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EC NEUROLOGY
Review Article

The Role of Oxidative Stress in Pathophysiology of Alzheimer's Disease

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Received: April 03, 2019 **Published:** July 17, 2019

Abstract

Alzheimer's disease (AD) is a common neurodegenerative disorder, which is characterised by amyloid plaques and neurofibrillary tangles. AD patients show progressive loss of memory, reduced brain functioning, abnormal behaviour, reduced learning ability, loss of synapsis and neuronal death. Oxidative stress in known to be involved in a number of neurodegenerative disorders like Alzheimer's disease, Parkinson's disease etc. Oxidative stress leads to formation of reactive oxygen species, which interact with various biological systems and have been found to be involved in amyloid beta deposition, neurofibrillary tangle formation and mitochondrial dysfunction. A large no antioxidants show beneficial effects in AD in cell line studies, in vivo studies and in clinical trials, however no antioxidant drug has yet got an FDA approval for AD treatment. In this review, we will discuss about the basic concept of oxidative stress, involvement of oxidative stress in various aspects of AD pathophysiology like amyloid beta formation, neurofibrillary tangles and mitochondrial dysfunction etc. Antioxidant drugs used in latest animal studies and clinical trials for the management of AD have also been discussed herein.

Keywords: *Amyloid Plaques; Neurofibrillary Tangles; Synapsis; Oxidative Stress; Mitochondrial Dysfunction; Antioxidants*

Introduction

Oxidation is a process, in which there is a gain of oxygen molecule, whereas reduction is the process in which there is loss of oxygen molecule. Oxidation and reduction occurs side by side in the biological systems. These are known as redox reactions. Reductants are the chemical entities which cause removal of oxygen or donators of electrons, whereas oxidants are the chemical entities which cause gain of oxygen or acceptors of electrons. Reductants and oxidants are known as antioxidants and pro-oxidants respectively in biological systems [1]. The redox potential or balance between pro-oxidants and antioxidants is very important for normal functioning of the cell. Imbalance between pro-oxidants and antioxidants i.e. presence of more amount of pro-oxidants or less amount of antioxidants leads to oxidative stress [2]. Oxygen derived pro-oxidants or reactive oxygen species (ROS) are very important as these cause damage to important parts of the cell such as lipids, proteins and DNA [2]. Examples of ROS include nitric oxide radical, hydroxyl radical, superoxide ion radical, hydrogen peroxide etc. Various exogenous and endogenous sources are responsible for the production of ROS. Exogenous sources include radiations like γ-radiations, air pollutants such as cigarette smoke and various xenobiotics like pesticides, herbicides etc. In endogenous sources, mitochondria are the main source of ROS [3]. Mitochondria produce ROS during ATP production by ETC. Along with mitochondria other endogenous sources which are responsible for the production of ROS are enzymes, WBC, various pathogens and diseases. Under normal physiological conditions, ROS act as signalling molecules in redox hemostasis and in cell signalling e.g. for activation tyrosine kinase and MAPK. Oxidative stress is found to be involved in pathophysiology of a large no of diseases including neurodegenerative disorders like Alzheimer's disease (AD) [4]. AD is a type of neurodegenerative disorder, which is characterised by the progressive loss of memory, reduced brain functioning, abnormal behaviour, reduced learning ability, loss of synapsis and neuronal death. Main characteristic neurological features of Alzheimer's disease are presence of amyloid plaques and neurofibrillary tangles (NFT). Amyloid plaques consist of extracellular deposition of Amyloid beta oligomers which clump together in brain parenchyma, whereas NFT consist of hyper-

phosphorylated tau proteins. These amyloid plaques and NFT leads to neurodegeneration with time, which results into appearance of behavioural and functional symptoms in the patients.

In this review, we discuss about the role of oxidative stress in pathophysiology of alzheimer's disease and involvement of oxidative stress in various characteristics features of AD like amyloid beta, neurofibrillary tangles, mitochondrial dysfunction etc. Antioxidant drugs used in latest animal studies and clinical trials for the management of AD have also been discussed herein.

Amyloid beta and oxidative stress

Amyloid beta is the constituent of amyloid plaques in AD brain. Amyloid beta deposition is an early event of AD pathogenesis and it is considered as central basis of AD pathogenesis [5]. Oxidative stress is also a well known established factor in the AD pathogenesis. A large no of studies have been done to establish a link between amyloid beta and oxidative stress in AD pathogenesis. As stated earlier, oxidative stress leads to lipid peroxidation, protein oxidation and DNA damage. A number of studies have shown the involvement of amyloid beta in oxidative stress induced neuronal alterations. Level of polyunsaturated fatty acids (PUFA) for example arachidonic acid and docosohexenoic acid are have been reported to be decreased in AD brain [6]. This indicates that lipid peroxidation is involved in AD pathogenesis. Also, Amyloid beta synaptosomes show increased level of free fatty acid release and an antioxidant vitamin E, has been shown to reverse these changes. The concentration of HNE (24-hydroxy-2-transnonenal), which is a product of lipid peroxidation, is observed to be increased in AD as well as in hippocampal neuronal culture exposed to amyloid beta [7]. IsoP (isoprostanes) and neuroprostane (NP) are the products of ROS induced degeneration of arachidonic acid and docosohexenoic acid [8]. Levels of IsoP and NP have been found to be increased in AD CSF and amyloid beta treated culture of rat brain hippocampus.

Similar evidence of association between amyloid beta and oxidative stress are observed in protein oxidation, where creatine kinase (CK) level have been observed to be declined in AD brain, due to oxidation, as well as amyloid beta treatment. Another example include significant decrease in glutamine synthase (GS) activity in AD hippocampus and cortex as well as in the amyloid beta treated brain homogenate and hippocampal neuronal culture [9].

Association between oxidative stress and amyloid beta is also supported by the presence of more lipid peroxidation and protein oxidation in amyloid beta rich brain area as compared to other sites [10]. Also, it has been shown that neuroblastoma neuro 2a cells are resistance to amyloid beta as they contain the high level of an antioxidant glutathione [11]. In another example, patients of Down's syndrome had higher level of amyloid beta due to APP overexpression, and they also show remarkable increase in ROS level. Another study has shown that increased anticholinesterase within and around amyloid plaques is responsible for accumulation of amyloid beta into fibrils. The activity of anticholinesterase has also been found to be increased in retinal cells incubated with amyloid beta 25 - 35 when compared with reverse sequence of peptide or untreated. Increase in Calcium influx lead to generation of ROS and NOS which causes oxidative stress and proceed to cause lipid peroxidation. Increased oxidative stress leads to increased activity of anticholinesterase by decreasing the cholinergic function. When pre-treated with antioxidants, decrease in anticholinesterase activity is observed which shows increased acetylcholine activity in AD is due to oxidative stress and ROS production [12]. Further, Oxidative stress occurs in *C. elegens* strain CL4176 (a temperature inducible strain which express human amyloid beta peptide) without the formation of fibrils, which shows that prefibillar amyloid beta can be responsible for oxidative stress and neurodegeneration instead of amyloid fibrils. Also, in transgenic animals, less deposition of amyloid beta has been shown to be associated with reduced free radical generation and oxidative stress. Homocysteine acts as NMDA receptor agonist and it elicits excitation of cerebellar neurons and increases the influx of calcium. Oxidative stress is produced due to calcium influx, and homocysteine produces synergistic effect with amyloid beta in the induction of oxidative stress and calcium influx. Although, a large number of studies have shown that amyloid beta is responsible for the production oxidative stress, yet there are some studies which show that oxidative stress is also responsible for increased amyloid beta production. APP is cleaved by beta secretase (BACE1) and forms app c-terminal fragment which is further acted upon by gamma secretase and lead to formation of amyloid beta peptides. Oxidative stress and HNE (lipid peroxidation product) activates JNK/C- JUN signalling pathway, which further increase the expression of PS1 (catalytic subunit of gamma secretase) and hence increase the activity of gamma secretase and production of amyloid beta [13].

These studies show that there is strong correlation between amyloid beta and oxidative stress in Alzheimer's pathogenesis.

Hyperphosphorylation of Tau and oxidative Stress

Hyperphosphorylated tau is second hallmark of AD pathogenesis after amyloid beta deposition. Hyperphosphorylated tau leads to formation of neurofibrillary tangles (NFT), which is an important characteristic in AD pathogenesis. In normal physiological condition, tau proteins are responsible for microtubule assembly and their stabilization. Their phosphorylation can occur at more than 30 sites, which are regulated by protein kinases and phosphatases. In normal physiological condition, there is a balance between phosphorylation and dephosphorylation by kinases and phosphatases. An imbalance between kinase and phosphatase activity leads to hyperphosphorylation of tau, which ultimately leads to neurofibrillary tangles formation. In kinases, GSK-3β is majorly involved in controlling phosphorylation of tau. GSK-3β causes the hyperphosphorylation of tau whereas inhibition of GSK-3β, results into decreased hyperphosphorylation of tau. In case of phosphatases, PP2A is most important in hyperphosphorylation of tau. Inhibition of PP2A leads to hyperphosphorylation of tau. This is also responsible for hyperphosphorylation of tau in Down's syndrome. In AD, oxidative stress is also involved in hyperphosphorylation of tau. Oxidative stress leads to increased activity of GSK-3β, which leads to hyperphosphorylation of tau. Various antioxidant drugs have been shown to exert beneficial effects in prevention of NFT by inhibiting the GSK-3β, such as melatonin. DAB cause tau hyperphosphorylation due to GSK-3β activation whereas NAC (an antioxidant) reverses the changes by inhibiting GSK-3β. Linkage between oxidative stress and tau is also favoured by berberine, which inhibits the self-perpetuating cycle of neuro-inflammation and oxidative stress and this leads to decreased tau hyperphosphorylation [14]. Studies also show that there is linkage between phosphatase and oxidative stress. Oxidative stress leads to inactivation of PP1/ PP2A. This leads to increased ERK1/2 activity, which causes tau hyper phosphorylation. Hyperphosphorylated tau accumulates in somatodendritic portion of neurons, where it disrupts glutamate receptor trafficking. It also leads to impairment of NMDA receptor and PSD-95 functioning (a synaptic plasticity regulator) [15]. These studies shows that oxidative stress interfere with kinases and phosphatases activity, and are thus, responsible for hyperphosphorylation of tau.

Mitochondrial dysfunction and oxidative stress

Mitochondria are one of important organelles of the cell. Mitochondria control ATP production, oxidative phosphorolysis, and apoptosis. Mitochondrial dysfunction is noted in number of neurodegenerative disorders like Alzheimer's disease, Parkinson's disease and Huntington's disease. Mitochondrial dysfunction and oxidative stress are closely related to each other, because mitochondria are not only the main source of reactive oxygen species, but also a main target for oxidative stress. Mitochondrial dysfunction leads to the overproduction of ROS and lesser production of ATP [16]. Various aspects of mitochondrial dysfunction are observed in AD, like reduced brain metabolism i.e. reduced glucose metabolism, decreased neuronal expression of gene encoding for key enzymes of ETC like alpha –keto glutarate dehydrogenase complex and pyruvate dehydrogenase complex etc [16]. calcium dyshomeostasis due to impaired buffering capacity, mutation in MTDNA particularly in parietal cortex and cerebellum, because it is prone to ROS attack due to absence of histone in MTDNA and close proximity with site of gene responsible for ROS, and activation of components of intrinsic apoptosis pathway in AD. These observations show a strong relationship between mitochondrial dysfunction and oxidative stress in Alzheimer's disease.

Mitochondrial function is markedly affected by mitochondrial dynamics, i.e. mitochondrial fusion and fission. If mitochondrial fission is inactivated then it leads to elongation and if fusion is inactivated then it lead to fragmentation of mitochondria [17]. Imbalance between fission and fusion leads to mitochondrial dysfunction. Mitochondrial fission is regulated by two main proteins named as DLP-1 and Fis-1, in which DLP-1 punctate the fission spot whereas Fis-1 helps in recruitment of DLP-1. On the other hand, mitochondrial fusion is regulated by 3 proteins – Mfn-1, Mfn-2 [18] and OPA [19]. Here, Mfn-1 and 2 forms the homo and hetero oligomers which tie up the neighbouring mitochondria. Mitochondrial fusion and fission are very important for normal functioning of mitochondria, because when fusion take place it allows the exchange of intra mitochondrial content, which helps the mitochondria to replenish the store, whereas fission allows the elimination of damaged mitochondrial content. Thus, fusion and fission helps in maintaining the healthy population of mitochondria in cell. Equilibrium between fission and fusion is also required for normal cell metabolism and energy production, controlling ROS production and apoptosis [20]. In AD, there is significant decrease in percentage of normal mitochondria, which may occur due to the abnormal mitochondrial dynamics [21]. Amyloid Beta overproduction leads to mitochondrial fragmentation and mitochondrial dysfunction like increased ROS, decreased ATP, decreased mitochondrial potential, etc. These changes are reversed by fusion protein optic atropy (OPA) overexpression, which confirms the imbalance of mitochondrial dynamics in AD [22]. As stated earlier, random loss of essential components like MTDNA of mitochondria are overcome by exchange of content by fission and fusion. In AD, APP overpro-

duction, Amyloid beta and oxidative stress leads to the decrease in rate of mitochondrial fusion, which decrease the rate of exchange of mitochondrial content, thus mitochondria lacking MTDNA are also formed. These mitochondria lack respiratory subunit, and this leads to formation of dysfunctional mitochondria. Their function cannot be overcome by other functional mitochondria, which ultimately leads to reduced ATP production and metabolism in neurons in AD [22]. In AD, significant change in level of fission and fusion proteins is observed, like level of DLP-1 is increased, which leads to formation of damaged and swollen mitochondria, eventually causing increased ROS production and oxidative stress [23]. Various evidences show the relation between altered mitochondrial dynamics and oxidative stress in AD, like inhibition of mitochondrial pyruvate, does not affect mitochondrial fragmentation, whereas genetic inhibition of DLP-1 leads to decreased ROS production. Also, ETS inhibition by 1-methyl-4-phenylpyridinium leads to mitochondrial fragmentation and ROS generation [24]. Antioxidant treatment only partially reverses ROS production and mitochondrial fragmentation, whereas inhibition of mitochondrial fission leads to significant inhibition of ROS and mitochondrial fragmentation [24]. These evidences show that imbalance of mitochondrial dynamics is responsible for increased mitochondrial fragmentation, ROS generation and oxidative stress in AD. Defective mitochondria lead to set up of cascade of events which leads to oxidative stress in AD. There is a defective microtubule metabolism, which leads to decreased mitochondrial transport, which in turn results into abnormal mitochondrial turnover, thus initiating the cascade of events including oxidative stress. Oxidative stress results in damage of MTDNA, which leads to increased perikaryal MTDNA and mitochondrial protein accumulation [25].

Role of VDAC-1

Voltage dependent anion channel 1 (VDAC) is a multifunctional membrane protein in outer mitochondrial membrane. It regulates the metabolic and energetic functions of mitochondria. VDAC occurs in three isoforms – VDAC1, VDAC2 and VDAC3. VDAC1 is mainly involved in AD because VDAC2 and VDAC3 have low expression in neurons. In normal physiological conditions, VDAC1 occurs as monomer and dimer, but upon the induction of apoptosis, VDAC1 undergoes conformational changes, due to which VDAC1 oligomer assemble to form VDAC1 oligomers. This leads to binding of hexokinase and creatine kinase, which leads to release of cytochrome c and ultimately causes apoptosis. VDAC1 overexpression is observed in AD, and since VDAC1 initiates apoptosis, it may be involved in neuronal death in AD [26]. Normally, hexokinase remains bound with VDAC1 in outer mitochondrial membrane, which directly uses ATP produced by mitochondria and help in protection against apoptosis. GSK3B activity is increased in AD, due to which GSK3B induced phosphorylation of VDAC1 occurs and thus, hexokinase detach from VDAC1, which leads to VDAC1 oligomerization and thus initiates apoptosis This also leads to a decrease in availability of ATP, which makes the cells prone to apoptosis [27]. Therefore, this can be the possible mechanism involved in VDAC1 derived neuronal apoptosis in AD (Figure 1).

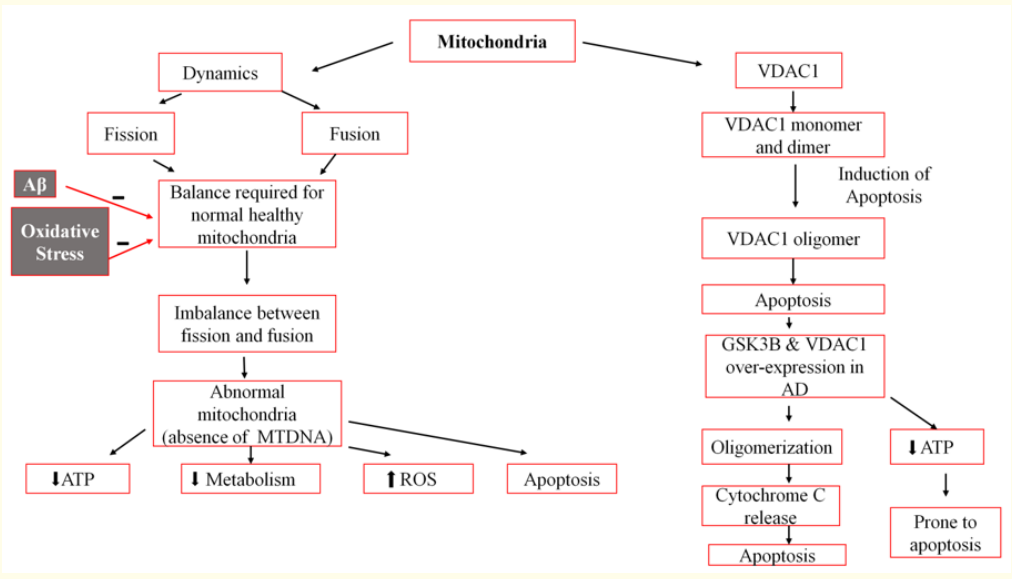

***Figure 1**: Mechanism of mitochondrial dysfunction in AD.*

Down's syndrome and oxidative stress in AD

Down's syndrome is a genetic disorder which is characterised by chromosome 21 trisomy. Chromosome 21 encode for a number of genes, which play role in neurodegeneration, for example SOD-1, Ets-2, BACE-2 and DSCR1 [28]. Down's syndrome is also associated with AD. Various studies has shown that oxidative stress and lipid peroxidation are increased in Down's syndrome. Chromosome number 21 trisomy in this disease produces an extra copy of gene encoding for SOD-1. This extra copy of SOD-1 produce imbalance between SOD-1 and glutathione. Normally, SOD-1 and glutathione act side by side. SOD-1 acts on superoxide radicals and convert them into H_2O_2 and O_2. H_2O_2 is further acted upon by glutathione peroxidase but in case of Down's syndrome, due to an extra copy of gene encoding for SOD-1, SOD-1 is present in more amount than glutathione due to which, whole H_2O_2 produced by SOD-1 cannot be processed by glutathione. Thus, H2O2 reacts with transient metal to initiate the Fenton reaction, which results into the formation highly reactive hydroxyl radicals. These hydroxyl radicals react with DNA, protein and lipids and cause their peroxidation. This results into neuronal damage due to disruption of mitochondria and other cell organelles. Also, SOD-1 levels are observed to be increased in AD patients [29], which indicate that the correlation between Down's syndrome and AD may involve SOD-1.

Ets-2 is another enzyme which is encoded on chromosome 21 [30]. ETS-2 level is increased in Down's syndrome directly by gene trisomy [30] and indirectly by oxidative stress. The increased level of Ets-2 initiates a P-53 dependent mitochondrial death pathway, which further results into neuronal damage [30,31].

Amyloid beta accumulation is also associated with Down's syndrome induced AD. Chromosome21 also encode for APP, so, 21 chromosome trisomy leads to increased APP production [32]. Also, chromosome no 21 encode for BACE-2, which has 64 percent similar amino acid sequence as that of BACE-1 [33]. BACE -2 leads to increased amount of amyloid beta [34]. Along with overproduction of amyloid beta, there is also a decreased clearance of amyloid beta in Down's syndrome. Because amyloid beta is cleared by IDE [35], Neprilysin [36] and T-PA [37], and in AD Neprilysin exists in oxidised form, this leads to amyloid beta accumulation [36]. Thus, it is possible that in Down's syndrome, similar oxidation of neprilysin can occur, which leads to amyloid beta accumulation in Down's syndrome. Increased oxidative stress in Down's syndrome is also associated with amyloid beta accumulation [38]. Thus, increased APP, BACE-2, neprilysin oxidation and oxidative stress all contribute to increased amyloid beta in Down's syndrome (Figure 2).

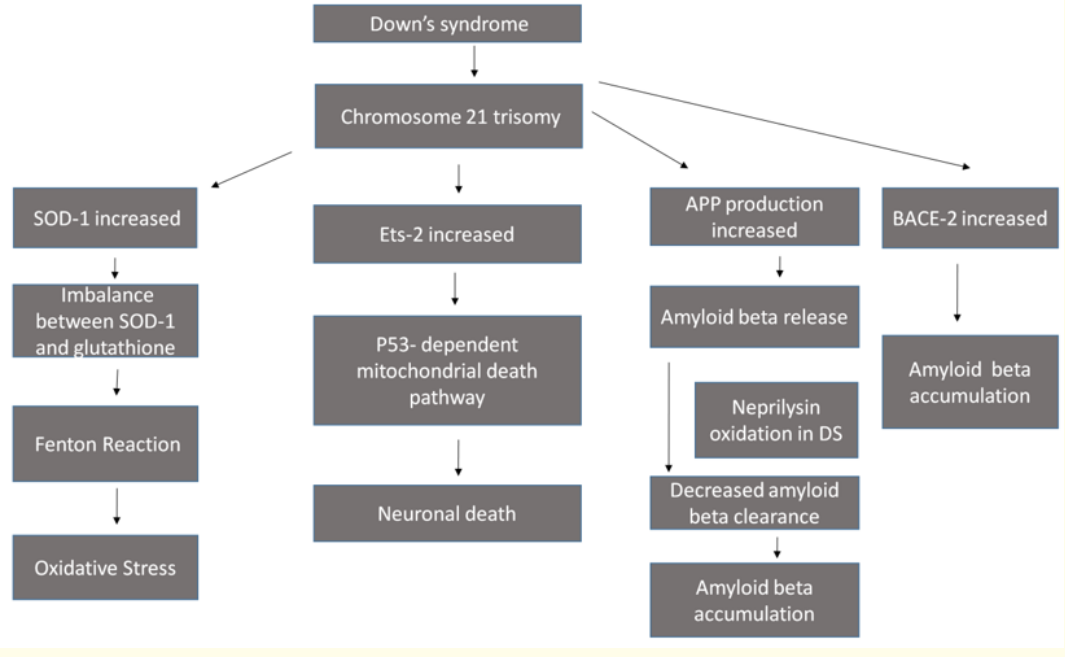

***Figure 2**: Mechanism of Down's syndrome induced AD.*

Lipid peroxidation, protein damage, DNA and RNA damage in AD and their association with oxidative stress

Some studies suggest that lipid peroxidation, protein damage and nucleic acid degradation occurs in AD due to oxidative stress. Knowingly, brain contains a large no of PUFA phospholipids mainly docosahexanoic acid and arachidonic acid. Increased amount of ROS has been found to be associated with decreased amount of PUFA in AD brain. Also, carbonyl levels have been reported to be increased in AD, which are a biomarker of oxidative damage to protein [39]. In AD brain, 8-OHdG levels have been found to be significantly increased in mitochondrial DNA of cortex. 8-OHdG is DNA oxidation product, so increase in its level shows that there is oxidative damage to DNA in AD. DNA strand break is also increased in AD, which is also a marker of oxidative damage [40]. These findings show that oxidative stress in AD is responsible for lipid peroxidation, protein damage and DNA oxidation.

The information provided above shows that oxidative stress is a major cause of all the neurological, biochemical and pathological changes occurring during AD. Due to this reason, a large number of antioxidants have been screened for their potential to reverse or prevent AD pathogenesis. A list of antioxidants that have been recently used in various research studies involving AD is mentioned here.

S. No.	Antioxidant Drug	Study Type	Effects	Reference(S)
1.	Sodium Selenate	Phase IIa Randomized control trial	Stimulate PP2a activity, safe and well tolerated	[41]
2.	Resveratrol	Phase II randomized, placebo- controlled, double blind trial	Higher CSF and plasma Aβ40 levels	[42]
3.	Souvenaid	Randomized, controlled, double blind, parallel –group, multi-country study	Preserve the brain network organisation to maintain synaptic integrity and function	[43]
4.	Vitamin E	Randomized , parallel group placebo- controlled, double blind	Slower functional decline	[44]
5.	Omega-3 acid, lipoic acid	Randomized placebo-controlled pilot trial	Slower cognitive and functional decline	[45]
6.	Vitamin E, Vitamin c, α-lipoic acid, coenzyme Q	Double blind, placebo controlled clinical trial	CSF F2- isoprostane level decreased	[46]
7.	Kaempferol	STZ and Ovariectomized rat model of sporadic dementia	Alleviation of STZ induced memory impairment, elevation of antioxidant level, reduction of neuro inflammation	[47]
8.	Phloroglucinol	5X Familial AD mice model	Decreased no of amyloid plaques, protein level of BACE1	[48]
9.	Pyridoxine	AD cell model	Decreased ROS level, decreased cytosolic Nrf2 expression	[49]
10.	Coenzyme Q10	Aβ-induced AD	Decrease the effect of Aβ on LTP	[50]

Table 1: *Recently used antioxidant drugs in AD.*

Conclusion

In this paper, we discussed about the role of oxidative stress in pathophysiology of Alzheimer's disease. Oxidative stress leads to protein oxidation, DNA damage and lipid peroxidation by amyloid beta production. This is supported by the studies showing that amyloid beta treatment leads to increased lipid peroxidation, DNA damage and protein oxidation due to ROS production and oxidative stress. Oxidative stress leads to activation of JNK/C- JUN signalling pathway, which increase the expression of gamma secretase and thus amyloid beta production. Oxidative stress also activates anticholinesterase, which increase the deposition of amyloid beta whereas by increasing the activity of GSK-3β, it leads to hyperphosphorylation of tau. Oxidative stress is also closely related to mitochondrial dysfunction and an imbalance between mitochondrial fission and fusion. Dysfunctional mitochondria lead to formation of ROS and oxidative stress. Oxidative stress is also associated with AD induced by Down's syndrome where an increased amount of SOD and Ets-2 leads to increased oxidative

stress and mitochondrial dysfunction. A large no of antioxidants shows beneficial effect in AD. Recently, Sodium selenite, resveratrol, souvenaid, Vitamin E, omega-3 acid, lipoic acid, vitamin C, coenzyme Q3 are under clinical trials for AD, however, no antioxidant drug has got an FDA approval so far for AD treatment. Thus, it could be concluded that oxidative stress is an important hallmark in AD pathophysiology and antioxidants are beneficial in prevention of disease. Still, a lot more research is required in this area for the purpose of understanding the role of oxidative stress in AD and antioxidants in treatment.

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