

# Amyloid Beta ( $A\beta$ ) and Oxidative Stress: Progression of Alzheimer's Disease



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## Abstract

Alzheimer's Disease (AD) is a complex neurodegenerative disease where aged brain considered as a pot player which supplies the machineries for formulating this disease. Amyloid beta ( $A\beta$ ) and oxidative stress are the key contributing factors for the progression of AD.  $A\beta$  can perform both neuroprotective and neurodegenerative role and oxidative stress reflects pathophysiological change associated with AD. Additionally, glycogen synthase kinase 3 $\beta$  (Gsk3 $\beta$ ) and cyclin dependent kinase 5 (Cdk5) are persist in  $A\beta$  and oxidative stress induced pathogenesis of AD. In this review, we focused on the condition in which  $A\beta$  stimulates the progression of AD preterming the neuroprotective activity. We also pay attention on the different mechanism of oxidative stress in the pathogenesis of AD. It has been found that, there is a direct relationship between  $A\beta$  and oxidative stress where Gsk3 $\beta$  and Cdk5 play the central role. This review reveals the convincing effect of trolox in the possible treatment of AD. Conversely, the damage of Blood Brain Barrier (BBB) is found to have an association with AD but the mechanism still unknown. Finally, this review provides insight into the molecular mechanism for the development of AD which might be helpful for therapeutic direction towards this disease.

**Keywords:** Amyloid beta; Oxidative stress; Senile plaque; Glycogen synthase kinase; Trolox

**Abbreviations:** BBB: Blood Brain Barrier; AD: Alzheimer's Disease; GSK: Glycogen Synthase Kinase; CDK: Cyclin Dependent Kinase; APP: Amyloid Precursor Protein; ER: Endoplasmic Reticulum; PI3K: Phosphatidylinositol 3 Kinase; MAPK: Mitogen Activated Protein Kinase; IDE: Insulin-Degrading Enzyme; ACE1: Angiotensin 1 Converting Enzyme; HNE: Hydroxynonenal; LRP: Lipoprotein Receptor-Related Protein; ApoE: Apolipoprotein E; MDR: Multidrug Resistance; LTP: Long-Term Potential; ISF: Interstitial Fluid; CRD: Cysteine Rich Domain; Fz: Frizzled; SF: Straight Fragment; MCI: Mild Cognitive Impairment; MDA: Malondialdehyde; NFT: Neurofibrillary Tangle; JNK: Jun N-Terminal Kinase; SOD: Superoxide Dismutase

## Introduction

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder that has a devastating effect on elderly people which brings about multifactorial pathological changes in brain [1]. It is clinically differentiated by a gradual loss of memory and cognitive functions where episodic memory is affected first [2] followed by executive functions, semantic memory, language and spatial orientation skill deterioration [3]. Around 44.4 million of people throughout the world who are living above 65 years are suffering from dementia and 70 percent of them are Alzheimer patients. It will probably cross 135 million by 2050 [4-5]. Moreover, approximately 5.2 million peoples in America and 59% people in Asia whose age is over 65 are affecting by this disease [6-7]. However, the mystery behind the understanding of its cellular, molecular and pathological initiation and development are not clear. Senile plaques and neurofibrillary tangles are two most common principles for AD progression where Amyloid beta ( $A\beta$ ) and oxidative stress are two common reasoning factors for these two phenomena

[8-9]. Amyloid beta ( $A\beta$ ) is a derivative product of Amyloid precursor protein (APP) [10]. The proteolytic cleavage of the amyloid precursor protein (APP) produces  $\beta$ -peptide ( $A\beta$ ) which is oligomerized to form senile plaques [11] that ultimately progress the Alzheimer's Disease. In addition,  $A\beta$  causes the hyperphosphorylation of tau through activation of glycogen synthase kinase 3 $\beta$  (Gsk3 $\beta$ ) and cyclin dependent kinase 5 (Cdk5) which accelerate the neurofibrillary tangle [12].

On the other hand, Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates [13]. It has been 3 increasingly recognized as a contributing factor in various forms of pathophysiology like oxidation of macromolecule, hyper phosphorylating tau proteins during the procession of Alzheimer's Disease [14,15]. These two contributories are frequently occurring in the aged brain cell. Although there are commonalities exist between them, but the exact relationship between them remains elucidate.

Finally, numerous causes have been revealed towards the formation of AD. However, the precise treatment is still unrevealed. Many scientists claimed that antioxidant may be a good strategy to slow or reverse the progression of AD [16-18]. From this view trolox is a useful antioxidant to combat AD [19]. But the mechanism remains unmask. Therefore, the objective of this review is to accumulate the knowledge of A $\beta$  and oxidative stress underlying their mechanism towards the Alzheimer's Disease and build up a relationship between these two phenomena to reach the possible target for therapy. We also study the possible mode of action of trolox for strategic treatment of Alzheimer's Disease.

### Role of Amyloid Beta

The most significant pathological feature that promotes Alzheimer's Disease (AD) is the characterization of Amyloid Beta (A $\beta$ ) which is derived from Amyloid precursor protein (APP) [10]. The aggregation of this peptide precedes neuronal plaque causes synaptic dysfunction, neural loss and atrophy within temporoparietal and hippocampal regions that leads to the Alzheimer's Disease [20].

### APP protein family

Amyloid precursor protein is a type 1 integral membrane glycoprotein synthesize from 'APP' gene available in human chromosome [21]. It is synthesized in the endoplasmic reticulum (ER) but the highest concentration is found in the trans-Golgi-network (TGN) [22]. Three major isoforms are identified in human from alternative splicing; APP695, APP751 and APP770. APP695 is highly expressed in neurons which lack the KPI domain [23]. The orthologs of APP have been found in other species like *Drosophila*, *C. elegans*, Zebra fish, Puffer fish, *Xenopus Laevis*, but they are evolutionary conserved in their sequence. Three APP homologs, namely APP (APP like protein 1 (APLP1) and 2 (APLP2) are found in mammals (human) [24], while in *Drosophila* Appl (fly), and in *C. elegans* apl<sup>-1</sup> (worm) [25] are namely found. But all are processed in similar fashion in the cytoplasm.

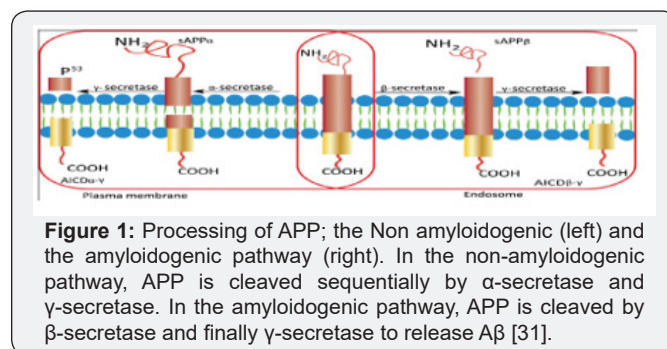
The physiological function of APP is still unclear. It is believed to play significant role in neurite outgrowth and synaptogenesis, cell adhesion, neuronal protein trafficking along the axon, transmembrane signal transduction, calcium metabolism [26].

### A $\beta$ is a derivative product of APP

APP is abundantly expressed in a variety of tissues and its processing is a normal event in nearly all neural and non-neural cells [26]. The proteolysis of APP mainly occurs at the cell surface or in the endosomal membrane system. The sequential cleavage of APP governed by three secretase enzymes called  $\alpha$ ,  $\beta$  and  $\gamma$  secretase. All the 4

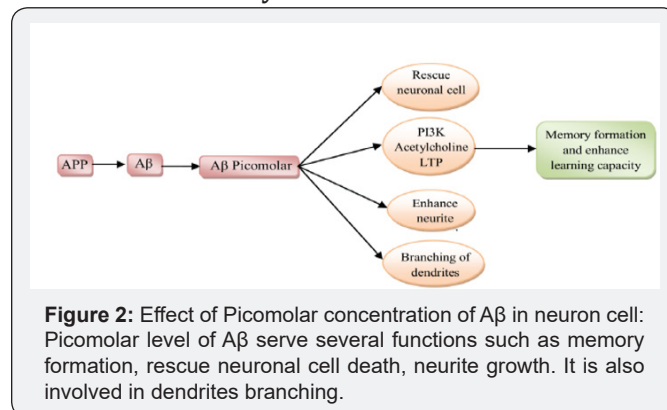
three enzymes are type-I transmembrane proteins and found different region of cell. The entire processing of APP is mediated by two discrete pathways; the non-amyloidogenic pathway

and amyloidogenic pathway (Figure 1). Like other integral membrane proteins APP is transported to the cell surface via the secretory pathway after synthesis [27]. It is cleaved by  $\alpha$ -secretase resulting soluble form of APP (sAPP $\alpha$ ) and a membrane-bound C83 ( $\alpha$ -CTF) fragment [28]. C83 is further cleaved by  $\gamma$ -secretase resulting APP intracellular domain  $\alpha$ - $\gamma$  (AICD  $\alpha$ - $\gamma$ ) and p3 peptide fragments [29]. This is known as the non-amyloidogenic pathway. Conversely, amyloidogenic pathway occurs in the endosome where APP can be re-internalized via endocytic pathway [30]. In endosome,  $\beta$ -secretases cleave the APP to produce a soluble  $\beta$  fragment of APP (sAPP $\beta$ ) and a (CTF) fragment, called C99 ( $\beta$ -CTF) (Figure 1). The C99 fragment then becomes a direct substrate for  $\gamma$ -secretase resulting APP intracellular domain  $\beta$ - $\gamma$  (AICD  $\beta$ - $\gamma$ ) and the A $\beta$  peptide [10]. The activity of  $\beta$ -secretase increases with aging, infection stress etc. A $\beta$  may be of different sizes (38 to 43 amino acid), but the most common isoforms are A $\beta$ -40 and A $\beta$ -42. Healthy neurons are found to secrete A $\beta$ -40 yet may be toxic [31]. However, the A $\beta$ -42 isoform is more toxic peptide. They are insoluble and aggregated into amyloid plaques which result neuronal cytotoxicity and promotes neuropathological effect leading to neurodegeneration of the brain [32].



**Figure 1:** Processing of APP; the Non amyloidogenic pathway (left) and the amyloidogenic pathway (right). In the non-amyloidogenic pathway, APP is cleaved sequentially by  $\alpha$ -secretase and  $\gamma$ -secretase. In the amyloidogenic pathway, APP is cleaved by  $\beta$ -secretase and finally  $\gamma$ -secretase to release A $\beta$  [31].

### Hormesis role of amyloid beta



**Figure 2:** Effect of Picomolar concentration of A $\beta$  in neuron cell: Picomolar level of A $\beta$  serve several functions such as memory formation, rescue neuronal cell death, neurite growth. It is also involved in dendrites branching.

Hormesis refers to a compound that has a beneficial effect in low concentration but shows the toxicological role when applied at a higher concentration. The low doses of A $\beta$  increase neuronal plasticity, hippocampal long-term potentiation and enhance memory [33-34] where excessive A $\beta$  induce neurodegeneration [35]. Picomolar levels of A $\beta$  rescue neuronal cell death by inducing the inhibitors of  $\beta$ -or  $\gamma$ -secretases probably through regulating the potassium ion channel [36]. Moreover, Picomolar

Aβ peptide activates phosphatidylinositol 3 kinase (PI3K) which is important for memory formation while even micromolar concentrations inhibit its function [37] (Figure 2). Aβ also increases mitogen activated protein kinase (MAPK) and the nicotinic acetylcholine receptor that speed up acetylcholine production in the hippocampus [38]. Finally, low doses of amyloid-beta produce presynaptic enhancement governing the branching of dendritic processes and enhance neurotrophic outgrowth [39].

**Role of Aβ in Alzheimer’s disease**

Many evidences have manifested that the overrun of Aβ causes neurodegenerative cascade resulting synaptic dysfunction, neuronal loss. Aβ directly involve of causing two key pathological features of Alzheimer’s Disease; the senile plaque and the intraneuronal fibrillary tangles [11,35].

**Senile plaque formation:** Amyloid beta can either be degraded proteolytically, or they may be cleared from the brain, or they may be accumulated and develop the AD. Enzymes like ACE1 (angiotensin 1 converting enzyme 1), insulin-degrading enzyme (IDE), neprilysin (derived from NEP gene) can significantly degrade Aβ [8]. ACE1 can degrade naturally secreted Aβ in vitro [40] (Figure 3). IDE degrades varieties of substrates e.g., insulin and amylin that tend to adopt β-pleated sheet conformation (Figure 3) [41]. Another Aβ-degrading enzyme NEP found on chromosome 3 (in the region of 3q25) neprilysin but its action is unclear as, yet its full genome screens is not published [42]. In case of aged brain, a decrease amount of neprilysin enzyme have been found [43]. Oxidatively modified neprilysin in the form of 4-hydroxynonenal (HNE)-protein accumulates in AD brain.

affinity soluble forms of Aβ especially to Aβ42 [44]. Additionally, P-glycoprotein (P-gp) is a 170-kD protein product of the multidrug resistance-1 (MDR1) gene which is highly expressed on the luminal surface of brain capillary endothelial cells. It accelerates the transportation of Aβ through BBB. Mice without P-gp have decreased amyloid-beta efflux result an increase in brain amyloid beta [45].

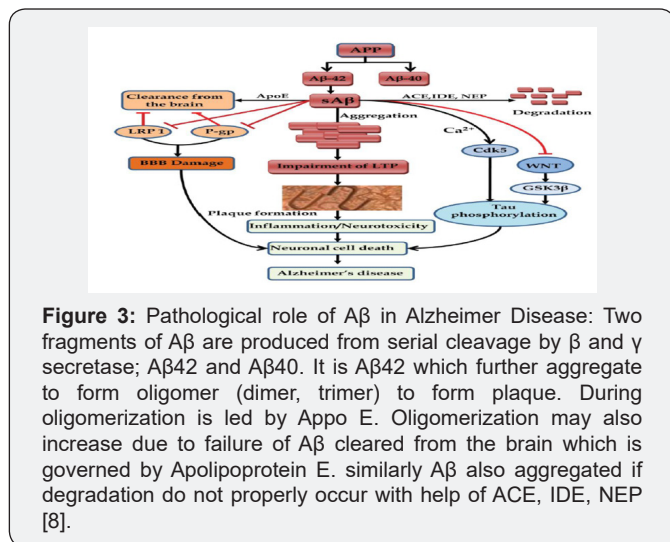
Despite these, Aβ started to accumulate where Aβ42 play key role. It aggregates rapidly into two different shapes, Non-fibrillar non-β sheet and the fibrillar β sheet. The fibrillar β-sheet is more cytotoxic and finally deposits into plaques [46]. The accumulation of Aβ is influenced by Apolipoprotein E (ApoE) with the help of ApoE, Cu, Zn etc. [47] (Figure 3). Aβ accumulation also increased due to failure of clearance from the brain. Moreover, increase amount of β secretase and destruction of neurolysis have found highly expressed in adult brain due to myelin breakdown that facilitate the over production of Aβ [43,48]. The formation of senile plaque starts with oligomers like dimers and trimers that damage of long-term potential (LTP) (Figure 3). Aβ oligomers can further aggregate into fibrils, which finally developed into senile plaques.

Senile plaque progresses slowly in the neocortex and continues through the allocortex that finally to the brainstem nuclei and the cerebellum [49]. These plaques are deadly to the surrounding brain parenchyma, which results several phenomena including swollen neurite, dystrophic morphologies phosphorylation of tau and multiple cellular components which altogether disrupted cellular transport [50]. The trajectories of axons and dendrites are interrupted due to amyloid plaques and cause negative impact on synaptic integration of signal [51]. There appear gliosis and related oxidative stress around plaques, which can also lead to synaptic changes that causes the death of neuronal cell [52].

Amyloid beta induced hyperphosphorylated tau: Tau is a microtubule associated protein which is found in chromosome 17 [53]. They stabilize the microtubules by enhancing the assembly and maintenance of their structure. The activity of tau is highly regulated by its degree of phosphorylation which inhibit the ability of tau to promote the assembly of microtubule. AD brains contain 4 to 8-fold more of abnormally phosphorylated tau compared to normal brains [54]. However, glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (Cdk5) are the two key enzymes that accelerate the phosphorylation of tau where Aβ play a crucial role [55].

GSK3β phosphorylates tau is near about 42 sites and 29 of them are found in AD brains [56]. GSK3β activity is regulated by different regulatory proteins in Wingless canonical pathway (Wnt/b-catenin pathway) where Aβ play a significant role. Aβ is naturally released into interstitial fluid (ISF) and involve in down regulation of want to signal either by

- a) Directly interact with the Fz receptor



Aβ can be transported out of the brain through the Blood Brain Barrier to the periphery (Figure 3). The low-density lipoprotein receptor-related protein (LRP1) accelerates the efflux of Aβ from the brain to periphery. LRP1 forms a complex with many ligands like Apolipoprotein E (ApoE), α2-macroglobulin (α2M), and APP [42] to accelerate the process. Aβ can be transported from the brain by directly binding with LRP1 as it has higher

- b) An increase in GSK-3β activity
- c) A decrease in Wnt target gene transcription
- d) Induction of Dkk-1 [57].

A recent report has shown that Aβ bind to the Cysteine rich Domain (CRD) of Frizzled (Fz) close to the wnt binding site [58]. They suggested that Aβ might compete with Wnt ligands for binding to Fz and inhibits downstream signaling via this pathway. Aβ also induces Dkk-1 (a glycoprotein) which is a negative modulator of wnt signaling pathway. The expression of Wnt antagonist Dkk1 is increasingly found in the hippocampus region in AD brain (especially surrounding the Aβ deposition) of transgenic mouse models [59-60].

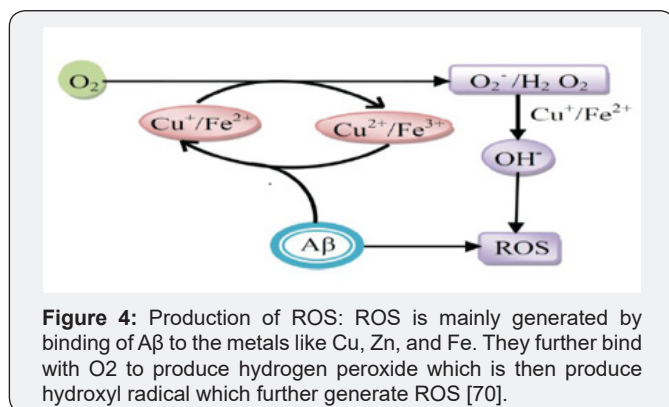
On the other hand, CDK5/p25 complex is the most active form of CDK5 pathway that is found to involve in tau phosphorylation. CDK5 phosphorylates tau at 11 sites, and all these sites are found phosphorylated in AD patients. The proteolysis of p35 to form p25 is governed by Ca<sup>2+</sup>-dependent protease calpain under neurotoxic conditions. sAβ directly promotes increased levels of intracellular Ca<sup>2+</sup> in neurons and causes neuronal injury and apoptosis [11].

After phosphorylation some conformational changes occur in tau. Free taus are rapidly polymerized into neurofibrillary tangle

**Table 1:** Role of oxidative stress in different neurodegenerative disease.

Disease Name	Affected brain region	Disease causing Agent	Mode of action	Reference
Alzheimer's Disease	hippocampus and cortex	Oxidative stress	Activation of macromolecule, glial cell & tau phosphorylation	[64]
Parkinson's Disease	substantia nigra and the basal ganglia	Oxidative stress	Lipid peroxidation & mutation in α-synuclein	[65]
Huntington's Disease	caudate nucleus, putamen, and globus pallidus	Oxidative stress	Lipid peroxidation	[66]
Amyotrophic Lateral Sclerosis	upper and lower motor	Oxidative stress	SOD1 activation, inflammation	[67]

**Generation of oxidative stress**



The key step of oxidative stress is the generation of reactive oxygen species (ROS) that disturbs the normal functioning of cell [13]. They are generated continuously in cells because of oxidative biochemical reactions which produce unstable cytotoxic molecules known as free radicals under physiological conditions. In fact, several types of free radicals depending on

via aggregation of PHF with the mixture of straight fragment (SF) even they do not require any co-factor [61]. Neurofibrillary tangles may impair axoplasmic flow and lead to slow progressive retrograde degeneration and loss of connectivity of the affected neurons [54] and causes cell death and ultimately Alzheimer's Disease. A recent report has manifested that expression of wild-type human tau knockout in mice results cognitive impairment and alterations in synaptic transmission [62].

**Oxidative Stress**

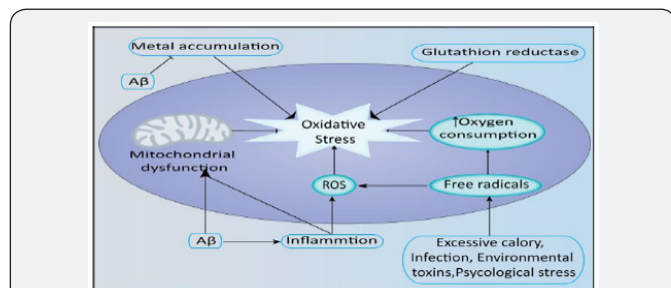
Human brain contains only 2% of the body weight, but it takes up to 20% oxygen supplied by the respiratory system therefore, more sensitive to oxidative stress as compared to other organs. The high levels of oxidative stress can cause necrosis, ATP depletion, apoptosis, resulting various disease like cancer, diabetes and especially neurodegenerative disease. Interestingly, oxidative stress is eminent biochemical phenomenon in almost all types of neurodegenerative diseases like Parkinson Disease, amyotrophic lateral sclerosis, and Huntington Disease [63]. But they are region specific for a disease (Table 1). A recent study found that oxidative stress (and neuronal damage) occurs in hippocampus and cortex region of AD affected brain, but not in the cerebellum, midbrain, or pons (Table 1) [64-67].

their structure involve in the neurodegenerative disease like superoxide anion (O<sub>2</sub><sup>-</sup>), hydroxyl radical (HO<sup>-</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) [68]. In AD brain ROS are produced by the interactions between Aβ and metals such as Cu and Fe etc. (Figure 4). Additionally, diverse physiological and pathological processes such as aging, excessive caloric intake, infections, inflammatory states, environmental toxins, certain drugs, emotional or psychological stress, tobacco smoke, ionizing radiation, alcohol or unbalanced nutrition causes ROS in brain cell (Figure 5) [69].

However oxidative stress is produced by ROS due to the dysfunction of mitochondria, metal accumulation, inflammation, and β-amyloid (Aβ) accumulation [14,70].

**Mitochondrial dysfunction:** The mitochondria are much more sensitive for oxidative stress. Cytochrome oxidase is the key enzymes for electron transport in turn deficiency of which generate ROS as a result of energy reduce in brain [71]. Aβ shakes up the electron transport chain by shrinking the

activities of key enzymes Cytochrome oxidase (Figure 5) and interrupts mitochondrial dynamics [72]. Soluble A $\beta$  interacts with increased hydrogen peroxide levels and decreased activity of cytochrome c oxidase in Tg2576 mice, prior to the appearance of A $\beta$  plaques [73].



**Figure 5:** Production of oxidative stress: The schematic shows how oxidative stress produced can be induced by the mitochondrial dysfunction, metal malmetabolism, and inflammation and A $\beta$  accumulation. Furthermore some exogenous also cause oxidative stress [14].

**Metal accumulation:** Severe histopathological changes are observed in AD patients near the hippocampus region of brain due to increase of abnormal copper, zinc, and iron. These metals interact directly with A $\beta$  to induce oxidative stress [74]. A $\beta$  binds Cu<sup>2+</sup> (Figure 4) and transferred an electron to Cu<sup>2+</sup> which produce Cu<sup>+</sup> and A $\beta$  radical (A $\beta$ +•). Additionally, Cu<sup>+</sup> can donate two electrons to oxygen to generate H<sub>2</sub>O<sub>2</sub> [75]. Moreover, Iron accumulation is also found in cells related to neuritic plaques in AD which binds to A $\beta$  and causes the reduction of Fe<sup>3+</sup> to Fe<sup>2+</sup> and H<sub>2</sub>O<sub>2</sub> in a similar fashion of copper-A $\beta$  interaction (Figure 4) [76].

**Inflammation**

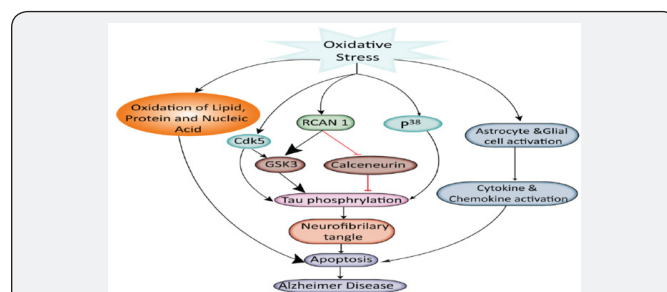
Cytokines, Chemokines, ROS, and complement proteins are proinflammatory intermediate that are released by both microglia and astrocytes [77]. A $\beta$  attracts and activates both microglia and astrocytes which are involving neuronal death [78].

Furthermore, reduction of various antioxidant enzymes may lead to the production of oxidative stress in our brain [79]. Among them, glutathione reductase lowers the level of glutathione which important for neuron however, causes oxidative stress [80]. Moreover, high oxygen consumption may lead to the oxidative stress by stimulating ROS production (Figure 4) [81].

**Mechanism of oxidative stress in AD:** A $\beta$  causes oxidative damage in surrounding cells through the activation of microglia and astrocytes that activated by multiple ROS pathways such as the kynurenine pathway [82]. Oxidative stress play role in AD pathogenesis by oxidation of macromolecule, glial cell activation tau phosphorylation and A $\beta$  accumulation.

**Oxidation of macromolecule:** Oxidative stress is highly vulnerable to post mitotic cell like brain and affect adversely on various cell and cellular housekeeping macromolecule. Our brain is rich in phospholipids which play a significant role

in neurotransmission, neuronal interactions and cognition. Brain phospholipids gradually decrease with production of free radical which release several reactive aldehydes including 4-hydroxy-2- nonenal (HNE), malondialdehyde (MDA), ketones and hydrocarbons (Figure 6) [83]. They impaired normal metabolism and mild cognitive impairment (MCI) in AD [2]. The oxidation processes also affect proteins especially the cytoskeleton proteins by addition of carbonyl groups (aldehydes or ketones) and nitration which become hydrophobic and resistant to proteolysis and causes accumulation numerous non-functional proteins in neuron and causes cell death [84]. Finally, the oxidation of DNA is governed by 8-hydroxy-2-deoxyguanosine (8-OHdG). 8-OHG seems to stimulate attribute of AD progression like neurofibrillary tangles (NFTs) and A $\beta$  plaques, and specifically occurs before A $\beta$  aggregation in AD patients (Figure 6).



**Figure 6:** Mechanism of oxidative stress in Alzheimer's Disease; the schematic shows how Oxidative stress in turn interacts with A $\beta$  and activates microglia, and astrocytes which release chemokines, cytokines and cause apoptosis of neuronal cell leading AD. On the other hand, oxidative stress can activate RCAN1 which further activates GSK3 $\beta$ , or inhibit the dephosphorylating action of Calcineurin and thus phosphorylate tau which can further polymerized into NFT and result AD. Moreover, oxidative stress is also responsible for A $\beta$  deposition.

**Activation of glial cell:** The Microglial activation occurs early in AD development, prior to neuropil damage, bearing a contributing role of microglia in disease pathology [85]. ROS induces several chemokines and cytokines, which work as inflammatory mediators and finally may cause neuronal damage. Astrocytes are also activated by oxidative stress and A $\beta$ , and hence produce chemokines, cytokines, and ROS that may result in neuronal damage [78].

**Oxidative stress induced tau hyperphosphorylation:** Most of the neuronal loss during neurodegeneration occurs where the levels of oxidative stress and neurofibrillary tangle (NFT) are highest. Oxidative stress play role in tau phosphorylation through the activation of reverse Calcineurin or directly involved in the activation of p-38. Calcineurin is a calcium-dependent serine–threonine protein phosphatase, which dephosphorylates tau protein. Calcineurin is regulated by RCAN1 (a Regulator of Calcineurin 1 gene) formerly known as Adapt78 or DSCR1, which is also strongly expressed in many regions of brain [86]. Chronic over expression of RCAN1 proteins results the inhibition of Calcineurin and accelerate the phosphorylation of Calcineurin specially tau protein [87]. Furthermore, RCAN1 transgene

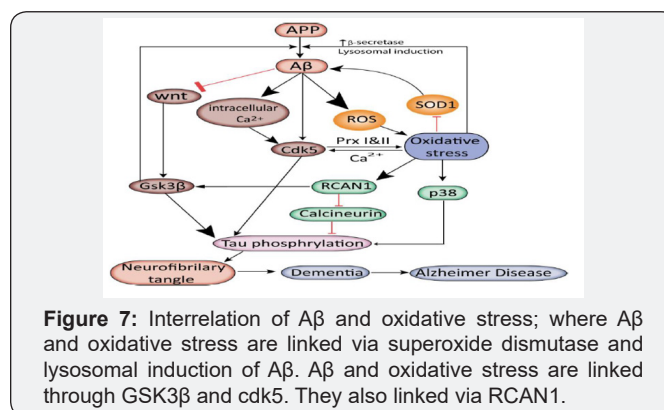
stimulates transcription and translation of the glycogen synthase kinase-3beta (GSK3β) in PC-12 cells [88], which is involve in phosphorylation of tau (Figure 6).

On the other hand, mitogen-activated protein kinases (MAPK) such as p38 found in tau phosphorylation at 21 sites where 15 sites are related to AD pathology patients' brains [89]. P38 also phosphorylates p53 and GSK3β addition to the tau. A recent report showed that oxidative stress induces p38 that leads to the phosphorylation of tau, whereas treatment with antioxidant trolox inhibits the p38 [90]. Oxidative stress also results Ca<sup>2+</sup> release, which eventually activate Cdk5 and other cytoskeletal proteins responsible for phosphorylation of tau [91].

**Oxidative stress induced Aβ deposition:** Faulty antioxidant defense system cause the raising of oxidative stress that significantly increased Aβ deposition. Deletion of cytoplasmic copper/zinc superoxide dismutase (Cu-Zn-SOD, SOD1) in Tg2576 APP-over expressing AD mouse model has been found to increase Aβ oligomerization [92]. Oxidative stress also decreases the activity of α-secretase and increase the expression and activation of β-secretase and γ-secretase which are critical for the generation of Aβ from APP [93-94] through c-Jun N-terminal kinase (JNK) pathway.

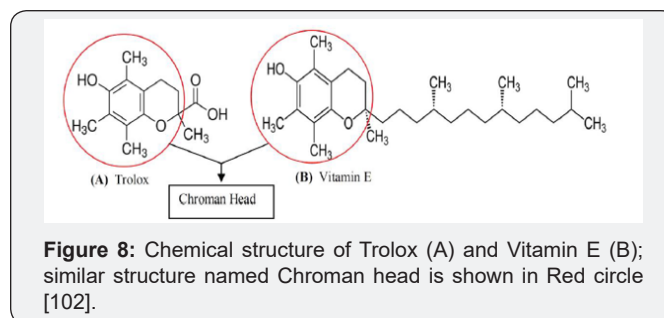
### Interrelation of Aβ and Oxidative Stress

Aβ and oxidative stress accelerate the progression of Alzheimer's Disease in numerous ways. But there is a convincing molecular relationship among them that may affect the progression and severity of AD. Aβ binds with metals and other factors that are responsible for oxidative stress via free radical. However, the relationship between Aβ and oxidative stress is not unipolar. β-amyloid also destabilizes lysosomal membranes that enhance Aβ production, [95]. Amyloid beta and oxidative stress may be linked via superoxide dismutase (SOD) which is available on chromosome 21 along with APP gene [96]. Interestingly Aβ and oxidative stress accelerate AD through the common pathway. Both stimulate the phosphorylation of tau [90]. Aβ can activate GK3β through want signaling pathway which is a major tau protein kinase causing hyperphosphorylation of tau. Furthermore, GSK3β can alternatively involve in the processing of APP to produce Aβ by activating the β-secretase and γ-secretase (Figure 7) [97,98]. On the other hand, Aβ can activate cdk5 which stimulates the tau phosphorylation by increasing the intracellular Ca<sup>2+</sup> [99]. Alternatively, Cdk5 can activate β-secretase that demonstrates the increase of Aβ production and its accumulation in the cell body and neurites [100]. Oxidative stress induces RCAN1 that can activate GSK3β (Figure 7) and causes Aβ [87] and tau pathogenesis. Furthermore, Aβ activates cdk5 which may induce oxidative stress by generation of ROS. Cdk5 phosphorylates. Peroxiredoxin-I (Prx-I) and peroxiredoxin-II (Prx-II) and lessen the enzymatic activities which leads to the accumulation of ROS within the cells [101,102].



**Figure 7:** Interrelation of Aβ and oxidative stress; where Aβ and oxidative stress are linked via superoxide dismutase and lysosomal induction of Aβ. Aβ and oxidative stress are linked through GSK3β and cdk5. They also linked via RCAN1.

### Possible Treatment with Trolox



**Figure 8:** Chemical structure of Trolox (A) and Vitamin E (B); similar structure named Chroman head is shown in Red circle [102].

Although vitamin E and trolox both shows the antioxidant activity, trolox has some advantage over vitamin E. Vitamin E is only lipid soluble but trolox can penetrate both water and lipid [103]. Vitamin E causes serious side effect and brings conformational changes in some functional protein that increase mortality in AD brain [104]. Although, many scientists claimed that trolox has the antioxidant and the protective activity against neurodegenerative and cerebrovascular diseases. But the mechanisms underlying these effects remain unclear. Therefore, researchers pay interest on trolox underlying its protective effect on Alzheimer's Disease.

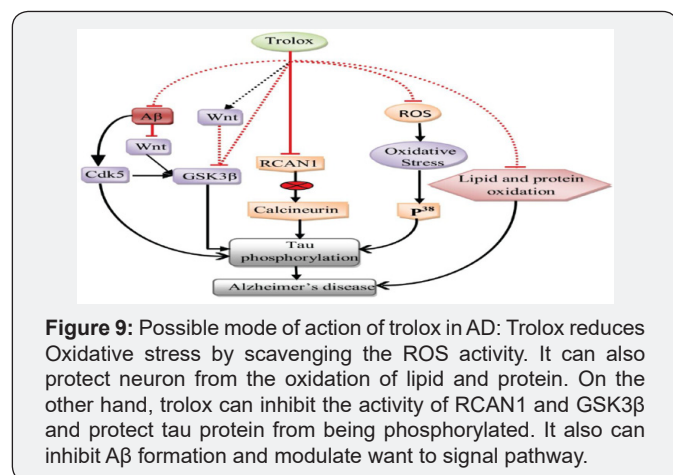
### Effect of trolox on oxidative stress

Trolox mainly combat with oxidative stress in AD patient in several ways. Trolox play the protective role against H<sub>2</sub>O<sub>2</sub> induced neurotoxicity either by

- i. Change in cellular uptake of H<sub>2</sub>O<sub>2</sub> or in vitro scavenging activity,
- ii. Induction of antioxidant enzymes (glutathione peroxidase, catalase) or
- iii. Direct scavenging activity of Trolox [19].

Human keratinocytes treatment with Trolox was also found to decrease the intracellular H<sub>2</sub>O<sub>2</sub> generation in a dose-dependent manner [105]. Carbonyl group is a major biomarker of protein oxidation. Pre-treatment with trolox decrease protein oxidation scavenging H<sub>2</sub>O<sub>2</sub> in *S. pombe* cell when assayed with

protein carbonyl [19]. Trolox can also protect neuronal protein from oxidative stress by increasing the activity 20S proteasome (Figure 9). On the other hand, Trolox is found in the aqueous phase and partly in the lipid phase of phospholipid membrane system where it diffuses into the bilayer phase and traps two peroxy radicals per molecule when oxidation is initiated in the lipid phase [102]. It donates hydrogen from the hydroxyl group to peroxy radical (ROO•) converting it into a lipid hydroperoxide and Trolox radical and thus terminating the chain reaction [106]. The activation of p38 and RCAN1 by oxidative stress can be inhibited by co-incubation with trolox [90].



### Effect of trolox on Aβ induced toxicity

Since Aβ play a major role during the initiation and progression of AD, it can be attenuated by the induction of trolox. Decrease in cell viability was partially prevented by the presence of Trolox when hippocampal neurons disputed with Aβ were pretreated with Trolox. Co-incubation of Aβ with trolox prevented 70% of the apoptotic neuronal population [107].

Moreover, Trolox can reduce the activity of GSK-3β and help in the stabilization of β-catenin (Figure 9). The radioactive labeling on GS-2 correlates with the GSK-3β activity by phosphorylating the Tyr-216 residue by decreasing the phosphorylation of P-Ser-9 residue, which down-regulates GSK-3β [108]. Neurons pretreated with trolox showed a significant decrease in the activity of GSK-3β by incorporating 32P on GS-2 and accelerates P-Ser-9 production [18]. Furthermore, trolox induces a modest increase in the Wnt-7a and Wnt-5A mRNA levels [109].

### Conclusion

This review has set out the emphasis that Alzheimer's Disease is heterogeneous events where multiple factors ranging from Aβ to oxidative stress mechanism are regulating the complex process. One of the key finding is that the excessive form of Aβ (not low dose of Aβ) stimulates the progression of Alzheimer's Disease. So, it would not be a better idea to disrupt Aβ to terminate AD rather than to lower the concentration. On the other hand, oxidative stress completes a vicious pathological

cycle with Aβ accumulation, tau phosphorylation which is regulated by mitochondrial dysfunction, metal toxicity etc. We also combine the amyloid beta hypothesis and oxidative stress hypothesis where Aβ and oxidative stress are linked to the hyperphosphorylation of tau. This allows that either dysregulation of Aβ or balancing of oxygen uptake in brain may helpful for Alzheimer's patient. Moreover, GSK3β and Cdk5 is the central point where Aβ, oxidative stress and tau meet alternatively in the disease progression. So, GSK3β and Cdk5 may also be a target for therapeutic purpose. We also investigate the positive effect of trolox over Alzheimer's Disease. It shows greater beneficial effect on both Aβ and oxidative stress. It also suppresses the activity of GSK3β by phosphorylating Ser-9. These evidences emphasis that trolox may be therapeutic approach to combat against Alzheimer's Disease.

Until recently many evidences have been elucidated about the role of Aβ and oxidative stress in Alzheimer's Disease. However still some question remains unsolved. The exact mechanism of BBB damage in Alzheimer's Disease is still unclear. The fate of Aβ after clearance from brain remains unmask? The exact mechanism of lipid per oxidation, protein and nucleic acid oxidation that progress the AD pathogenesis is still to be elucidated. From this review we observed that tau pathology occurs mainly downstream to the Aβ pathology and oxidative stress. This may arise a question whether tau gene play role in tau pathology or not? Finally, trolox is water soluble. The cell membrane may be a barrier to the transportation of trolox. So, the truncation of trolox into the cell may be further research of interest.

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### References

1. Blennow K, de Leon MJ, Zetterberg H (2006) Alzheimer's disease. *Lancet* 368(9533): 387-403.
2. Butterfield DA, Reed T, Perluigi M, De Marco C, Coccia R, et al. (2006) Elevated protein-bound levels of the lipid peroxidation product, 4-hydroxy-2-nonenal, in brain from persons with mild cognitive impairment. *Neurosci Lett* 397(3): 170-173.
3. Ralph MAL, Patterson K, Graham N, Dawson K, Hodges JR (2003) Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer's disease: a cross-sectional and longitudinal study of 55cases. *Brain* 126(Pt 11): 2350-2362.
4. (2013) Alzheimer's disease International. Dementia statistics.
5. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, et al. (2010) Decreased clearance of CNS beta amyloid in Alzheimer's disease. *Science* 330(6012): 1774.
6. (2014) Alzheimer's disease facts and figures. *Alzheimers Dement* 10(2): 47-92.
7. Bonda DJ, Wang X, Lee HG, Smith MA, Perry G, et al. (2014) Neuronal failure in Alzheimer's disease: a view through the oxidative stress looking-glass. *Neurosci Bull* 30(2): 243-252.

8. Bertram L, Tanzi RE (2008) Thirty years of Alzheimer's disease genetics: Systematic meta-analyses herald a new era. *Nat Rev Neurosci* 9(10): 768-778.
9. Zhao Y, Zhao B (2013) Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxid Med Cell Longev* 2013: 316523.
10. De Strooper B, Vassar R, Golde T (2010) The secretases: enzymes with therapeutic potential in Alzheimer disease. *Nat Rev Neurol* 6(2): 99-107.
11. Mattson MP (2004) Pathways Towards and Away from Alzheimer's Disease. *Nature* 430(7000): 631-639.
12. Iqbal K, del A, Alonso C, Chen S, Chohan CO, et al. (2005) Tau pathology in Alzheimer disease and other tauopathies. *Biochimica et Biophysica Acta* 1739(2-3): 198-210.
13. Chong ZZ, Li F, Maiese K (2005) Stress in the brain: novel cellular mechanisms of injury linked to Alzheimer's disease, *Brain Res. Brain Res Rev* 49(1): 1-21.
14. Chen Z, Zhong C (2014) Oxidative stress in Alzheimer's disease. *Neurosci Bull* 30(2): 271-281.
15. Mohsenzadegan M, Mirshafiey A (2012) The Immunopathogenic Role of Reactive Oxygen Species in Alzheimer Disease. *Iran J Allergy Asthma Immunol* 11(3): 203-216.
16. Feng Y, Wang X (2012) Antioxidant Therapies for Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity* 17.
17. Pratico D (2008) Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. *Trends Pharmacol Sci* 29(12): 609-615.
18. Quintanilla RA, Munoz FJ, Metcalfe MJ, Hitschfeld M, Olivares G, et al. (2005) Trolox and 17 $\beta$ -Estradiol Protect against Amyloid  $\beta$ -Peptide Neurotoxicity by a Mechanism That Involves Modulation of the Wnt Signaling Pathway. *J Biol Chem* 280(12): 11615-11625.
19. Hamad I, Arda N, Pekmez M, Karaer S, Temizkan G (2010) Intracellular scavenging activity of Trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) in the fission yeast, *Schizosaccharomyces pombe*. *J Nat Sci Biol Med* 1(1): 16-21.
20. Jack Jr CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, et al. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 9(1): 119-128.
21. Newman M, Musgrave FI, Lardelli M (2007) Alzheimer disease: Amyloidogenesis, the presenilins and animal models. *Biochimica et Biophysica Acta* 1772(3): 285-297.
22. Greenfield JP, Tsai J, Gouras GK, Hai B, Thinakaran G, et al. (1999) Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer beta-amyloid peptides. *Proc Natl Acad Sci USA* 96(2): 742-747.
23. Zhang Y, Thompson R, Zhang H, Xu H (2011) APP processing in Alzheimer's disease. *Molecular Brain* 4: 3.
24. Coulson EJ, Paliga K, Beyreuther K, Masters CL (2000) What the evolution of the amyloid protein precursor supergene family tells us about its function. *Neurochem Int* 36(3): 175-184.
25. Thinakaran G, Koo EH (2008) Amyloid Precursor Protein Trafficking, Processing, and Function. *J Biol Chem* 283(44): 29615-29619.
26. Zheng H, Koo EH (2006) The amyloid precursor protein: beyond amyloid. *Mol Neurodegener* 1: 5.
27. Sannerud R, Annaert W (2009) Trafficking, a key player in regulated intramembrane proteolysis. *Semin Cell Dev Biol* 20(2): 183-190.
28. Lichtenthaler SF (2011) Alpha-secretase in Alzheimer's disease: molecular identity, regulation and therapeutic potential. *J Neurochem* 116(1): 10-20.
29. De Strooper B, Annaert W (2010) Novel research horizons for presenilins and gamma-secretases in cell biology and disease. *Annu Rev Cell Dev Biol* 26: 235-260.
30. Caporaso GL, Takei K, Gandy SE, Matteoli M, Mundigl O, et al. (1994) Morphologic and biochemical analysis of the intracellular trafficking of the Alzheimer beta/A4 amyloid precursor protein. *J Neurosci* 14(5): 3122-3138.
31. Rajendran L, Annaert W (2012) Membrane Trafficking Pathways in Alzheimer's Disease. *Traffic* 13(6): 759-770.
32. Kirkitadze MD, Kowalska A (2005) Molecular mechanisms initiating amyloid beta-fibril formation in Alzheimer's disease. *Acta Biochim Pol* 52(2): 417-423.
33. Puzzo D, Privitera L, Leznik E, Fa M, Staniszewski A, et al. (2008) Picomolar amyloid-beta positively modulates synaptic plasticity and memory in hippocampus. *J Neurosci* 28(53): 14537-14545.
34. Morley JE, Farr SA, Banks WA, Johnson SN, Yamada KA, et al. (2010) A physiological role for amyloid-beta protein: enhancement of learning and memory. *J Alzheimers Dis* 19(2): 441-449.
35. Shankar GM, Walsh DM (2009) Alzheimer's disease: synaptic dysfunction and Abeta. *Mol Neurodegener* 4: 48.
36. Plant LD, Webster NJ, Boyle JP, Ramsden M, Freire DB, et al. (2006) Amyloid beta peptide as a physiological modulator of neuronal A-type K<sup>+</sup> current. *Neurobiol Aging* 27(11): 1673-1683.
37. Puzzo D, Privitera L, Fa M, Staniszewski A, Hashimoto G, et al. (2011) Endogenous amyloid- $\beta$  is necessary for hippocampal synaptic plasticity and memory. *Ann Neurol* 69(5): 819-830.
38. Morley JE, Farr SA (2012) Hormesis and amyloid- $\beta$  protein: physiology or pathology? *J Alzheimer's Dis* 29(3): 487-492.
39. Abramov E, Dolev I, Fogel H, Ciccotosto GD, Ruff E, et al. (2009) Amyloid- $\beta$  as a positive endogenous regulator of release probability at hippocampal synapses. *Nat Neurosci* 12(1): 1567-1576.
40. Hemming ML, Selkoe DJ, Farris W (2007) Effects of prolonged angiotensin-converting enzyme inhibitor treatment on amyloid  $\beta$ -protein metabolism in mouse models of Alzheimer disease. *Neurobiol Dis* 26(1): 273-281.
41. Kurz A, Perneczky R (2011) Amyloid clearance as a treatment target against Alzheimer's disease. *J Alzheimers Dis* 24(2): 61-73.
42. Tanzi RE, Moir RD, Wagner SL (2004) Clearance of Alzheimer's Abeta peptide: the many roads to perdition. *Neuron* 43(5): 605-608.
43. Sinha M, Bir A, Banerjee A, Bhowmick P, Chakrabarti S (2015) Multiple mechanisms of age-dependent accumulation of amyloid beta protein in rat brain, Prevention by dietary supplementation with N-acetylcysteine,  $\alpha$ -lipoic acid and  $\alpha$ -tocopherol. *Neurochem Int* 95: 92-99.
44. Jaeger LB, Dohgu S, Hwang MC, Farr SA, Murphy MP, et al. (2009) Testing the neurovascular hypothesis of Alzheimer's disease, LRP-1 antisense reduces blood-brain barrier clearance, increases brain levels of amyloid-beta protein, and impairs cognition. *J Alzheimers Disease* 17(3): 553-570.
45. Cirrito JR, Deane R, Fagan An M, Spinner ML, Parsadanian M, et al. (2005) P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model. *J Clin Invest* 115(11): 3285-3290.
46. Cuajungco MP, Faget KY (2003) Zinc takes the center stage: its paradoxical role in Alzheimer's disease. *Brain Res Rev* 41(1): 44-56.
47. Tanzi RE, Bertram L (2005) Twenty Years of the Alzheimer's Disease Amyloid Hypothesis: A Genetic Perspective. *Cell* 120(4): 545-555.



48. Bartzokis G (2011) Alzheimer's disease as homeostatic responses to age-related myelin breakdown. *Neurobiology of Aging* 32(8): 1341-1371.
49. Thal DR, Rub U, Orantes M, Braak H (2002) Phases of A beta deposition in the human brain and its relevance for the development of AD. *Neurology* 58(12): 1791-1800.
50. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* 1(1): a006189.
51. Spire TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, et al. (2005) Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *J Neurosci* 25(31): 7278-7287.
52. Serrano-Pozo A, Mielke ML, Gomez-Isla T, Betensky RA, Growdon JH, et al. (2011) Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. *Am J Pathol* 179(3): 1373-1384.
53. Goedert M, Spillantini MG, Jakes R, Rutherford D, Crowther RA (1989) Multiple isoforms of human microtubule-associated protein tau: Sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron* 3(4): 519-526.
54. Iqbal K, Liu F, Gong CX, Alonso Adel C, Grundke-Iqbal I (2009) Mechanisms of tau-induced neurodegeneration. *Acta Neuropathol* 118(1): 53-69.
55. Zhou XW, Winblad B, Guan Z, Pei JJ (2009) Interactions between glycogen synthase kinase 3beta, protein kinase B, and protein phosphatase 2A in tau phosphorylation in mouse N2a neuroblastoma cells. *J Alzheimers Dis* 17(4): 929-937.
56. Sergeant N, Bretteville A, Hamdane M, Caillet-Boudin ML, Grognet P, et al. (2008) Biochemistry of Tau in Alzheimer's disease and related neurological disorders. *Expert Review of Proteomics* 5(2): 207-224.
57. Palop JJ, Mucke L (2010) Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. *Nature Neuroscience* 13(7): 812-818.
58. Magdesian MH, Carvalho MMV, Mendes FA, Saraiva LM, Juliano MA, et al. (2008) Amyloid-Binds to the Extracellular Cysteine-rich Domain of Frizzled and Inhibits Wnt/-Catenin Signaling. *J Biol Chem* 283(14): 9359-9368.
59. Rosi MC, Luccarini I, Grossi C, Fiorentini A, Spillantini MG, et al. (2010) Increased dickkopf-1 expression in transgenic mouse models of neurodegenerative disease. *J Neurochem* 112(6): 1539-1551.
60. Killick R, Ribe EM, Al-Shawi R, Malik B, Hooper C, et al. (2014) Clusterin regulates beta-amyloid toxicity via Dickkopf-1-driven induction of the Wnt-PCP-JNK pathway. *Mol Psychiatry* 19(1): 88-98.
61. Kopke E, Tung YC, Shaikh S, del A, Alonso C, et al. (1993) Microtubule associated protein tau: abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. *J Biol Chem* 268(32): 24374-24384.
62. Polydoro M, Acker CM, Duff K, Castillo PE, Davies P (2009) Age-Dependent Impairment of Cognitive and Synaptic Function in the tau Mouse Model of Tau Pathology. *J Neurosci* 29(34): 10741-10749.
63. Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443(7113): 787-795.
64. Sultana R, Butterfield DA (2013) Oxidative modification of brain proteins in Alzheimer's disease: perspective on future studies based on results of redox proteomics studies. *J Alzheimers Dis* 33(1): 243-251.
65. Sherer TB, Greenamyre JT (2005) Oxidative damage in Parkinson's disease. *Antioxid Redox Signal* 7: 627-629.
66. Davies S, Ramsden DB (2001) Huntington's disease. *Mol Pathol* 54(6): 409-413.
67. Rowland LP, Shneider NA (2001) Amyotrophic lateral sclerosis. *N Engl J Med* 344(22): 1688-1700.
68. Shukla V, Mishra SK, Pant HC (2011) Oxidative stress in neurodegeneration. *Adv Pharmacol Sci* 572634.
69. Ranjana K, Negi R, Pande D, Khanna S, Khanna HD (2012) Markers of Oxidative Stress in Generalized Anxiety Psychiatric Disorder: Therapeutic Implications. *Journal of Stress Physiology & Biochemistry* 8(2): 32-38.
70. Barnham KJ, Masters CL, Bush AI (2004) Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov* 3(3): 205-214.
71. Silva DF, Selfridge JE, Lu J, EL, Cardoso SM, et al. (2012) Mitochondrial abnormalities in Alzheimer's disease: possible targets for therapeutic intervention. *Adv Pharmacol* 64: 83-126.
72. Yan MH, Wang X, Zhu X (2013) Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease. *Free Radic Biol Med* 62: 90-101.
73. Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, et al. (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. *Hum Mol Genet* 15(9): 1437-1449.
74. Eskici G, Axelsen PH (2012) Copper and oxidative stress in the pathogenesis of Alzheimer's disease. *Biochemistry* 51(32): 6289-6311.
75. Opazo C, Huang X, Cherny RA, Moir RD, Roher AE, et al. (2002) Metalloenzyme-like activity of Alzheimer's disease beta-amyloid. Cu-dependent catalytic conversion of dopamine, cholesterol, and biological reducing agents to neurotoxic H<sub>2</sub>O<sub>2</sub>. *J Biol Chem* 277(43): 40302-40308.
76. Altamura S, Muckenthaler MU (2009) Iron toxicity in diseases of aging: Alzheimer's disease, Parkinson's disease and atherosclerosis. *J Alzheimers Dis* 16(4): 879-895.
77. Tuppo EE, Arias HR (2005) The role of inflammation in Alzheimer's disease. *Int J Biochem Cell Biol* 37(2): 289-305.
78. Smits HA, Rijmsus A, van Loon JH, Wat JW, Verhoef J, et al. (2002) Amyloid-beta-induced chemokine production in primary human macrophages and astrocytes. *J Neuroimmunol* 127(1-2): 160-168.
79. Ansari MA, Scheff SW (2010) Oxidative stress in the progression of Alzheimer disease in the frontal cortex. *J Neuropathol Exp Neurol* 69(2): 155-167.
80. Pocernich C, Butterfield D (2012) Elevation of glutathione as a therapeutic strategy in Alzheimer disease. *Biochim Biophys Acta* 1822(5): 625-630.
81. Halliwell B (2006) Oxidative stress and neurodegeneration: where are we now? *J Neurochem* 97(6): 1634-1658.
82. Bonda DJ, Mailankot M, Stone JG, Garrett MR, Staniszewska M, et al. (2010) Indoleamine 2, 3-dioxygenase and 3-hydroxykynurenine modifications are found in the neuropathology of Alzheimer's disease. *Redox Rep* 15(4): 161-168.
83. Skoumalova A, Hort J (2012) Blood markers of oxidative stress in Alzheimer's disease. *J Cell Mol Med* 16(10): 2291-2300.
84. Massaad CA (2011) Neuronal and vascular oxidative stress in Alzheimer's disease. *Curr Neuropharmacol* 9(4): 662-673.
85. Ray B, Lahiri DK (2009) Neuroinflammation in Alzheimer's disease: different molecular targets and potential therapeutic agents including curcumin. *Curr Opin Pharmacol* 9(4): 434-444.
86. Mitchell AN, Jayakumar L, Koleilat I, Qian J, Sheehan C, et al. (2007) Brain expression of the calcineurin inhibitor RCAN1 (Adapt78). *Arch Biochem Biophys* 467(2): 185-192.
87. Loret AL, Badia MC, Giraldo E, Ermak G, Alonso MD, et al. (2011) Alzheimer's amyloid-beta toxicity and tau hyperphosphorylation are linked via RCAN1. *J Alzheimers Dis* 27(4): 701-709.

88. Ermak G, Harris CD, Battocchio D, Davies KJA (2006) RCAN1 (DSCR1 or Adapt78) stimulates expression of GSK-3 $\beta$ . *FEBS J* 273(10): 2100-2109.
89. Hanger DP, Anderton BH, Noble W (2009) Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. *Trends Mol Med* 15(3): 112-119.
90. Giraldo E, Lloret A, Fuchsberger T, Vina J (2014) A $\beta$  and tau toxicities in Alzheimer's are linked via oxidative stress-induced p38 activation: Protective role of vitamin E. *Redox Biol* 2: 873-877.
91. Shea TB, Zheng YL, Ortiz D, Pant HC (2004) Cyclin dependent kinase 5 increases perikaryal neurofilament phosphorylation and inhibits neurofilament axonal transport in response to oxidative stress. *J Neurosci Res* 76(6): 795-800.
92. Murakami K, Murata N, Noda Y, Tahara S, Takao Kaneko T, et al. (2011) SOD1 (copper/zinc superoxide dismutase) deficiency drives amyloid  $\beta$  protein oligomerization and memory loss in mouse model of Alzheimer disease. *J Biol Chem* 286(52): 44557-44568.
93. Tamagno E, Guglielmo M, Aragno M, Borghi R, Autelli R, et al. (2008) Oxidative stress activates a positive feedback between the  $\gamma$ -and-secretase cleavages of the  $\beta$ -amyloid precursor protein. *J Neurochem* 104(3): 683-695.
94. Quiroz-Baez R, Rojas E, Arias C (2009) Oxidative stress promotes JNK-dependent amyloidogenic processing of normally expressed human APP by differential modification of  $\alpha$ - and  $\gamma$ -secretase expression. *Neurochem Int* 55(7): 662-670.
95. Zheng L, Roberg K, Jerhammar F, Marcusson J, Terman A (2006) Oxidative stress induces intralysosomal accumulation of Alzheimer amyloid beta-protein in cultured neuroblastoma cells. *Ann N Y Acad Sci* 1067: 248-251.
96. Webster R (2003) *Neurotransmitters, Drugs and Brain Function*. John Wiley & Sons, USA.
97. Inestrosa NC, Toledo EM (2008) The role of wnt signaling in neuronal dysfunction in Alzheimer's Disease. *Mol Neurodegener* 3: 1-13.
98. Inestrosa NC, Varela-Nallar L (2014) Wnt signaling in the nervous system and in Alzheimer's disease. *J Mol Cell Biol* 6(1): 64-74.
99. Town T, Zolton J, Shaffner R, Schnell B, Crescentini R, et al. (2002) p35/Cdk5 Pathway Mediates Soluble Amyloid-Peptide-Induced Tau Phosphorylation *in vitro*. *J Neurosci Res* 69(3): 362-372.
100. Cruz JC, Kim D, Moy LY, Dobbin MM, Sun X, et al. (2006) p25/cyclin-dependent kinase 5 induces production and intraneuronal accumulation of amyloid beta *in vivo*. *J Neurosci* 26(41): 10536-10541.
101. Sun KH, De Pablo Y, Vincent F, Shah K (2008) Deregulated Cdk5 promotes oxidative stress and mitochondrial dysfunction. *J Neurochem* 107(1): 265-278.
102. Lucio M, Nunes C, Gaspar D, Ferreira H, Lima JLFC, et al. (2009) Antioxidant Activity of Vitamin E and Trolox: Understanding of the Factors that Govern Lipid Peroxidation Studies *in vitro*. *Food Biophysics* 4(4): 312-320.
103. Satoh K, Kadofuku T, Sakagami H (1997) Effect of Trolox, a synthetic analog of alpha-tocopherol, on cytotoxicity induced by UV irradiation and antioxidants. *Anticancer Res* 17(4): 2459-2463.
104. Farina N, Isaac MGEKN, Clark AR, Rusted J, Tabet N (2012) Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst Rev* 11: 1-31.
105. Peus D, Meves A, Pott M, Beyerle A, Pittelkow MR (2001) Vitamin E analog modulates UVB-induced signaling pathway activation and enhances cell survival. *Free Radic Biol Med* 30(4): 425-432.
106. Rezk RM, Haenen GRMM, van der Vijgh WJF, Bast A (2004) The extraordinary antioxidant activity of vitamin E phosphate. *Biochim Biophys Acta* 1683(1-3): 16-21.
107. Silvestrelli G, Lanari A, Parnetti L, Tomassoni D, Amenta F (2006) Treatment of Alzheimer's disease: From pharmacology to a better understanding of disease pathophysiology. *Mech Ageing Dev* 127(2): 148-157.
108. Shaw M, Cohen P, Alessi DR (1997) Further evidence that the inhibition of glycogen synthase kinase-3 $\beta$  by IGF-1 is mediated by PDK1/PKB induced phosphorylation of Ser 9 and not by dephosphorylation of Tyr 216. *FEBS Lett* 416(3): 307-311.
109. Yoon WJ, Woon SJ, Ryu BJ, Gwang BJJ (2003) Blockade of ionotropic glutamate receptors produces neuronal apoptosis through the Bax-cytochrome C-caspase pathway: the causative role of Ca<sup>2+</sup> deficiency. *J Neurochem* 85(2): 525-533.



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