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Nutraceuticals: The New Generation Therapeutics for Alzheimer's Disease

Nutraceuticals in the treatment and prevention of Alzheimer's Disease

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Abstract

Current pharmacological strategies for Alzheimer's disease (AD), the most common age-related neurological disorder worldwide, are often plagued with undesirable side effects after prolonged treatment. Despite this, pharmacological strategies remain the mainstay for treatment of AD as better and safer alternatives doesn't exist. In the recent past, there has been no development of new drugs that can reverse the onset and progression of this disease. In this connection, nutraceuticals have certain therapeutic value and the advent of which has opened doors to the use of alternative strategies to tackle neurodegenerative diseases such as AD. Significant efforts have been put into better comprehending the role of nutraceuticals in AD as nutraceuticals have been able to position themselves as a safer and better alternative due to the fact that they are naturally derived compounds having fewer side effects. The aim of this presentation is to summarize the effects of selected nutraceuticals against this age-related cognitive impairment and dementia. This presentation highlights the beneficial impact of flavonoids, some vitamins and other natural substances on AD for the maintenance of a good cognitive performance.

Index Terms Nutraceuticals, Alzheimer's disease, vitamins, flavonoids, natural substances.

Introduction

Alzheimer's Disease (AD) is the most commonly recognized cause of dementia in the aging population where low levels of acetylcholine (Ach) has been reported in the Alzheimer's brain arising from the accumulation of beta amyloid (βA) protein fragments forming hard plaques that interferes with the ability of ACh to effect synaptic transmission and initiate inflammatory processes [1]. Research suggests that βA opens channels in cell membranes, permitting calcium ions to enter the cell and triggering several processes leading to mitochondrial dysfunction, inflammation and cell death [2]. Alteration in the chemical nature of a specific protein – tau also leads to cell death in AD wherein neuron's microtubules pair with other tubules producing neurofibrillary tangles that result in tubule disintegration and blocking neurotransmitters, leading to cell death. The aim of this review was to present evidence on plant and animal food components, the so-called nutraceuticals, which have displayed the ability or a strong potential to act as neuro-protectants and/or delay cognitive impairment in AD. Presently therapeutic strategies mainly include FDA-approved pharmaceuticals for

AD, however, less than 20 percent of AD patients have even a moderate response to approved drugs [3]. Also approved drugs offer little or no neuro-protection, are effective for only a short duration, often produce serious side effects, and are expensive. Another option is to use FDA- approved drugs of label, such as rosiglitazone and ACE inhibitors. This approach also has risks of adverse effects and no conclusive evidence of benefit. Thus nutraceuticals are able to position themselves as a safer and better strategy due to the fact that they are naturally derived compounds, therefore possibly having fewer side effects.

Polyphenols

Polyphenols are a group of plant-derived chemical substances with more than one phenol unit. Polyphenols are mainly known to protect plants from stress induced by ultraviolet radiation, disease, pests and physical damages and also from animals by activating a number of intracellular processes that preserve neurons. Curcumin, is one such important polyphenol, extracted from the plant *Curcuma longa* (turmeric), having several neuroprotective properties, including anti-inflammatory, antioxidant, inhibition of βA formation, clearance of existing βA and copper and iron chelation [4,5,6]. Curcumin readily penetrates the blood-brain barrier, but oral administration may produce barely detectable blood levels at doses of 2g and low levels at 8g [7]. The best approach for increasing curcumin bioavailability is by blocking the metabolic pathways by use of adjuvants like piperine.

Resveratrol, another important polyphenol, found in red wine, peanuts, and other plants, reduces oxidative stress, decreases inflammation, reduces βA, protects DNA, decreases cell death, and modulates various other systems that protect cells [5,8]. Research on animal models clearly suggest that resveratrol mimics the effects of caloric restriction on longevity and lowers the harmful effects of high fat diet [9], enhances resistance to muscle fatigue [10], reduces neurotoxicity and cell death and prevents learning impairment [11]. Moderate consumption of red wine reduces the risk of developing AD has been proved by different studies [12].Besides, resveratrol has been known to attenuate AD-type cognitive deterioration and amyloid neuropathology [13].

Ginkgo biloba

Ginkgo biloba (Gb) is a living fossil tree prone to undergone little evolutionary change over almost 200 million years, which has high tolerance to urban & industrial pollution and are extremely resistant to insects, etc [14]. There are more than thousands of studies on Gb, the same is not only used for dementia, but also in its mode of action which includes increased blood flow, mild hypoxia and protection against ischemia, reducing edema, effects on nerve cell energy metabolism, protection of myelin etc. Gb herbal extracts (mainly EGb761) are often used as an alternative treatment to improve cognitive function whose extracts include several components, such as the flavonols, quercetin and kaempferol as well as terpenoid lactones that are considered to be responsible for the neuroprotective functions of Gb [15].

General use of standardized extracts of Gb leaves for improvement of memory and cognitive function are in use. Evidences from *in vivo* studies from humans have shown the beneficial effects of Gb in prevention and treatment of neurodegenerative disorders like AD have been shown. Improvement of cognitive performance [16, 17], memory [17] and attention [18,19] were consistently observed. Gb being a very powerful free radical scavenger, has its effects on receptor systems and various cerebral neurotransmitter. Therefore, it has a wide range of actions in pharmacology, yet in comparison to other drugs it has few side effects, if found effects are very mild. [20]. However, there exist certain reports that show the failure of Gb in improving the cognitive performance of AD patients, paving the way for further experimentation.

Coenzyme Q10

A large amount of polyunsaturated fatty acids are present in brain tissue which are particularly vulnerable to free radical attacks [21]. Coenzyme

Q10 is essential for mitochondrial energy production. Mitochondrial dysfunction can result in oxidative stress by generation of reactive oxygen species [22]. Mitochondrial dysfunction occurs in AD involving disruption of energy production, apoptosis deregulation, altered calcium homeostasis, and others [23]. For these reasons, mitochondria are viewed as promising therapeutic targets [24]. CoQ10 has proved beneficial in reducing oxidative stress and tau pathology in mice [25], and metabolized βA and inhibition of its formation *in vitro* [26].The reduction of βA found in a mouse model was attributed to the antioxidant properties of CoQ10 [27].

Vitamins and Minerals

Low levels of vitamin B_{12} and folate appear to be associated with an increased rate of cognitive decline. Also, in a study of 107 normal elderly individuals, those with low normal vitamin B_{12} had the greatest five-year loss of brain volume [28]. Since AD patients typically have high levels of homocysteine [29], researchers have examined the possibility that lowering homocysteine would be therapeutic. A combination of vitamins B_{12} and B_6 and folate lowered homocysteine both in normal seniors [30] and in those with mild-to-moderate AD [31,32],but had no efect on cognition. Homocysteine levels appear to correlate with aging but not with cognition [33]. Vitamin A has received attention because it is essential for learning, memory, and cognition and because vitamin A levels in the brain decline with age and are lower still in individuals with AD [34]. A metabolic product of vitamin A, retinoic acid, is known to slow cell death and ofer protection from βA [35]. Vitamin E is low in AD patients [36].The risk of AD was inversely related to the intake of α, γ, and δ but not β tocopherol. In general, higher levels of dietary vitamin E is known to lower the risk of AD and slow down the cognitive decline if taken over a considerable period of time.

Melatonin

Melatonin is a naturally occurring hormone whose production level decreases with aging. Recent studies revealed that melatonin, which is an indoleamine secreted by the pineal gland acts as an antioxidant and neuroprotector in aging and AD. Decrease in level of melatonin is seen during aging and more profound reduction in this hormone is found in patients with AD. [37]. Melatonin is a powerful antioxidant, easily crosses blood-brain barrier and provides mitochondrial support, protects against tau tangles, and reduces βA toxicity [38]. A case study by Brusco et al. 1998 revealed that the melatonin-treated twin had less memory loss compared to the twin receiving no melatonin for the same duration [39]. However, there exists few reports that highlight the inefficiency of melatonin in treating AD.

Omega-3 fatty acids

Omega-3 fatty acids are known to improve brain function though there exists limited data as to whether they offer protection against AD.Recent experimental evidences suggests that omega-3 polyunsaturated fatty acids(PUFAs) may play an important role in cognitive function in AD patients [40]. Morris *et al.* [41] studied 815 aged 65 to 94 years for about four years, to see if they would develop AD. Results showed that participants who ate fish had less risk of AD compared to those who rarely or ever ate fish. Total intake of omega-3 and DHA was associated with a reduced AD risk, thus we can conclude that dietary intake of omega-3 fatty acids and weekly fish consumption may reduce the risk of AD.

Alpha-lipoic acid

Alpha-lipoic acid (ALA), a powerful antioxidant, plays a role in brain function by improving glucose metabolism and utilization in the brain. ALA is found to have a wide range of properties that interferes with the pathogenesis or progression of AD, i.e. it increases the production of acetylcholine (Ach) by the activation of choline acetyltransferase and thereby increases glucose uptake, this supplies more acetyl coA for the production of Ach .[42] Hager *et al.* [43] gave 600 mg ALA daily to nine patients with AD and related dementias, who were

already receiving standard acetylcholinesterase inhibitors, in an open study lasting about 337 days. Results showed that those receiving the ALA had stabilization of cognitive function demonstrated by constant scores on the MMSE scale and AD assessment scales. Despite potential benefits, there has been a paucity of human studies.

Conclusion

Recent research developments in neutraceuticals have led to a great public and scientific interest about the potential of nutraceuticals to prevent age-related diseases in general and cognitive decline in particular by counter-acting deleterious neurodegenerative and pathological processes. This short review highlights several components of common diets and phytochemicals that have been shown to have benefits on AD. Despite current developments, there is a substantial lack of well conducted studies in humans addressing the impact of short-term or long-term dietary intake of nutraceuticals on AD that can reduce the severity and incidence of this neurodegenerative disease.

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Table.1 Common Nutraceuticals for treatment of AD

Nutraceuticals	Mechanism	Clinical Trials / In vivo / In vitro
Polyphenols	Curcumin has at least 10 protective properties including inhibition of oxidative stress, inflammation, βA, benefits cognition, resveratrol has similar benefits, both are well tolerated	Curcumin needs more human trials, little human research on resveratrol therapy on AD
Gingko biloba	Has antioxidant and antiinflammatory properties, retards cell death, well tolerated, considerable research backing cognitive benefit	Appears to work for AD, does not reduce the risk of getting AD
Coenzyme Q10	Protects mitochondria and promotes energy production, reduces oxidative stress, βA, apoptosis and brain atrophy.	More research would be welcome, few research has been carried out till date
Vitamins and minerals	AD patients typically have low levels of βA, supplementation has shown benefit for vitamin E, and some nutrient combinations	Insufficient research to draw conclusions in most cases
Melatonin	Antioxidant, protects mitochondria, reduces tau tangles and βA toxicity, readily penetrates the blood-brain-barrier, enters all cell structures, cognitive benefits in several studies, well tolerated	Few studies on AD, insufficient research
Omega-3 Fatty acids	Many beneficial effects but not specific to AD, well tolerated	Limited research, little benefit except in mild impairment
Alpha-lipoic acid	Powerful antioxidant (outside and inside cells),	Limited AD research, good benefit

	easily penetrates the blood-brain barrier, reduces inflammation, well tolerated	