Review Article

iMedPub Journals
www.imedpub.com

Journal of Clinical Epigenetics
ISSN 2472-1158

2021
Vol.7 No.7:001

Nutrients that Optimize Aging Brain Functioning: A Systematic Review

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Received date: October 19, 2021; **Accepted date:** November 02, 2021**; Published date:** November 09, 2021

Citation: Alsogair SS (2021) Nutrients that Optimize Aging Brain Functioning: A Systematic Review. J Clin Epigen Vol.7 No.7:001.

Abstract

Alzheimer's disease is the most common neurodegenerative disease amongst the elderly population and aging is the most significant factor that is linked to its pathogenesis. Its pathology is characterized by the formation of senile plaques and neurofibrillary tangles, but the exact mechanisms of its progression are still unclear. Oxidative stress and inflammation are considered the major epigenetic factors for aging of the brain and maintaining the redox balance is shown to be crucial in the early development of the disease. A plant-based diet, that is rich in antioxidants and other essential micronutrients have proven to be a successful strategy in fighting oxidative stress and inflammation in the brain. Coupled with caloric restrictions and physical exercises, such a diet can reduce the formation of senile plaques and neurofibrillary tangles and may be used as a preventive therapy for people who are vulnerable to this ailment.

Keywords: Nutrient; Alzheimer's; Aging

Introduction

Alzheimer's Disease (AD) is the most common neurodegenerative disease amongst the elderly population and aging is the most significant factor that is linked to its pathogenesis. Its progression can be devastating as it affects cognition and memory, and requires additional attendance for the patients [1]. Despite its prevalence, the effects of established treatment are not entirely clear, and medications only aim to slow the progression of the disease rather than curing it.

Literature Review

AD pathology is characterized by the formation of senile plaques and neurofibrillary tangles (NFTs). Plaques are composed of amyloid β (Aβ), which is a product of the abnormal cleavage of Amyloid Precursor Protein (APP), a trans membrane glycoprotein, whose function is not well understood. Tangles are mainly composed of hyper phosphorylated tau, a microtubule-associated protein. Aβ plaques exhibit neurotoxic properties and cause inflammation [2]. The role of tangles is still not well understood. Some studies suggest that they exhibit protective properties, rather than harmful. Although the exact mechanisms of action of this ailment are still unknown, studies have suggested that oxidative stress and neuro-inflammation are strongly related to the development of plaques and NFTs, as well as a consequence of it [3].

Oxidation products occur consequently to the natural metabolic processes of aerobic cells. That is why animal cells have endogenous antioxidant enzymes like Superoxide Dismutase (SOD) and catalase. However, as the cell ages, free radicals accumulate, leading to the point where enzymatic antioxidant defense is insufficient and antioxidant molecules become reactive [4]. Accumulation of oxidants can cause serious damage to important proteins, membrane lipids, and DNA, altering the normal processes of the cell and eventually killing it [2]. Moreover, damaged cells induce pro-inflammatory responses that activate the cells of the immune system. That is why exogenous antioxidants, like vitamin C, vitamin E, and phenolic compounds, are crucial for maintaining the redox balance in cells and a healthy plant-based diet can be very beneficial for this purpose [5].

Neurons are more vulnerable to oxidative stress due to the high oxygen consumption, high content of easily peroxidizable unsaturated fatty acids, and low levels of antioxidant enzymes, compared to the other cells [6,7]. Oxidative stress triggers events linked to AD pathogenesis, such as Aß formation, redox metal accumulation, neuro-inflammation, and mitochondria dysfunction [8]. This leads to the suggestion that antioxidants may be a key for early prevention and treatment.

Interestingly, recent studies show that neurogenesis can occur in the adult brain. Neural stem cells and precursor cells can differentiate into new neurons [9-11]. Although the exact molecular mechanisms of adult neurogenesis are unknown, there are studies that show the positive effects of several dietary supplements, as well as caloric restrictions and physical activity [12-14].

An adequate diet may achieve lower oxidation levels as well as decreased inflammation, in addition to increased neurogenesis and improved overall health, which prompts for a better quality of life and lower risk of developing neurodegenerative ailments [15,16].

In the current study, we aim to present the main groups of nutrients that can be beneficial for the prevention and early treatment of AD and how they exert their properties.

A literature search was made through PubMed, utilizing the following keywords “aging brain nutrients” and “brain aging nutrition”. 344 articles were selected for review. Free full-text articles were chosen and abstract-only articles were excluded. A total of 67 free, full-text articles were examined for the current study. References were also checked for relevant sources.

Discussion

Early diagnosis and prevention may be a key strategy to reducing the symptoms of AD. Keeping a healthy diet and regular exercising are known to have a positive impact on overall health, including the fitness of the brain [15]. Nutrients that exert free radical scavenging and anti-inflammatory properties have been suggested as factors that improve cognition and neuro protection in the brain and can be used as preventive supplements for AD, as well as enhancers for neurogenesis [5].

Ascorbic acid

Ascorbic Acid (AA), or vitamin C, is the most essential exogenous antioxidant in human cells, including the cells of the Central Nervous System (CNS), acting as a direct scavenger of reactive oxygen species (ROS) and regenerating endogenous antioxidant enzyme [17,18]. Its neuro-protective role is linked to its antioxidant and chelation properties, as well as its regulatory role in neuro inflammation. Studies suggest that AA directly reduces Aβ fibrils formation while administering oxidative stress and neuro inflammation, triggered by ROS. Another piece of evidence for the participation of AA in the response against AD is its low levels in the plasma of AD patients, even when their symptoms are still mild [19,20].

Aß plaques contain metal-binding sites and can attract iron, copper, and zinc [21], which may alter their morphology and accelerate the fibrillation process and cytotoxicity [22]. These events lead to the accumulation of hydroxyl radicals and reactive nitrogen species, damaging DNA, proteins, and lipids. In addition, advanced glycated end products also appear. These molecules trigger inflammation responses, inducing pro-inflammatory cytokines, such as IL-6, and are biomarkers for neurodegenerative disease recognition [23]. Aβ injected rats, treated with AA showed reduced neuroinflammation and oxidative stress [24]. In SH-SY5Y neuroblastoma cells, AA acts as a defense molecule against apoptosis mediated by Aβ [25].

However, AA may also exhibit pro-oxidative properties. Due to its chelating potential, AA tends to interact with free iron and copper ions and make them reactive. Reduced metal ions can later interact with hydrogen peroxide and yield ROS [26,27]. Even though there is a number of studies that prove the pro-oxidative potential of AA *in vitro*, evidence of such *in vivo* activity is insufficient, which may be due to the strictly controlled metabolism of metal ions in the cell [28]. This leads to the conclusion that AA can be used in the prevention and early treatment of AD.

Vitamin E

Vitamin E is also a very important exogenous antioxidant that can act in the cell membranes due to its hydrophobic nature. It is also well known for its anti-inflammatory properties. Along with AA, this group of micronutrients is essential for the antioxidant defense in the nervous system and reduces Aβ and NFTs. Vitamin E deficiency in elderly patients shows poor memory performance [29,30]. A cross-sectional study reports decreased memory amongst elderly patients consequently to low serum levels of vitamin E. Studies have shown that vitamin E can modulate adult neurogenesis [31] and when insufficient in the diet of rats, results in increased cell proliferation and early death of the cells of the dentate gyrus (DG) [32]. In contrast, supplementation with vitamin E decreased neurotoxicity and increased cell survival in the DG.

Docosahexaenoic Acid (DHA)

Docosahexaenoic Acid (DHA) is an omega-3-fatty acid that is a structural component of the human brain and is crucial for the formation of neuronal membranes [33]. Changes in its normal distribution in the brain can affect synaptic function, the function of enzymes, receptors, and ion channels, as well as gene expression. DHA neuroprotective properties are represented by its anti-oxidant and anti-inflammatory properties, as well as the ability to inhibit apoptosis. This is due to the capacity of DHA to reduce oxidative stress, lower pro-inflammatory mediators, maintain low nitric levels, and enhance endogenous antioxidant enzymes, such as glutathione peroxidase and glutathione reductase [34]. DHA can also affect neurological function by modulating signal transduction pathways, neurogenesis, myelination, membrane integrity, and membrane organization. The adequate formation and development of the brain are highly dependent on the DHA availability. DHA supplementation is connected to better cognition [35] and a lower risk of depression [36]

AD patients are showing lower levels of DHA, compared to control groups, and recent data shows they also have a problem processing the fatty acid, which makes adequate supplementation even harder [37]. Morris et al. [38] showed that 200 mg of DHA per week lowered the risk of developing AD by 60%.

Melatonin

Melatonin acts as a hormone that regulates the circadian and seasonal rhythms, but also has been shown to exert antioxidant and neuroprotective properties and is suggested as prophylaxis for preventing the progression of neurodegenerative diseases [39].

Increasing the number of NFTs is a main pathological hallmark of AD and it correlates with the severity of cognitive decline. Melatonin inhibits tau hyperphosphorylation in neuroblastoma cells, by inhibiting the wortmannin-induced glycogen synthase kinase-3 (GSK-3) activation, isoproterenol-induced Protein Kinase A (PKA) activation, and CA-induced protein phosphatase-2A (PP-2A) inactivation [40,41], and reduces Aβ

formation in different cell lines, as it interferes with APP maturation [42].

Phenolic phytochemicals

Phenolic compounds have been well known for their antioxidant properties and recent studies suggest a great potential in dealing with cognitive impairment with a diet rich in phenolics [43,44]

Resveratrol, a potent polyphenolic antioxidant, has been shown to improve cognitive performance and learning in rat AD models [45] and decrease hippocampal neurodegeneration [46]. In a primate study, supplementing with resveratrol showed improved spatial memory, compared to the control group [47]. Resveratrol reduces oxidative damage and chronic inflammation, by activating longevity genes and improving vascular function [48].

Turmeric has been used widely for food preservative and a source of bioactive ingredients. Curcumin, the most studied compound of turmeric, is known for its antioxidant and immunomodulating properties [49]. Recent studies show that curcumin can exhibit neuroprotective activity by inhibiting the secretion of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α [50,51] and protecting dopaminergic neurons from microglia-mediated neurotoxicity [52]. In addition, curcumin may also play a role in the epigenetic expression of pro-inflammatory mediators in the microglia, promoting a phenotype with higher anti-inflammatory and neuro-protective potential [53,54]. However, evidences of these effects in human trials are scarce [55].

Carotenoids are potent antioxidants that can be obtained from a plant diet. Studies show a link between cognitive performance and carotenoid-rich diet, as well as reduced depression amongst non-demented older adults, as a result of supplementation with carotenoids [56,57].

Retinol is a carotenoid that exhibits a neuro-protective potential by lowering the oxidant load in mitochondria. Retinol can also regulate genes, involved in APP processing, by its nuclear receptors and is known to protect embryonic neurons from oxidative damage and apoptosis by managing glutathione reduction [58,59] Moreover, Retinol can restore the levels of intrinsic antioxidant enzymes Cu, Zn-superoxide dismutase (SOD-1), and Mn-superoxide dismutase (SOD-2) in primary hippocampal cultures [58,60] and aids nerve growth factor-induced protection in chick embryonic neurons.

Flavonols, like catechin and epicatechin, are also known to exert neuroprotective activity [61].

Selenium

Selenium plays a fundamental role in the functioning of cells and the whole organism, as it contributes to the formation of protein-protein complexes and for the regeneration of muscle tissue, as well as protecting neurons from oxidative stress [62]. Selenium is also associated with the immune response, as it regulates the functions of macrophages and the production of prostaglandins [63]. Selenoproteins are a big group of essential proteins that have Selenium incorporated in the polypeptide chain as part of the amino acid Selenocysteine. This group of proteins includes antioxidant enzymes, such as Glutathione peroxidases (GPXs), as well as enzymes that are crucial for the proper growth and survival of the cell, like thio-redoxin reductase [64,65]

Selenium-enriched diet can yield increased content of exogenous antioxidant enzymes, such as GPX and SOD, in mice, as well as improved total antioxidant action. Studies show that selenium levels decrease in elderly patients, as well as vitamin E, which leads to increased inflammation indexes [64].

Zinc

Zinc is also an essential microelement for the cells. It is greatly involved in transcription regulation and when insufficient can lead to cognitive compromising, as well as other dysfunctions in the development [66]. Its role in the immune response is also fundamental, as it regulates cytokine and antibody production, impacts cell signalling and functionality of B, TH, and NK cells [67,68]. A study on healthy adults (age 55-87) shows that zinc supplementation reduces TNF levels and oxidative markers, compared to the control placebo group [69]. In addition, Zn ions are associated with DNA binding proteins and transcription factors through zinc-finger domains. Zn is also a component of the enzymatic antioxidant defense of the organism, as it is incorporated in Zn/Cu-SOD [70] and regulates the action of metalloproteinase [71,72].

Conclusion

The incidence of Alzheimer's disease doubles every five years after the age of 60, reaching up to 40% prevalence amongst 85 years old or older. With the progression of this ailment, symptoms become more devastating and the cost of care for the patient's increases significantly. Although scientists still don't understand well the exact ways in which the disease acts and progresses, we have more evidence about the importance of lifestyle and diet in its pathogenesis. Studies about the inflammatory and oxidative origin of the disease's hallmarks – the Aβ plaques and NFTs, shape a preventive strategy that may lower the risk of developing the illness and mitigate its symptoms. There are already multiple studies, showing the positive effects of antioxidant and anti-inflammatory supplementation on reducing the risks of developing AD and its symptoms, in animal models, as well as in humans. AD patients are showing a shortage of microelements, such as vitamin C, E, zinc, and selenium which makes them more susceptible to oxidative stress. Well-known and accessible supplements such as vitamins, polyphenols, and PUFAs, which can be either be obtained through the diet or by taking food additives, show great potential and are more often prescribed for early treatment and prevention of the most common neurodegenerative disease. A deeper understanding of the nutrition pathways and pathogenesis is necessary for improving AD prophylaxis and treatment.

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