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REVIEW

Oxidative stress in Alzheimer's disease: current knowledge of signaling pathways and therapeutics

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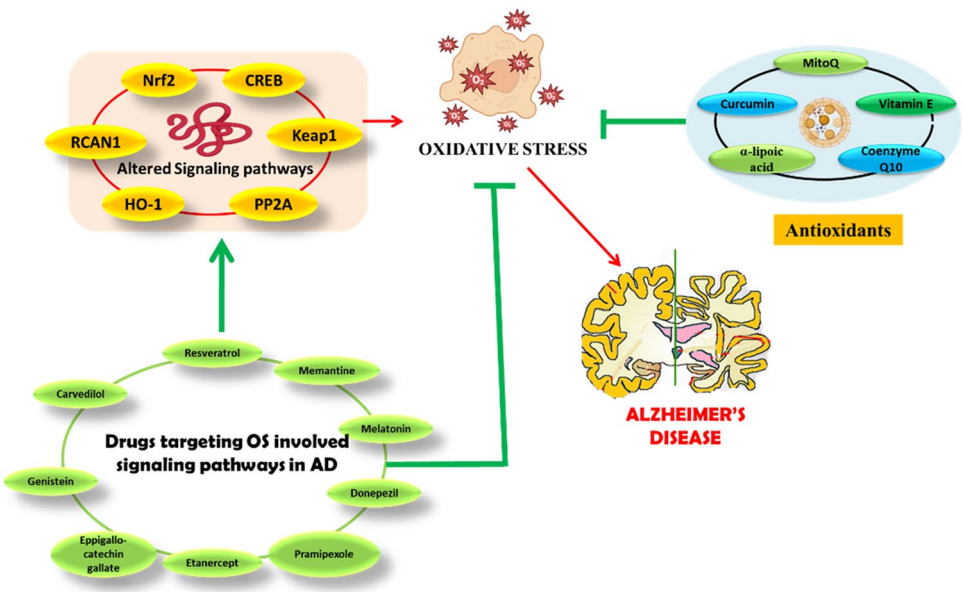
Abstract

Alzheimer's disease's pathophysiology is still a conundrum. Growing number of evidences have elucidated the involvement of oxidative stress in the pathology of AD rendering it a major target for therapeutic development. Reactive oxygen species (ROS) generated by altered mitochondrial function, dysregulated electron transport chain and other sources elevate aggregated Aβ and neurofibrillary tangles which further stimulating the production of ROS. Oxidative stress induced damage to lipids, proteins and DNA result in neuronal death which leads to AD. In addition, oxidative stress induces apoptosis that is triggered by the modulation of ERK1/2 and Nrf2 pathway followed by increased GSK-3β expression and decreased PP2A activity. Oxidative stress exaggerates disease condition by interfering with various signaling pathways like RCAN1, CREB/ERK, Nrf2, PP2A, NFκB and PI3K/Akt. Studies have reported the role of TNF-α in oxidative stress stimulation that has been regulated by drugs like etanercept increasing the level of anti-oxidants. Other drugs like pramipexole, memantine, carvedilol, and melatonin have been reported to activate CREB/RCAN1 and Nrf2 pathways. In line with this, epigallocatechin gallate and genistein also target Nrf2 and CREB pathway leading to activation of downstream pathways like ARE and Keap1 which ameliorate oxidative stress condition. Donepezil and resveratrol reduce oxidative stress and activate AMPK pathway along with PP2A activation thus promoting tau dephosphorylation and neuronal survival. This study describes in detail the role of oxidative stress in AD, major signaling pathways involving oxidative stress induced AD and drugs under development targeting these pathways which may aid in therapeutic advances for AD.

Graphical abstract



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Keywords Alzheimer's disease · Oxidative stress · Signaling pathways · CREB · Nrf2 · Drugs

Introduction

Alzheimer's disease is a rapidly progressing neurodegenerative disorder leading to the decline of cognitive functions [1]. Major pathologies of the disease include amyloid plaque deposition, neurofibrillary tangle formation, oxidative stress, cholinergic insufficiency, platelet aggregation [2], excitotoxicity and neuroinflammation [3, 4] (Fig. 1). Currently there are only few FDA approved drugs for the treatment of AD which provide only symptomatic relief. That include galantamine, donepezil and rivastigmine which are acetylcholinesterase inhibitors and memantine which is a NMDA receptor blocker [5]. Recently, anti-Aβ monoclonal antibodies (mabs) (viz., aducanumab, bapineuzumab, gantenerumab, solanezumab, and lecanemab) that can alter the root cause of AD have been proposed. These are under clinical trials based on the hypothesis that a systemic malfunction of cell-mediated removal of Aβ plays a role in the onset and progression of AD [6]. As the exact causative factor for AD is still unknown, drug development for the treatment of AD has become very challenging [5]. Oxidative stress is reported to be a crucial contributor in the progression of Alzheimer's disease [7]. Imbalance in the production of free radicals (FRs) and anti-oxidants of the body is mainly responsible for it. Oxidative stress also results in the disruption of biomolecules including lipids, proteins and nucleic acids of the cells [8, 9]. This damage leads to the destruction of various cells in the brain. The major contributors of reactive oxygen species in the body are believed to be energy transform systems. In these, an electron is transferred from electron donor to acceptor and during this process various intermediates are formed which are harmful free radicals (FRs) like OH., OH^-, NO. and H_2O_2 [10]. The role of mitochondria is also well established in the generation of FRs. Mitochondria contribute as a major source of generation of energy in the form of ATP that generates reactive oxygen species while producing energy [3]. Due to mitochondrial dysfunction, there occurs leakage of electron from the mitochondrial respiratory chain leading to oxidative stress induced AD [11].

Brain is considered highly susceptible towards the damage caused by oxidative stress due to many reasons. The major ones include excessive amount of iron, high availability of polyunsaturated fatty acids, high demand of energy, and relatively high consumption of oxygen. Aβ oligomers present in the AD brain may also promote the generation of reactive oxygen species which further damage the neurons and affect the cognitive functions [12]. ROS generated during dysregulated cellular respiration is also responsible for damage caused to neuronal functions. Due to reduction in the generation of ATP as a result

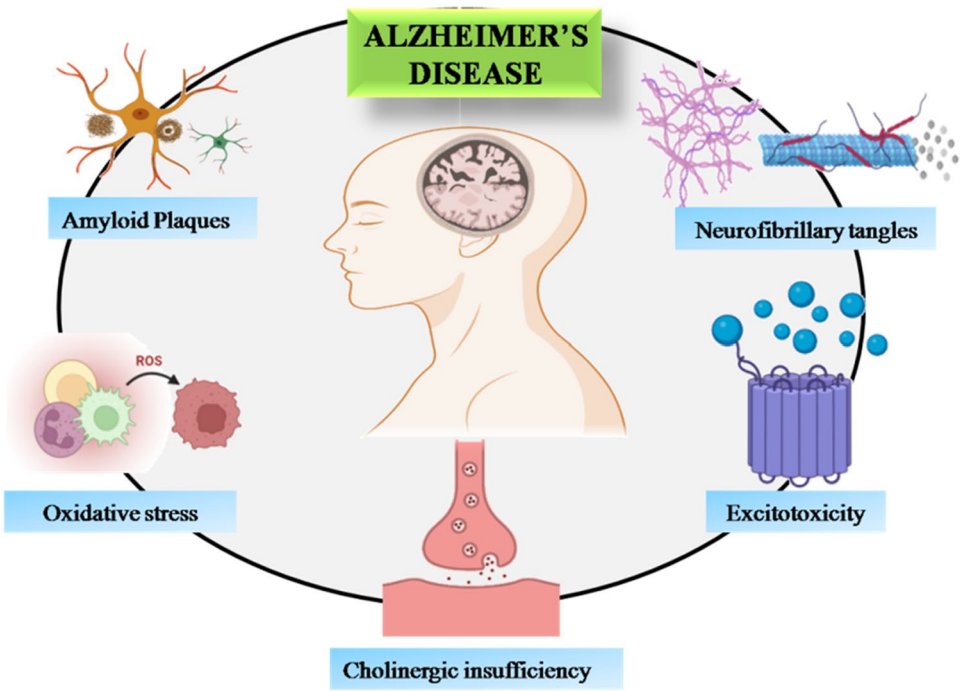


Fig. 1 Pathophysiological cascades in Alzheimer's disease. Figure shows various pathologies responsible for the development of Alzheimer's disease including amyloid plaque deposition in the brain extraneuronally and neurofibrillary tangle formation due to destabilization of microtubules as a result of tau hyperphosphorylation intraneuronally. Besides these, other major pathological hallmarks are oxidative stress which is in line with mitochondrial dysfunction. Further, neuroinflammation, cholinergic insufficiency and excitotoxicity also contribute in the disease progression

of damaged mitochondria in AD and damage caused to DNA, proteins and lipids, the functions of neurons get disturbed [13]. Brain cells require efficacious anti-oxidant mechanism to protect against oxidative stress condition which is compromised in AD patients [14]. Lipid peroxidation associated with oxidative stress results in the generation of 4-hydroxynonenal which is toxic to neuronal cells. This causes loss of long-term potentiation and disrupted memory and learning functions of the brain [15]. In addition, calcium influx modulations caused by mitochondrial dysfunction results in the hindrance of signal transduction which can cause synaptic loss and neurodegeneration [16, 17]. Reduction in cholinergic neurons due to degeneration caused by oxidative stress leads to the downfall in acetylcholine. The expression of choline acetyl transferase enzyme required for the synthesis of acetylcholine has also been found to be reduced that progresses to synaptic dysfunction [18]. Various molecular pathways are involved in oxidative stress induced AD that includes RCAN1, CREB, Nrf2 and PP2A. These pathways are dysregulated due to ROS in the brain of AD patients ultimately leading to neurodegeneration. RCAN1 is a calcineurin regulator which is over-expressed in Alzheimer's disease. It is correlated with increased GSK3-β activity and consequently contributes in tau hyperphosphorylation. cAMP response element binding protein (CREB) is responsible for the proteasomal degradation of RCAN1 but under oxidative stress CREB expression is also modulated [19–21]. Another pathway regulating oxidative stress involves Nrf2, which is essential for controlling mitochondrial dynamics, mitophagy, and biogenesis. Age-related changes in Nrf2 activity have been seen in experimental animals accompanied by reduced glutathione synthesis. It has been reported that Nrf2 pathway is compromised during aging [22]. In addition, ROS promotes PP2A inhibition and GSK3β gets overactivated leading to hyperphosphorylation of tau protein. It also activates NF-κB mediated neuroinflammatory pathway linking oxidative stress with neuroinflammation and contribute in AD progression [13, 15, 23]. Modulating these pathways by using various drugs including carvedilol, donepezil, memantine, melatonin, pramipexole, resveratrol, etanercept, epigallocatechin gallate and genistein may combat oxidative stress induced Alzheimer's disease. Considering this, present study explains in detail the mechanism behind oxidative stress induced AD along with the signaling pathways involved. It focuses on the drugs in clinical trials targeting the pathways like RCAN1, CREB/ERK, PP2A, NFκB and PI3K/Akt, modulating which can be beneficial for the treatment of AD.

Materials and methods

Various databases and search engines have been used to collect the data for the manuscript including Google Scholar, PubMed, PubChem and Clinicaltrials.gov.in.

Impact of oxidative stress on lipids

Cell membrane is majorly composed of lipids which are highly prone to the destruction caused by free radicals. Lipids undergo peroxidation which results in the production of ketones, lipid peroxides and aldehydes. The propagating radicals withdraw a hydrogen atom from a molecule and render it reactive and form a new free radical. These free radicals attack unsaturated fatty acids which further react with molecular oxygen to form peroxy radical which is highly reactive. Consequently, other toxic compounds are formed like malondialdehyde, formaldehyde, propionaldehyde, and acetaldehyde which cause cross linking of lipids and proteins rendering them non-functional [24]. Due to oxidation of arachidonic acid, isoprostanes and isofurans are formed. Similarly, oxidation of docosahexaenoic acid leads to the production of neuroprostanes or neurofurans and oxidation of adrenic acid yields homo-isoprostanes or di-homo-isofurans. These oxidation products of lipids are harmful to the cell survival. As brain is having high lipid content as well as its oxygen demand is also high, it is more susceptible to the damage caused by these lipid oxidation products [25].

Impact of oxidative stress on proteins

Free radicals attack the amino acids and interfere in the functions of proteins by initiating cross-linking. Disulfide bonds present in the proteins make them susceptible towards damage caused by free radicals. Protein oxidation products may react with lipid oxidation products as well as carbohydrate oxidation products resulting in the conformational change of proteins making them non-functional. It is believed that carbonyl groups in proteins make them susceptible towards oxidative damage but it is still not clear [24]. As proteins are abundantly present and they have very high-rate constants for reactions, they are more susceptible to oxidative damage. The backbone and side chains of proteins get damaged resulting in their modifications. The damage caused to proteins include breakdown of protein backbone and side chain fragmentation, cross-linking resulting in accumulation of proteins, conformational changes and abnormal or loss of functions. Free radicals produce peroxyl radicals and peroxides which further oxidize other proteins hindering several physiological functions [26].

Impact of oxidative stress on DNA

ROS results in the generation of DNA-protein cross-links, damage to the DNA backbone and modify the purine and pyrimidine bases leading to highly cytotoxic compounds. These modifications can also lead to mutations which can come out to be carcinogenic. Free radicals cause breakage

of DNA backbone. Hydroxyl radicals react with the bases and cause alterations in them like modification of guanine to 8-hydroxyguanosine. Similarly, nitric oxide free radicals cause deamination of DNA bases [24]. Mitochondrial DNA is more susceptible to the disfigurement caused by reactive oxygen species and reactive nitrogen species because they are in close proximity of the source of these free radicals. ROS attack pyrimidine and purine bases and withdraw hydrogen from them leading to the formation of adducts like thymidine glycol, 5-hydroxydeoxyuridine, 5-formyl uracil, alloxan, etc. The adducts formed by the attack of free radicals in sugar moieties of DNA are erythrose, glycolic acid and 8-hydroxydeoxyguanosine. These adducts are carcinogenic and also act as biomarker for oxidative stress induced DNA damage. Peroxynitrite, a reactive nitrogen species also produces DNA lesions with 8-nitrogunanine and 8-oxydeoxyguanosine. Studies revealed that RNAs are more prone to oxidative damage than DNAs as they are less protected by proteins and due to their single stranded nature [27].

ROS and associated neurological Complications

ROS have crucial pathophysiological role which enhances the vulnerability of brain cells towards oxidative damage. The higher oxygen demand and lipid-rich content in brain makes it susceptible to oxidative stress. ROS are reported to stimulate various molecular cascades that result in neurodegeneration and related neurological disorders including AD. The major pathological damage caused by ROS and their related neurological complications have been described in Table 1.

Insight into the role of oxidative stress in AD progression

Oxidative stress is considered to be a major contributor in the pathology of many neurodegenerative diseases [28] including AD. In various examinations of AD brains massive oxidative damage has been found. ROS are originated by endogenous substances and processes or by exogenous factors like toxins, environmental pollutants and smoking. These undergo redox reactions and cause damage to the cell by promoting mitochondrial dysfunction and peroxidation of lipids, proteins and nucleic acids [29]. Along with the increased concentration of FRs there was reduced level of anti-oxidants like catalase and superoxide dismutase. It has been observed that majority of oxidative biomarkers were at synapses of neurons indicating that oxidative stress induces damage to neuronal synapse and disrupt signal transduction [30].

Mitochondrial dysfunction is a major contributor in neurodegenerative diseases like AD. Mitochondria act as source of ROS generation as well as the target of oxidative damage leading to AD progression. There is accretion of Aβ plaques which form chelates with metal ions like Cu^{2+}, Zn^{2+}, and Fe^{3+} in AD. These chelates then undergo various chemical reactions leading to altered oxidation states. These metal ions with transformed oxidation states interact with hydrogen peroxide and form highly reactive and destructive FRs [31]. Zn is important for cognitive functions of brain but due to the activation of inflammatory mediators towards aggregated Aβ, the homeostasis of Zn is altered in AD. This leads to the accumulation of Zn in the brains along with Aβ leading to cytotoxicity. In the brain, increased oxidative stress can cause rise in free calcium levels, excitotoxicity and subsequently neurotoxicity [32]. The nervous system is abundant in unsaturated fatty acid levels and iron content which make it susceptible to oxidative damage. It also acts as source of origination of hydroxyl and other FRs due to the presence of iron in large quantities. In AD, due to loss of synaptic function, increased ROS production, decreased anti-oxidant activity and presence of Aβ and tau tangles, there occurs degeneration of neuronal cells [33]. Oxidative stress also gives rise to the generation of stress granules. Stress granules are condensed clusters of proteins and untranslated mRNAs that emerge during stress condition in

Table 1 Neurological complications associated with ROS

S. No.		Effect	Consequence	References
1)	ROS	Brain glucose hypometabolism	Energy deprivation leading to neuronal death	[116]
2)		Increased APP expression	Aggregation of Aβ	[117]
3)		Presynaptic mitochondrial damage	Synaptic dysfunction	[118]
4)		Mitochondrial electron transport chain (ETC) complex modification	Further increase in oxidative stress condition	[119]
5)		Reduction in CREB and subsequent increase in GSK-3β expression	Tau hyperphosphorylation and NFTs formation	[19, 20, 21].
6)		mTOR dependent autophagy reduction	Protein oxidative damage and accumulation of damaged proteins	[120]
7)		Decreased Nrf2 activity	ROS induced apoptotic death of neuronal cell	[121]
8)		Increased caspases activity	Apoptotic neuronal cell death	[13]

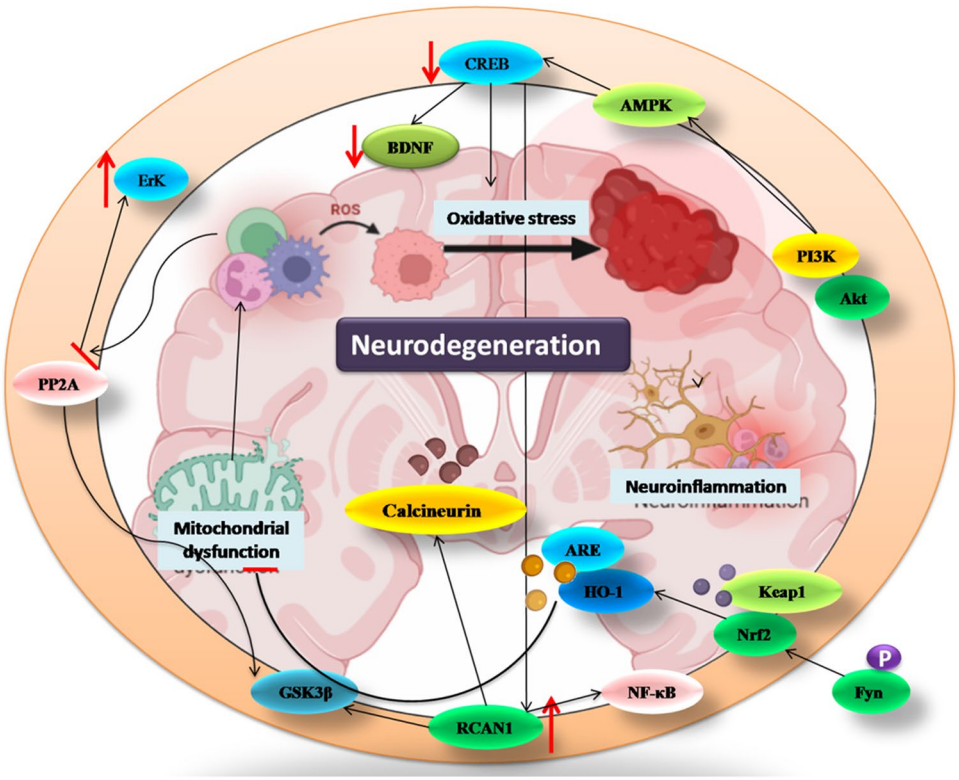


Fig. 2 Molecular pathways involved in the aggravation of oxidative stress induced neurodegeneration in AD. It shows various pathways involved in the damage induced by oxidative stress. These pathways influence various downstream pathways like PI3/Akt pathway, NFκB pathway, PP2A/Erk pathway, Nrf2, HO-1, kelch-like ECH-associated protein 1 (Keap-1), antioxidant response elements (ARE), cAMP response element-binding protein (CREB) and GSK3β which contribute in the disease progression by altering normal physiological condition

cytosol [34]. The composition of nuclear and cytoplasmic stress granules is different from one another. The nuclear one consists of factors responsible for pre-mRNA processing and heat shock transcription factor 1/2 and the latter one contains mRNA which are non-translating. The cytoplasmic stress granules disappear as soon as the stress is removed. These stress granules can also convert into persistent aggregates in pathological conditions like in AD. Acute stress derived stress granules are protective in action and reduce apoptosis. In AD, the stress granules alter the functions of neurons and engulf the vital proteins including ribonucleoproteins which progresses the disease [35].

Another factor responsible for oxidative stress induced AD is ferroptosis. It is an emerging concept explaining iron-dependent programmed cell death. It has been found to be linked with the neuronal cell death due to oxidative stress. Studies have shown the involvement of BID (a pro-apoptotic protein) in ferroptosis leading to dysfunction of mitochondria and cell death under oxidative stress. Ferroptosis involves the production of iron mediated production of FRs. Many studies are going on to determine the exact mechanism and consequences of ferroptosis in AD [9]. Oxidative stress is also supposed to interfere in acetylcholine dependent neuronal functions. It destroys the neurons which supply cholineacetyl transferase required for the synthesis of acetylcholine. Therefore, it indirectly affects the cognitive functions and signal transduction processes in the neurons. Reduced levels of glutathione, an antioxidant found in the brain, is also seen in AD patients, which further stimulates the generation of FRs and cause subsequent damage to the neuronal cells [18]. In addition, oxidative stress and Aβ deposition increase the stress in endoplasmic reticulum which can give rise to neuronal cell death. Phosphatase and tensin homolog (PTEN), is a tumor suppressor gene which is important for cell survival and death. In various studies it is seen that PTEN inhibitors activate PI3/Akt pathway and reduce oxidative stress induced ER stress thus inhibit apoptosis. PI3/Akt pathway dysregulation has been found to be associated with the pathology of AD [36]. Similarly, nuclear factor-kappa light chain enhancer of activated B-cells (NFκB) is also accountable for the regulation of various genes implying in stress conditions. Heat shock proteins reduce the levels of oxidative stress by reducing the levels of ROS inside the cells via increasing the concentration of reduced glutathione. It is evident from many studies that activation of Erk/Akt pathway increases the action of heat shock proteins and suppress the damage caused by hydrogen peroxide FRs [37]. Protein kinase C is also indulged in the stimulation of NFκB which is a crucial regulator of oxidative stress [38] (Fig. 2). Therefore, targeting these pathways may aid in ameliorating the disease condition.

Oxidative stress and advanced glycation end-products in AD progression

The products formed upon glycation of proteins non-enzymatically give rise to irreversible products known as

advanced glycation end-products (AGEs). This process is mediated by reducing sugars and dicarbonyls. In AD, there occurs dyshomeostasis in the generation and clearance of AGEs leading to their accumulation. Excessive aggregation of AGEs and dicarbonyls result in disruption of mitochondrial respiratory chain and alter the mitochondrial membrane permeability resulting in oxidative stress [39]. AGEs by binding with receptor for advanced glycation end products (RAGE) and by the generation of protein cross-links, bring out various biological consequences. By activating other downstream pathways RAGE is involved in the regulation of neurite outgrowth, cell survival, cell proliferation and apoptosis [40]. Oxidative stress has been reported to stimulate the generation of AGEs by glycoxidation and lipid peroxidation. Numerous reactive carbonyl compounds are produced by the ROS-mediated glycoxidation and lipid peroxidation processes. Protein cross-linking and DNA damage arise from these electrophilically triggered carbonyl compounds' subsequent reactions with cellular proteins, lipids, and nucleic acids. These prolonged and intricate reactions result in the generation of a range of AGEs. By interacting with RAGEs, AGEs further stimulate signal transduction, leading to the production of proinflammatory cytokines like interleukin-6 (IL-6) which may lead to neuroinflammation [41]. The peroxidation end products help in the determination of destruction caused by FRs. These lead to the generation of malondialdehyde, peroxynitrate, protein carbonyls and many other AGEs. These end product levels are measured in the blood samples of AD patients which are likely to be increased with age. As these products are generated due to peroxidation, a destructive mechanism of oxidative stress indicates the part of oxidative stress in the progression of AD. Various studies show the interlink between increased malondialdehyde levels and progression of AD [42]. The formation of ROS by RAGE is also mediated by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), and NOX-dependent ROS is directly linked to hippocampal damage and cognitive decline. NOX4 is abundantly present in the brain and widely involved in the pathological progression of AD. The activity of oxidative stress-related proteins such hemeoxygenase-1 (HO-1) can be influenced by NOX4 via nuclear erythroid factor 2-related factor 2 (Nrf2). When oxidative stress stimulates a cell, Nrf2 migrates to the nucleus so that it may associate to antioxidant response elements by activating a variety of cytoprotective molecules including HO-1. Therefore, attenuating oxidative stress and inflammation by inhibiting the AGE/RAGE/NOX4 signaling pathway could be an effective therapy for AD [43].

Oxidative stress and Aβ toxicity in AD progression

Zn, Cu and Fe are required for the cognitive functions of the brain. But in AD brain, the levels of these metal ions have been found to be significantly elevated. Aβ proteins are highly susceptible to these metal ions. The exact binding mechanism of Zn with Aβ proteins is not well reported, but it is believed to bind with imidazole ring of histidine derivatives. Cu and Fe directly bind to Aβ and trigger the synthesis of FRs. Cu is considered to be more susceptible to Aβ binding due to higher redox potential. Cu-Aβ complex undergoes catalytic reaction and produces hydrogen peroxide and hydroxyl radicals by interacting with molecular oxygen [10].

Aβ has been reported to cause lipid peroxidation and protein oxidation which results in elevated levels of peroxidation products like malondialdehyde and 4-hydroxy-2-nonenal (HNE) and cause neuronal cell death. It also stimulates the intracellular rise in calcium levels. These products bind to the proteins like cysteine and render them non-functional. Acrolein, another lipid peroxidation product, causes damage to the lipid bilayers and leads to neuronal cell damage. Aβ induced oxidation of proteins also leads to the formation of protein carbonyls which promote the pathogenesis of AD [44]. High concentration of FRs also influences the inflammatory gene transcription and gives rise to the stimulation of interleukins and cytokines. Other inflammatory mediators including tumor necrosis factor alpha (TNF-α) and chemokines cause inflammation in the neurons. This can result in the degeneration of neurons subsequently activating microglia and astrocytes exacerbating the disease condition. Both oxidative stress and neuroinflammation cause the accretion of amyloid β peptides in the brain causing neurodegeneration and progression of AD [45].

Oxidative stress and hyperphosphorylated tau in AD progression

Tau protein is crucial for the stabilization of microtubules and facilitate smooth neuronal transduction processes. Several studies have proven that oxidative stress is intricated in increasing the hyperphosphorylation of these tau proteins. Carbonyl-4-HNE, a peroxidation end product, is responsible for the accumulation of hyperphosphorylated tau. But the relation between tau hyperphosphorylation and oxidative stress is still unclear. In some animal studies, treatment with oxidative stress inducing compounds led to the overactivity of glycogen synthase kinase 3β (GSK3β). It is a Ser/Thr kinase that causes hyperphosphorylation of tau protein promoting the pathology of the disease. Apart from GSK-3β, oxidative stress also modulates other kinases and promotes hyperphosphorylation of tau proteins. Some other studies have shown that there is oxidative stress induced reduction of peptidyl prolyl cis-trans isomerase 1 (Pin1) in AD brains. This enzyme is involved in the dephosphorylation of tau protein [46]. Oxidative stress leads to the decrease in glutathione and buthionine sulfoximine resulting in increased hyperphosphorylation of tau protein. Oxidative stress can

also directly cause hyperphosphorylation of tau by modulating protein phosphatase 2 A (PP2A). GSK3β activity is enhanced in oxidative stress conditions and PP2A activity is hindered which subsequently leads to the stimulation of extracellular signal regulated kinase 1/2 (ERK1/2) pathway and cause apoptosis. Further studies need to be performed for better understanding of the involvement of oxidative stress in tau pathologies [47].

Oxidative stress and mitochondrial dysfunction in AD progression

Mitochondrial dysfunction is getting immense focus due to their role in neurodegenerative disorders including AD. It is well known that mitochondrial dysfunction leads to massive energy loss in the neurons which may hinder their normal physiological functions including neurotransmission, synaptic plasticity and membrane excitability. Accumulating evidences have suggested the role of mitochondrial dysfunction in the production of ROS and exhibiting oxidative stress condition [48]. It has been reported that mitochondria generated ROS trigger tau hyperphosphorylation and its aggregation. This was proven by a study in mice, in which mitochondria targeted anti-oxidant, mito-TEMPO, suppressed the accumulation of hyperphosphorylated tau by reducing ROS generation from mitochondria. This suggests the involvement of mitochondrial ROS in the pathogenesis of AD mediated by hyperphosphorylated tau accumulation [49]. In addition, mitochondria mediated glucose hypometabolism is also a major concern associated with the progression of AD. As glucose is the key source of energy for the functioning of brain, alteration in cerebral glucose metabolism is the trigger for AD progression. IRS (Insulin receptor substrate)/PI3k/Akt pathway is responsible for regulating gene expression related to lipid metabolism, gluconeogenesis and stress resistance via forkhead box transcription factors (FOXO) transcription factors. But under insulin resistance condition FOXO is hyperactivated which stimulates heme oxygenase 1 (HMOX1) rendering it to consume heme. This disturbs electron transport chain (ETC) [50] as heme are embedded in the proteins of ETC [51]. Further, it leads to abrupt production of ROS from mitochondria causing oxidative stress, mutations in mitochondrial DNA and apoptosis resulting in neurodegeneration. Evidences have suggested that Kreb's cycle and oxidative phosphorylation are altered in AD which eventually leads to glucose hypometabolism and oxidative stress [50]. Further, it has been observed that there is build-up of oxidative stress, damaging mitochondrial DNA (mtDNA) which keeps on increasing with age. Due to lack of protective histones and impaired repair mechanism, mtDNA are more vulnerable to ROS induced mutilations. Oxidative stress condition also alters the levels of nuclear proteins like Nup93 which hinders the nucleocytoplasmic transmission. In addition, the oxidative phosphorylation enzymes are compromised due to ROS induced damage which eventually leads to ATP depletion in AD. Studies have suggested that the glycolysis enzymes hexokinase and lactate dehydrogenase are expressed in AD cortical regions. This indicates the shift towards anaerobic respiration to compensate ATP depletion by aerobic respiration [52]. Therefore, mitochondrial dysfunction associated oxidative stress may result in decreased ATP synthesis, increased calcium release from the stores and opening of mitochondrial permeability pores. Dysregulated calcium influx can cause various signal transduction anomalies which can cause neuronal synapse loss and ultimately neurodegeneration [16]. Thus, dysfunctional mitochondria induced oxidative stress leads to the progression of AD by increasing oxidative stress (Fig. 3).

Oxidative stress and gut microbiota in AD progression

Gut eubiosis, nutrition, and physiology are all influenced by gut microbiota (GM). Additionally, they control immunological responses, oxidative stress, inflammation, and central and peripheral neurotransmission. The pathology of neurological conditions including AD, can be attributed to aging and poor lifestyle choices. It is also influenced by oxidative and inflammatory reactions brought on by gut dysbiosis [53]. Initially the crosstalk between intestinal microbiota and brain was elucidated by Elie Metchnikoff and colleagues in 1900s. There are four ways by which gut microbiota interacts with brain. That includes activation of vagal neurons, serotonin released by enterochromaffin cells, systemic cytokines and chemokines and direct transfer of chemical signals by fermentation of dietary fibers like short chain fatty acids (SCFAs) [54]. Gut microbiota is involved in the regulation of microglial activation. It was observed in a study that gut microbiota stimulated oxidative stress condition via accumulation of N^6-carboxymethyllysine (CML) which leads to the generation of reactive oxygen species. It also resulted in the reduction of brain ATP levels and altered mitochondrial functions. It was proven by the study that upon removal of gut microbiota the oxidative stress and mitochondrial dysfunction in rat was ameliorated. It suggests the pathogenic link between gut-microbiota and oxidative stress [55]. Through leaky gut, pro-inflammatory cytokines and bacterial byproducts (TMAO, SCFA, amyloids, LPS, and peptidoglycans) may penetrate the bloodstream, approach the brain and result in cognitive decline promoting AD. In addition, they might stimulate glial cells that cause the production of neurotoxic Aβ plaques and neuroinflammation. Further, this may lead to degeneration of neurons as well as disruption of the connections between Aβ1-40 and Aβ1-42 peptides along with tau hyperphosphorylation [53].

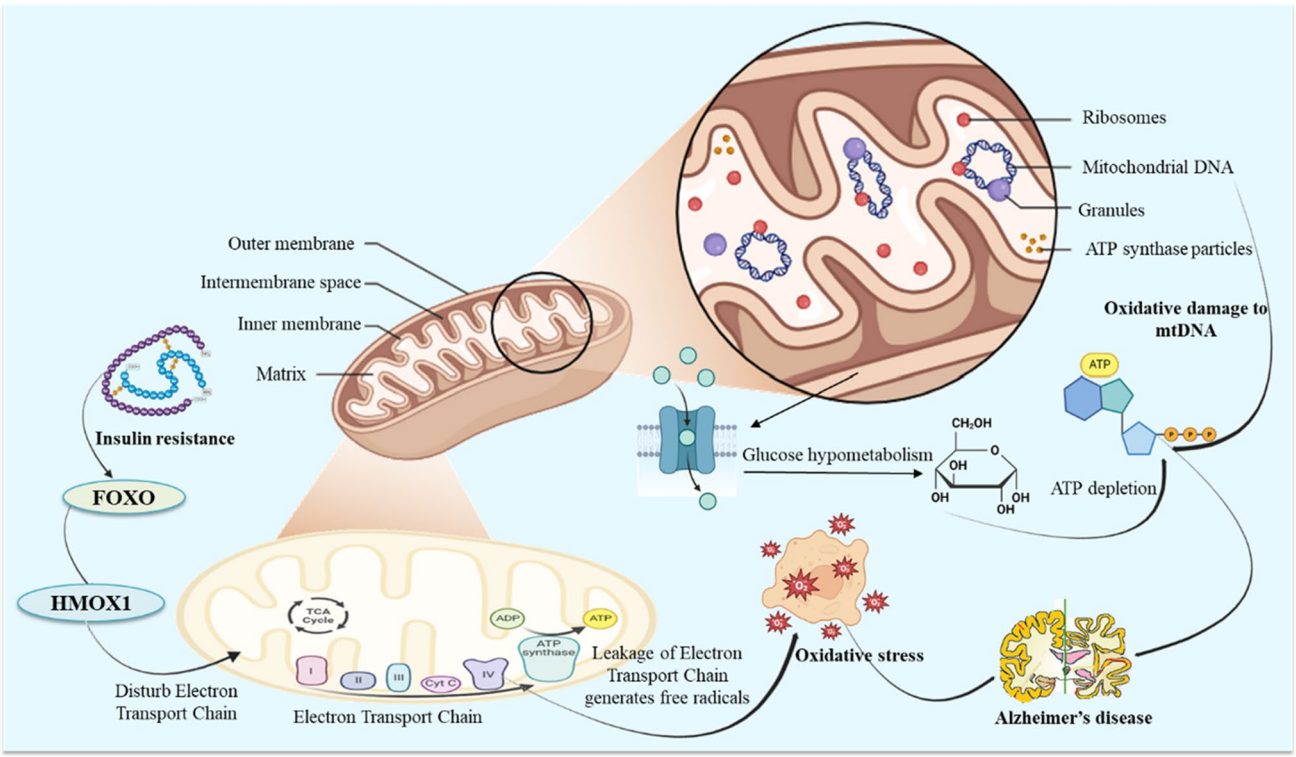


Fig. 3 Mitochondrial involvement in oxidative stress induced Alzheimer's disease. The figure shows various pathways which lead to the progression of AD. The leakage of electron from the electron transport chain during cellular respiration is the major cause of production of ROS which further damages the neurons and progress AD. Further insulin resistance disrupts the electron transport chain via FOXO/HMOX1 pathway contributing to oxidative stress. Due to ROS induced mitochondrial DNA damage, there occurs further increase in the disease condition as a result of alteration of mitochondrial functions including production of energy for various brain functions resulting in neurodegeneration and cognitive decline

Oxidative stress induced signaling pathways involved in the pathogenesis of AD

Various molecular pathways including RCAN, CREB, Nrf2 and PP2A have been reported to be implicated in the progression of AD induced by oxidative stress. These signaling pathways get altered under stress condition and activate or inhibit downstream pathways leading to AD progression. Thus, modulating these pathways can be a major target for therapeutic development of AD (Fig. 2).

Regulator of calcineurin (RCAN1) signaling pathway and AD progression

Calcineurin is involved in many facets of synaptic plasticity and memory formation. This is due to its ability to directly dephosphorylate critical targets in both the presynaptic and postsynaptic compartments of neurons. Regulator of calcineurin (RCAN1) is upregulated in Alzheimer's disease. Increased RCAN1 level is also associated with increased activity of GSK3β [19]. It is well reported that overexpression of RCAN1 increases the susceptibility of neurons towards oxidative stress. As mitochondria plays a crucial role in oxidative stress regulation, RCAN1 is involved in the normal functioning of mitochondria [56]. The transition of short-term memory to long-term memory is mediated by long-lasting alterations in synaptic plasticity, which are dependent on CREB signaling [21]. CREB promotes the proteasomal degradation of RCAN1 which is overexpressed in AD brains [20]. Elevated oxidative stress levels are linked with decreased CREB activation [21]. Calcineurin regulated by RCAN1 is a calcium dependent serine/threonine phosphatase which stimulates the transcription of various genes promoted by dephosphorylation of nuclear factor of activated T-cells (NFAT) and its transfer into the nucleus. NFAT then contributes in proliferation of cells, apoptosis, synaptic plasticity maintenance, angiogenesis and muscle development. Based on its phosphorylation levels, RCAN-1 exhibits the regulation of calcineurin. It has been justified by *in-vitro* studies where high RCAN-1 levels were responsible for inhibition of calcineurin and low levels account for increased expression of calcineurin. Dysregulation of calcineurin has frequently been observed in AD patients [57–60]. This dysregulation is as a result of upregulation of

RCAN-1 which occurs due to increased glucocorticoid levels, ApoE4 allele, ischemic stroke and elevated NF-κB [61]. In a study on SHSY5Y cells, RCAN1 expression for a short period inhibited apoptosis via inhibition of oxidative stress mediated caspase-3 activation. But when the exposure time was increased the effect was reversed and caspase-3 was activated under oxidative stress [62]. RCAN1 promotes neurodegeneration via inhibition of calcineurin and increased expression of GSK3-β. It stimulates the formation of neurofibrillary tangles and neuronal apoptosis [63].

Cyclic AMP response element binding protein (CREB) signaling pathway and AD progression

Pro-survival protein, CREB is regulated by AMPK family member proteins. As a transcription factor, the CREB protein controls the expression of genes that are important for the survival, differentiation, and growth of neurites. It has been demonstrated that a number of kinases, including protein kinase A (PKA), protein kinase C, calmodulin kinases, pp90 ribosomal S6 kinase and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) facilitate the phosphorylation of CREB at its transcriptional activation location [64]. In a study on PC12 cells the ERK/CREB signaling was observed to be modulated under oxidative stress. Increased levels of H_2O_2 elevate phosphorylation of ERK1/2 and reduce phosphorylation of CREB. Some studies have also shown that oxidative stress is inhibited by CREB/Erk pathway also CREB activation mitigates apoptosis mediated by oxidative stress [65]. The ERK/MAPK pathway consequently modulates other downstream pathways to regulate gene transcription for maintaining synaptic plasticity and alleviating oxidative stress. ERK/CREB signaling is linked to brain-derived neurotrophic factor (BDNF) which is involved in the regulation of cognitive functions and neuronal plasticity and contributes in the management of AD [66]. Many drugs are targeted towards CREB for the treatment of oxidative stress condition and the related disorders including AD [67] which are enlisted in Table 2.

Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway and AD progression

Growing number of studies indicate the involvement of Nrf2 in the oxidative stress mediated pathology of AD. Oxidative stress and persistent neuroinflammation in AD patients may be reduced by activating the Nrf2/HO-1 pathway and associated antioxidant molecules. NAD(P)H dehydrogenase quinone 1 (NQO1), heme oxygenase 1 (HO-1), and other antioxidant enzymes are expressed more frequently when Nrf2 is activated. These activities enhance ATP generation and mitochondrial activity, as well as prevent against oxidative damage. Nrf2 plays a crucial role in regulating the biogenesis, mitophagy and dynamics of mitochondria. Nrf2 activity declines with age in rats resulting in decreased glutathione production. This indicates that the expression of Nrf2/ARE pathway is decreased with age [22]. Under physiological condition, kelch-like ECH associated protein 1 (Keap1), which is known to inhibit Nrf2, clusters with Nrf2 [68]. Physiologically, Nrf2 must first be activated by ROS before it can be dissociated from the Keap1-CuI-Rbx1 complex and translocated into the nucleus [69]. Heme oxygenase-1 (HO-1) is one endogenic oxidoreductase whose expression is further regulated by Nrf2 after it binds to antioxidant response elements (AREs) in the nucleus [70]. A study on transgenic AD mice with Aβ accumulation and cognitive deficits suggested that with the increased AD pathology the activity of Nrf2 was declined consequently altering the expression of HO-1. By means of a GSK-3β and TrCP-β dependent Cul1-based ubiquitin ligase, Nrf2 undergoes degradation. Ser334–338 of the Nrf2 protein are phosphorylated by GSK-3β, forming a disintegration region that is recognized by β-TrCP and marked for enzymatic digestion by the Cullin 1 (Cul1) and Rbx1 complex [71–73]. Through the phosphorylation of the Fyn protein, which is brought on by GSK-3β, Nrf2 controls its function during oxidative stress environments like those in AD. The nuclear transfer, ubiquitination, and degradation of Nrf2 are caused by phosphorylated Fyn protein [22]. Nuclear Nrf2 levels in the hippocampus of AD human brains are found to be decreased. In spite of oxidative stress, Nrf2-mediated transcription is not enhanced in AD patients. Histochemical investigations show that Nrf2 is mostly localized in the cytoplasm of hippocampus neurons during the disease [74]. The Keap1-Nrf2 expression acts as biomarker for the severity of oxidative stress. Keap1-Nrf2 is linked to ageing and regulate the transcription of several antioxidant enzymes. A complicated regulatory system, comprising phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), protein kinase C, and mitogen-activated protein kinase (MAPK), is also involved in Keap1-Nrf2 signaling [75]. Targeting this pathway may be therapeutically beneficial in AD.

Protein phosphatase 2 A (PP2A) signaling pathway and AD progression

The protein phosphatases (PPs) are highly conserved between species and regulate a variety of cellular functions in eukaryotic cells, including cell division, differentiation, apoptosis, gene regulation, and cellular metabolism [76]. Different opinions exist regarding how ROS affects PP2A [77]. PP2A is inhibited in the presence of ROS and activates GSK-3β. Thus, it increases tau hyperphosphorylation due to activated GSK3β in AD [13]. Additionally, phosphatase is essential for regulation of oxidative stress and inflammation. Reactive oxygen species have been demonstrated

Table 2 Therapeutic agents under clinical trial targeting oxidative stress for the treatment of AD

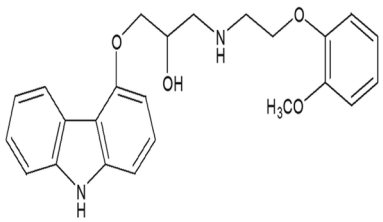
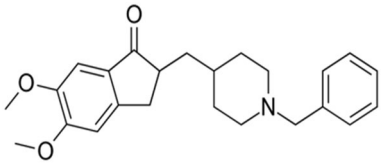
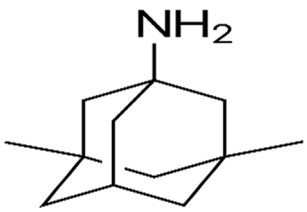
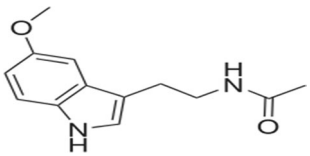
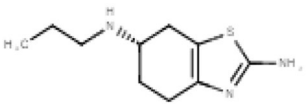
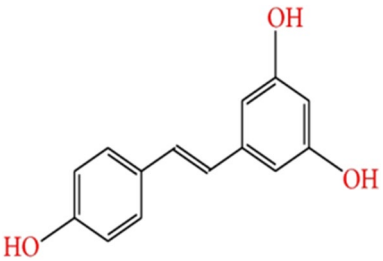
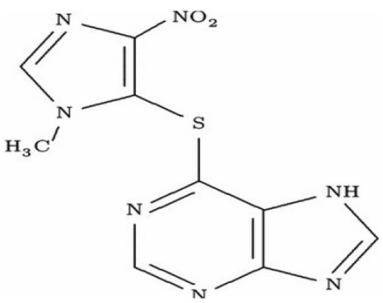
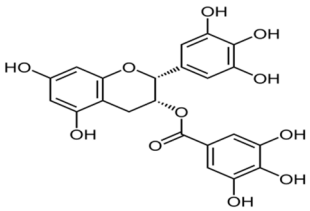
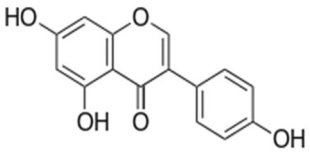
S.No.	Drug	Structure	Molecular mechanism of action	Route of administration	NCT No.	References
1)	Carvedilol		Activation of Nrf2/ARE pathway	Oral	NCT01354444	[89]
2)	Donepezil		AMPK activation	Oral	NCT00000173	[92]
3)	Memantine		Activation of Nrf2 and BDNF/TrkB pathway	Oral	NCT00235716	[94, 95]
4)	Melatonin		Activation of Nrf2/HO-1 pathway	Oral	NCT00000171	[97]
5)	Pramipexole		Modulates CREB/RCAN1 signaling; Activation of Nrf2/HO-1 pathway	Oral	NCT01388478	[100, 101]
6)	Resveratrol		Activation of PP2A; AMPK/PI3K/Akt inhibition	Oral	NCT01504854	[103, 104]
7)	Etanercept		TNF-α inhibitor; Increase the levels of anti-oxidants and decrease ROS generation	S.C.	NCT01716637	[106, 109]

Table 2 (continued)

S.No.	Drug	Structure	Molecular mechanism of action	Route of administration	NCT No.	References
8)	Epigallocatechin gallate		Activation of Nrf2/ARE and Nrf2/Keap1 pathway	Oral	NCT03978052	[111]
9)	Genistein		Activation of CREB pathway and PI3K/Akt/Nrf2/Keap1 pathway	S.C.	NCT01982578	[115]

to inactivate PP2A, which activates NFκB-mediated pro-inflammatory signaling. The dissociation of the highly functional PP2A holoenzyme trimer to a less functional dimeric form is caused by oxidative stress [23]. Memory impairment and tau hyperphosphorylation are the major hallmarks of AD. Rats with impaired memory were subjected to OKA-induced PP2A inhibition, which resulted in tau hyperphosphorylation. It has been demonstrated by in-vitro and in-vivo studies that oxidative stress-induced deactivation of PP1/PP2A is responsible for tau hyperphosphorylation and extended ERK 1/2 phosphorylation. Therefore, it is intriguing to hypothesize that increased ERK1/2 activity, which leads to tau hyperphosphorylation and the development of neurofibrillary tangles, is caused by oxidative stress-mediated PP1 and PP2A suppression in AD. Additionally, a reduction in PP2A activity contributes to aberrant tau hyperphosphorylation in AD brain by decreasing its dephosphorylation, activating ERK1/2, MEK1/2, and p70 S6 kinase [78]. Thus, PP2A stimulation has been suggested as a potential therapeutic target for alleviating oxidative stress.

Recent development in potential therapeutics for AD targeting oxidative stress

Current FDA approved drugs for the treatment of Alzheimer's disease include galantamine, donepezil, memantine, rivastigmine and a combination of donepezil and memantine known as Namzaric. However, they provide only symptomatic relief without inhibiting the progression or changing the outcomes of the disease. Tacrine was the first drug to be approved for the treatment of the disease but later it was withdrawn due to hepatotoxicity [79]. Acetylcholinesterase inhibitors are beneficial in almost all stages of dementia but their role in mild cognitive dysfunction and prodromal AD is still not proved. Memantine is effective in moderate to severe forms of the disease and is not efficient in ameliorating cognitive decline [80]. Recently, anti-amyloid-β antibodies, aducanumab, lecanemab and gantenerumab are in focus for the treatment of AD. These are monoclonal IgG1 antibodies targeting aggregated forms of Aβ. Growing evidence from clinical trials suggest the beneficial role of Aβ immunotherapy in ameliorating AD condition [81]. Developing therapeutics involve naturally occurring polyphenolic compounds that act as antioxidants and play a neuroprotective role in AD. Polyphenolic compounds either reduce the production of reactive oxygen species or enhance the release of antioxidants. They are able to cross the blood brain barrier (BBB) and promote neuroprotection [29]. α-lipoic acid is one of the polyphenolic compounds which acts as free radical scavenger and reduces hydrogen peroxide or iron induced pathologies by inhibiting ferroptosis. It reduces the level of iron required for the conversion of hydrogen peroxide into hydroxyl radicals via Fenton reaction by forming chelates with iron. It also reduces calcium content in the brain and activity of calpain preventing neuronal cell death [82]. Polyphenols have beneficial properties and a wide range of biological activities against a number of human diseases, including type 2 diabetes mellitus, cancer, cardio-metabolic diseases, and neurodegenerative diseases including AD and potentially modulate gut dysbiosis [83]. Green tea polyphenols, which are abundant in (-)-epigallocatechin-3-gallate (EGCG), scavenge free radicals, chelate metal ions, and block the nuclear transfer of NF-κB. As a result, they alleviate oxidative stress and protect against a number of the AD promoters [84]. Reactive oxygen species have also been found to disrupt BBB by triggering a variety of signaling pathways leading to tight junction activation, adherent junction modification, mitochondrial membrane pore activation and cytoskeletal disorganization. This results in BBB dysfunction and further stimulates other pathological conditions

including neuroinflammation progressing to AD. Naturally occurring polyphenols include stilbenes, flavanones, isoflavones and phenolic acids. These act as anti-oxidants alleviating the BBB dysfunction associated with increased oxidative stress [85]. Thus, polyphenols are considered to be potential therapeutic molecules for the treatment of oxidative stress induced AD.

In addition, targeting mitochondria for decreasing the production of FRs is a major pathway ameliorating oxidative stress induced AD. Anti-oxidants like coenzyme Q10, MitoQ, dimebon and α-lipoic acid are potent in alleviating mitochondrial dysfunction and associated oxidative damage (Fig. 4). They reduce cognitive decline associated with AD patients [86]. ROS activate protein kinase C and MAPK pathway and trigger inflammatory cytokines and chemokines. The inflammatory cells lead to the synthesis of FRs that further stimulates other inflammatory mediators. Therefore, anti-inflammatory drugs can be used to reduce the oxidative stress induced damage and prevent neurodegeneration [31]. TNF-α is a major stimulator of cytokines and various other inflammatory mediators and lead to the abnormal cleavage of APP. TNF-α is also a stimulator of NFκB pathway which leads to production of Aβ. Inhibiting TNF-α in AD patients have been found to mitigate cognitive defects [87]. TNF-α inhibitor like etanercept can be used to reduce TNF-α induced damage to the neurons (Table 2) (Fig. 4). Drugs undergoing clinical trials targeting oxidative stress induced AD are described herein.

Carvedilol

Carvedilol is under phase IV of the clinical trials. 29 participants have been enrolled in the trial. This study has a randomized, triple-blind and parallel assignment design. Carvedilol is a β-blocker and it inhibits apoptosis, reduces ROS level and toxicity caused by Aβ. It regulates IL-1β

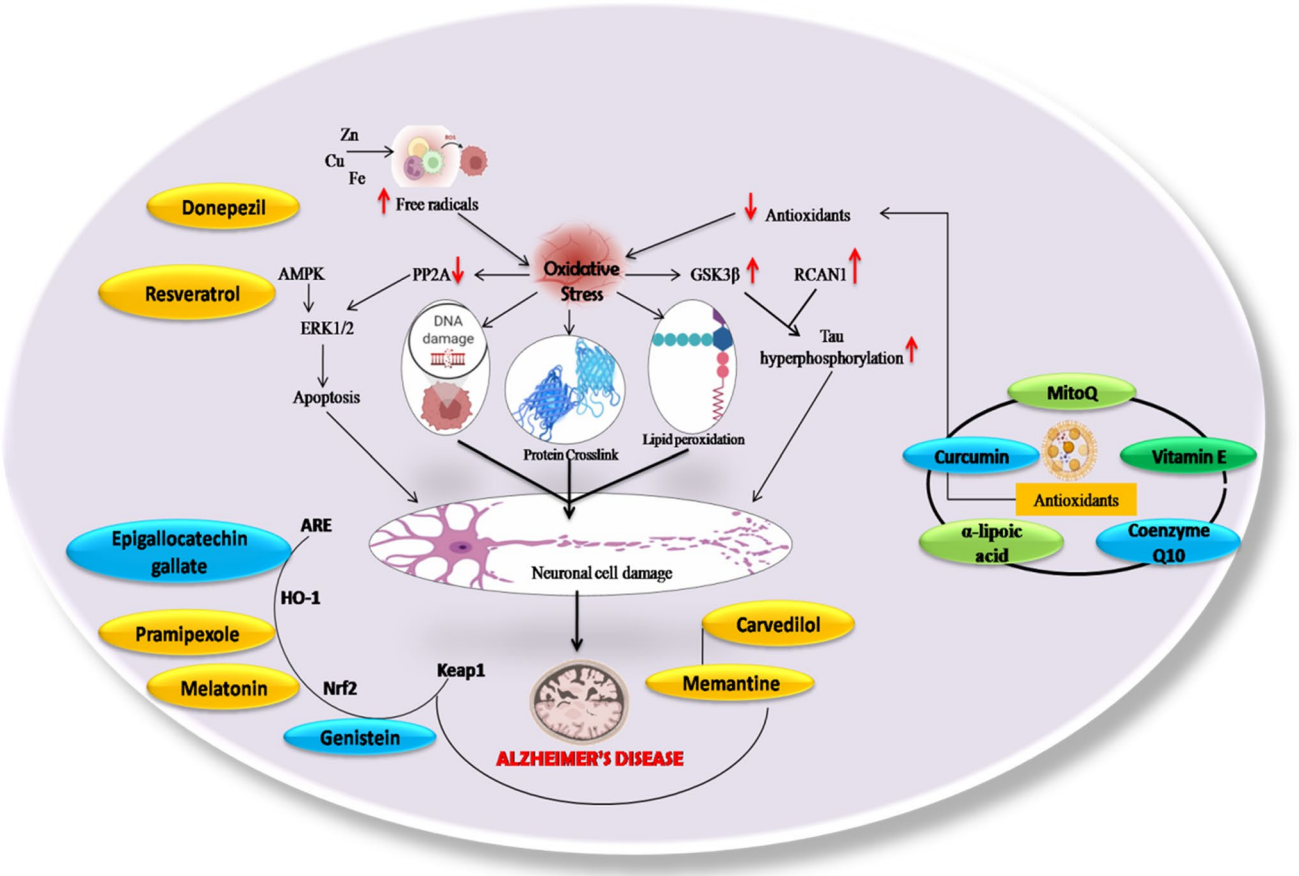


Fig. 4 Therapeutic implications to combat oxidative stress in AD. Figure shows that the antioxidants like Vitamin E, Mito Q, curcumin, etc. reduce the generation of FRs from various sources and along with the reduction in the generation of FRs antioxidant system is also stimulated with the help of various drugs preventing the damage induced by oxidative stress conditions. Further drugs like pramipexole, memantine, melatonin and carvedilol promote activation of Nrf2/HO-1 pathway and epigallocatechin gallate and genistein activate Nrf2/ARE and Keap1 pathway respectively. Donepezil and resveratrol can be seen activating AMP activated protein kinase (AMPK) pathway. These all ultimately lead to the attenuation of oxidative stress condition and ameliorate AD pathogenesis

expression which is implicated in reducing neurogenesis thus promotes neuronal growth and survival [88]. Carvedilol activates the Nrf2/ARE pathway and increases the levels of heme oxygenase-1(HO-1) and NAD(P)H quinone oxidoreductase-1(NQO-1) in HT22 cells alleviating oxidative stress [89].

Donepezil

Donepezil is in phase III for evaluating its therapeutic potential by diagnosing cognitive functions in AD patients. The study has a double-blind, randomized, and parallel assignment design. In murine macrophages cell line RAW 264.7, it was seen that donepezil suppresses NF κB. Similarly, in cuprizone induced mouse model donepezil was found to promote remyelination of neurons [90]. It is a piperidine derivative which reversibly inhibits acetylcholinesterase enzyme which is responsible for hydrolysis of acetylcholine. Thus, it also improves cholinergic transmission in neurons by increasing acetylcholine levels [91]. Donepezil has also been found to activate AMPK and modulate other downstream pathways to mitigate oxidative stress conditions [92].

Memantine

Memantine is in phase III clinical trials to determine the effectiveness and safety for the management of Alzheimer's disease. Randomized quadruple masking and factorial assignment make up the study design. There are 613 participants altogether enrolled for the study. Memantine blocks NMDA, a glutamate receptors sub-family, which has very important role in the functioning of brain [93]. Recently, memantine has been shown to mitigate oxidative stress condition via activation of BDNF/TrkB signaling in human umbilical vascular endothelial cells (HUVECs) [94]. It has also been reported that memantine reduces oxidative stress directly or indirectly via activation of Nrf2 pathway in SHSY5Y cells [95].

Melatonin

Melatonin is in phase III clinical trial with the objective of treatment of AD. Melatonin is a pineal hormone and is an inhibitor of β and γ secretase enzymes and increases the activity of α secretase thus reducing amyloidogenesis. If AD is detected in early stages melatonin is highly efficient drug inducing neuroprotection [96]. It has been reported to directly scavenge ROS along with activation of Nrf2/HO-1 pathway and attenuating oxidative stress. The levels of antioxidants including catalase, superoxide dismutase and glutathione peroxidase were found to be elevated upon melatonin treatment [97].

Pramipexole

Pramipexole is in phase II study for evaluating the effectiveness and safety in Alzheimer's disease patients. The design of the study is open label with single group assignment model. Actual enrollment is of 20 participants. Preclinical studies in APPswe/PS1dE9 mice models showed that pramipexole, a dopamine agonist has a potent neuroprotective role as it prevents neurodegeneration [98]. It is a dopamine agonist which functions as a free radical scavenger that mitigates oxidative stress in the mitochondria and prevents its dysfunction exhibiting neuroprotective effect [99]. Pramipexole acts via attenuating oxidative stress condition by activating Nrf2/HO-1 pathway and treatment with it elevated IL10 generation and improved cognitive functions in rats [100]. It also activates CREB pathway and subsequently reduces over-expressed RCAN1 levels [101].

Resveratrol

Resveratrol is in phase II clinical trials to determine the effectiveness of resveratrol supplement in the prevention of Alzheimer's disease progression. The study design is randomized and single centered. It is a study with quadruple masking and parallel group assignment model. Actual enrollment is of 119 participants. Preclinical studies were conducted in Tg19959 transgenic AD mice model and APP/PS1 transgenic mice model which resulted in reduced tau pathology by increasing the activity of AMPK and reduced oxidative stress [102]. Resveratrol further inhibits the phosphoinositide-3 kinase (PI3K)/AKT pathway and promotes neuronal survival [103]. It also stimulates PP2A activation and promotes tau dephosphorylation [104].

Etanercept

This study design is open label with crossover assignment model and randomized allocation. The study is in Phase I of clinical trials for effectiveness and safety measurements of etanercept in AD patients. 12 participants are enrolled for this study. Studies in AD mouse model have shown that there is decreased level of TNF-α in brain. TNF-α is responsible for the production of ROS via NADPH oxidase. Upon administration of etanercept cognitive function was found to be improved [105, 106]. It is an anti-TNF-α drug efficient in reducing cognitive defects in AD patients [107, 108]. It was found to reduce oxidative stress, suggested by decreased malondialdehyde level and increased anti-oxidants level including superoxide dismutase and glutathione peroxidase [109].

Epigallocatechin-gallate (EGCG)

The goal of the study is to assess beneficial effects of EGCG in the early stages of Alzheimer's disease. There are 200 people enrolled in the trial, which has a randomized, double-blind, and crossover assignment design. EGCG attaches to FRs and neutralizes them because it contains hydroxyl groups. It also modulates the pro-apoptotic proteins Bax and Bad and regulates mitochondrial permeability [110]. EGCG was found to activate Nrf2/ARE and modulate Nrf2/KEAP1 signaling pathway alleviating oxidative stress resulting in neuroprotection [111].

Genistein

The study has randomized, parallel assignment, quadruple masking study design. There are 27 people enrolled in the study. Experiments on streptozotocin induced rat models showed that genistein induces autophagy and promotes Aβ clearance [112]. Genistein hinders the activity of kinases including cAMP-dependent protein kinase, protein kinase C and phosphorylase kinase [113]. Genistein promotes neuronal cell survival by attenuating oxidative stress via activation of PI3K/Akt/Nrf2/Keap1 pathway and decreased malondialdehyde and lactate dehydrogenase levels [114]. The cAMP/CREB-BDNF-TrkB signaling pathway was activated by the effective upregulation of cAMP levels and the phosphorylation of CREB and TrkB upon genistein treatment. It is also a potent regulator of PI3K/Akt signaling [115].

Conclusion

Alzheimer's disease is a highly progressive neurodegenerative disorder affecting the memory and cognitive functions. Existing drugs only target the symptoms and are involved in improving the longevity of life of the AD patients. Due to lack of proper evidences for the cause of the disease complete cure is still on the way. Recent findings have shown that oxidative stress has major role in the pathogenesis of the disease. Oxidative stress via different mechanisms damages the neurons and alters the signal transduction process contributing to AD. Peroxidation of lipids present in the brain, cross-linking of various proteins and damage to the nucleic acids cause neuronal cell death. Dysregulation of signaling pathways like Nrf2, PP2A, RCAN1 and CREB are involved in the disease progression. Natural antioxidants like polyphenolic compounds either reduce the generation of reactive oxygen species or enhance the release of antioxidants, thus prevent oxidative stress induced damage. Potent anti-oxidants are Vitamin E, Curcumin, α lipoic acid, Mito Q, Coenzyme Q10 and epigallocatechin gallate. α-lipoic acid acts as free radical scavenger and reduce hydrogen peroxide or iron induced pathologies of AD by inhibiting ferroptosis. Ferroptosis leads to cell death by stimulating lipid peroxides in the presence of iron. Mitochondrial respiratory chain is also a major producer of FRs due to dysfunction of mitochondria. Therefore, drugs like Mito Q target mitochondria for reduction of free radical generation. TNF α is major stimulator of cytokines and various other inflammatory mediators resulting in abnormal cleavage of APP. Along with this, it also stimulates the production of ROS via NADPH oxidase dependent pathway. Drugs like etanercept inhibit TNF-α activity and reduce oxidative stress and elevate the levels of antioxidants. Various drugs directly or indirectly contributing in the reduction of oxidative stress are under various phases of clinical trials. Pramipexole, memantine, carvedilol and melatonin target Nrf2/HO-1 pathway. Pramipexole also reduces the overexpression of RCAN1 and attenuates oxidative stress. Further, epigallocatechin gallate and genistein activate NRF2/ARE/Keap1 and modulate CREB signaling contributing in the management of oxidative stress. Donepezil and resveratrol have been found to activate AMPK pathway promoting neuronal growth and survival. Thus, targeting oxidative stress is the major choice for developing therapeutics against Alzheimer's disease.

Author contributions DHKR and SKS designed the manuscript. RD wrote the manuscript and prepared the illustrated figures, SKB and PS wrote the manuscript and prepared tables. DHKR. and SKS revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All persons designated as authors qualify for author-ship, and all those who qualify for authorship are listed.

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Data availability Not applicable.

Declarations

Competing interest The authors declare no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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