in neurotoxicity by overstimulation of NMDA receptors or by increasing the vulnerability of hippocampal neurons to excitotoxicity and Aβ toxicity.

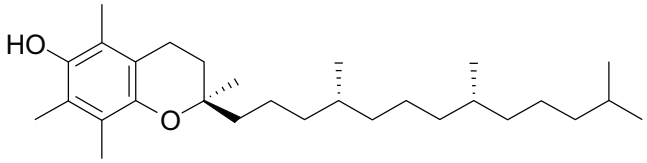


Fig. (8). Chemical structure of α -tocopherol form of vitamin E ($C_{29}H_{50}O_2$).

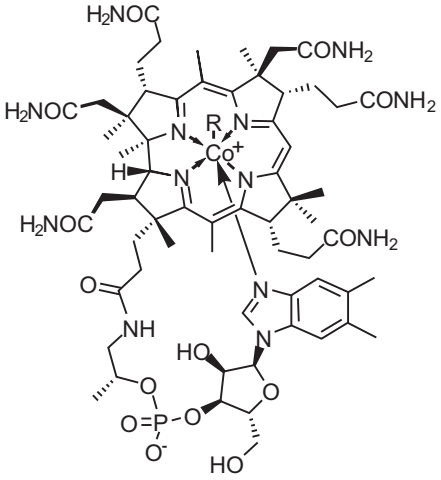


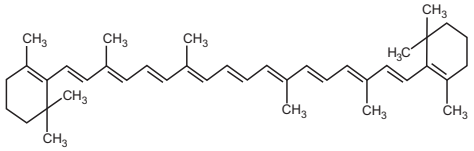
Fig. (9). Chemical structure of vitamin B12 ($C_{63}H_{88}CoN_{14}O_{14}P$).

A relationship between dietary carotenoids and age-related cognitive function has been reported. Perrig *et al.* [126] noted that the higher level of β-carotene in plasma was associated with better memory performances (priming, working-memory, free recall, recognition and vocabulary test) in old and very old subjects. β-Carotene (a major precursor to vitamin A; Fig. **10**) might have beneficial effects via its antioxidant or Aβ anti-oligomerisation effects [127-128]. Certain carotenoids also may modulate the functional properties of synaptic membranes [128], enhance gap junctional communication [67].

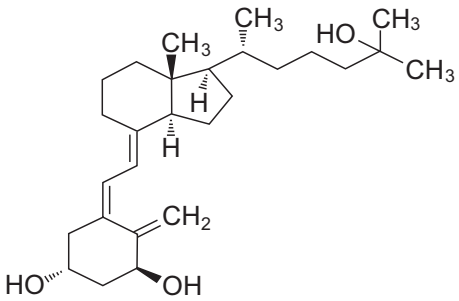
Vitamin D is a steroidal hormone and exerts its effects via vitamin D receptor (VDR) that located in the nucleus. Traditionally, vitamin D regulates the metabolism of bone, however, the recent studies shown that VDR are abundantly present in neurons and glial cells in CNS and participated in some physiological processes. The active form of vitamin D, 1,25 dihydroxy-vitamin D3 (1,25-D3 or cholecalciferol; Fig. **10**), upregulates neurotrophin expression, such as nerve growth factor (NFG), neurotrophin 3 (NT3), and glial-derived neurotrophic factor (GDNF) [129] those affects the survival and differentiation of neurons. Consistently, hypovitaminosis D is associated with prevalent cognitive impairment and AD dementia in elder [68]. Mechanistically, vitamin D reduced the risk of AD and other neurodegenerative diseases through several mechanisms including neuro-protection and synaptic plasticity-enhancing effects through detoxification pathways by inhibiting iNOS and enhancing antioxidant system, regulates calcium homeostasis and protects neurons from excess calcium, inhibits neuroinflammation by down regulating NF-κB activity and modulates angiogenesis by down regulating angiogenin 2 and vascular endothelial factor expression (VEGF) [130-131]. Furthermore, vitamin D activates glyoxalase 1 that catalyze methylglyoxal, the major precursor to AGE formation [132]. *In vivo*, vitamin D inhibits β-secretase, affects the expression and processing or APP and increases the phagocytic clearance of Aβ plaques by NGF-stimulated astrocytes [133-135]. Moreover, *in vitro*, vitamin D reduces Aβ-induced inflammation and apoptosis in primary cortical neurons [136].

ROLE OF OMEGA-3 IN AD

Omega-3 fatty acids are polyunsaturated fatty acids with a double bond after the third carbon atom in its carbon chain from the terminal methyl end and commonly found naturally in marine and plant oils. The backbone of omega-3 is lino-



β-Carotene



1,25Dihydroxy-vitamin D3

Fig. (10). Chemical structures of β-carotene ($C_{40}H_{56}$) and 1,25Dihydroxy-vitamin D3 ($C_{27}H_{40}O$).

lenic acid and human must be obtained it in diet, human cannot synthesize it. Consuming omega-3 fatty acids versus other fatty acids reduce the risk of cancer, cardiovascular disease, inflammation, and neurological disorders.

Docosahexaenoic acid (DHA; Fig. **11**) is the most important components of omega-3 fatty acid with potent anti-inflammatory and antioxidant prosperities. In brain, DHA is modified to neuroprotectin 1 (NPD1) through the action of phospholipase A_2 and lipoxygenase. NPD1 has been shown to have potent anti-inflammatory and neuroprotective effects in neural systems [137] by regulating the redox state of neurons. The action of NPD1 includes up regulation of Bcl-2 family, down regulation of pro-apoptotic proteins and suppressing the production of prostaglandin that participated in neuronal damage. Furthermore, there is a growing body of evidence that DHA modifies the expression of many genes that regulate a variety of biological functions including neurogenesis and neuronal functions and survival that important for cognitive health [138]. Thus, the intake of DHA can reduced the risk of AD [139]. For this, it is not surprising that, supplementation of aged transgenic mouse containing the human Swedish APP mutation with DHA-depleting rich safflower oil diet exhibited oxidative damage and significant (70–95%) loss of postsynaptic proteins that are seriously depleted in AD brains by 70–90% [140].

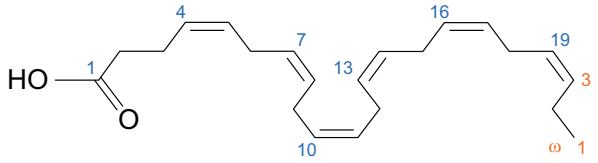


Fig. (11). Chemical structure of docosahexaenoic acid (DHA; $C_{22}H_{32}O_2$).

DHA exerts protective effects against neurotoxicity induced by Aβ [141, 142]. DHA limits the production and accumulation of neurotoxic Aβ from its APP [69, 70] by facilitating the interaction of α-secretase with APP to produce non-amyloidogenic sAPPα. Elevated sAPPα levels were associated with substantial protection against mitochondrial dysfunction and apoptosis [143]. Further, DHA prevents the action of γ-secretase by forming shield over the essential recognition sequence site for γ-secretase, and also inhibits Aβ formation and fibrillation. Additionally, omega-3 effectively reduces cholesterol and prevents its oxidation. High cholesterol levels in the brains directly stimulate β- and γ-secretase activities [144].

Additionally, dietary DHA increased cerebral acetylcholine levels *in vivo* [145, 146], and improved memory through the influence of DHA on the phospholipids of neuronal membranes. Thus, DHA increases the learning ability in rats [147] and prevents the loss of neurons longevity, discrimination-learning ability and memory in aged rats [148].

Finally, DHA has a number of potential mechanisms as an antioxidant by binding to membrane and trapping the generated ROS [149] and enhancing the activity of endogenous antioxidant system [150]. Furthermore, DHA may reduce the generated ROS by increasing nitric oxide (NO) synthesis, which may decrease the cellular oxygen pool and subsequently reduce ROS and lipid peroxidation [151]. Additionally, NO significantly increases blood flow and supply of nourishment and facilitates the removal of toxic metabolites and proteins from the brain.

ROLE OF COQ_{10} IN AD

In 1955, Festenstein *et al.* [152], the British scientists in Morton's Laboratory in Liverpool isolated a new unsaponifiable lipid from the intestinal mucosa of horses. The substance was identified later as a quinone and was found to be distributed in the most animal tissues, Morton named it ubiquinone "the name derived from ubiquitous quinone that meaning everywhere present quinine". In David Green's Laboratory at the Wisconsin University in USA after two years, Crane *et al.* [153] observed a novel quinone in the inner membrane of mitochondria and named it coenzyme Q because of its important role in the electron transport chain and ATP synthesis.

Coenzyme Q_{10} (CoQ_{10}; Fig. **12**) exerts a potential neuroprotective effect. In brain, CoQ_{10} protects the neuronal cells by increasing the stability of the cell membranes, decreases free radical that may attack DNA, and shows capability to recycle and regenerate the other antioxidant molecules, such as tocopherol and ascorbic acid [154].

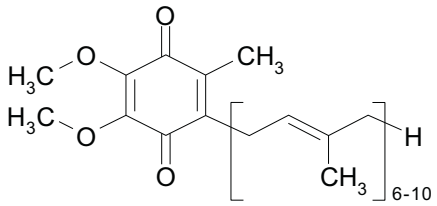


Fig. (12). Chemical structure of coenzyme Q_{10} ($C_{59}H_{90}O_4$).

CoQ_{10} is a potent antioxidant in mitochondrial membranes [155]. More specifically, CoQ_{10} facilitates efficient transport of electrons and defends mitochondria against oxidative injury. However, the levels of CoQ_{10} have been reported to decline with age, making mitochondria increasingly vulnerable and hazardous [156]; this malfunction may contribute to the development of neurodegenerative diseases. As such, considerable interest has been placed on the therapeutic use of CoQ_{10} in AD [157]. Nevertheless, the preclinical and clinical evaluation of CoQ_{10} has been hindered by its hydrophobicity, severely limiting its use *in vitro* and *in vivo* [158]. CoQ_{10} was able to modestly restore autophagic activity [159] and exerts anti-inflammatory effects by inhibiting NF-κB [160]. CoQ_{10} administration to aged APP/SP-1 transgenic mice led to a reduction in cortical levels of $A\beta_{42}$ and reduction of oxidative stress markers [161]. Moreover, CoQ_{10} supplementation improved brain bioenergetics [71] and partially prevented Aβ overproduction and deposition in the cortex of transgenic mice brain [72] and suppressed brain AGEs levels.

CLINICAL TRIALS WITH ANTIOXIDANTS THERAPIES IN AD

Unfortunately, the outcomes of many clinical trials with different antioxidants demonstrated no or minimal effects. For example,

- *Curcuma longa* exerts potent antioxidant and anti-inflammatory properties and capable of inhibiting Aβ aggregation *in vitro*, but when it tested in clinical trial showed no significant effect [162]. Low absorption of curcumin through gastrointestinal tract may be a cause for that, however, a carrier mediated transport or nanotechnology based delivery system can potentiate its effect [163].
- *Ginkgo biloba* has many properties including antioxidant effect and used in Chinese medicines. However, when *Ginkgo biloba* standardized extract (EGb 761) tested in a large randomized controlled trial did not show any difference in cognitive decline from the control group [164].
- CoQ10 or its analog are potent antioxidants, however, when CoQ10 tested in 563 patients with mild AD for one year did not show any changes in cognitive decline compared to the placebo group [165].

CONCLUSION

According to the predominantly symptoms those caused by acetycholine signaling dysfunction, the cholinergic hypothesis was conceived at the beginning. However, amyloid and tau hypothesizes are used nowadays based on the AD pathogenesis. APP was degraded with β-secretase to sAPP that subsequently degraded by γ-secretase to release Aβ, amyloid hypothesis. While in tau hypothesis, NFT was formed as a result of tau protein hyperphosphorylation. Even though the toxicity of Aβ is well established in AD pathogenesis, oxidative stress may play an important role in the initiation and progression of AD. Furthermore, oxidative stress amplifies the key events in AD.

Currently, acetylcholinesterase inhibitors and NMDA receptor antagonists alone or in combination are used to treat mild to moderate AD symptoms. High intakes of antioxidants low the risk for AD, and show beneficial effects in the prevention of the disease in several *in vitro* studies.

Unfortunately, the outcome of clinical trials with antioxidants demonstrated minimal effect. For this reason, when it comes to the use of these studies as examples to deny the oxidative-stress hypothesis of AD, at best they can only be considered inconclusive. Since, AD is a heterogeneous disorder, multimodal strategies using different molecular targets and delivery methods with antioxidants should be examined.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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