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# Physiology of Possible Role of Vitamin E in Management of Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD), a progressive neurodegenerative disorder, is characterized by cognitive decline, memory loss, and behavioral disturbances. Its pathogenesis is complex and multifactorial, involving amyloid-β (Aβ) plaque deposition, neurofibrillary tangle formation, oxidative stress, and neuroinflammation. While currently no cure exists, therapeutic strategies aim to mitigate disease progression and improve patient quality of life. Vitamin E, a potent lipid-soluble antioxidant, has emerged as a potential therapeutic agent due to its multifaceted physiological effects relevant to AD pathology. This article explores the potential mechanisms through which vitamin E might contribute to AD management. Its primary role is scavenging free radicals, reducing oxidative stress, a hallmark of AD. Oxidative stress damages neuronal membranes, mitochondria, and proteins, contributing to neuronal dysfunction and death. Vitamin E, specifically α-tocopherol, effectively neutralizes reactive oxygen species (ROS) and lipid peroxides, protecting neuronal structures from oxidative damage. Furthermore, vitamin E's influence extends beyond direct antioxidant activity. It modulates inflammatory pathways by inhibiting the production of pro-inflammatory cytokines, thereby reducing neuroinflammation, another key contributor to AD pathogenesis. Studies suggest that vitamin E can also influence Aβ metabolism, potentially reducing its aggregation and plaque formation. This may involve influencing Aβ-related signaling pathways or interacting with Aβ itself, thereby preventing its neurotoxic effects. However, the clinical efficacy of vitamin E in AD remains a subject of ongoing debate. While some clinical trials have demonstrated modest cognitive benefits, particularly in the early stages of the disease, others have yielded inconsistent results. This variability may be attributed to factors such as dosage, disease stage at intervention, and patient heterogeneity. Furthermore, the precise mechanisms through which vitamin E exerts its effects in the complex milieu of the AD brain require further investigation. Future research should focus on elucidating the optimal dosage, treatment duration, and patient selection criteria for maximizing the therapeutic potential of vitamin E. Investigating the synergistic effects of vitamin E with other therapeutic interventions, such as cholinesterase inhibitors or disease-modifying therapies, may also prove beneficial. Ultimately, a comprehensive understanding of vitamin E's physiological actions in the context of AD is crucial for developing effective and targeted therapeutic strategies.

**Keywords:** *Vitamin E, Alzheimer's Disease*

**Introduction.**

The neurodegenerative disease Alzheimer's disease (AD) has a slow onset and typically manifests in old age. On the other hand, a paradigm shift in AD has occurred in recent years. A long time ago, scientists believed that AD was a disease that develops naturally with getting older. We now know that the disease starts anywhere from fifteen years (in genetic cases) to twenty to thirty years (in sporadic cases) before any sort of clinical symptom manifests [1]. There is currently no treatment that can stop or reverse the condition, and doctors have a tough time doing their jobs because they don't know when symptoms first appear. The fact that we still don't know what causes the disease to start is another obstacle.
This is one way in which various theories attempt to account for the genesis of AD. It is possible that various theories will coexist and overlap with one another. The theories can be categorized into three main areas: Protein deposits form the basis of the hypotheses. The tau theory and the beta-amyloid (Aβ) cascade hypothesis are part of this category.

Seen as senile plaques, the deposits mostly created by Aβ peptide [2]. The amyloid precursor protein (APP), a membrane protein, is the source of Aβ by proteolysis. Arguments in support of the Aβ cascade theory include the following: AD is caused by mutations in genes involved in Aβ genesis [3,4], amyloid deposition is not caused by mutations in the tau protein gene [5,6], the ApoE4 allele increases the risk of AD by reducing the clearance of the Aβ peptide [7], memory impairment, loss of synapses, and hyper-phosphorylation of tau [8] are symptoms of Aβ oligomers isolated from AD brains [8], and Aβ peptide can induce hyper-phosphorylation of tau [9].
Neurofibrillary tangles are the name given to the deposits mostly created by the tau protein. The stability of the cytoskeleton depends critically on the cytoskeleton protein tau. In the pathophysiology of Alzheimer's disease, Tau becomes hyperphosphorylated, which disrupts the cytoskeleton. There is neurodegeneration and cell death in neurons that have a high concentration of hyper-phosphorylated tau [10]. Evidence supporting this theory includes the following: a strong correlation between the severity of Alzheimer's disease (AD) and the accumulation of neurofibrillary tangles in the brain [11,12,13]; a correlation between the degree of cognitive impairment in AD patients and the amount of hyper-phosphorylated tau species in their cerebrospinal fluid (CSF) [14]; and a reduction in tau filaments caused by medications targeting this therapeutic target improves cognitive function [15].

Neuroinflammation is the initial event in Alzheimer's disease, according to the theory of reactive processes. In AD, there is an increase in inflammatory cytokines [16,17]. Blood and brain samples from patients show elevated amounts of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), in comparison to those from controls. Animal models of Alzheimer's disease show elevated levels of several inflammatory markers, including interleukin (IL)-1, interleukin-6, GM-CFS, interleukin-12, interleukin-26, and tumor necrosis factor (TNF). On histological examination, reactive astrocytes and microglia encircle distinctive amyloid plaques in the brains of AD patients [18]. Additionally, astrocyte activation appears to happen relatively early in the pathogenic process, according to investigations with cerebral amyloidosis mice [19]. It has been observed that the increase of cells and proinflammatory cytokines happens prior to the accumulation of Aβ [20].

Hypotheses based on functional impairment include the oxidative stress, vascular, and calcium imbalance theories. Each mutation in early-onset Alzheimer's disease changes the cell's calcium equilibrium, lending credence to the calcium idea [21]. Prior to the development of Aβ or any other histological change in sporadic

AD, there is evidence that neurons in the brain may be too excited because their calcium levels are higher than normal [22].
Proponents of the vascular theory argue that: (1) vascular risk factors are clearly linked to AD; (2) people with AD exhibit early vascular damage; (3) neurodegeneration can be caused solely by vascular damage; and (4) intravascular deposits of Aβ are found in the early stages of AD [23].

**Oxidative Stress Theory and AD**

When antioxidant defenses are inadequate and oxidant species formation is strong, a condition known as oxidative stress occurs [24]. This leads to a disruption in the homeostatic equilibrium that is caused by oxidant insult [25]. The process by which mitochondria convert oxygen to water. Mitochondrial oxygen reduction to water yields reactive oxygen species (ROS), a class of molecules that interact with a variety of adjacent biological components due to their reactivity. The brain, in contrast, uses more oxygen than any other organ in the body. It may only make up a little fraction of your body weight (approximately 2-3%), yet it accounts for 20-25% of your basal metabolic rate. Hence, it is the organ that produces the most reactive oxygen species (ROS). In Alzheimer's disease, metabolic control decreases and reactive oxygen species (ROS) production increases at an early stage [26].

It is early in the course of Alzheimer's disease for the brain to exhibit oxidation of all macromolecules. In Alzheimer's disease, oxidation occurs in lipids, proteins, nucleic acids, and polysaccharides.
Glycation is the process by which reduced sugars combine with protein side chains to produce advanced glycation end products (AGE). Inside neurons, in senile plaques, and in neurofibrillary tangles, glucation products tend to accumulate because they are relatively stable compounds [27].
An enzyme's physiological function can be rendered inactive when reactive carbonyls and aldehydes, which are highly reactive byproducts of hydroxy radical attack on unsaturated lipids, are produced during lipid peroxidation. Moreover, oxidized membranes exhibit different mobility. The cell bodies of susceptible neurons are the most prevalent sites for aldehyde adducts of proteins, which are also present on neurofibrillary tangles and senile plaques [28].

Protein oxidation poses a threat of peptide bond compromise and cleavage. Protein nitration is another similar process that occurs regularly, and reactive carbonyls are also formed. Neuronal cell bodies are involved in all of these protein changes [29].
Last but not least, oxidation may also influence nucleic acids. ROS have the ability to modify purinic and pyrimidinic bases, potentially leading to harmful or even mutagenic outcomes. Presumably oxidized nucleic acids build up in the cell bodies of susceptible neurons [30].
Vitamin E Protects Nerves and Antioxidants
The group of eight molecules known as vitamin E is a member of the class of vitamins that are soluble in fat. The fundamental characteristic of the tocopherols and tocotrienols found in this group is their antioxidant capacity. On the other hand, vitamin E is important for brain health because of its neuroprotective, anti-inflammatory, and hypocholesterolemic characteristics [31,32,33].

Vitamin E's ability to neutralize free radicals, such as reactive oxygen species (ROS), is due to the presence of a hydroxyl group on the phenolic group on the chromanol ring, which is responsible for its antioxidant effect [34]. An inert byproduct and a radical form of vitamin E are the end results of this process. When this happens, vitamin E radicals can either react with other free radical lipids or be restored to their original form by vitamin C [35,36,37,38]. In this way, vitamin E protects cellular membranes by destroying peroxyl radicals and preventing lipid peroxidation [39], particularly that which occurs with polyunsaturated fatty acids.
Compared to other antioxidants such as glutathione or β-carotene, Vitamin E possesses more antioxidant ability against peroxyl radicals [40]. Multiple in vitro and in vivo investigations have demonstrated this

antioxidant effect. In 1997, researchers Ham and Liebler reported on the effects of supplementing rats' diets with vitamin E, providing crucial evidence of the vitamin E's antioxidant ability. By using t-Bu-OOH to induce lipid peroxidation in liver cells, they assessed the antioxidant capabilities of vitamin E. Vitamin E-treated rats had less metabolic alterations, according to their findings [41].

Additionally, the α-tocopherol form of vitamin E is particularly revered as one of the brain's most crucial antioxidants. The reason behind this is because the brain contains high amounts of the transporter α-TTP, which is responsible for regulating and distributing vitamin E levels in various tissues [42,43]. The fact that those who carry a mutation in the α-TTP gene experience progressive spinocerebellar ataxia, areflexia, loss of proprioception, and abnormally low vitamin E levels highlights its crucial involvement in brain function [44,45]. The cerebellum, particularly in astrocytes that provide vitamin E to nearby neurons, has the highest α-TTP expression in the encephalon [46]. The expression of α-TTP is elevated in the brains of individuals suffering from neurodegenerative disorders, which is a crucial finding [42,47]. Because of its antioxidant properties, vitamin E is clearly involved in neuroprotection.
Earlier it was noted that AD is characterized by an obvious increase in ROS generation, which in turn increases the oxidation of all macromolecules. Given that Aβ is involved in the production of reactive oxygen species (ROS) by the mitochondria and endoplasmic reticulum, it should come as no surprise that it is a significant stimulator of oxidative stress within cells. Additionally, Aβ prevents the transmission of action potentials by interfering with cellular calcium homeostasis. Aβ can stimulate lipid peroxidation and produce pro-oxidant species, such as malondialdehyde (MDA) or 4-hydroxynonenal (4HNE), when it gathers and accumulates close to the cell membrane. The final one is an aldehyde that can covalently alter nearby lipids and proteins, tau included [48,49].

Tau aggregation in vitro can be facilitated by oxidative modification [50], which may also stimulate tau hyper-phosphorylation and neurofibrillary tangle formation [51]. Furthermore, the activation of glycogen synthase kinase-3 beta (GSK3β) is enhanced by oxidative stress, which in turn promotes tau hyper-phosphorylation. GSK3β phosphorylates tau on the majority of serine and threonine residues in paired helical filaments and is expressed everywhere [52]. Lastly, tau hyper-phosphorylation occurs as a result of 4HNE's direct activation of p38, a mitogen-activated protein (MAP) kinase [53]. Actually, researchers observed a link between active p38 and the amount of aggregated tau in transgenic mice with hyper-phosphorylated tau [54].

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**Vitamin E as an Anti-Inflammatory and Cell Signaling**

In addition to protecting cells from free radical damage, vitamin E can boost the immunological response of the aged. The immune system becomes dysregulated with age and in certain neurological illnesses like Alzheimer's, leading to an overproduction of inflammatory reactions. Several studies have shown that vitamin E, when taken as a dietary supplement, can reduce inflammation in the elderly.

Among other positive benefits, these investigations demonstrate in vitro T cell proliferation, IL-2 generation, and suppression of E2 prostaglandin [32]. The levels of IL-2 receptors in the T-lymphocyte population were reported to rise when Lee and colleagues administered 233 mg of vitamin E daily for 28 days [55]. De La Fuente et al. demonstrated that α-tocopherol had a positive impact on the adhesion capacity of lymphocytes, enhanced IL-2 production, NK activity, and lymphocyte proliferation in aged individuals when given a similar dose for three months [56].

Having a coexisting condition, such as allergic rhinitis [57], makes this positive impact diminish [58], and in adult smokers it even causes detrimental effects [59,60].
Vitamin E inhibits prostaglandins E2 and D2 without inhibiting the activities of cyclo-oxygenase (COXs) and 5-lipoxygenase (5-LOX) [61,62,63]. This is the mechanism by which vitamin E acts on the immune system. One side of the coin is that COX activity is inhibited by vitamin E metabolites that result from the ϋ- and β-oxidation of its hydrophobic side chain [62]. To counter this, vitamin E inhibits 5-LOX activity by blocking ionophores, which in turn prevents membrane alterations that lead to calcium influx blockage [63]. Both inhibitions activate a signaling pathway that finally induces the inhibition of the prostaglandins. Then IL-2 production is generated and, therefore, an immune response (Figure 1).

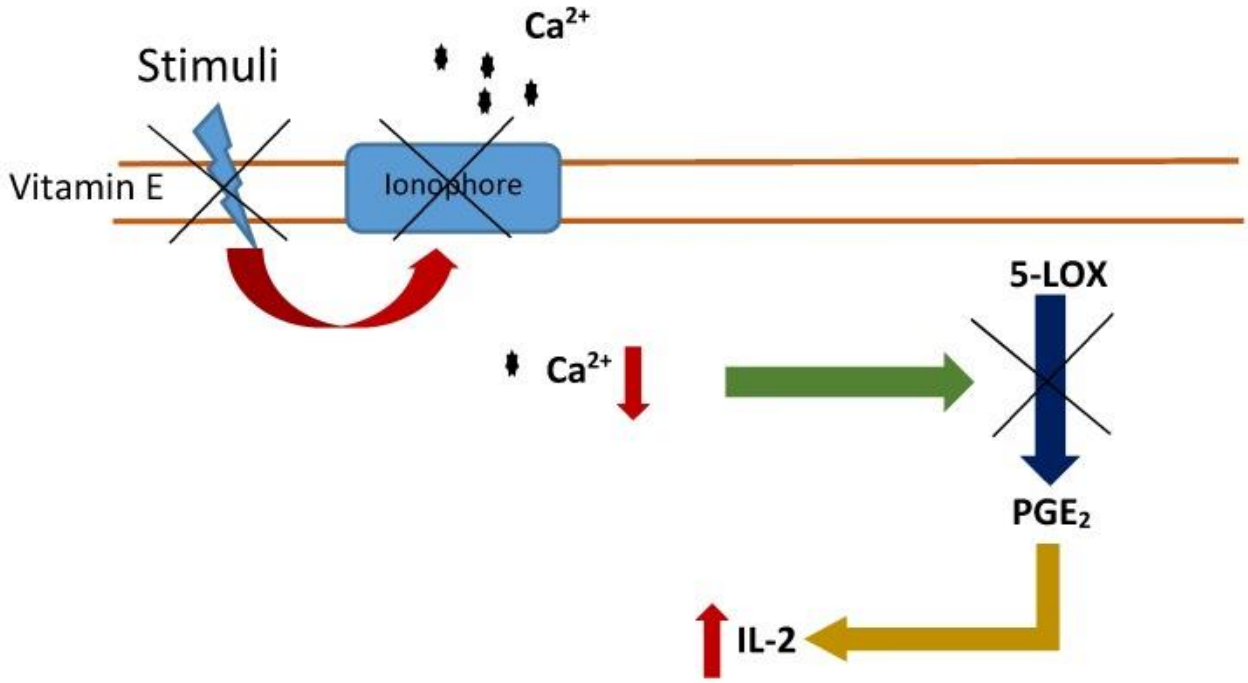


**Figure 1: Vitamin E effects. Vitamin E can act as anti-inflammatory through protein kinase C (PKC) inhibition and has antioxidant and neuroprotection properties through the attack to reactive oxygen species (ROS).**

Research has demonstrated that vitamin E inhibits protein kinase C (PKC) without affecting its antioxidant properties [64]. Both the diacylglycerol kinase activity and the phosphatase (PP)2A, which inhibits the active form, can be activated by vitamin E, therefore the process is two-fold [65,66]. Vitamin E isoform determines the outcome; α-tocopherol blocks PKC in vascular smooth muscle, halting cell proliferation, while β-tocopherol prevents this effect [64,67,68].

On the other hand, vitamin E's PKC inhibitory actions may not be harmless in certain cases of AD pathogenesis. An instance where PKC is significant in immune response is when distinct isoforms of PKC are expressed by the subpopulation of T-cells that are reactive to Aβ1-42 at various clinical stages of Alzheimer's disease [69]. In addition, the non-amyloidogenic APP processing relies on PKC regulating α-secretase activity. This limits the amyloidogenic pathway and, by extension, the production of the harmful amyloid beta peptide [70].
Some genes that can be transcriptionally regulated by vitamin E in a manner that is not dependent on protein kinase C include intracellular adhesion molecule-1 [73], SR class A [72], and CD36 [71].

There was a published finding over 30 years ago that vitamin E levels were lower in 55 AD patients compared to non-demented controls [74]. Countless subsequent studies have confirmed these findings. Even with a small sample size, we consistently get meaningful results. Eighty articles examining the relationship between micronutrients and AD were included in a 2014 meta-analysis. Among other things, researchers found that AD patients had reduced plasma levels of vitamin E. In addition, the authors hypothesized that micronutrient status may be compromised prior to malnutrition [75:78], and they failed to detect a correlation between patients' vitamin E levels and their malnutrition state. Evidence from a recent meta-analysis of 116 papers supports the idea that vitamin E levels in cerebrospinal fluid and the brain of AD patients are much decreased [79:82]. Serum vitamin E concentrations were lower in Alzheimer's disease patients compared to healthy older controls, according to a recent meta-analysis that included 17 trials and a total of 904 AD patients and 1,153 controls [83].

In terms of epidemiological studies, it was also found that taking vitamin E supplements reduced the likelihood of acquiring Alzheimer's disease. After 4.3 years of follow-up, none of the 27 people who took vitamin E supplements developed AD in a 1998 prospective research that included 633 people [84:86]. With a six-year follow-up, Engerhalt et al. (2002) confirmed this finding in a separate Dutch sample [87:89]. Another prospective study was published in the same year. It tracked 815 people, all 65 and up, who were free of AD at baseline and were followed for an average of 3.9 years. The study ran from 1993 to 2000. This study found that vitamin E-containing foods may lower the chance of acquiring Alzheimer's disease, but no other antioxidants were linked to this effect. Nevertheless, this link was noted exclusively in people who did not possess the APOE ε4 gene [91]. Cache Country Study, a prospective research out of Utah, USA, found that persons who took vitamin E and multivitamin complexes that included vitamin C had a significantly reduced incidence of AD. Taken individually, these chemicals did not appear to have any protective effects [92].

Data from the Rotterdam Study, which included 365 individuals with AD, also shown a slight decrease in the long-term risk of AD. It is worth noting that the subjects who consumed more vitamin E-rich meals were the only ones who showed beneficial benefits. Dementia risk was not reduced in people with average vitamin E consumption, albeit [93]. In a cohort trial of 560 AD patients conducted from 1991 to 2002 in Canada, researchers found that taking vitamin E supplements lowered the incidence of cognitive deterioration [94].

But three other research found no link between vitamin E consumption and Alzheimer's disease risk. The first study found no protective effect of vitamin E or vitamin C supplementation against Alzheimer's disease or dementia in general, after following 2969 people every six months for 5.5 years [95:98]. Vitamin E and C supplements may enhance cognitive performance in old age, according to the second study, which included 3385 men from The Honolulu-Asia Aging Study [96]. However, the study did not find any protective effect for Alzheimer's disease specifically. Finally, it was discovered that neither dietary, supplementary, nor total intake of vitamin E was linked to a decreased risk of Alzheimer's disease [99:101] in another trial involving 980 older people in the Washington Heights-Inwood Columbia Aging Project.

Vitamin E's effectiveness as a therapy for Alzheimer's disease was initially demonstrated in a 1997 study by Sano et al. Supplemental vitamin E was the primary focus of this placebo-controlled, randomized, multicenter clinical trial in Alzheimer's disease patients with moderate to severe impairment [102]. Vitamin E at 2000 IU/d or a placebo was given to 321 participants for two years [102]. The researchers looked at the duration until death, institutionalization, incapacity to carry out BDDs, or severe dementia occurred [102]. They concluded that this dose of vitamin E slows AD progression. Twenty-two years later the controversy still exists. Table 1 summarizes Clinical trials about the effectiveness of vitamin E in AD treatment.

Table 1: Clinical trials about the effectiveness of vitamin E in the AD treatment.

| Authors and Publication Year | Number of Patients and Diagnosis | Isoform | Doses | Time | Method | Results |
|---|---|---|---|---|---|---|
| Sano et al., 1997 [102] | 341 AD | α-tocopherol | 2000 IU/d for 2 years | Two years | Alzheimer's Disease Assessment Scale (ADCS); Mini–Mental State Examination (MMSE); Blessed Dementia Scale; Dependence Scale | Decline progression of AD |
| Petersen et al., 2005 [103] | 769 AD | not specified | 2000 IU/d for 3 years | Three years | A battery of fifteen cognitive tests (MMSE, The Clinical Dementia Rating (CDR), ADCS . . . ) | No benefit |
| Lloret et al., 2009 [104] | 33 AD | α-tocopherol | 800 IU/d for 6 months | Six months | MMSE; Blessed-Dementia Scale; Clock Drawing Test | Cognitive status was maintained in some cases but in others it was detrimental in terms of cognition |
| Dysken et al., 2014 [105] | 613 mild to moderate AD | α-tocopherol | 2000 IU/d | 6 months–4 years | Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory; MMSE | Reduced functional decline |
| Kryscio et al., 2017 [106] | 7540 asymptomatic older men | | 400 IU/d | 6 years | Memory Impairment Screen (MIS); Consortium to Establish a Registry for AD (CERAD) battery | No prevention of dementia |

At the present time, clinical studies have revealed unreliable findings on the effect of vitamin E on AD-developing risk. Thus, it remains unclear whether vitamin E levels are genetically associated with AD risk or if the supplementation with this compound could be beneficial in delaying the progression of dementia.

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