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OPINION

A Micronutrient Mixture may Reduce the incidence and Improve the Effectiveness of Drug Therapy of Alzheimer's Disease

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ABSTRACT

Costus species is a significant restorative and decorative plant used to fix various illnesses. In India 6,000 plants are used for traditional and herbal medicine. The plant *Costus spicatus* commonly known as 'Spiral ginger' as 'insulin plant', a wonder drug down blood sugar level and hypoglycemic properties. The plant has been found to have numerous pharmacological exercises, for example, antibacterial, antifungal, anticholineesterase, cancer prevention agent, antihyperglycemic, calming, pain relieving, antipyretic, antidiuretic, antistress and estrogenic action. The rhizomes of *Costus species* are harsh, astringent, bitter, cooling, love potion, laxative, anthelminthic, depurative, febrifuge, expectorant, tonic, improve assimilation, and is an energizer herb that clears poisons. It additionally has against richness, anabolic properties. This audit plainly demonstrates the need to perform logical investigations with therapeutic vegetation featuring potential for *Costus species* because of its antidiabetic, pharmacological and cell reinforcement properties. The rhizome is credited with purgative and tonic properties. India is a botanical garden of the world for natural resources.

Alzheimer's Disease (AD) is a progressive complex neurodegenerative disorder, which is characterized by the gradual loss of cognitive function due to degeneration and death of cortical and hippocampal neurons in the brain. This disease alone accounts for 60-70% of dementia. More than 90% of cases are acquired during the lifetime, while 5-10% of AD are considered familial. In the USA, 15-20% of individuals 65 years or older have mild cognitive impairment. It is the 5th leading cause of death in the USA. In 2021, approximately 6.2 million Americans of 65 years or older have AD dementia; this number may increase to 12.5 million, if no effective preventive strategy is developed and implemented [1]. In 2021, approximately 50 million persons are affected with AD and other forms of dementia worldwide [2]. The cost of AD and other dementia is estimated to be $355 billion in 2021; this value is likely to increase to $1.1 trillion (in 2021 dollar). Emotional cost of the family members cannot be measured.

Despite extensive research during last decades it has not been possible to develop any effective prophylactic remedy for reducing the incidence of AD. Treatment with drugs have produced only modest benefits for a short period of time. Since AD is a multifactorial diseases involving number of neurons signaling systems; attenuating one of the neuron signaling systems is unlikely to be useful in reducing the risk of AD. To develop an effective remedy for reducing the incidence of AD, an early biochemical defect that participate in the onset of AD should be identified. Similarly, biochemical defects that contribute to neuronal degeneration and death should be identified in order to improve the efficacy current drug therapy in AD.

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Biochemical defects associated with the onset and progression of AD

Several reviews show that increased oxidative stress and chronic inflammation [3,4] play an early and central role in the onset and progression of AD. Neuronal injury such as oxidative damage triggers activation of microglia and astrocytes that release anti-inflammatory cytokines to heal the injury. As soon as the neuronal injury is healed, activation of microglia and astrocytes is turnoff. However, if oxidative damage of the neurons is not healed, chronic inflammation occurs by activating microglia and astrocytes, which releases pro-inflammatory mediators that are toxic to neurons.

Based on published studies, it has been proposed that increased oxidative stress is one of the earliest biochemical defects in the development of AD [3]. This hypothesis is supported by the fact that markers of oxidative damage and chronic inflammation were present in asymptomatic individuals carrying mutated presenilin1 and APP AD genes [5]. Other contributors to AD such as increased production of Aβ1-42 from the cleavage of APP [6,7], mitochondrial dysfunction [8-10], proteosome inhibition [11], and tau phosphorylation [12,13] occur subsequent to increased oxidative stress. Increased oxidative stress and inflammation also play an important role in the progression of AD by enhancing neuronal death.

Current drug treatments in AD

Cholinesterase inhibitors such as Razadyne (galatamine), Exelon rivastigmine), and Aricept (donepezil) are used to treat mild to modest AD. Namenda (memantine), an antagonist of N-Methyl-D-Aspartate (NMDA) and Namzarich, a combination of Namenda and Aricept are used to treat moderate to severe AD [14]. Cholinesterase inhibitors increase the levels of acetylcholine in the cholinergic neurons, which store memory. Thus, the benefits of these drugs depend upon the viability of cholinergic neurons. Since these drugs do not affect oxidative stress and inflammation that contribute to the death of neurons, the effectiveness of these drugs last only for a short period of time. If these drugs are combined with antioxidants that would reduce oxidative stress and chronic inflammation, the effectiveness of these drugs in improving cognitive function may last for a longer period of time.

Aducanumab, a monoclonal antibody that targets aggregated beta-amyloid proteins, developed by Biogen for the treatment of AD is under review by the FDA. The rationale for the development of this antibody was that beta amyloid protein causes neurodegeneration and death of cholinergic neurons; therefore, removal of this protein may improve clinical symptoms of the disease. Since AD involves other cellular defects discussed earlier, removing only beta-amyloids may not produce any significant benefits in improving cognitive function.

Use of antioxidants in AD

Increased oxidative stress is one of the earliest events which initiates and participated in the progression of AD. Therefore, supplementation with antioxidants may be useful in reducing the risk as well as improving the efficacy of drug therapy of AD.

Although the use of a single antioxidant produced impressive results in cell culture and animal models of AD, it was ineffective in treating patients with AD; however, it produced minimal benefits in early phase of sporadic AD. This issue has been discussed in a previous reviews [3,4]. The role of antioxidants in combination with drugs has never been investigated.

The potential reasons for the failure of a single antioxidant to yield expected benefits that were observed in animal models of AD, but not in human AD, have been discussed in previous reviews [3,4]. Some of them are listed here.

(a) The patients with AD have high levels of markers of oxidative damage. Administered single antioxidant in a high oxidative environment of such patients would be oxidized, which then would act as a pro-oxidant rather than as an antioxidant.

(b) Different antioxidants are distributed in different amounts in various organs. Even within the cell, they are distributed in varying amounts in the sub-cellular compartments. Administration of a single antioxidant cannot accumulate equally and in sufficient amounts in all organs and all parts of the cell to provide adequate protection against oxidative stress.

(c) Alpha-tocopherol is a more effective scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure. Therefore, administration of one antioxidant may not provide adequate protection again oxidative damage in the whole body.

(d) Elevation of both the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds are essential for optimally reducing oxidative stress. This is due to the fact that antioxidant enzymes and antioxidant compounds reduce oxidative damage by different mechanisms. For example, antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes destroy H_2O_2 by catalysis, converting them to harmless molecules such as water and oxygen. Administration of a single antioxidant cannot achieve this goal.

(e) Administration of a single antioxidant cannot protect both the aqueous and lipid compartments of the cell against enhanced oxidative stress.

The failure of individual antioxidants to yield expected benefits in human AD led us to propose that in order to simultaneously reduce oxidative stress and chronic inflammation, the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds should be elevated at the same time. Oral supplementation with a mixture of antioxidant compounds can enhance their levels in the body; however, increasing the levels of antioxidant enzymes require an activation of a nuclear transcriptional factor Nrf2. A brief description of steps needed to activate Nrf2 is presented here.

Processes of activation of Nrf2

The processes of activation of Nrf2 has been described in a previous review [4]. Briefly, under normal physiological conditions, Reactive Oxygen Species (ROS) is required to activate Nrf2. Activated Nrf2 dissociates itself from Keap1-CuI-Rbx1 complex in the cytoplasm and migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of cytoprotective enzymes including antioxidant enzymes.

During the prolonged oxidative stress commonly observed in human AD, activation of Nrf2 becomes resistant to ROS. This is evidenced by the fact that increased oxidative stress continues to occur in AD despite the presence of Nrf2. However, some antioxidants can activate this ROS-resistant Nrf2. Activation of Nrf2 and antioxidant compounds decrease oxidative stress as well chronic inflammation.

Proposed mixture of micronutrients for reducing the incidence and improving the efficacy of drug therapy of AD

A comprehensive mixture of micronutrients containing vitamin A, mixed carotenoids, vitamin C, alpha-tocopheryl acetate, alpha-tocopheryl succinate, vitamin D3, alpha-lipoic acid, N-acetylcysteine, coenzyme Q10, curcumin, resveratrol, all B-vitamins, and minerals selenomethionine, and zinc for reducing the risk of sporadic AD has been proposed [4]. This micronutrient mixture may increase the levels of antioxidant enzymes by activating the ROS-resistant Nrf2 and enhancing the levels of dietary and endogenous antioxidant compounds at the same time. It is suggested that such a micronutrient mixture may reduce the incidence of AD by simultaneously addressing the reduction of oxidative stress and chronic inflammation. Such a micronutrient mixture may improve the efficacy of drug therapy of AD.

The efficacy of proposed mixture of micronutrients has never been tested in human AD. Therefore, the question can be asked whether a mixture of micronutrients has ever produced beneficial effects in any human diseases. Two clinical studies with a commercial preparation of multivitamin in certain human diseases have produced beneficial effects. For example, oral administration of a multivitamin reduced the risk of cancer in men by about 10% [15], and attenuated the progression of HIV disease, and prolonged the time period of initiating the anti-viral therapy [16]. Therefore, it is likely that oral administration of the proposed micronutrient mixture may reduce the incidence of AD, and may improve the efficacy of drug therapy. Pre-clinical and clinical studies on the efficacy of the proposed micronutrient mixture in prevention and improved management with drug therapy should be tested in AD.

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