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Role of Tocopherols in Treatment of Depression related Alzheimer's Disease

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Introduction

Depression is a common and serious medical illness that involves the body, mood, and thoughts and affects the way a person eats, sleeps, feels about himself or herself. The signs and symptoms of depression comprise loss of interest in activities that were one interesting or enjoyable, loss of appetite or overeating consequential in weight loss or weight gain respectively; loss of emotional expressions, anxious and no emotional reaction or expression. Depression gradually leads to the Alzheimer's disease (AD) [1,2].

Alzheimer has (attributed to Alois Alzheimer), is a physical disease that affects the brain commonly. AD is a neurodegenerative defect in the CNS, clinically characterized by gradual loss of memory and other cognitive skills, resulting in severe dementia [3,4]. Most of patients present for diagnosis at 65 years of age and above, the guides suggest that the pathological processes underlying this destructive neurodegenerative disease start years ago or decades, before the clinical diagnosis. Therefore, aging is a main risk factor for the progress of AD, but subclinical of AD probably beginning in younger people [5]. Through this disease, proteins gathering up in the brain to create structures called tangles and plaques and tangles that build-up in an around nerve cells. This process leads to lack of the links between nerve cells, damage and death of nerve cells and loss of brain tissue [6].

The correlation of socioeconomic status and Alzheimer risk is composite and insufficient. The only reason is lower socioeconomic status that contributes with lifetime exposures to environmental pollutants, stress, poor nutrition, unhealthy behaviors and depression. Commonly, researches explained that less education is main reason of Alzheimer's disease. One of them reveals that smoking, unhealthy lifestyle and less education are the risk of Alzheimer's disease [7,8]. When socioeconomic status and education have analyzed, less education determined more important risk factor and increased threefold, compared to community with higher education and high socioeconomic status [9]. The symptoms of Alzheimer's disease appears earlier in lower socioeconomic community [10]. These studies determined that less and lower socioeconomic status are playing important role to accelerate the Alzheimer's disease, which can be only diminish with more education.

Psychosocial stress has a significant impact in the growth of Alzheimer's disease. Few studies determined that stress is major problem for later development of Alzheimer's disease [11,12]. While few researches explained that, psychosocial stress is not only a risk factor but it is the early symptom of Alzheimer's disease [13,14].

Furthermore, Alzheimer's patients have a lack of some important chemicals (neurotransmitter acetylcholine) in the brain that work as a messengers help to transmit signals around the brain. When there is a lack of these chemicals, the signals are not transmitted as efficiently. The case often begins with mild memory slips and then gradually advances to dementia gradual deterioration of memory and most mental functions [15]. Recent genetically studies have identified four genes linked with inherited risk for AD, including amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2), apolipoprotein E (apo E) and α_2-macroglobulin gene. These genes consider to about half of the total hereditary risk for AD [16]. The concentration of Aβ in the tissue shows to be critical for keeping of the peptide's structure, and the increase in concentration of Aβ in the tissue is the probable cause of aggregation and misfolding. Whereas, increase production of Aβ, leaded by mutations in the genes encoding APP, PS1 and PS2, all feature increased production of this peptide, thus accounts for the hereditary form of AD [17]. Researchers have long known that that depression and Alzheimer's disease are linked but it was not clear whether depression was a risk factor for Alzheimer's or a symptom of a disease. Exactly why the plaques and tangles form is a mystery but previous brain anatomical studies suggested that depression is to be blamed. Precisely how a mood disorder like depression can contribute to Alzheimer's disease is not known, but the effect is probably cumulative [18].

One theory suggested that depression weakens the body's defense mechanism against dementia by affecting the brains blood supply. CVD (another risk factor for Alzheimer) and depression are often clinically linked to each other, because of reduced blood flow to the brain. The vascular change might render the brain more vulnerable to Alzheimer's related damage [19].

One recent study, indicating that genetic factor, neuron atomic changes, vascular risk factors and the imbalance of neurotransmitters might contribute to depressive symptoms in AD [20]. Tau pathology and amyloid-β accumulate also correlate with depression in AD. In addition, the alteration of hypothalamic-pituitary-adrenal axis, inflammatory pathway and neurotrophin deficiency are the possible biological mechanism linking depression and AD [21].

Oxidative stress is defined as a defect in the balance between output of free radicals and reactive metabolites (antioxidants) [22]. This imbalance can conduct to harm of important cells and biomolecules, with possible impact overall body [23.] Free radicals are unsettled molecules with electrons that could impair the cell membrane fatty acids and proteins, function by reacting with them [24]. Free radicals could be a predisposing factor for many health problems because of their effects on mutation and DNA damage [25]. Free radicals are generated endogenously in our body or exogenously as when exposed to different physiochemical conditions or pathological states. Even though a low or moderate ROS have a good physiochemical effect including the killing of invading pathogens, wound healing, and tissue renovation

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processes [26]. The disproportionate generation of ROS will badly affect homeostasis and causes oxidative tissue damage, which is a big serious problem. The reverse impact of ROS can be limited by natural antioxidant pathways, but also can be stimulated by many oxidative stressors contributing to tissue damage [27]. ROS are produced in response to exogenous and endogenous agents include stress response. Disorder of normal cellular homeostasis by redox signaling gives a shone in an actual disease for every organ [28].

Free radicals and antioxidants have become commonly used terms in modern discussions of disease mechanisms [29]. NADPH oxidase, NADPH oxidase isoforms (NOX), Peroxidases, lipoxygenases (LOXs), xanthine oxidase (XO), glucose oxidase, nitric oxide synthase, myeloperoxidase (MPO) and cyclooxygenases (COXs) are all enzymes that catalyze ROS-generating chemical reactions [30,31]. Intracellular compartments including mitochondria, the endoplasmic reticulum, nuclei, peroxisomes, the cytosol, plasma membranes and even extracellular spaces are capable of ROS generation [32,33]. The mitochondrial electron transport chain is the major site of ROS production in most mammalian cells [34].

An antioxidant is any substance, synthetic or natural, that inhibits oxidation in the cell of living organisms. Oxidation can produce free radicals which, when left unattended, may cause oxidative stress within the body. Oxidative stress has been thought to be a major contributor to the development of many diseases in human body [35]. Antioxidants are known as "free radicals scavengers", which help the body combat free radicals by donating an electron safely neutralize free radicals. Antioxidants may also help reduce the overall formation of free radicals. The body needs antioxidants in order to maintain a safe balance of free radicals [36].

In the oxidative stress, free radical hypothesis of aging was subtracts that the age-related accumulation of ROS results in damage to major components of cells: nucleus, membranes, mitochondrial DNA and cytoplasmic proteins. Depending on suggested by many authors for many years, an imbalance between the generation of free radicals and ROS might be involved in the pathogenesis of most of the neurodegenerative disorders, including AD [37-39]. The impact of free radicals can be carried out by identification of end-products of biomolecular peroxidation [40]. This process can leads to the formation of protein carbonyls (CRBNLs), melanodialdehyde (MDA) molecules, peroxynitriate, and other advanced glycation products [41,42]. Researchers focused on the measurement of MDA levels and catalase, glutathione peroxidase, superoxide dismutase and reductase in blood samples from patients with AD. Results indicated an increasing level of MDA with age, because these molecules are formed during biomolecular peroxidation, the results indicate on correlation between oxidative stress and stages of AD [20]. Free radicals affect protein, RNA and DNA. The studies were based on correlation between protein modifications with level of oxidative stress. Many researchers suggested that oxidative stress could be produced by aggregation of oxidative-damaged protein in plasma; they believe that protein carbonyl groups are better marker for the level of oxidative stress. Whereas, increased levels of the mentioned protein was reported in plasma from patients with AD [43].

There are two types of vitamin concerned in antioxidant alleyway, which are vitamin E and vitamin C [44]. Vitamin E family includes eight natural compounds: four tocopherols and four tocotrienols. Vitamin E occurs naturally in the diet. It has several biological activities, including functioning as an antioxidant to scavenge toxic free radicals [45]. Evidence that free radicals may contribute to the pathological processes behind cognitive impairment has led to interest in the use of vitamin E supplements to treat AD [46].

Vitamin E is a fat-soluble vitamin also found in your body to prevent the development of the ROS (reactive oxygen species) chemical through its concentrated antioxidants. A lipid-soluble antioxidant; prevents the *in vitro* oxidation of the membrane lipids and the accumulation of oxidative metabolites induced by Ab peptide neurotoxicity affects the expression of genes that are involved in the clearance of Ab [44,47,48]. The antioxidant quality of vitamin E works to counteract the potential damage caused by free radicals and ROS, and vitamin E may help to prevent or offset the development of certain chronic diseases linked to free radicals [49]. In the study of vitamin E it was suggested through *in vitro* cell studies that vitamin E also supports healthy immune system function, gene expression, cell signals and hinders blood platelet aggregation. Vitamin E is stored in the liver and is measured through serum concentrations. A study found that patients suffering from major depression had lower vitamin E serum concentrations then those without major depression. The researchers hypothesize that those with major depression may be suffering from an increase in lipid per oxidation due to a lack of antioxidants. Yet suggested a lack of vitamin E through dietary sources may be the cause of low vitamin E levels. Compared with cognitively normal subjects, AD and MCI had lower levels of tocopherols and total tocorienols and total vitamin E [45].

Alpha-tocopherols is traditionally recognized as the most active form of vitamin-E in humans and is a potent antioxidant that is believed to be important in protecting cells from oxidative stress, regulating immune function, maintaining endothelial cells integrity and balancing normal coagulation. Alpha-tocopherols traps free radicals, and interrupts the chain reaction that damages cells. It reduces the degeneration of hippocampal cells after cerebral ischemia and enhances the recovery of motor function after spinal cord injury [50,51]. In hypoxic cultured neurons, alpha-tocopherols inhibited lipid per oxidation and reduce cell death associated with β-amyloid protein [52].

Vitamin E from foods may be safer and effective than alpha tocopherols provided in supplement form. Vitamin E can delay or prevent a clinical diagnosis of Alzheimer disease in elderly persons with mild cognitive impairment. Treatment with antioxidants might theoretically act to prevent propagation of tissue damage and improve both survival and neurological outcome [53]. Administration of vitamin E correlated with cognitive decline and long-time supplementation of vitamin E results in a better cognitive condition and prevents brain oxidative damage [49,50].

We suggest using the tocopherols to be an integrated supplement as a part of diet for Alzheimer could be efficient and mechanisms are subjected to future understandings at molecular levels as per dose and efficacy.

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