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REVIEW ARTICLE

Role of Oxidative Stress and Metal Toxicity in the Progression of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is one of the life-threatening neurodegenerative disorders in the elderly (>60 years) and incurable across the globe to date. AD is caused by the involvement of various genetic, environmental and lifestyle factors that affect neuronal cells to degenerate over the period of time. The oxidative stress is engaged in the pathogenesis of various disorders and its key role is also linked to the etiology of AD. AD is attributed by neuronal loss, abnormal accumulation of Amyloid-β (Aβ) and neurofibrillary tangles (NFTs) with severe memory impairments and other cognitive dysfunctions which lead to the loss of synapses and neuronal death and eventual demise of the individual. Increased production of reactive oxygen species (ROS), loss of mitochondrial function, altered metal homeostasis, aberrant accumulation of senile plaque and mitigated antioxidant defense mechanism all are indulged in the progression of AD. In spite of recent advances in biomedical research, the underlying mechanism of disruption of redox balance and the actual source of oxidative stress is still obscure. This review highlights the generation of ROS through different mechanisms, the role of some important metals in the progression of AD and free radical scavenging by endogenous molecule and supplementation of nutrients in AD.

Keywords: Alzheimer's disease (AD), oxidative stress, metal toxicity, mitochondrial dysfunction and neurodegeneration, Reactive Oxygen Species (ROS).

1. INTRODUCTION

AD is one of the main propagating neurodegenerative diseases in the elderly population worldwide [1]. Through extensive research has been performed, but there is no efficient and effective treatment available until now for AD. Hence the overall results have been disappointing and people are continuously working in the direction of drug discovery for such complex disease. There are various factors that are involved to comprehend the etiology and pathogenesis of AD, but oxidative stress is one of the major and leading causes (Fig. **1**). Oxidative stress is the perturbation between the production of both reactive oxygen species (ROS) and reactive nitrogen species (RNS) and antioxidant defense hence, responsible for the development of neurodegenerative disorders [2-12]. In the progression of AD, the basic landmarks for the induction of oxidative stress are mitochondrial dysfunction, increased metal accumulation, inflammation, hyper-phosphorylation of tau protein (microtubule-associated protein) and Amyloid beta peptides (ABP) aggregation [13-15]. Inactivation and deficiency of antioxidant enzymes machinery including glutathione peroxidase (GSH-Px), Lipid peroxidase (LPO), Superoxide dismutase (SOD) and Catalase (Cat), play a major role in the induction of oxidative stress (Fig. **1**) [14, 16].

Ageing is the major risk factor for the advancement of AD right from initiation to progression [17] and it is the most widespread neurodegenerative disease with a deadly outcome [18-21]. The presence of extracellular amyloid plaque also named senile plaques [22-24] mainly composed of Aβ (Fig. **1**) and Neurofibrillary tangents (NFTs), which consist of the filament protein tau, are the two most peculiar histopathological hallmarks of AD [25, 26]. NFTs are found in both degenerated and dying neurons and composed of an insoluble polymer of hyper-phosphorylated tau protein.

There are various evidences that indicate that the brain is more prone to oxidative stress than the rest organ during the progression of AD [5] because of the higher metabolic rate of the neurons (the basic functional unit of the brain) [27, 28]. Due to the overproduction of free radicals, the most affected regions of the brain are frontal, parietal, and temporal lobes in the case of AD [29]. The components of neurons like nucleic acids, proteins and lipids can be easily oxidized and promote Aβ deposition, hyper-phosphorylation of tau protein and the subsequent loss of synapses and neuronal

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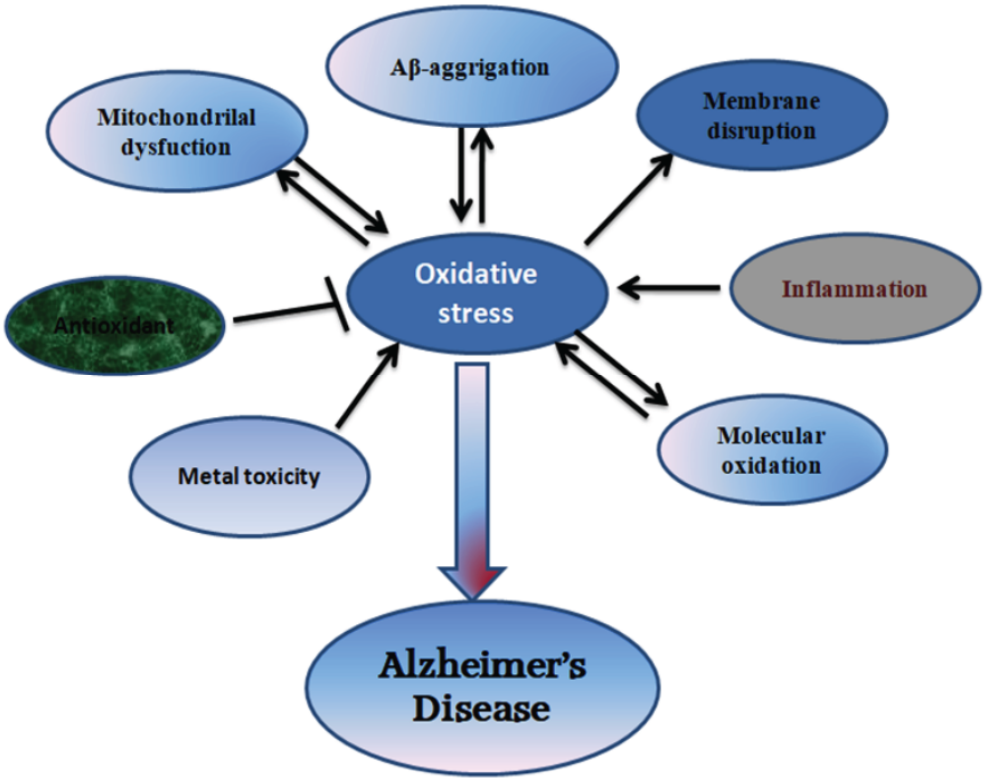

Fig. (1). Schematic representation depicting the role of ROS in the progression of Alzheimer's disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

death which are the most common features in the development of AD [30, 31]. The neurons are rich in phospholipids that contain polyunsaturated fatty acids (PUFAs) in high proportion, especially docosahexaenoic acid (DHA) and arachidonic acid [14]. These phospholipids are engaged in the neuronal interaction and also in the processes of neurotransmission. Neurons are highly vulnerable to oxidative stress because of the large amount of PUFAs and low levels of antioxidant enzymes especially glutathione [8, 14, 32, 33]. PUFAs can interact with ROS, leading to a self-propagating lipid peroxidation cascade and molecular destruction [33, 34]. It has been reported that as the level of free radicals increases, the content of PUFAs and oxidative enzymes gradually declines in the case of AD progression [35]. The free radical theory of aging suggests that oxidative stress is one of the crucial players, which plays a central role in the deterioration and degeneration of neurons (Fig. **2**) [27, 36-40].

There are two stages of AD: early-onset or familial stage (<5%) and the late-onset or sporadic stage. Most Cases of AD have been reported in the category of sporadic stage [14]. Evidence indicates the key role of Aβ in the pathogenesis of AD. Aβ itself being neurotoxic in nature induces oxidative stress in neurons and promotes the neuronal cell death [27, 41].

2. OXIDATION AND OXIDIZED PRODUCTS IN THE PROGRESSION OF AD:

The oxidative stress is generally characterized by a serious imbalance between the generation of free radicals and the capability of cells to nullify their damaging effects on the cellular components such as DNA, proteins, and lipids [42]. The failure of anti-oxidative defense cascade is envisaged as a major player in the onset and progression of neurodegenerative disorders [19]. Various studies have demonstrated that oxidative load is responsible for the production of the high level of end products of lipid peroxidation, such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE) and isoprostanes (F2-IsoPs and F4-IsoPs), various oxidized proteins and oxidative modifications in nuclear and mitochondrial DNA [16, 41]. MDA and 4-HNE are produced from lipid hydroperoxides decomposition in the presence of iron (Fe) (Fig. **2**) [27] and an increase of MDA and 4-HNE levels have been reported in the brains of AD patients [16]. In addition, Isoprostane (F2-IsoPs and F4-IsoPs) are the products of esterification of arachidonic acid [14, 30] and an increased level of isoprostanes has also been reported in the cerebrospinal fluid (CSF) of AD patients [43]. An elevated level of oxidative stress biomarkers in the circulation has been reported in sporadic AD cases and also in AD-related animal models. These biomarkers are protein carbonyls, 3-nitrotyrosine, MDA, 4-HNE, F2-isoprostanes (F2-IsoPs), 8-hydroxyguanosine (8-OHG) and 8-hydroxydeoxyguanosine (8-OHdG) [14, 44-46]. 8-OHdG and 8-OHD are the oxidized products of DNA and RNA respectively and are used as blood markers of oxidative stress in AD patients [47].

ROS can directly react with nucleic acids either DNA or RNA. Oxidative stress produces breaks in either dsDNA or ssDNA and also liberate carbonyls in the nuclei of nerve and glial cells, hence an increased level of strand breakage is found in the cerebral cortex of AD patients [16]. Besides that

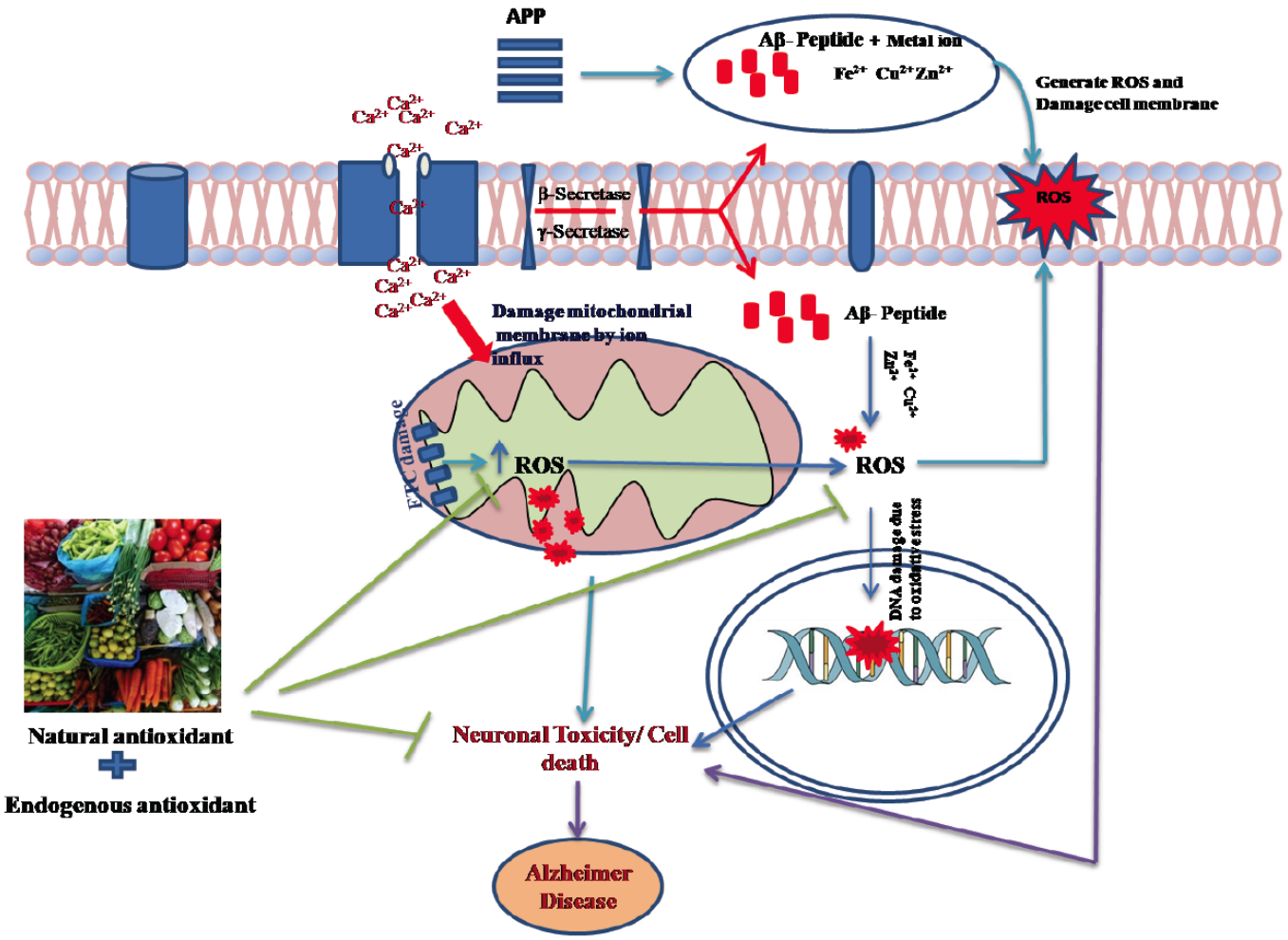

Fig. (2). The schematic diagram demonstrates the proposed mechanism of ROS induced neurodegeneration in APP leads to Aβ plaque accumulation. Extracellular Aβ oligomer and metal toxicity result in lipid membrane disruption, protein and DNA peroxidation *via* generation of ROS and its metabolites. Aβ accumulation causes Ca^{2+} channel imbalance that leads to mitochondrial membrane potential. Cytosolic Aβ aggregation directly binds to the components of Electron transport chain (ETC) and mitigates its activity. Decreased activity of ETC leads to the generation of ROS and promotes extreme mitophagy. Excessive production of ROS in mitochondria leads to the disruption of mitochondrial membrane potential and damage cytosolic proteins and enzyme and enters into the nucleus. Overload of ROS is the result of mitochondrial dysfunction that leads to the progression of neurodegenerative diseases. Various phytochemicals that are the natural sources of antioxidants as well endogenous antioxidants prevent the progression of neurodegenerative diseases induced by ROS. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

excessive ROS production mediates the oxidation of protein side chains and introduced hydroxyl group or carbonyl group [16]. The oxidation of side chains of lysine, arginine, proline and threonine residues side-chain results in the generation of carbonyl derivatives. 3-nitrotyrosine and di-tyrosine are the biomarkers for the oxidative damage to protein, produced by the reactions of various ROS and RNS with tyrosine [14]. Protein carbonyl substance is one of the frequently used biomarkers of oxidative stress in AD patients, Identification and assessment of carbonylated proteins is considered to be a good diagnostic approach in the pathogenesis of AD (Fig. **3**) [48, 49].

Evidence suggested the progressive decline in glucose metabolism, cellular energy production (ATP) and synthesis of neurotransmitters such as acetylcholine, glutamate, aspartate, γ-aminobutyric acid and glycine in the brain of AD patients [18]. Oxidative stress inactivates several enzymes that are implicated in the process of glucose metabolism and ATP synthesis including pyruvate kinase, enolase, triose phosphate isomerase, fructose-bisphosphate aldolase, glyceraldehyde phosphate dehydrogenase, phosphoglucomutase and also modifies ATP synthase in AD brain [51] (Fig. **3**). Impairment in ATP synthase activity and brain energy metabolism has been suggested to contribute to the progression of AD [52, 53].

3. MITOCHONDRIAL DYSFUNCTION

Dysregulated bio-energetics and bio-metabolism are the prominent features in the progression of various neurodegenerative disorders and Alzheimer's is one of them. Mitochondria are maternally inherited organelles that are indulged in multiple cellular functions including energy me-

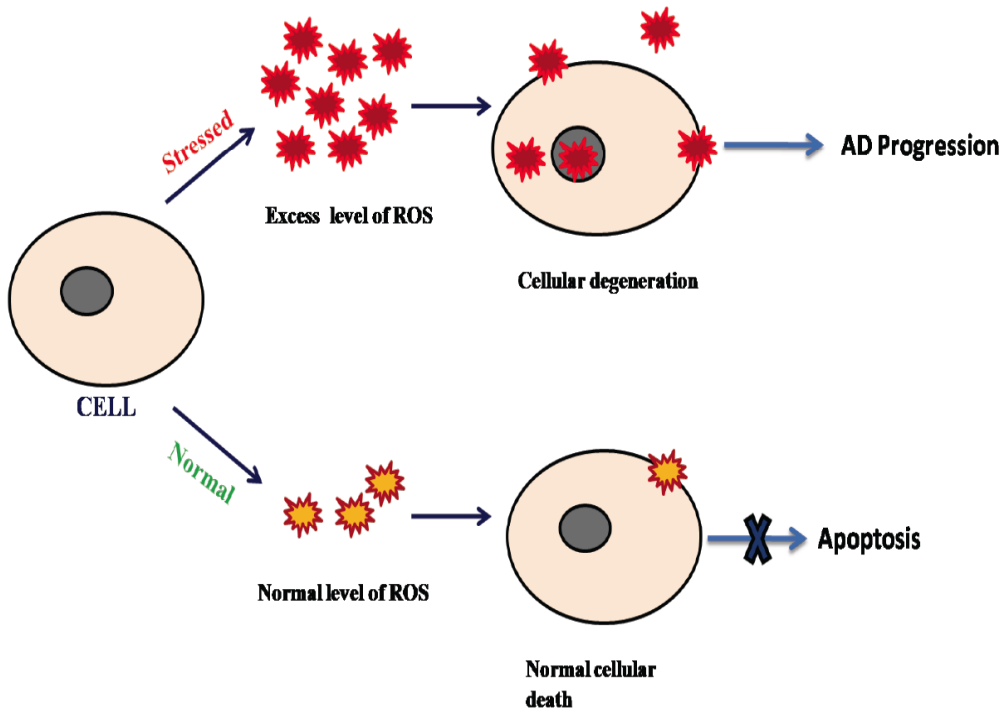

Fig. (3). Illustrating the role of various factors in the generation of oxidative stress responsible for the progression of Alzheimer's disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tabolism, ATP synthesis, second messenger signaling, and cell survival to programmed cell death [19, 54]. Mitochondria is the powerhouse of the cell and hence the main source of ROS generation and any anomaly in the function of electron transport chain (ETC) may not only damage several biomolecules (Nucleic acids, proteins and lipids) but also mitochondria themself become more vulnerable to oxidative damage [41]. There are various anti-oxidant enzymes, such as Catalase (CAT), Superoxide dismutase (SOD), Glutathione Peroxidase (Gpx) that plays a crucial role in the pathogenesis of AD. The mitigation in the activity of these enzymes further encourages mitochondrial dysfunction and generates oxidative stress and promotes apoptosis [14, 41]. The level of hydrogen peroxide (H_2O_2) is regulated by catalase and glutathione peroxidase (GSH-Px) by causing its degradation [44]. Impaired mitochondria generate excess H_2O_2 through the conversion of superoxide radical anion (O_2^-) by mitochondrial superoxide dismutase [41]. Catalase is one of the crucial enzymes of oxidative defense that converts H_2O_2 to water and oxygen whereas, GSH-Px utilizes glutathione to reduce H_2O_2 and fatty acyl peroxides to water and lipid alcohols respectively [16, 55]. An increase in the level of H_2O_2 and a decrease in the activity of cytochrome c oxidase suggest the loss of function of mitochondria. The mitochondrial-targeted study may be one of the efficient approaches to comprehend the onset and progression of AD [19, 56]. In addition to this, any deficiency in the key enzymes of ETC alters the redox balance and disrupts mitochondrial membrane potential which ultimately leads to oxidative stress [50]. Cytochrome c oxidase (complex IV) is one of the crucial enzymes of ETC that can trigger two harmful events that have an influence on the development of AD (Fig. **2**) [25]. The first event includes the excessive production of destructive free radicals and second includes the mitigation in brain energy resources. Many observations have confirmed that the level of oxidative phosphorylation gets lowered in AD patients [57, 58]. Mutisaya et.al, reported a significant reduction in the function of Cytochrome c oxidase (complex IV) in the cerebral cortex of AD patients [59, 60].

Many studies have confirmed that any impairment in mitochondrial function is because of aggregation of Aβ in the proximity of mitochondria and due to this level of oxidative phosphorylation is lowered in AD patients [57]. Accumulation of Aβ is the key feature in the advancement of AD and is associated with impaired oxidative phosphorylation and ROS generation in the mitochondria that contributes to the reduction of energy stores and neurodegeneration in AD [60-62]. Aggregation of Aβ is responsible for the loss of mitochondrial membrane permeability and increases the release of cytochrome c by inhibiting the key enzymes of ETC within mitochondria [17]. Besides that, calcium homeostasis is another parameter that contributes to mitochondrial dysfunction [63]. Calcium accumulation in mitochondria causes neuronal and muscular disorders in animals and humans [64]. Any imbalance in calcium homeostasis initiates a cascade of events that explains many of the AD pathophysiologies [65]. Mitochondrial calcium uniporter (MCU), one of the mitochondrial transporters that has recently been investigated assists in the pathological hallmarks of AD [66]. Several studies have ignited the effect of calcium accumulation in mitochondria and the influence of MCU complex in mitochondrial function [67]. Some natural phytochemicals have been reported to possess anti-oxidant property and acts as an a potent drug candidate for AD in preclinical studies like

Berberine [68], Bergenin [69], Quercetin [70], Rhodiola Crenula [71], Flavonoid [72, 73], Crocus Sativus L. and modulated cannabinoid [74, 75]. Some drug delivery methods reported like Dendrimer and nano-particle coated drug *etc*. [76-78]. Besides that, exercise and calorie restriction is another prominent effective approach to suppress mitochondrial dysfunction by increasing the level of cytochrome c, nuclear PGC-α and Sirtulin 1 that plays an interesting role in mitochondrial biogenesis [79-81].

4. CEREBRAL HYPOPERFUSION AND ALZHEIMER DISEASE

Chronic hypoperfusion plays a crucial role in the progression of AD. Chronic hypoperfusion is a central initiating factor for vascular alterations by inducing mitochondrial dysfunction, Aβ- transporter, increasing ROS production, reducing NO bioavailability *via* ROS scavenging, and damaging vascular functions as well as severely affecting regional CBF, ultimately leading to cognition decline and the disease [82-87]. De la Torre [99] proposed that advanced aging with a comorbid condition decreases cerebral perfusion and promotes a critically attained threshold of cerebral hypoperfusion (CATCH) [88]. Vascular cells are prone to oxidative stress that plays a prominent role leading to vascular anomalies in AD [89, 90]. In vascular cells, chronic and sustained hypoperfusion is responsible for the mitochondrial dysfunction which enhances the production of ROS in brain tissues. Oxidative stress of brain tissues, could also stimulate overexpression of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) in brain cells and produce secondary damage [91, 92]. continuous accumulation of oxidative stress products, such as peroxynitrite accumulation appear to be secondary and accelerating factors for damage and for compromising the blood brain barrier (BBB) in hypoxia/hypoperfusion or AD [93]. All of these alterations probably contribute to the progressive cognitive decline characteristic of patients with AD [93, 94].

5. ROLE OF METALS IN AD

Nowadays, metals are involved in each and every sphere of human life. Some are essential for the regulation of cellular physiology while others are important for industrial use. Due to increased Urbanization and industrialization exposure to heavy metals has prolonged and increasing day by day. Humans are more prone to the exposure of toxic metals through diversity of sources, such as diet, industrial and occupational exposures and these metals enter into the body through various routes and finally reaches to the blood [95]. Thereafter, they may be destined to reach to the brain from the blood by crossing either the blood-brain barrier or choroid plexus and from there diffuses into the central nervous system and advances the production of Aβ and phosphorylation of tau protein (P-tau), both are responsible for the formation of senile/amyloid plaques and NFTs respectively [3]. Several studies have ignited that the excess of heavy metals poses a critical risk for the development and progression of AD. Patients suffering from AD possess the abnormal level of metals such as copper (Cu), zinc (Zn), Iron (Fe), Aluminum (Al) and Mercury (Hg) that have been reported to disrupt the cell redox system and to induce oxidative load and increased deposition of extracellular amyloid plaque (Fig. **2**) [13, 17, 41]. Among the various heavy toxic metals, mercury (Hg), aluminum (Al), lead (Pb) and cadmium (Cd) are more prone to the progression of the AD because of neurotoxic nature and high industrial use.

6. MERCURY

Mercury is the ubiquitous toxic heavy metal that participates in the progression of AD. Several findings have revealed the existence of high mercury levels in the blood of Alzheimer's patients and also in nervous tissues [96-98]. The presence of mercury in the nervous tissues is responsible for the formation of NFTs and senile plaques which ultimately leads to tremor, insomnia, impaired cognitive dysfunction, muscle atrophyweakness, cardiac and renal dysfunction, memory loss, attention deficits and dementia which are the manifestations of AD [99-101]. In neuronal tissues mercury alters the function of tubulin protein, as the metal interacts with the tubulin, the configuration of the protein gets altered resulting in an inhibition of polymerization of tubulin to micro-tubulin and promoting the formation of NFTs and amyloid plaques [102]. Food is the primary source of mercury poising and People with high fish consumption may have an increased risk of methylmercury exposure. The BBB of fetuses is less tight than of adults and therefore circulating methylmercury in mother´s blood may enter fetus´s brain. Therefore, pregnant females must avoid the intake of such fish taken from polluted waters [103, 104].

7. CADMIUM

Cadmium is the other heavy metal that also plays a crucial role in the progression of AD. Cadmium is neurotoxic in nature and due to this attribute it has been detected in high concentrations in brain tissues and blood in AD patients. Recent studies have revealed that blood cadmium levels were associated with AD-related mortality among older adults [105-107]. The interaction of cadmium with Aβ peptides clearly enhances the risk of progression of AD because it is responsible for the formation of NFTs and aggregation of AβPs [108]. The prolonged exposure of cadmium leads to the neuronal impairment in attention, psychomotor speed and memory [109]. Furthermore, it has been postulated that cadmium accumulation downregulates the expression of α-secretase (ADAM10) and neutral endopeptidase which are responsible for reducing Aβ levels in the brain [110, 111]. In addition to this, cadmium is also involved in the conformation and self-aggregation of tau protein in the brain of AD patients [112, 113].

8. LEAD

Occupational and prolonged exposure of lead (Pb^{+2}) assists in the progression of AD. The correlations between lead exposure and AD progression is well depicted by the generation of free radicals but the molecular mechanism is still an enigma [114, 115]. During the advancement of ageing the oxidative stress has been enhanced in the brain which is the major risk factor for the pathogenesis of AD [114-119]. Lead overload-induced oxidative stress not only increases the Aβ aggregation but also damages the neuronal cells that ultimately lead to irreversible deficits in intelligence and behav-

ior [115, 120, 121]. According to Bolin *et al*., lead exposure in early life is responsible for the hypo-methylation of the APP gene which causes the APP gene to over express and increases APP production [120, 122]. As the concentration of APP is enhanced the activity of transcription factor Sp1 is increased which regulates proteins associated with AD and due to this over expression, expedite Aβ aggregation and plaque formation takes place in the brain [120, 121]. Various evidences pave the way that air and water can enhance the susceptibility to Pb at the developmental stage that trigger neurodegeneration in older age [123, 124]. Lead exposure hampers several biological processes and is hazardous to the various organs of the body with the nervous system being the most affected [125]. Though the toxic effect of Pb exposure on the developing nervous system is well documented but past exposure effect remains a serious issue and needs to be probed further. Thus, accumulating evidences suggest that pb exposure accounts for the 1% of global disease burden and past exposure to Pb is associated with cognitive decline [126-128].

9. ZINC

The brain has the highest concentrations of zinc among all the other organ of the body. Zinc acts as a structural and catalytic component of the proteins present in the brain contributing to the efficient performance of transcription factors and enzymes [129, 130]. Basically, Zinc (Zn^{+2}) element is present in all body organs and tissues but found in abundance in the amygdala, hippocampus and cortex. During the advancement of Alzheimer, zinc homeostasis gets altered and increased Zn accumulation is connected to the progression of AD as it induces a rapid amyloid formation in AD but not in AD-related models [41, 131]. Zinc accumulation not only alters Aβ aggregation, but also the level of hyperphosphorylated tau and the formation of NFTs. Interaction of Zn (II) with APP results in the conformational change of APP structure that causes inhibition of APP cleavage by α-secretase [13]. Binding of Zn (II) also increases the affinity of APP for heparin-binding [132]. Zinc accumulation causes oxidative stress, enhances the osmotic fragility of erythrocyte membranes, and decrease the protein turnover number lead to AD [133, 134].

10. IRON

Iron is the most abundant element found on the earth and also the part of several metalloproteins. At physiological concentrations, it performs various cellular functions such as enzyme catalysis, oxygen transport, cell growth and differentiation, mitochondrial respiration, regulation of protein expression, neurotransmission and myelin biosynthesis. However, the modulation in its physiological concentration has been linked with the pathogenesis of several neurodegenerative disorders along with AD. "R. M. Uranga and G. A. Salvador" have studied the toxic effects of iron overload on the brain and concluded that iron overload results in the production of oxidative stress and aggregation of various neurodegenerative diseases linked proteins that contribute to the progression of AD. They also postulated that the exploration of factors involved in iron-induced ROS and their role in AD pathogenesis will pave the way to understand the molecular mechanisms in its progression and also the development of possible therapeutic tools. In AD patients the concentration of p97 (Fe binding protein) has been elevated that could be used as a marker of AD pathogenesis (Fig. **2**) [135].

11. COPPER

Copper (Cu) acts as a vital element and catalytic factor for several enzymes, particularly those involved in cellular respiration, neurotransmission, iron metabolism, transcription of the gene and antioxidant defense [136]. The interconversion of Copper between Cu^{1+} and Cu^{2+} has made it very productive for several biological attributes. Copper pollution mainly occurs through manufacturing operations, mining, farming, and municipal and industrial wastewater. Short term exposure of copper generates mild symptoms include vomiting, hypotension, jaundice, and abdominal pain with gastrointestinal distress while prolonged exposure of copper damage the vital organs of the body such as liver, brain, and kidney [137-139].

All these metals interact with Aβ but the binding affinity of Cu with Aβ is higher than other metals [17]. Aβ plays a very efficient role in the failure of Fe and Cu homeostasis and increases the concentration of free Fe and Cu which results in the production of ROS [18, 27, 132]. Aβ directly interacts with Cu^{+} or Fe^{+2} and after binding changes their oxidation states to Cu^{+2} or Fe^{+3} respectively [25]. Change in the Oxidation state of Cu^{+} to Cu^{+2} and Fe^{+2} to Fe^{+3} are examples of Fenton reaction leading to the cytotoxic ROS generation [17, 25]. Both Cu and Fe behave as pro-oxidants or antioxidants depending on their coordination site *i.e*. they can act as pro-oxidants by promoting the production of superoxide and hydroxyl radicals [61] and antioxidants as they are present in the catalytic center of antioxidant enzymes like Cu in complex IV, Cu/Zn in SOD or Fe in catalase and conserve the cell from free radicals by decomposition of superoxide anion and H_2O_2 [140].

12. FREE RADICAL SCAVENGERS AND ANTIOXIDANTS

A number of studies have revealed that various antioxidants have been employed for the treatment of AD pathogenesis. Majority of antioxidants belong to the category of phytochemicals while a few are hormones. These antioxidants are Quercetin, curcumin, ascorbic acid (vitamin C), Vitamin E, lipoic acid, β-carotene, creatine, melatonin and the red-wine micronutrients that have beneficial effects in eliminating ROS [27]. Dietary intake of plant-based food source those are rich in antioxidants like vitamin E and C can reduce the risk of AD [141]. Nevertheless, intake of vitamin B and vitamin B6 reduces the elevated level of plasma homocysteine that has been connected with increased risk of dementia, a characteristic feature of AD [19]. Redox-active nanoparticles (RNPs), containing covalently bound antioxidants like cerium oxide, boron clusters, silica and nitroxide create a new therapeutic perspective for the prevention of AD [142]. Ubiquinone or CoQ10 (metabolic antioxidant), latrepirdine (a non-selective antihistamine), mitoquinone or mitoQ (CoQ10 derivative) has been shown to have a protective effect in ROS-mediated damage [14]. Inhibitors of free

radicals or activators of the antioxidant enzyme system have shown protective against AD treatment (Fig. **1** and Fig. **2**) [143].

CHALLENGE AND FUTURE PROSPECTIVE

AD still remains one of the progressive and leading causes of mortalities in the ageing population worldwide after exhausting various resources in the treatment. The patients suffering from AD receive relevant treatments but overall existing rates are still unsatisfactory. Despite that various prevention trials are also found profoundly disappointed hence to understand the underlying causes for this failure may lead to accelerate the development and application of new and effective approaches for the prevention and treatment of this chronic disorder. In order to cope with this situation, we need to identify various crosslink's that gives the glimpse of the progression of AD with more refined and efficient strategies. Oxidative stress is a vital component in the progression of AD hence antioxidant therapy for the prevention and treatment of AD is of major concern. A prominent feature in the AD is the presence of the products of oxidized proteins and lipid in neuronal and glial cells, which share a remarkable link between oxidative stress and the progression of AD. Various oxidative markers have been employed for the treatment of H_2O_2 mediated Aβ toxicity that can be prevented by the treatment of antioxidant enzymes catalase and GSH-Px (Fig. **1**). Mitochondrial key enzymes serve as a possible target in the development of new therapy for the treatment of AD. Targeted therapy against the interaction of metals and Aβ would be effective for introducing new therapeutic options for the treatment of AD. Various approaches coupled with more refined and efficient trial designs, may lead to deliver a new avenue of preventive discovery in this challenging area.

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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