Review Article

# Study About Alzheimer's Disease and Their Management by Using Antioxidants

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**ABSTRACT**

Alzheimer is a neurodegenerative disease caused by neuronal cell death, and it is the most common type of dementia which produces progressive impairment of behavioral ad cognitive functions including memory, language, attention, judgment and reasoning. In the United States they are the sixth leading cause of death. Depend upon the stages of Alzheimer the symptoms will be exposed. It typically begins from the entorhinal cortex in the hippocampus. For increase the risk of Alzheimer Disease by Traumatic head injury, depression, cerebro vascular disease, family history of dementia and also presence of APOE e4 allele. By the report of global prevalence of dementia to be high as 24 million, and it is increased 4 times by the year 2050. In the United States estimated health care amount for Alzheimer disease is $172 billion per year. Multiple factors cause AD by genetics, environmental factors, and general lifestyles and also senile plagues and intracellular neurofibrillary tangles are the pathology of Alzheimer. In this review, I focus that stress is an important phenomenon for correlates with free radicals and antioxidant in organism that is due to an oxidative Stress imbalance between free radicals and antioxidant production of reactive oxygen and nitrogen species will be increased. That oxidative stress plays on very essential role in stimulating and activating multiple cells signaling cause lesion formation of toxic substance cause promotes to develop AD.

**Keywords:** Dementia, Alzheimer disease, amyloid protein, Apolipoprotien, Neurofibrillary Tangles, Antioxidants.

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## INTRODUCTION

Alzheimer is the most common type of dementia that seriously affecting in daily life[1]. At an initial stage, their symptoms such as memory defect are mild but at late stage Alzheimer patients have loss the memory to reply and convey the message in their surroundings[2]. For communication, the brain has billions of nerve cells called neurons attached each other and they are performing several jobs such as memory, thinking, identifying, remembering and smelling, etc. But they are totally impacted due to deposition of extracellular beta amyloid protein in the form of senile plagues and intracellular neurofibrillary tangles that is microtubule associated protein that causes neuron function is discontinued and communication is failed leads to neuronal death in Alzheimer patient[3]. This neuronal loss occurs particularly in hippocampus and cerebral neocortex[4]. In world more than 47 million peoples are influenced by dementia. About 60 to 80% of the Alzheimer cases are in the form of dementia[5] where 5 to 10% of dementia cases include vascular dementia, Lewy body dementia, parkinson's with dementia[5]. Aging is the most important strongest factor in Alzheimer patient and the prevalence is 10% for individuals 65 years and over 80 years for 40%[6]

### Normal Neuron Cell and its Function

Normally all cell contains nucleus and their site of function is to produce neuronal protein and membrane. In Dendron some proteins are synthesized, but there are no proteins are synthesized in axon and axon terminal, because they do not contain ribosome. Where, for renewal of axon and nerve terminal, proteins and membranes are required which are synthesized in cell body. In body every neuron has a single axon but their diameter varies, from nerves of brain to millimeter in giant fiber.

### Action Potential

Electric impulse called as action potential which are the specialized conduction present in axon. Across the plasma membrane action potential produces serious sudden change in the voltage. An action potential is present in axon, and it is actively conducted move down the axon to axon terminals and to small branches of axon this forms synapse. In body many neurons have multiple dendrites which are extended outward, and they are specialized to receive the chemical signal produced from axon terminal of other neurons. By dendrites these signals are converted into small electric impulse and transmit them into inward[7].

### Synapses

Generally, synapse transmit signal in one direction. From axon terminal presynaptic cell send signal which are picked up by postsynaptic cell. An action potential which are produced in terminal of presynaptic cell contains vesicles

filled with a specific neurotransmitter, and it reaches an axon terminal, that time it induces rise in the level of calcium ion in the cytosol. This produces some vesicles to fuse with plasma membrane, and releasing their contents into the synaptic cleft in between the cells, and it takes 0.5millisecond for them to bind to receptor on postsynaptic cells[7].

## OXIDATIVE STRESS MARKERS IN AD

### Amyloid Plaques

Senile Amyloid Plaque are also known as military foci, and they are described in AD, and they are formed by extracellular nonvascular accumulation of Aβ40 and Aβ42 peptides that causes by the abnormal processing of amyloid precursor protein by the β and γ secretases. And are imbalance in production[8,9,10]. And also additional Aβ peptides have 38 and 43 amino acids detected, but in this Aβ42 have a most fibrillogenic and also the predominant compound of amyloid plaque in AD[11]. In AD have two types of amyloid plaques are observed that is diffuse plaque and dense core plaque[10]. Where dense cored neuritic plaque have also presence of synaptic loss, reactive astrocytes and activated microglia[12,13,10]. In Diffuse Plaque the neuritic components are lacked, and also the diffuse neuritic plaque are observed in advanced AD[14].

### Amyloid Precursor Protein

From amyloid precursor protein, the generation of amyloid-β peptides of either 40 or 42 amino acids and their frequently accumulation, aggregation in brain parenchyma produce Senile plaque and in perivascular regions produces cerebral amyloid angiopathy are the pathogenesis for AD[15]. Senile plague and intracellular neurofibrillary tangles are the problems found in pathogenesis of AD. In contrast, soluble Aβ oligomers are also cause injury to the synapses and produce neurodegeneration and cognitive deficits through modifying normal synaptic functions and their downstream toxic pathways are triggered[16].

### Genetic Factor and their types

Inherited genetic mutations in APP, PSEN1 and PSEN2 caused the Alzheimer disease in 1% of cases[17]. Early onset familial AD is the development of alzheimer usually before the age of 60, due to inheriting any of these genetic mutation increases Aβ production. In the majority of AD, Late Onset AD can be occurred later in life. In presence of LOAD there producing modification in Aβ clearance it leads to accumulation of Aβ in brain[18].

### Apolipoprotien Synthesis and their Function

Apolipoprotien E have a central role in neurobiology, lipid metabolism and neurodegenerative disease, and also they have multifunctional protein. They have three isoforms that is apoE2, apoE3, apoE4 have different effect on lipid and neuronal homeostasis. And their major role is to mediate the binding of lipoprotein in plasma by binding to specific receptor present in cell surface. Thus, apoE with its cellular origins and have multiple structural and functions of lipid metabolism and neurobiology, with variety of disorders such as neuronal repair, remodeling etc through various pathway[19].

### Synthesis from other region of body

From variety of tissue as well as plasma and several types of cells and also abundant in lymph and interstitial fluid where ApoE was synthesized [20,21,22]. ApoE mainly secreted by cells in poor form of lipid, they always exist in association with lipids, and also the plasma, lymph, cerebral spinal fluid ApoE produced and to be associated with lipids to phospholipids disc or lipoprotein particle, and their synthesize is also detected on brain, adrenal gland, testis, skin, spleen and adipose tissue and also in macrophages in variety of tissues.

### Synthesis from Central Nervous System

In central nervous system, the primarily responsible for the production of ApoE is astrocytes [23,20,22,24]. In CNS the ApoE are secreted by different types of cell, and they have distinct role in physiology and pathophysiological pathway. But in peripheral nervous system in glia surrounding, the ApoE was present in sensory and motor neuron. They are not presented in myelinating Schwann cells. Where injured in peripheral nerves macrophages are responsible for ApoE synthesis and secretion. When injury occurs production of large quantities of ApoE from resident macrophages and monocyte derived macrophages recruited to the site and causes accumulation in the extracellular matrix to regenerating nerve from degenerating stump [25,21,22].

### Function of Apolipoprotien

Basically, in CNS ApoE are the major apolipoprotein and play a vital and central role for transport of lipid in the nervous system[26]. Homeostasis of cholesterol in the CNS and they are regulated independently due to presence of BBB. To maintenance of cholesterol pool in CNS and it is based on three important steps- synthesis, transport and regulation[27].

### Synthesis

Mature brain containing neuron can synthesis cholesterol for neuronal maintenance, growth, repair and dendritic re-establishment [28,29]. ApoE act as a central significance for maintaining cholesterol synthesis through series of interdependent pathway. APOJ are identified and act one of the genetic risk factor for AD, and APOE is produces in brain they are secreted by astrocytes, microglia and is afterwards lapidated by ATP- Binding Cassette Transporter A1 and to produce lipoprotein particle [30,31].

### Transport

ABCA1 act as a catalyst for initial transfer of cholesterol onto the lipid poor APOE and finally produces full lipidation of apolipoprotien[32]. By specific members of LDLR family, includes LDLR-Related Protein which are present in neuronal and non-neuronal cell and endocytosed the APOE-HDL like lipoparticles when fallowing lipidation[30,31].

After that APOE endocytosis which gives cholesterol to the neuron for synthesis of plasma membrane, synaptic formation and dendritic proliferation. The function of APOJ is the homeostasis of lipid and metabolism of Aβ and very similar to that of APOE that is carrier of cholesterol in the CNS and both have ability to change amyloid fibrillogenesis and clearance[33,34,35]. Due to sterol ring, excess cholesterol cannot be degraded in brain.

**Regulation**

The pathway for excrete cholesterol from the CNS by convert that more lipophilic because can cross the BBB[32,36], these type of metabolite only produced in neuron, and they are excreted as form of bile acids when they are directed to the liver[37]. APOE lipoprotein are act as a scavenger for soluble beta amyloid peptides through they are more bind to the soluble nonaggregated Aβ fragments by APOE receptor internalization pathway, after internalization the Aβ fragments are ready to degrade and released through endosomal pathway[38]. APOE have an antioxidant property, when oxidative damage or stress occur in individuals who carry APOE4 allele in one or two copies[39,40].

**Biological Function**

For growth, repair, neuronal maintenance, and re-establishment APOE plays on important role[41]. Enough cholesterol is produced in CNS neuron helps to survive and grow inefficient synapse[42], by the glial system which provides additional cholesterol supplies when injured occur in adult brain[29]. For increase the risk of familial and sporadic AD by APOE4 [43,44].

## OTHER RISK FACTOR TO CAUSE ALZHEIMER'S DISEASE DUE TO OXIDATIVE STRESS

**Lipid oxidation in AD**

Lipoperoxidation is one of the most essential phenomenon for the pathogenesis of AD. Lipoperoxidation of the membrane and stimulate lipid peroxidation products are due to Aβ accumulation. ROS modifies the lipids and their link among antioxidant enzymes, lipid peroxides, senile plaques and NFTs in AD brain very strong. Depletion of membrane phospholipids is the major cause and to produce AD due to lipid peroxidation

## NATURAL ANTI-OXIDANTS

**Antioxidant and their Role**

STRESS is one of the major factor produce variety of the disease and also from obesity, long term health issue, immune suppression and some eating disorder stress also can exist. Free radicals are derived from oxygen that is called as reactive oxygen species and reactive nitrogen species. When imbalance occurs between free radicals and antioxidants oxidative stress will be produced, decreases endogenous antioxidant defenses and increases the production of reactive oxygen species[45].

**Regulation**

By the help of antioxidant mechanism, maintaining organism from oxidative stress, and homeostasis will be occurred. Antioxidant may be in the form of natural or synthetic both are helps to protect the cell from damage during oxidative stress occur. Normally the natural antioxidants are present in food which can helps to give better health and quality life, and also several natural antioxidants which helps to prevent oxidation in lipid peroxidation. Some natural antioxidant such as medicinal plants, curcuma, clove, aloe vera, etc. are used for health maintenance and some compounds such as carotenoids, polyphenols, flavonoids, phycocyanin etc. have an important biological activity. By these compounds and antioxidant which helps to produce an anti-inflammatory action, prevention of cell damage, regulation of gene, and enzyme detoxification[46,47].

**Mechanism between free radical and antioxidant**

Reactive oxygen species and their subgroup include reactive nitrogen species called as Free Radicals these are the products in normal cellular metabolism. If these overproductions occurs leads to produce increase oxidative stress causes damages to lipids, proteins, DNA[48]. For proper functioning, it is necessary to occur balance in between free radical's and antioxidant. If free radicals mechanism increases stress will be occurred and the stress will be considered as two-way that is acute, and another one is chronic.

**Acute and Chronic Stress**

Acute stress called as short term stress occurs that time release of hormone from the sympathetic nervous system and to produce response in either flight or fight response. Where chronic stress occurs, stress produce over a period of long time. Oxygen is most important essential element in all life form of species in earth, through electron transport chain they are used for energy production for both prokaryotes and eukaryotes[48]. When stress occurs in cellular metabolism production of Reactive oxygen Species, and they damage the carbohydrate, proteins, lipids and nucleic acids. The effect of free radicals in fatty acids produces lipid peroxidation and also produces some damage

Normally antioxidant can be divided into two enzymatic and non-enzymatic, where enzymatic antioxidant called as glutathione, catalase, glutathione peroxidase, super oxide dimutase have an significant role in free radical elimination[49]. And the non-enzymatic antioxidants such as vitamins are C, E and beta-carotene, polyphenol etc.,[50,51].

## CONCLUSION

In this review, I explain that APOE isoforms are the main effect on risk of AD through effect on APOE on Aβ metabolism and deposition of Aβ in both brain parenchyma and vasculature, these continue accumulation on neuronal cells produce AD and some dementia and cognitive disorder. Normal 50+ years old

individual has more likelihood of cognitive impairments when APOE4 increases. Normally APOE4 proteins have an effect for facilitating the metabolism of Aβ forms, and alternatively APOE4 produce deleterious effect of reduced protein expression on cholesterol homeostasis and cause increased the risk of Alzheimer Disease. Normally Alzheimer based on two types that is familial AD (genetic mutation cause increase production of Aβ resulting development of AD) and another one is late onset of AD (represent many cause), so I conclude that some stress occurs in CNS neuron that produce deleterious effect on apolipoprotien (they are important for transport of cholesterol and lipid) and also affect APOJ (they are used for metabolism of Aβ) they cause accumulation of amyloid beta and lipid peroxidation occurs. So synaptogenesis, plasma membrane synthesis, reorganisation also impacted, they produce dementia and cognitive disorder and AD occur. They are prevented by suitable administration of antioxidants they help to prevent the stress formation in CNS neuron and maintain the mechanism properly and also helps to prevent that such disease's formation.

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