Role of potential antioxidant in management of memory deficit disorder

Mr. Ainulsha Feequ[1], Mrs Jaswandi Mehetre[2], Mr. Vimal Kumar[3]

School of Pharmacy, ITM (SLS) Baroda University Vadodara

Email- ainulshafeequ@gmail.com[1]

ABSTRACT:

Alzheimer's disease (AD) is a neurodegenerative disorder (ND) that impacts memory, cognition, and motor functions, ultimately resulting in individuals needing assistance with basic activities. According to epidemiological projections, the prevalence of AD the number of people is projected to rise significantly from 26.6 million in 2006 to 106.8 million by 2050. This review intends to provide a concise summary of the pathophysiology involved in a particular topic management of AD, with a focus on the potential benefits of antioxidant nutrients and supplements for everyday life. The importance of dietary antioxidants for patients with NDs has increased due to the recognition of oxidative stress in brain health. The review seeks to examine the current evidence on antioxidant therapies for NDs and their future prospects, highlighting their importance in preventing these disorders. NDs impair the brain and its neurons, causing symptoms such as impaired balance, breathing problems, movement disorders, reflex abnormalities, cardiac irregularities, and cognitive deterioration. Antioxidants, such as beta-carotene, vitamins E and C, flavonoids, and polyphenols, are active substances that have shown promise as preventive and protective agents against NDs. These antioxidants have a crucial role in lowering the risk of Alzheimer's, Parkinson's, and other NDs. Dementia is a term used to describe a decline in cognitive function, which can interfere with daily life. Dementia can result from various diseases, such as AD, vascular dementia, Lewy body dementia, frontotemporal dementia, and others. Some types of dementia may be reversible if the underlying cause is addressed. Antioxidants, particularly dietary antioxidants, have been increasingly considered as possible therapeutic options for patients with NDs and dementia. Antioxidants include beta carotene, vitamins E and C, flavonoids, and polyphenols. These substances may help prevent or delay the development of NDs and dementia by reducing the risk of oxidative injury to the brain cells. This review presents the current evidence on antioxidant therapy of ADs, and its future challenges and implications. It also emphasizes the potential value of antioxidants for preventing ADs and dementia in the first place.

Keyboard: Neurodegenerative diseases, Oxidative stress, Antioxidants, Vitamin C, flavonoid, lycopene.

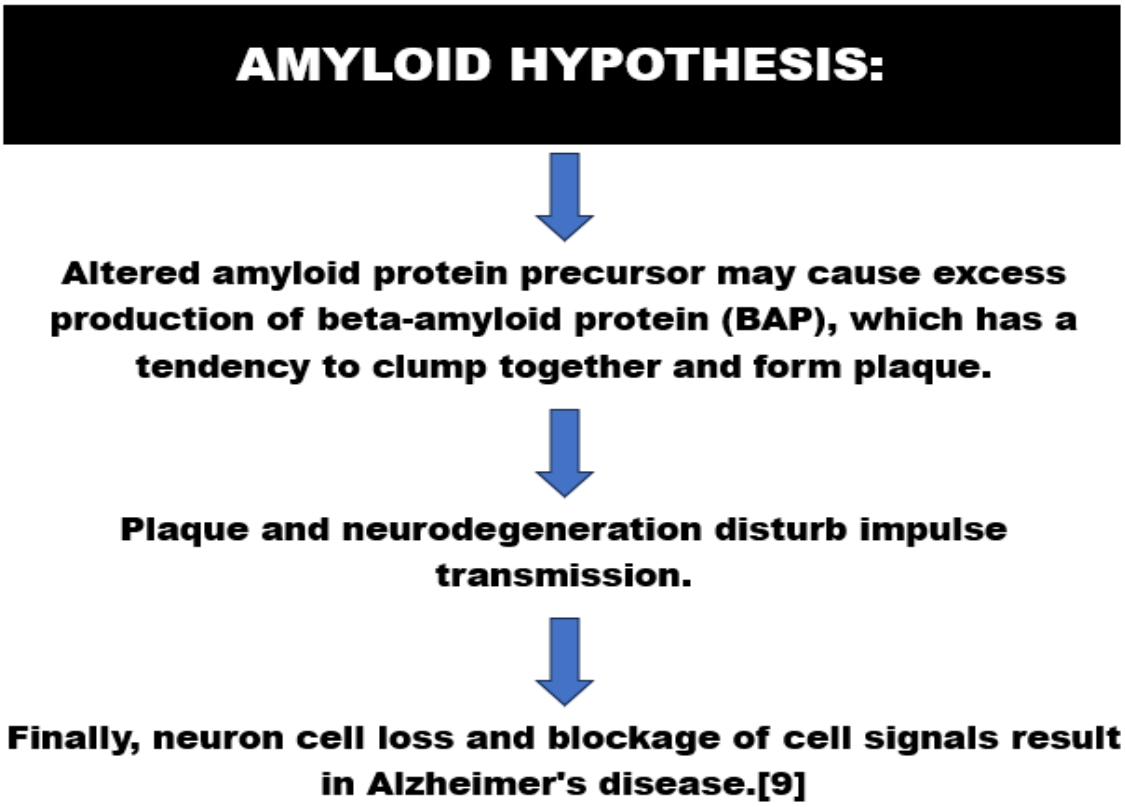
INTRODUCTION:

Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, was the first to describe a dementia condition that was later identified as Alzheimer's disease. Alzheimer's disease (AD) is a severe form of dementia that causes impairments in memory, language, and behaviour.[1]

Alzheimer's disease stands as the predominant factor behind the onset of dementia around the globe among the elderly, accounting for over 80% of cases of neurodegenerative disorders.[2] AD is marked by the progressive deterioration of mental, behavioural and functional capacities, as well as the ability to learn. One of the factors that may influence the onset and advancement of Alzheimer's disease is oxidative stress, which is the mismatch between the production and elimination of reactive oxygen species (ROS) inside the body. ROS are molecules that can harm cells and tissues by reacting with proteins, lipids, and DNA. Oxidative stress arises from a disparity between pro-oxidants and antioxidants, marked by elevated levels of reactive oxygen and nitrogen species and reduced levels of innate antioxidants.[3].

Alzheimer's disease (AD) is a common type of cognitive impairment that impacts over 50 million people around the world [4]. It is characterized by the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) made up of hyperphosphorylated tau protein in the brain. These pathological features disrupt the functioning of synapses and communication among neurons, resulting in memory loss and cognitive decline. The significance of oxidative stress plays a pivotal role in the development and advancement of AD. It can trigger Aβ production and aggregation, tau hyperphosphorylation and aggregation, synaptic dysfunction, neuronal death, and neuroinflammation [5].

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE AND DEMENTIA:



AD is a complex disorder that involves various factors, but it is mainly defined by two different pathologies. The first mechanism involves the hyperphosphorylation of tau proteins, while the second mechanism involves the increase in the aggregation of amyloid plaques. Tau is a microtubule protein that acts as a scaffold in axons. When these proteins become hyperphosphorylated and impaired in AD patients, it leads to an abnormal cytoskeleton, disruption in cell function, neuronal atrophy, and damage to axonal transport. [6] AD is also associated with the accumulation of amyloid-β (Aβ), which is highly resistant to protease degradation and remains in high levels. These beta-sheet structures aggregate and form amyloid plaques in the brain, causing neurodegeneration and damage. [7] In vitro studies using neurons from AD brains showed reduced long-term potentiation, synaptic dysfunction, and impaired dendritic spines, all leading to neuronal death. All aggregated misfolded proteins induce oxidative stress. Besides these two mechanisms, there is another pathology that is involved in AD, which is inflammation.[8]

NEUROFIBRILLARY TANGLES:

Abnormal phosphorylation leads to the formation of tau protein, which provides structural support to microtubules and transportation of nutrients.

Microtubules collapse, which stops nutrient supply and may result in cell death.

Neuronal loss results in Alzheimer's disease.[10]

CHOLINERGIC REGULATION:

The first neurotransmitter defect discovered in AD involved acetylcholine (ACH).

Abnormal release of ACH from cholinergic neurons to the brain at the hippocampus and cortex inhibits the regulation of learning and memory, resulting in Alzheimer's disease.[11]

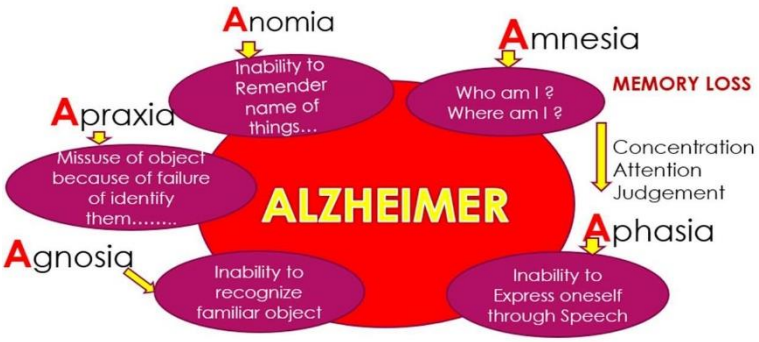


Figure: Symptoms of Alzheimer Disease [1,2]

ROLE OF ANTIOXIDANTS IN ALZHEIMERS:

Antioxidants are suggested as a possible therapeutic approach for AD and other neurodegenerative disorders, as they can eliminate free radicals, regulate redox signalling pathways, preserve mitochondrial function, prevent protein aggregation, decrease neuroinflammation, and stimulate neurogenesis [12]. Antioxidants can be obtained from natural sources (such as fruits, vegetables, herbs, spices, tea, coffee, wine, etc.) or synthetic compounds (such as vitamins, minerals, polyphenols, flavonoids, carotenoids, etc.). Several studies have demonstrated that dietary intake or supplementation of antioxidants can enhance cognitive function and postpone the onset or progression of AD and other neurodegenerative disorders in animal models and human trials [13].

However, there are also some drawbacks and challenges related to the use of antioxidants for neurodegenerative disorders. For example, some antioxidants may have pro-oxidant effects under certain conditions or doses; some antioxidants may have low bioavailability or poor penetration across the blood-brain barrier; some antioxidants may interfere with other drugs or nutrients; some antioxidants may have negative effects or toxicity; some antioxidants may have inconsistent or inconclusive results in different studies; and some antioxidants may have unknown long-term effects or safety. Therefore, more research is required to determine the optimal types, doses, combinations, timings, and mechanisms of action of antioxidants for different neurodegenerative disorders.[14]

Vitamin E:

Vitamin E, classified as a fat-soluble vitamin, possesses antioxidant characteristics. It can shield the cells from oxidative stress Caused by unstable molecules termed free radicals, it has the ability to harm the cell membranes, proteins, and DNA. Oxidative stress contributes to the development of various neurological conditions, including but not limited to Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).[15].

Vitamin E can alter the expression of genes involved in inflammation, apoptosis, and neuroprotection. It can also control the synthesis of prostaglandins, which are hormone-like substances that affect the function of neurons and glia. Vitamin E can also affect the metabolism of neurotransmitters, including dopamine and acetylcholine, which play a vital role in cognitive and motor functions [16].

Several clinical studies have explored the outcomes of vitamin E supplementation on the prevention or treatment of neurological disorders. The results have been varied and inconclusive. Certain research findings suggest that vitamin E might possess beneficial effects on cognitive decline, motor symptoms, and the advancement of the disease in individuals diagnosed with Alzheimer's disease or Parkinson's disease [14]. However, other studies have not confirmed these findings or have reported negative effects of high doses of vitamin E [16]. Therefore, more research is required to determine the optimal dose, duration, and formulation of vitamin E for different neurological disorders.

In summary, vitamin E stands as a potent antioxidant that may have neuroprotective effects in various neurological disorders. However, the evidence from clinical trials is not reliable and persuasive. Further studies are needed to clarify the mechanisms of action and the safety and efficacy of vitamin E supplementation in different populations and settings. [14,16]

Coenzyme Q10:

Coenzyme Q10 (CoQ10) is a potential therapeutic agent for neurodegenerative diseases. CoQ10 functions as a crucial cofactor in the electron transport chain, aiding in the transfer of electrons from complexes I and II. CoQ10, also known as ubiquinone, has a significant antioxidant role in both mitochondria and lipid membranes. It mediates some of its antioxidant effects through interactions with α-tocopherol.[17] Coenzyme Q10 inhibits apoptosis by preventing the activation of the mitochondrial permeability transition independently of its free radical scavenging abilities.[18] Another possible neuroprotective mechanism of Coenzyme Q10 is its role as a cofactor for mitochondrial uncoupling proteins. It is also a mandatory cofactor for these proteins. Activation of these proteins lowers mitochondrial free radical generation.[19]

CoQ10 reduced ischemia-induced neuronal damage in the hippocampus. It also protected cultured cerebellar neurons from excitotoxin-induced degeneration. Our study explored the effects of CoQ10 administration on lesions induced by mitochondrial toxins.[20] The oral administration of CoQ10 showed dose-dependent neuroprotective effects against malonate induced striatal lesions and alleviated ATP depletion while increasing lactate concentrations. Moreover, CoQ10 administration offered significant protection against dopamine depletions induced by MPTP administration, as shown by Beal and Matthews et al. [21] Oral administration of CoQ10 for one week before co-administration of 3-nitropropionic acid resulted in a remarkable 90% neuroprotection against 3-nitropropionic acid-induced striatal lesions. Remarkably, we observed that starting CoQ10 administration at 50 days of age significantly prolonged the lifespan of ALS transgenic mice and increased the survival of HD transgenic mice by 14.5%. CoQ10 administration significantly postponed the onset of motor deficits, weight loss, cerebral atrophy, and the formation of neuronal inclusions [20,21].

Curcumin:

Curcumin, the phytochemical that gives turmeric its bright yellow color and Indian curry its distinctive flavour, has a long history of use in traditional Indian medicine. It has been used for centuries as a wound-healing agent and a remedy for various diseases. Modern pharmacology has recently discovered the antioxidant, anti-inflammatory, antiproliferative, and other beneficial properties of curcumin. The mechanism of action of curcumin is complex and diverse. Partially, curcumin operates by triggering diverse cytoprotective proteins that are in the phase II response. [22]

In the past decade, research on curcumin has increased. Both in vitro and in vivo studies have revealed its potential to target pathways that contribute to the pathophysiology of Alzheimer's disease (AD), including the β-amyloid cascade, tau phosphorylation, and neuroinflammation, and oxidative stress. [23]

These results imply that curcumin holds promise as a potential candidate for the development of AD therapy. Yet, its limited water solubility and inadequate bioavailability have posed constraints clinical trials and for therapeutic applications. For curcumin to be efficacious as a drug therapy, it must either be combined with other drugs or require the development of new delivery strategies [24].

Curcumin may bind to amyloid-beta, the toxic protein accountable for the generation of plaques in the brains of individuals with Alzheimer's disease, and prevent its aggregation and deposition [25]. Curcumin may also dissolve existing amyloid-beta plaques and increase their clearance by the immune system [26].

Curcumin may regulate various signalling pathways that are involved in inflammation, oxidative stress, and apoptosis (cell death) in the brain, which are all involved in the pathogenesis of Alzheimer's disease [25, 26]. Curcumin may also protect the brain from damage caused by metal ions, such as iron and copper, that accumulate in Alzheimer's disease [25].

Curcumin may enhance the function of mitochondria, the energy-producing organelles in the cells, and synapses, the connections between neurons, which are both impaired in Alzheimer's disease[12]. Curcumin may also increase neurogenesis, the generation of new neurons, and neuroplasticity, the ability of the brain to adapt and reorganize [22,26].

Curcumin may reduce the risk factors for Alzheimer's disease, such as cerebrovascular disease, hypertension, and hyperlipidaemia, by improving blood circulation, lowering blood pressure, and reducing cholesterol levels [26].

However, it should be noted that most of these studies have been performed in animal models or cell cultures, and the evidence from human trials is still scarce and inconclusive. Therefore, more research is required to verify the safety and efficacy of curcumin in Alzheimer's disease. Moreover, curcumin has low bioavailability, meaning that it is not well absorbed or distributed in the body. Therefore, various strategies have been devised to improve its delivery and stability, such as using nanoparticles, liposomes, or other molecules [22,25,26].

Omega-3 fatty acid:

Omega-3 fatty acids are categorized as polyunsaturated fatty acids (PUFA) that have anti-inflammatory and antioxidant effects in the brain. They can regulate the function of neurons and glia, and protect them from oxidative stress and neuroinflammation, which are involved in the development of many neurological disorders [27].

Some of the neurological disorders that may benefit from omega-3 fatty acids supplementation are:

Omega-3 fatty acids can inhibit or postpone the creation of amyloid-beta plaques and neurofibrillary tangles, both of which are the characteristics of Alzheimer's disease. They can also enhance the synaptic plasticity and memory-related learning, which are compromised in this disorder. Some clinical trials have indicated that omega-3 fatty acids can reduce the cognitive decline and disease progression of patients with Alzheimer's disease [28].

Omega-3 fatty acids have multiple neurological benefits, as they can act as antioxidants and anti-inflammatory agents in the brain. However, the evidence from clinical trials is not reliable and persuasive, and more research is required to determine the optimal dose, duration, and formulation of omega-3 fatty acids for different neurological disorders.[27]

Alpha-lipoic acid:

Alpha-lipoic acid is a disulfide compound that acts as the coenzyme for mitochondrial alpha keto acid dehydrogenases. It has powerful antioxidant properties and can restore supplementary antioxidants like vitamin C, vitamin E, and glutathione.[29]

In a study, nine patients with Alzheimer's disease and related dementias took a daily dose of 600 mg of alpha-lipoic acid for an average of 337 days. Cognitive assessments remained unchanged during this period. Although the study was small and not randomized, the results suggest that further research with alpha-lipoic acid may be beneficial [30].

ANTIOXIDANT TOXICITY:

Antioxidant toxicity is a condition that occurs when the consumption of antioxidants surpasses the body's capacity to utilize them. Antioxidants are substances that can inhibit or delay the oxidation of other molecules, thus protecting them from free radical damage. Free radicals are exceptionally reactive molecules capable of harm cellular structures and contribute to various diseases. However, excessive amounts of antioxidants can also have detrimental effects, such as disrupting the normal function of enzymes, hormones, and immune cells, or diminishing the effectiveness of some medications. [31,32]

Some examples of antioxidants are vitamin C, vitamin E, beta-carotene, selenium, flavonoids, and polyphenols.

- **Vitamin C toxicity:** Vitamin C is a nutrient that dissolves in water that has antioxidant properties and is involved in various metabolic processes, such as collagen synthesis,

wound healing, immune system regulation, and iron absorption. Vitamin C is commonly considered safe, and nontoxic, but excessive intake of vitamin C supplements can cause gastrointestinal problems, such as diarrhoea, nausea, abdominal pain, and gas. Elevated quantities of vitamin C can also raise the probability of kidney stone formation, particularly in individuals with a history of kidney-related issues or oxalate stones. Moreover, vitamin C can interfere with some medications, such as anticoagulants, chemotherapy drugs, and statins.[33]

- **Vitamin E toxicity:** Vitamin E is a type of fat-soluble vitamin that has antioxidant properties and is involved in various biological processes, such as cell signalling, gene expression, and immune system regulation. Vitamin E is generally regarded as safe and nontoxic, but excessive intake of vitamin E supplements can cause bleeding disorders, such as increased bleeding time, bruising, and haemorrhage. Elevated doses of vitamin E can also heighten the risk of haemorrhagic stroke, prostate cancer, and mortality. Furthermore, vitamin E can interact with some medications, such as anticoagulants, antiplatelet drugs, and statins.[34]
- **Selenium toxicity:** Selenium is a trace element that has antioxidant properties and is involved in various metabolic processes, such as thyroid hormone synthesis, DNA repair, and immune system regulation [35]. Selenium is essential for human health, but excessive intake of selenium supplements can cause selenium toxicity or selenosis.[36] Symptoms of selenosis include nausea, vomiting, diarrhoea, hair loss, nail brittleness, skin rash, garlic breath odour, fatigue, irritability, nervousness, and muscle weakness. Severe cases of selenosis can lead to liver damage, kidney failure, respiratory distress, cardiac arrest, and death.[37] Additionally, selenium can interact with some medications, such as anticoagulants and chemotherapy drugs.[36]
- **Flavonoids and polyphenols:** Flavonoids and polyphenols are generally regarded as safe and beneficial for human health when ingested in moderate quantities from natural sources. However, excessive intake of these compounds from supplements or fortified foods may cause adverse effects or interactions with some medications. [38] Some of the possible side effects or interactions of flavonoids and polyphenols are gastrointestinal problems (such as nausea, vomiting, diarrhoea), bleeding disorders (such as increased bleeding time or risk of haemorrhage), kidney stones (due to increased oxalate excretion), thyroid dysfunction (due to interference with iodine uptake), estrogenic or anti-estrogenic effects (due to modulation of hormone receptors or enzymes), and altered drug metabolism (due to inhibition or induction of cytochrome P450 enzymes).[39]

CONCLUSION:

In conclusion, this article has discussed the pathophysiology of Alzheimer's disease and dementia, the role of antioxidants in preventing and treating these conditions, and the potential toxicity of excessive antioxidant intake. The main points of the article are:

- Alzheimer's disease and dementia are marked by the buildup of amyloid plaques and neurofibrillary tangles within the brain, resulting in the formation of neuronal abnormalities.

- Antioxidants are substances capable of counteracting free radicals, which are reactive species that can damage cellular components and contribute to oxidative stress and inflammation in the brain.
- Antioxidants may have beneficial effects on Alzheimer's disease and mitigating the impact of oxidative stress and inflammation, modulating amyloid production and clearance, and enhancing neuronal survival and function.
- However, antioxidants may also have adverse effects on Alzheimer's disease and dementia by interfering with normal redox signalling, disrupting the balance between pro- and anti-inflammatory mediators, and inducing pro-oxidant or cytotoxic effects at high doses or in certain conditions.

Therefore, the use of antioxidants for Alzheimer's disease and dementia requires further investigation and optimization, taking into account the type, dose, timing, and combination of antioxidants, as well as the individual characteristics and stage of the disease. Future research should also explore the mechanisms and biomarkers of antioxidant action and toxicity, as well as the potential interactions and synergies between antioxidants and other therapeutic strategies.

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