Interplay of antioxidants in Alzheimer’s disease

Sajjad N1, Wani A2, Hassan S4, Ali R5, Hamid R6, Akbar S7, Ganai BA8 and Bhat EA9

1Department of Biochemistry, University of Kashmir, Hazratbal, Srinagar, India
2Indian Institute of Integrative Medicine (IIIM), Jammu, India
3Regional Research Institute of Unani Medicine, Kashmir University Campus, Srinagar 190006, India
4Centre for Research for Development, University of Kashmir, Hazratbal, Srinagar, India
5Life science institute and school of medicine, Zhejiang University, Hangzhou, Zhejiang, 310058, P.R. China
6Centre of Research for Development, University of Kashmir, Hazratbal, Srinagar, India
7Author contributed equally
8Centre of Research for Development, University of Kashmir, Hazratbal, Srinagar, India
9Indian Institute of Integrative Medicine (IIIM), Jammu, India

Abstract

The generation of reactive oxygen species (ROS) results in oxidative stress, leading to damage of tissue via many cellular molecular pathways. ROS can result in damage of principal cellular components of the cell such as lipids, proteins, and nucleic acids which then cause cell death via different modes of necrosis or apoptosis. Therefore, it is very important to maintain the redox status in our body. This is maintained by balance in the production of free radicals and antioxidants. Oxidative stress is the main phenomena which occur in progression of many diseases such as diabetes, neurodegenerative diseases, cancers etc. Alzheimer disease (AD) is one of the neurodegenerative disease and is common form of dementia in elderly people. The etiology of this disease is multifactorial; pathologically it is accompanied with accumulation of amyloid beta and neurofibrillary tangles. Accumulation of amyloid beta and mitochondrial dysfunction leads to oxidative stress. There is natural antioxidant defence system in our body which helps us to prevent us from various diseases via different mechanisms. Antioxidants are believed to act against the detrimental effects of ROS and thereby preventing or treating oxidative stress-related diseases. The nuclear factor erythroid 2-related factor 2 (Nrf2) is an emerging regulator of cellular resistance to oxidants. It controls the basal and induced expression of antioxidant response element-dependent genes. The current review examined the extensive role of oxidative stress in AD. Further investigation into the role that oxidative stress mechanisms seem to play in the pathogenesis of Alzheimer disease may lead to novel clinical interventions.

Oxidative stress

Oxidative stress is generated by pertubance of balance between reactive oxygen species (ROS) and antioxidants. Damage of biomolecules- lipids, proteins and nucleic acids in response to increased ROS levels leads to oxidative stress. It plays a very crucial role in the pathogenesis of many diseases like cardiovascular diseases, cancers, neurodegeneration, cancers, immune disorders, diabetes, aging, etc [1]. There arises a shift in the balance between oxidants and antioxidants in favour of oxidants in oxidative stress. Regulation of redox state is very crucial for cell viability, activation, proliferation, and cellular integrity. Therefore, redox homeostasis plays a paramount role in disease prevention [2]. Aerobic organisms have evolved integrated antioxidant systems, which include many enzyme systems such as superoxide dismutase, catalase, and glutathione system [3]. Furthermore, various transcriptional factors get activated by oxidative stress. These systems tend to repair oxidative damage as they act as oxidative sensors in signal transduction pathway [4]. Recent interest has focused on the intricate ways by which redox signalling integrates these converse properties. Redox balance is maintained by prevention, interception, and repair, and concomitantly the regulatory potential of molecular thiol-driven master switches such as Nrf2/Keap1 or NF-kB/IκB is used for system-wide oxidative stress response [5]. Organisms come across various types of oxidants from internal metabolism and external environmental toxic exposure. The reactive oxygen and nitrogen species result in oxidative stress and are considered as harmful [6,7]. On the other hand, regularized generation of oxidants in normal cells serve to regulate various signalling pathways. Our intricate antioxidant defence systems which is regulated by web of various pathways is adequate to counterbalance the reactive oxidants [8]. The nuclear factor erythroid 2-related factor 2 (Nrf2) emerges as a regulator of cellular resistance to oxidants. It regulates and controls the basal expression of an array of ARE antioxidant response element-dependent genes to regulate various physiological outcomes of oxidant exposure [9].

The vulnerability of the nervous system

The neuronal system is vulnerable to ROS mediated injury as compared to other biological systems due to different physiological and biochemical properties of the brain [10]. The nervous system - including the brain, spinal cord, and peripheral nerves - is very prone to oxidative damage [11]. It is due to various reasons such as; high oxygen consumption of the brain as it demands higher energy, which in turn, results in excessive ROS produced; the neuronal membranes possess higher polysaturated fatty acids (PUFA), PUFA being susceptible to free radical damage; high aerobic metabolic activity; elongated axonal morphology which is vulnerable to peripheral injury [12] the excitotoxic glutamate is the major effector that causes oxidative stress; the high Ca2+ traffic across neuronal membranes and

*Correspondence to: Bashir Ahmad Ganai, Centre of Research for Development, University of Kashmir, Hazratbal, Srinagar, India, E-mail: bbscganai@gmail.com
Eijaz Ahmed Bhat, Life science institute and school of medicine, Zhejiang University, Hangzhou, Zhejiang, 310058, P.R. China, E-mail: eijazbhat05@gmail.com

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interference of ion transport increase intracellular Ca++; often leading to oxidative stress [13]. Moreover, the elevated levels of iron which can be essential during brain development, facilitates oxidative stress via iron-catalysed formation of ROS [14]. Furthermore, the regions of the brain which possess substantial amount of catecholamines, adrenaline, noradrenaline and dopamine are exceptionally very prone to free radical generation. Catecholamines can generate free radicals via spontaneous breakdown or by being metabolized by endogenous enzymes such as monoamine oxidase [15]. Antioxidant defines mechanisms are modest, in particular, low levels of catalase, glutathione peroxidase, and vitamin E; activated microglia produce ROS and cytokines in a perpetual process; neuronal mitochondria generate O2 [16]. The interaction of NO with superoxide can be implicated also in neuronal degeneration [17] neuronal cells are nonreplicating and thus are sensitive to ROS (Figure 1).

Oxidative stress in Alzheimer disease

Alois Alzheimer a German physician for the first time described AD when he was practicing in Asylum state in Frankfurt. He investigated on patient August D, 51 year old lady in 1901, who suffered from symptoms of cognition, aggressive behaviour and hallucinations. AD is the common form of dementia in elderly people. According to World Health Organization (WHO) estimation, 71% of 81.1 million dementia cases will be reported by 2040 [18,19]. The majority of people which suffer from AD are older individuals usually aged 65 or more. They have sporadic or late onset form of AD, there can be rare case of early onset or we can say familial AD which occur in individuals before age 65 [20]. These people possess autosomal dominant mutation on either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, there is increased risk of developing early onset AD in individuals suffering from Down’s syndrome [21]. The genetics of sporadic AD is less understood and very complex. It is well known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD [22].

The etiology of this disease is multifactorial. Pathologically it is characterized by neuronal death, intracellular neurofibrillary tangles and extracellular amyloidotic protein deposits contributing to senile plaques [23]. Many different hypotheses have been given from time to time to elucidate the causative factors of this disease in order to explain the multifactorial nature of disease such as cholinergic hypothesis, Aβ hypothesis, tau hypothesis, oxidative stress hypothesis and inflammation hypothesis [24]. Aging has been associated with oxidative damage and is extensive in the brain in Alzheimer disease [25,26]. There are ample evidences supporting the exposure of brain tissue in patients with AD to oxidative stress (e.g., protein oxidation, lipid oxidation, DNA oxidation and glycoxidation) during the course of the disease [27]. The neurons are exposed to higher levels of ROS as compared to other systems of our body [28], and brain accounts for approximately 20% of body’s total oxygen. Moreover, AGES (Advanced glycation endproducts) found in amyloid plaques and its extracellular accumulation in AD is believed to be caused by an enhanced oxidation of glycated proteins [29]. AGEs cause neuronal cell death directly (chemical) and indirectly (cellular) by increasing oxidative stress due to generation of free radicals. AGEs, a diverse class of posttranslational modifications, are generated by the non-enzymatic reaction of a sugar ketone or aldehyde group with the free amino groups of a protein or amino-acid specifically lysine, arginine and possibly histidine. Accumulation of AGES in the brain is a feature of aging and it also is also implicated in the development of pathophysiology in age-related diseases such as diabetes mellitus, atherosclerosis, and AD [30].

The most notable feature of degenerative change in AD brain is increased lipid peroxidation as the membrane phospholipids of brains which mainly consists of PUFA is highly vulnerable to free radical attack [31]. Furthermore, the protein oxidation by free radicals might be significant in AD, as the oxidation of proteins of the brain, affect enzymes which are necessary to neuron and glial functions [32]. Two enzymes are very sensitive to oxidative modification namely glutamine synthetase and creatine kinase, which are remarkably low in AD brains, depicting the change of glutamate concentrations and increase of excitotoxicity. While as oxidative impairment of creatine kinase might cause decrease energy metabolism in AD [33]. Moreover neurofibrillary tangles results from aggregation and hyperphosphorylation of tau protein [34]. Phosphorylation is connected to oxidation via microtubule associated protein kinase pathway and through activation of the transcription factor nuclear factor-kB, thus potentially linking oxidation to the hyperphosphorylation of tau (τ) proteins [35]. Oxidation of proteins can also induce advanced glycation end products (AGEs) [36]. Furthermore, oxidation of the proteins can affect DNA, producing strand breaks, sister chromatid exchange, DNA-protein crosslinking, and base modification [37]. As aging process is connected with increase in production of ROS, together with the decrease in the defence system against them, not surprisingly, studies on Alzheimer’s disease over the past ten years have established that oxidative stress and damage are not only in the lesions of AD but also in the neurons at risk of death.

Various lines of evidence have shown that oxidative stress plays a crucial role in the initiation of the AD via various cell signalling pathways [38]. Among them, mitochondrial and metal abnormalities also contribute to oxidative stress. Mitochondria act as source of ROS production [26]. Damaged mitochondria have been observed in AD and the common defect in mitochondria is deficiency in many important enzymes which are responsible for oxidative metabolism including α-ketoglutarate dehydrogenase complex (KGDHC) and pyruvate dehydrogenase complex (PDEC) [39]. These enzymes are involved in rate limiting step of tricarboxylic acid cycle, and another enzyme being the terminal enzyme cytochrome oxidase responsible

![Figure 1](image-url)
for reducing molecular oxygen [40]. The production of ROS is the result of these functional abnormalities in mitochondria. Furthermore, damaged mitochondria and formation of mitochondria derived lysosomes and lipofuscin was evident in almost all of AD neurons [26]. Neurons in AD show significantly higher number of completely damaged mitochondria compared to an aged-matched control group [41]. Abnormality in mitochondrial morphology, membrane potential and ROS production was evident from the studies on cybrid cell lines with mitochondria DNA from AD patients [42]. Increased sporadic mutations in the mtDNA control region, with some being unique to AD, were found in AD patients compared to controls [43]. Another study in Tg2576 mice model demonstrated that at mRNA level, gene expression related with mitochondrial metabolism and apoptosis were changed, suggesting mitochondrial energy metabolism is impaired by the expression of APP/β [44].

Iron (Fe) is another cause of oxidative stress because of its excess concentration in brain. It has been found that it accumulates in other parts like hippocampus, cerebral cortex and basal nucleus of Meynert, and colocalizes with AD lesions, senile plaques and neurofibrillary tangles (NFT) [45].

Copper (Cu) is another metal ion that is important for many enzymes in brain metabolism and that has been implicated in disease pathogenesis [46]. The homeostasis of copper is disrupted in AD. There are two pathways connected with copper related oxidative stress. One being the changes in ceruloplasmin and second being the copper interaction with amyloid-β protein precursor (AβPP). The ceruloplasmin is a copper binding protein which is responsible for entry of copper in brain. It plays a pivotal role in protection of cell against oxidative stress. It is a key protein involved in interconversion of redox state of iron by converting the ROS catalytic-Fe (II) to a less reactive Fe (III). It is increased in brain and cerebrospinal fluid in AD, whereas neuronal levels of ceruloplasmin remain unchanged. Thus, higher levels of ceruloplasmin might indicate a compensatory response to oxidative stress, if it fails, so it plays a crucial role in metal catalyzed damage [46].

Copper has also shown to play a role in producing ROS through its binding to Aβ. As with iron, copper concentrations are highly concentrated within Aβ plaques; Aβ binds copper in AD tissue, and Aβ-Cu complexes form a catalytic centre of H₂O₂, reducing Cu (II) to Cu (I) involving an electron-transfer reaction that can enhance the production of radical •OH. A recent study also reported that tau protein can also bind to Cu, and inappropriately binding with tau protein may trigger oxidative stress [47].

Various studies have shown that Aβ exerts its toxic effects by generating oxidative stress. It induces the oxidation of biomolecules which include peroxidation of lipids and lipoproteins, generates H₂O₂ and hydroxynonenal (HNE) in neurons, damages DNA and inactivates transport enzymes [27,48]. But there are three conditions which are required by Aβ to induce oxidation. Fibrillation; presence of transition metals and methionine (met) 35. If the peptide is aged the Cu complexes form a catalytic centre of H₂O₂, reducing Cu (II) to Cu (I) involving an electron-transfer reaction that can enhance the production of radical •OH. A recent study also reported that tau protein can also bind to Cu, and inappropriately binding with tau protein may trigger oxidative stress [47].

A scavenger-receptor to increase ROS production [29] and modulate gene transcription of various factors involved in inflammation through NF kB activation [52]. Similar to situations in the periphery where damaged tissue and the chronic presence of inert abnormal materials cause inflammation, senile plaques, NFT and injured neurons may well provoke inflammation in the AD brain [53]. Indeed, both activated microglia and astrocytes cluster at sites of Aβ deposition and express a wide range of inflammatory mediators including cytokines and chemokines and cyclooxygenase [54]. Furthermore, Aβ might directly activate the NADPH oxidase of microglia resulting in generation of superoxide radicals and increased production of hydrogen peroxide [55].

Moreover, the production of ROS/reactive nitration species (RNS) by inflammatory cells is a major mechanism for attacking opsonized targets and activated microglia/astrocytes have the potential to produce large amounts of ROS/RNS by various mechanisms [56]. Activated microglia and astrocytes can produce large amounts of nitric oxide (NO), which in turn can react with superoxide to form peroxynitrite, leaving nitrotyrosine as an identifiable marker. The footprint of excess NO production in AD is confirmed by the increased amounts of nitrotyrosine-modified proteins. Plaques in AD brain have shown the expression of Inducible nitric oxide synthase (iNOS) [57]. Another mechanism producing free radical in microglia involves myeloperoxidase (MPO) and there is evidence that MPO immunoreactivity is present in selective highly activated microglia around amyloid plaques in the AD brain and that Aβ aggregates increase MPO mRNA expression in microglia-like cells in vitro [58]. MPO catalyzes a reaction between hydrogen peroxide and chloride to form hypochlorous acid which can further react with other molecules to generate other ROS including hydroxyl ions. MPO can also catalyse the formation of nitrotyrosine-modified proteins as well as cause advanced glycation end product modifications, both of which are evident in AD [59].

**Nrf2 signaling pathway**

Oxidative stress is crucial in the pathogenesis of various diseases and it leads to production of free radicals. It results in damage to macromolecules in cells [60]. Many studies have reported that the nuclear factor erythroid 2 related factor 2 (Nrf2) is a key regulator of endogenous inducible defense systems in the body and increase the level of many antioxidants, including glutathione-s-transferase [61]. Under oxidative damage conditions, Nrf2 translocates to the nucleus, then binds to the antioxidant response element (ARE), and enhances sequence to initiate transcription of cytoprotective genes (Figure 2). In general, Nrf2-ARE activation is a novel neuroprotective pathway that can be considered as a promising therapeutic strategy for the treatment of neurodegenerative disorders, such as AD [62].

NF-E2 related factor 2 (Nrf2) has been seen to get modulated in various neurodegenerative diseases. Its overexpression is considered as a potential therapeutic target for neurodegenerative disorders such as Amyotrophic lateral sclerosis, Alzheimer's and Parkinson's disease [63]. The expression of enzymes involved in phase II detoxification is governed by antioxidant response element (ARE), which is a cis-acting regulatory element. The transcription factor Nrf2 binds to ARE which results in multiplet transcription of antioxidant genes. Keap1, a culin 3-based E3 ligase that later degrades Nrf2 and sequesters it, is governed by antioxidant response element (ARE), which is a cis-

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that belongs to Cap’n collar/basic-leucine zipper family. It regulates the genes containing ARE. It has six erythroid-derived CNC homology protein (ECH) domains. The cytoplasmic association of Keap1 and Nrf2 is governed by a Neh2 domain. Keap1 functions as adaptor for the cullin 3-based E3 ligase [66]. Is it necessary to mention that Nrf2 is ubiquitinated and rapidly degraded by ubiquitin-proteasome system under normal condition, as it has half-life ~20 minutes. But under oxidative stress conditions induced by reactive species, toxins or ARE inducers, the association between Nrf2 and Keap1 is disrupted and Nrf2 translocates to the nucleus of the cell, where it binds to small Maf proteins that increase the transcription of genes driven by ARE [67]. In addition, Keap1 also has a role in shifting Nrf2 out of the nucleus by shuffling itself from the cytoplasm to the nucleus. Though the actual mechanism of Keap1-Nrf2 interaction disruption is indescribable, it is reported that direct modification of cysteine thiols groups in Keap1 by ARE inducers leads to the release of Nrf2, thereby increasing its activity [68]. Furthermore, involvement of various kinases through phosphorylation of Nrf2 at serine and threonine residues may also be responsible for translocation of Nrf2 to nucleus. Members of the fibroblast growth factor family have been reported to regulate the transcription of Nrf2, thereby increasing both its mRNA and protein levels. This factor could possibly contribute to the activation of Nrf2 and induction of ARE-driven genes [69].

A multitude of genes that are involved in redox status, detoxification and anti-inflammation are transcribed by activation of Nrf2-ARE pathway. These genes are involved in protection of cell from oxidative burden and cellular injuries in different organs including brain. Nrf2 regulates various antioxidant enzyme systems including peroxiredoxin (Prdx), superoxide dismutase (SOD), catalase (CAT), thioredoxin (Trx), sulfiredoxin (Srx), glutathione peroxidase (Gpx), glutathione reductase (GR), NAD(P)H quinone oxidoreductase (Nqo1) and heme oxygenase 1 (HO-1) and Ferritin.

Though all antioxidant enzymes are essential for brain cells but some antioxidant genes have been reported to have more active roles than others in brain depending on the cell type and disease condition [64]. There is ample evidence in support of the study that the AD brain is under tremendous oxidative stress. Expression of HO-1 gene is significantly increased in post-mortem temporal cortex and hippocampus of AD patients than compared to age-matched normal controls [70]. Furthermore, increase in expression and activity of Nqo1 was found in astrocytes and neurons of AD brain along with predominant cytoplasmic localization of Nrf2 in AD hippocampal neurons [71]. Additionally, increased protein oxidation is common in AD brain when compared to age matched normal controls. A study on aged APP/PS1 AD mouse models showed reduced expression of Nrf2, Nqo1, GCL catalytic subunit (GCLC) and GCL modifier subunit (GCLM) mRNA in addition to decreased Nrf2 protein levels. Another study on triple transgenic AD mouse showed reduced GSH/GSSG ratio [72]. Many studies have focused on neuroprotection role of Nrf2 against ROS generation [73,74].

**Role of antioxidants**

Antioxidants are the substances which protects cell from damage caused by reactive unstable species known as free radicals. The rate of oxidation is inhibited significantly by antioxidants when present in low concentrations [75]. The antioxidants remove the intermediates of free radical mediated reactions, thereby impeding the chain reactions. They themselves get oxidized in order to stop other oxidation reactions. They help in preventing the growth of many chronic diseases; therefore, antioxidants are emerging as preventive and therapeutic agents [76]. Cellular antioxidants regulate an oxidative phenomenon which is involved in signal transduction, effect gene expression and pathways of cell proliferation and death. Our body possess an intricate natural antioxidant system which prevents us from damage by pro oxidants [77]. Defective endogenous antioxidant system leads to accumulation of free radicals and finally leads to oxidative stress which in turn is involved in pathogenesis of various diseases such as various cancers, diabetes, and neurodegenerative diseases etc [78]. Apart from endogenous systems, there are various dietary sources of antioxidants such as polyphenols which possess antioxidant potential [79].

**Antioxidant systems**

Our bodies possess natural endogenous defines mechanisms which include both enzymatic antioxidant systems and cellular molecules which protect against free radical induced cellular damage [80]. Enzymatic machinery comprises of superoxide dismutase (SOD), catalase, and glutathione peroxidase which are considered as primary enzymes. They are involved in direct elimination of active oxygen species like superoxide radical and H$_2$O$_2$. In addition, there are various secondary enzymes such as glutathione reductase, glucose-6-phosphate dehydrogenase, and cytosolic GST that function to decrease peroxide levels or to maintain a steady supply of metabolic intermediates like glutathione (GSH) and NADPH for optimum functioning of the primary antioxidant enzymes (Meister, 1992) [81]. Apart from these systems, there are various cellular molecules which act as active antioxidants in our body like GSH, ascorbate (vitamin C), a-tocopherol (vitamin E), β-carotene, NADPH, uric acid, bilirubin, sodium selenite, mannitol, sodium benzoate, the iron-binding protein transferrin, dihydroxyacid acid, melatonin, plasma protein thiol, and reduced CoQ10 which are involved in protecting the body from ROS and their byproducts produced during normal cellular metabolism [82].

**Endogenous antioxidants**

The biological systems possess natural defense mechanisms to fight against free radical induced cell damage [83].

**Superoxide dismutase (SOD)**

SOD is an enzyme responsible for the reduction of the superoxide anion which is formed in the body via oxidative phosphorylation,
inflammation etc [84]. It is involved in conversion of superoxide anion into a product such as hydrogen peroxide that is metabolized easily to water by glutathione peroxidase (GPx) and catalase (CAT). It acts as a first line of defense in the detoxification of the superoxide anion and seems to be involved in processes of tumor removal or cellular differentiation.

**Coenzyme Q**

Reactive oxygen species are generated during oxidative metabolism in mitochondria. Coenzyme tend to protect mitochondria from these reactive species. Coenzyme Q is naturally occurring antioxidant. It is currently under investigation in amyotrophic lateral sclerosis and Parkinson disease [85]. It is a biologically active quinone. Furthermore, adenosine triphosphate which is a key source of intracellular energy in the human body is synthesized from CoQ [86]. It helps to neutralize free radicals and it tends to stabilize the cell membrane for most optimal functioning. It is the only known lipid which is produced directly within the body that maintains a redox function.

**α-Lipoic Acid**

α-Lipoic acid is a mitochondrial coenzyme and possess antioxidant action. It results in induction of many antioxidant enzymes [87]. Nrf2 is a transcription factor which is induced by α-Lipoic acid. The lipoic acid is very potent antioxidant as it is able to cross blood brain barrier therefore making it an ideal substance in the treatment of AD. As the formation of beta amyloid leads to pathogenesis of AD by formation of free radicals thereby making it a very important coenzyme [88]. Dihydrolipoic acid (DHLA) the reduced form of lipoic acid and lipoic acid are called "universal antioxidants" as they are involved in neutralization of free radicals.

**The glutathione antioxidant system**

The glutathione antioxidant system consists of reduced glutathione and the enzyme glutathione reductase. Glutathione serves as various functions in our cells. It acts as redox buffer of the cell [89]. It is a tripeptide composed of glutamic acid, cysteine, and glycine. It also serves as a reducer, conjugates to drugs to make them more soluble in water. In highly oxidizing environment the role of GSH as a reducing agent is significant. The sulfhydryl group of GSH can be used to reduce peroxides. The resulting form of oxidized GSH consists of two molecules of disulfide linked together (GSSG). GSSG is reduced to two molecules of GSH by the help of Glutathione reductase which uses NADPH as the cofactor. NADPH is produced via pentose phosphate pathway. Glutathione peroxidase is a selenium-dependent enzyme that catalyzes the reduction of hydrogen peroxide (H$_2$O$_2$) or liperoxide (L-OOH) using the reduced glutathione (GSH) [90].

**Glutathione peroxidases (GPX)**

GPX consists of multiple isoenzymes which catalyze the reduction of H$_2$O$_2$ and lipid peroxides utilizing GSH as an electron donor [91]. They are localized both in cytosol and mitochondria. There are five various isoforms of selenium-dependent glutathione peroxidases (GPX1-4 and 6) and three non-selenium congeners (GPX 5, 7 and 8) that have cysteine instead of selenocysteine, in mammals [92].

**Catalase**

Catalase (CAT) is one of the most abundant enzymes in nature and is widely distributed in the human body [93]. It is a tetrameric enzyme consisting of four identical tetrahedrally arranged subunits of 60 kDa, which contains a single ferriprotoporphyrin group per subunit and has a molecular mass of about 240 kDa. Catalases catalyze the conversion of hydrogen peroxide to water and oxygen, using either an iron or manganese cofactor [94]. Here, its cofactor is oxidized by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate [95].

$$\text{Catalase-Fe (III) } + \text{H}_2\text{O}_2 \rightarrow \text{Compound I } \rightarrow \text{Compound I+H}_2\text{O}_2 \rightarrow \text{catalase-Fe (III) } + 2\text{H}_2\text{O} + \text{O}_2$$

**Nrf 2**

Apart from endogenous enzyme systems, there occur a transcriptional mechanism to reduce cellular oxidative stress. Nrf2 is sequestered in the cytoplasm by interaction with the kelch like enoyl-CoA hydratase-associated protein 1 (ECH) associated protein (Keap1) which leads to its subsequent degradation by the proteasome and ubiquitination. Upon exposure to oxidative stress or electrophiles, Nrf2 translocate to the nucleus where it binds to antioxidant responsive elements (ARE). Nrf2 is released either by phosphorylation of keap 1 or oxidation of sulfhydryl groups on specific cysteines in keap1 [96]. After that Nrf2 is stabilized and translocate from the cytoplasm to the nucleus via bipartite nuclear localization signal where it then transactivates expression of detoxification enzymes, reducing molecules, antioxidant enzymes, and Nrf2 itself [97]. Oxidative damage is prevented by these gene products. When the antioxidant response is no longer needed Nrf is removed from nucleus with the help of nuclear export sequence near its nuclear localization signal.

**Nqo1**

NAD (P) H:quinone acceptor oxidoreductase 1 (NQO1) is a widely-distributed FAD-dependent flavoprotein that promotes obligatory 2-electron reductions of quinones, quinone imines, nitroaromatics, and azo dyes, at rates that are comparable with NADH or NADPH [98]. These reductions depress quinone levels and thereby minimize opportunities for generation of reactive oxygen intermediates by redox cycling, and for depletion of intracellular thiol pools. It is a highly-inducible enzyme that is regulated by the Keap1/Nrf2/ARE pathway. It protects cells from oxidative stress, redox cycling, and neoplastic lesion [99]. Additionally, Nqo1 is also involved in regeneration and α-tocopherol (vitamin E) metabolism.

**Exogenous antioxidants from the Diet/ Natural dietary antioxidants**

Apart from endogenous sources there are many dietary natural antioxidants such as vitamin C, vitamin E, and β-carotene which renders protection against free radicals. Natural dietary antioxidants include Vitamin A, C, and E, carotenoids, flavonoids, and polyphenols [100].

**Vitamin C**

It is one of the important water soluble antioxidant as it has the capacity to neutralize ROS [101]. It is involved in a number of metabolic reactions in plants and animals. It is a well-known antioxidant that protects the body against oxidative stress. One of the studies showed lower plasma levels of vitamin C in patients with AD despite adequate dietary intake. On the other hand, several studies provided evidence to support a therapeutic role of vitamin C in AD [102]. Combining other antioxidants with vitamin C may prove beneficial for AD prevention by providing a more comprehensive activation of pathways to reduce oxidative stress [103].
Vitamin E

Vitamin E is the major lipid-soluble, chain-breaking, non-enzymatic potent antioxidant in the body [104]. As vitamin E is essential for normal neurological functions, it is potentially useful in preventing and treating neurodegenerative diseases. Vitamin E represents a group of 8 antioxidants (containing 4 tocotrienols and 4 tocopherol. α-tocopherol is the most investigated form of vitamin E in relation to AD and MCI (Mild Cognitive Impairment). Reduced plasma levels of α-tocopherol have been detected in subjects with AD and MCI. It protects membranes fatty acids from lipid peroxidation [105]. The vast majority of literature from animal studies and randomized trials has related α-tocopherol to brain function. Higher levels of α-tocopherol were strongly associated with lower amyloid load as well as with less severe neurofibrillary tangle pathology.

β-carotene

β-carotene and other carotenoids also provide antioxidant protection to lipid rich tissues. Fruits and vegetables are major sources of carotenoids [106].

Phytonutrients

There are number of other dietary antioxidants which occur in nature other than vitamins, they are collectively known as phytochemicals or phytonutrients. Flavonoids are one such example. They are group of polyphenolic compounds widely distributed in plants and beverages like beer, tea and wine. Flavonoids show anti-inflammatory, anti-allergic, and anti-hepatotoxic activities. Several biological properties are attributed to their antioxidant properties and free radical scavenging capabilities.

Benfotiamine

Benfotiamine is a fat-soluble form of thiamine. It's considered a potent antioxidant that has been used over the past decade to treat pain symptoms. Benfotiamine is also useful in maintaining brain health. It is used as a broad-spectrum neuroprotector against neuropathies, neuralgia pathologies, and impaired coronary circulation. It is known to reduce amyloid plaque as well as tau levels in cortical regions of the transgenic mice brains. Moreover, it increases the phosphorylation level of glycogen synthase kinase-3alpha and -3beta, and reduced their enzymatic activities in the amyloid precursor protein/presenilin-1 transgenic brain [107]. Furthermore, in animal models it appeared to improve the cognitive function and reduce amyloid deposition via thiamine-independent mechanisms, which are likely to include the suppression of glycogen synthase kinase-3 activities. These results suggest that, unlike many other thiamine-related drugs, benfotiamine may be beneficial for clinical Alzheimer's disease treatment. This form of B1 could offer a safe and effective way to reverse memory-destroying plaque in the brain, helping to stop the progression of Alzheimer’s. Clinical trials are also ongoing for this analogy of vitamin B1.

Quercetin

Quercetin is one of the most prominent dietary antioxidant claimed to exert many positive effects on health, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease [108]. It is a member of the flavonoids family. Several in vitro and in vivo studies have provided supportive evidence for neuroprotective effects of quercetin, either against neurotoxic chemicals or in various models of neuronal injury and neurodegenerative diseases. It is currently in Phase II clinical trial [109].

SK-PC-B70M

SK-PC-B70M is an oleanolic-glycoside saponin-enriched fraction derived from the root of Pulsatilla koreana. Recently, it was reported that hederacliniside-E is an active ingredient of SK-PC-B70M that confers a neuroprotective effect against the cytotoxicity induced by amyloid β (1-42) in SK-N-SH neuroblastoma cells [110].

Curcumin

Curcumin has multiple desirable characteristics for a neuroprotective drug, including anti-inflammatory, antioxidant, and anti-protein aggregate activities [111]. Because of its oral safety, long history of use, and inexpensive cost, curcumin has great potential for the prevention of multiple neurological conditions. It has been found that curcumin reduced oxidative damage, inflammation, and cognitive deficits in rats receiving CNS infusions of toxic Aβ. Curcumin has repeatedly been investigated in clinical trials in AD patients; however, there were no significant positive results reported so far. The mechanism of action is not specified.

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is the most abundant catechin in green tea, a beverage widely consumed worldwide. It is a component of Japanese green tea extract [112]. It acts as a potent antioxidant. Furthermore, it has also showed anti-inflammatory and antiatherogenic properties in experimental studies conducted in vitro and in vivo [113]. EGCG also attenuated the increase in malondialdehyde levels caused by cerebral ischemia and reduced the formation of post ischemic brain edema and infarct volume. The neuroprotective effect of EGCG against ischemia-induced brain damage was found, in part, due to the modulation of NOS isoforms and preservation of mitochondrial complex activity and integrity. It is likely to have a multitarget mechanism of action similar to most herbal preparations with a strong antioxidant component.

Gingko biloba

Gingko biloba extract is a phytoestrogen that is registered with Ipsen and Schwabe in 1992 as a dietary supplement that improves the cognitive function of patients with senile and peripheral vascular dementia [114]. Ginkgo biloba extract has been therapeutically used for several decades to increase peripheral and cerebral blood flow as well as for the treatment of dementia [115]. The extract contains multiple compounds such as flavonoids and terpenoids that are thought to contribute to its neuroprotective and vasotrophic effects.

INM-176

It is another herbal medicine that is based on ferruginosa acid complexes and is used in some food additives [116]. It has an analgesic effect and is indicated to improve the condition of AD patients by improving blood circulation as well as reducing psychiatric symptoms. In primary microglial cells, INM-176 significantly inhibited LPS-induced nitric oxide release and expression of tumor necrosis factor-α and interleukin-1β.

Resveratrol

A widely used herbal medicine, Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) is a kind of polyphenol produced in several plants, especially grapes skin and seeds, and a phytoalexin against pathogens such as bacteria or fungi [117]. A typical multitargeted medicine and antioxidant, targets monoamine oxidase (MAO-A), beta-secretase,
xanthine oxidase, NF-kappaB, and several others enzymes. It has been found to exhibit neuroprotective function in animal models, mostly rat models [118,119]. It has been shown that resveratrol activates Nrf2/ARE signaling pathway [120].

Current treatment for Alzheimer disease

Currently "only" approved treatments by US Food and Drug Administration (FDA), includes five drugs that are used to treat the cognitive manifestations of AD. Acetylcholinesterase inhibitors AChEIs - rivastigmine (Exelon), galantamine ( Razadine, Reminyl), tacrine (Cognex), and Donepezl (Aricept) and NMDA receptor antagonist - memantine (Namenda) that target symptoms at its best [121,122] Reminyl, Exelon and Aricept are effective in the early stages of treatment. Each drug has different mechanism of action and a different way to decrease the breakdown of acetylcholine which is an important neurotransmitter in the brain [123]. In AD there is a decreased level of this neurotransmitter. Memantine (Namenda) is the only drug which is shown to be effective at the later development of the disease [124].

To date, established treatments are only symptomatic in nature, trying to counterbalance the neurotransmitter disturbance of the disease. All the treatments suffer from various side effects. Tacrine (Cognex) is rarely prescribed due to its serious side effects (liver damage). They have all been shown to modestly slow the progression of cognitive symptoms and reduce problematic behaviours in some people, but at least half of the people who take these drugs do not respond to them [125] At the same time antipsychotic and antidepressant treatments are used for the behavioural symptoms of the disease [126].

Novel strategies have been developed to modify the disease process. In this regard major development is targeted to the Aβ and tau based therapeutics, which is a major key to unlock this disease in the near future [127]. New approaches to develop drugs for the treatment of AD that prevent free radical production and hence neurodegeneration including AGE-inhibitors, antioxidants and anti-inflammatory substances are being emphasized. The development of disease-modifying drugs for AD is recognized as a worldwide necessity [128]. These must presumably be drugs that will modify, either by stabilizing or slowing, the molecular pathological steps leading to neurodegeneration and finally dementia.

Herbal therapy for Alzheimer disease

Natural products and herbal remedies have been a source of many beneficial drugs. About 80% of the world’s population is dependent on plant based medicines [129]. Herbal mixtures might have advantages as they have multiple target approach as compared with the single target [130]. It has been challenging to treat AD. Herbal therapy can be a novel treatment option for AD. Phytotherapy may be a potential corner stone based on which treatment strategies can be streamlined [131]. There is evidence which suggest that herbs or herbal formulations may provide complementary cognitive benefits to the approved drugs, however due to various methodological limitations, their use alone, it remain inconclusive. On the basis of various positive results from clinical trials, herbal therapy formulations may offer certain complementary cognitive benefits to the approved drugs [132,133]. As many drugs are available today for treatment of AD, various plant and their extracts are extensively employed in vivo models and AD patients. Herbal extracts produce a diverse range of natural products including alkaloids, indoles, phytosterols, isoflavonoids which exhibit complex pharmacological properties [134]. Plants provide wealth of bioactive compounds, which exert a substantial strategy for the treatment of neurological disorders such as Alzheimer’s disease [135].

The anti-alzheimeric property of phytochemicals has been attributed to them by either of the following mechanisms:

- Antioxidative and radical scavenging activities
- Acetylcholiesterase inhibition
- Anti-inflammatory activity
- Modulation of antioxidant machinery

Plants with traditional use of antioxidant and anti-alzheimeric activity have been studied [136]. Some of the examples are: Withania somnifera showed antioxidant activity in Alzheimer’s disease by increasing the levels of the major free-radical scavenging enzymes like superoxide dismutase, catalase and glutathione peroxidase in the frontal cortex and striatum [137]. Curcuma longa (Turmeric) has shown potent antioxidant and anti-inflammatory activity. It has shown to activate Nrf2/ARE signaling [138]. Antioxidant activity is shown by Centella asiatica. It reduces brain lipid peroxidation (LPO) and protein carbonyl levels [139]. It also reversed Aβ pathology [140]. Bacopa monnieri shows anti-alzheimeric activity by possessing antioxidant activity by increasing levels of superoxide dismutase, catalase and glutathione peroxidase in the prefrontal cortex, striatum, and hippocampus [141]. Ocimum sanctum inhibits lipid peroxide generation thereby showing antioxidant activity 159. The seeds of Cassia obtusifolia showed neuroprotective role in mice via attenuation of Ca2+ ion dysregulation. Moreover they inhibit AChE [142]. The neuroprotective role of extracts of Cassia obtusifolia might be due to group of phenolic compounds i.e., flavonoids [143]. Dried ginger showed Ca2+ antagonistic activity and butyrylcholinesterase inhibition activity which are effective in AD treatment [144]. Aqueous and ethyl acetate extract of Convulvulus pluricaulis has shown memory enhancement effect. Various secondary metabolites have been isolated from it such as terpenoids, anthocyanins, steroids which are responsible for its effects [145]. Zeatin shows protective role against Aβ induced neurotoxicity in neuronal cell line PC12 and ameliorate scopolamine induced amnesia in mice models [146]. Gingko biloba showed various health benefits to the patients of AD. It possess various antioxidants. It has various effects like anti amyloid aggregation. There are few substantial studies which support amelioration of AD. The clinical trials have been promising. Clinical evaluation of EGb761 is widely used for dementia. In many countries and is used as dietary supplement on large scale in US for memory enhancement. It has been found to improve AD symptoms both in vivo and in vitro studies [147]. Desmodium gangeticum commonly known as Salparrini has been used in ayurveda extensively for the amelioration of neurological symptoms. Various in vivo studies have been carried out. Furthermore, it also showed potent antioxidant property [148]. Rosmarinic acid which is isolated from Salvia officinalis attenuates many processes proved by reactive oxygen species, lipid peroxidation, DNA fragmentation, Caspase 3 activation and Tau protein hyperphosphorylation. Other pharmacological activities include antioxidant, anti-inflammatory, AChE inhibition yet the mode of action is elusive. It effectively inhibits hall mark events of AD-like formation of fibrils from Aβ, destabilization preformed Aβ fibrils in vitro and tau hyperphosphorylation [149], Melissa officinalis extract has been proven to ameliorate mild to moderate AD. It might present a natural treatment for AD by amelioration of cognition [150]. Huperzine A extracted from the serrate clubmoss herb is a potent, reversible and selective inhibitor of acetylcholinesterase. From various trails, it seems to have some beneficial effects on improvement of cognitive function [151,152]. Panaxasaponin main ingredient of Panax ginseng enhance cognitive performance. It decrease level of Aβ and
repair damaged neurons. Medhya Rasayanas or drugs from Ayurveda considerably ameliorate memory and intellect. In vivo studies on rats evaluated that the oral dose of Trasina, a herbal formulation, once daily 21 days effectively ameliorate colchicine induced effects. Herbal formulation may have advantages with multiple target regulation as compared with the single target antagonist. There have been few clinical trials examining the efficacy and safety of herbal formulations in AD patients.

Conclusion

As oxidative stress plays a crucial part in pathogenesis of AD, it remains a challenge to design some sort of treatment intervention because it lacks a typical treatment target. To combat oxidative stress involve augmenting antioxidant defence eg: with nutritional supplements or vitamins. Various epidemiological, clinical and basic researches provide a strong support for antioxidant treatment in AD. It is plausible that one single antioxidant may not be sufficient to resist the oxidative damage since the oxidative stress is modulated by a complex system of endogenous and exogenous antioxidants. In this regard, the combinatorial approach of antioxidants would be necessary to be studied in the treatment of neurodegenerative diseases. Antioxidant therapy can provide treatment option. The integrated approach is needed to combat the pathogenesis of AD. Several substances are considered as therapeutic candidates for oxidative stress; however, further preclinical and clinical studies are required before clinical application of these substances.

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