The Pharma Innovation Journal 2019; 8(4): 1129-1132

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(4): 1129-1132

www.thepharmajournal.com
Received: 12-02-2019
Accepted: 13-03-2019

PJ Josmi
MSc Scholar, Department of Veterinary Biochemistry, College of Veterinary and Animal Sciences, Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur, Kerala, India

PD Divya
Assistant Professor, Department of Veterinary Biochemistry, College of Veterinary and Animal Sciences, Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur, Kerala, India

JM Rosemol
Teaching Assistant, Department of Veterinary Biochemistry, College of Veterinary and Animal Sciences, Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur, Kerala, India

Correspondence
PD Divya
Assistant Professor, Department of Veterinary Biochemistry, College of Veterinary and Animal Sciences, Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur, Kerala, India

Role of Nutraceuticals in Alzheimer's disease

PJ Josmi, PD Divya and JM Rosemol

Abstract
Pharmacological statistics for Alzheimer's disease, the most common age related brain disorder in the world, are bedeviled with undesirable side effects after prolonged treatment. In this contest, nutraceuticals are gaining importance for prevention as well as in therapy. The advantage of nutraceuticals has opened doors to the use of alternative strategies to tackle neurodegenerative diseases such as Alzheimer's disease. The role of nutraceuticals in Alzheimer's disease as nutraceuticals have been able to position themselves as a safer and better alternative due to the fact that they are naturally occurring compounds having less side effects. The aim of this review is to summarize the effect of selected nutraceuticals against this age related cognitive impairment. It also highlights the beneficial impact of antioxidant, flavonoids, omega-3 fatty acids, vitamins and other natural substances on Alzheimer's disease for the maintenance of a good cognitive performance.

Keywords: Alzheimer's disease, nutraceuticals, cognitive, neurodegenerative

Introduction
Alzheimer's disease (AD) is the most common type of dementia and is a chronic neurodegenerative disease which usually starts slowly and worsens over time. It is the cause of 60 – 70 % of cases of dementia in the aging population where low levels of acetylcholine have been reported. Alzheimer's brain arising from the accumulation of beta amyloid protein fragments, forming hard plaques that interferes with ability of acetylcholine to effect synaptic transmission and initiate inflammatory processes and alteration in the chemical nature of specific protein – tau also leads to cell death in Alzheimer's disease wherein neuron's microtubules pair with other tubules producing neurofibrillary tangles that result in tubule disintegration and blocking neurotransmitters, leading to cell death. (Marianna *et al.*, 2010) [8].
Nutraceuticals are pharmaceutical grade and standardized nutrient. The word nutraceutical is a hybrid of the nutrients and pharmaceutical coined in 1989 by Stephen L. De Felice. Nutraceutical is a food or a part of food that provides medical or health benefits, including the prevention or treatment of a disease. (Falinska *et al.*, 2011) [4].
The aim of this review was to present evidence on plant or animal food components, which have displayed the ability or a strong potential to act as neuro-protectants and/or delay cognitive impairment in Alzheimer's disease.

Antioxidants
Antioxidants are very important in the treatment of all diseases because most of the chronic diseases carry with them a great deal of oxidative stress. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are the major cognitive disorders. (Katsuno *et al.*, 2018) [6]. Oxidative stress participates major roles in all of these cognitive disorders. Oxidative stress is due to the aging process and also by a lack of dietary antioxidants. Many studies have found an association between high dietary antioxidant intake and a decreased risk of AD. It is very important because preventing a disease is significantly easier than treating it. Treatment with antioxidants is a promising approach for slowing disease progression. Oxidative damage resulting from the beta-amyloid induced free radicals, inflammation, altered antioxidant defenses, and mitochondrial abnormalities can be reduced to some extent by the intake of foods rich in antioxidant potental. However, intervention studies have given us mixed results. The study mentioned above where patients were given 1000 IU of vitamin E, used a very large dose, but the problem with most of the studies with vitamin E is that they use synthetic vitamin E. But it can cause lot of problems with that. First reason, synthetic vitamin E, which is dl-alpha tocopherol, has about an eighth of the activity of natural vitamin E. The other reason is that synthetic vitamin E

could interfere with the absorption of other tocopherols, such as gamma tocopherol, tocotrienol, and other components of the vitamin E spectrum. Thus the use of synthetic and natural vitamin E causes lot of problem in research. The dosing is a problem as well. (Cristina *et al.*, 2014) [2].

Low concentrations of vitamin C and vitamin E have been observed in the cerebral spinal fluid of AD patients. (Zandi *et al.*, 2004) [12]. The combination of vitamin C and E significantly decreased susceptibility of the cerebrospinal fluid and plasma lipoproteins to oxidation. Because the combination of vitamin C and E, in fact, vitamin C regenerates vitamin E in the body. Antioxidants are best given before significant damage occurs. Mild damage can be reversed. Antioxidants protect the aging brain against oxidative damage associated with the pathologic changes of AD. The researchers looked at the use of vitamin E and vitamin C supplements in combination, and found that it was associated with a significantly reduced risk of Alzheimer's disease and prevalence. The study resulting that vitamin E, vitamin C, B vitamins, or multivitamins used alone did not reduce the risk of prevalence. So there is a real association between the cooperation of antioxidants used in combination.

Phosphatidyl Serine

Phosphatidyl serine is the major phospholipid in the brain and it makes up the basic structure of the cell membrane. Membrane Phosphatidyl serine and phospholipids play an important role in cell-to-cell communication and transfer of biochemical messages to the cell. Phosphatidyl serine enhances cellular metabolism and communication, and oral supplemental effects neuronal membranes, cell metabolism and specific neurotransmitters: acetylcholine, nor epinephrine, serotonin, and dopamine.

Phosphatidyl serine can lead to very significant improvements in early dementia, early AD, and age-related cognitive decline. The Food and Drug Administration has approved health claims for Phosphatidyl serine for reducing dementia and age-related memory decline. Several studies demonstrate that Phosphatidyl serine improves memory, brain wave activity, and brain metabolism in the early stages of AD. Numerous double-blind placebo-controlled studies have been carried out on phosphatidyl serine. Engel *et al* conducted a double-blind placebo-controlled study of 33 patients with AD. Participants were given 300 milligrams of phosphatidyl serine each day or a placebo for eight weeks. Results showed that significantly improved with phosphatidyl serine, but not with placebo. Furthermore, the improvement carried over to the following wash-out and treatment phases, and the EEG was improved by reducing higher power values in AD patients and shifting the EEG power more to normal. (Engel *et al.*, 1992) [3].

Alpha-Lipoic acid

Alpha-lipoic acid (ALA) also important in brain functions. Oxidative stress and energy depletion are biochemical characteristics are important symptoms of AD, as there is mitochondrial failure. ALA plays a powerful antioxidant, which also important in improves glucose metabolism and utilization in the brain. (Vayeda *et al.*, 2017) [11]. Hager *et al.*, gave 600 mg ALA intake daily in to nine patients with AD and related dementias, who were already receiving standard acetyl cholinesterase inhibitors, in an open study for the period of 337 days. The results that showed that those receive the ALA had stabilization of cognitive function demonstrated by constant scores on the MMSE scale and AD assessment scales (Hager *et al.*, 2001) [5].

Omega 3-Fatty Acids

Dietary Omega-3 fatty acids improve brain function; however, there is a limited amount of data as to whether they offer protection against AD. Morris *et al.* studied 815 aged 65 to 94 years for about four years, to see if they would develop AD. Studies showed that participants who ate fish just once a week or more had a 60% less risk of AD compared to those who rarely or ever ate fish. Total intake of omega-3 and DHA results 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. Human beings consume a diet with equal amount of Omega-3 (n-3) and Omega-6 (n-6) essential fatty acids. Over the past 100 - 150 years, the dietary intake of n-6 has increased enormously due to increased use of oils. The sources of these oils are corn, sunflower seeds, safflower seed, cottonseed, and soybeans. (Morris *et al.*, 2003) [10].

Flavonoids

Flavonoids are a group of polyphenolic compounds that are very common in the daily human diet. This can be found in most plants, including fruits, vegetables, and several types of natural drinks such as tea, cocoa and wine. On the basis of their chemical structure they can be divided into six subgroups such as flavanols, flavonols, flavones, isoflavones, flavanones, and anthocyanidins.

Flavanoids and their metabolites modulate several neurological processes as shown by studies in which an interaction with neuronal-glial signaling pathways involved in neuronal survival and function was observed. In addition, Flavonoids induce changes in cerebral blood flow upregulate antioxidant enzymes and proteins involved in synaptic plasticity and neuronal and inhibit neuropathological processes in brain regions typically involved in AD pathogenesis.

Flavanols are a major flavonoid group, found in cocoa and chocolate as well as in black and green tea and in grapes. Flavanols have beneficial physiological and antioxidant effects, particularly in the context of vascular function. Flavanols are most abundant in grape seeds and grape juice. A study on supplementation of grape juice helps in an inhibition of glutamate toxicity. In humans, few clinical trials with grape juice have shown that short- and moderate-term supplementation produces benefit in individuals with cerebrovascular diseases including increased serum antioxidant capacity and reduced LDL oxidation, improvement of endothelial function and reduction of platelet aggregation.

Consumption of cocoa flavanols has an influence on cerebral hemodynamics. It has been suggested that one consequence of the effect of cocoa flavanols on cerebral blood flow might be to improve performance on visual and cognitive tasks as shown after drinking of cocoa beverages.

One of the most studied bioflavonoid is found in many common foods, such as capers, apples, onions and green tea. Its primary activity is to prevent endothelial apoptosis caused by oxidants, thanks to a highly potent antioxidant activity and cytoprotective effects. It improves memory and hippocampal synaptic plasticity in models of impairment induced by chronic lead exposure and it could have a role in neuronal repairing, as shown in spinal cord injury models. It is widely distributed in the human daily diet such as fruits, beverages,

tea, and vegetables. It protects PC_{12} cells against the oxidative stress induced by H_2O_2 and improves cognitive learning and memory capability in mice.

Flavones (Luteolin, Apigenin)

It is the most abundant flavonoid in plants such as rosemary, celery, and parsley. It has several pharmacological properties including a protective role of DNA against hydrogen peroxide-induced toxicity and anti-inflammatory action.

Apigenin is a nutraceutical that is used to protect neurons against β-mediated toxicity induced by copper, to increase neuronal viability as well as to relieve mitochondrial membrane dissipation and neuronal nuclear condensation. Apigenin also modulates GABAergic and glutamatergic transmission in cultured cortical neurons.

Isoflavones (Soy-Genistein, Daidzein, Glycitin)

Soybean is a very rich source of phytoestrogens, especially isoflavones. Soybean contains several minerals, fibers, proteins and oligosaccharides. The isoflavones from soybean are considered agonists of estrogen receptors. Soy isoflavones helps memory-improving effects of soybean supplementation. Isoflavones improve cognitive function by the effects of estrogen, in particular through estrogen receptor β in the brain. Estrogen replacement can improve cholinergic function by increasing choline uptake and potassium-stimulated acetylcholine release. Former studies revealed that soy isoflavones improve visual spatial memory and learning ability as well as memory of male and female animals and humans.

Anthocyanidins (Pelargonidin, Cyanidine, Malvidin)

Blueberry, bilberry, cranberry, elderberry, raspberry seeds, and strawberry are sources of natural anthocyanin antioxidants. If a grape seed extracted it contain proanthocyanidins it is a potent anti-inflammatory, antioxidant, anti-nociceptive, and vasodilatative effects. It also shows antidepressant properties. Berry anthocyanins improve the brain function and protect genomic DNA integrity. Blueberries contain flavanols and other phenolic compounds which increases their beneficial effects.

Intake of blue berries, anthocyanidins are found in specific cerebral sites, including hippocampus and neocortex. This may represent one mechanism by which blueberry flavonoids improve memory. These improvements seem linked to the modulation of important structural and synaptic plasticity markers. One of the roles of anthocyanins in neuro protection could be mediated through phospholipase A_2 inhibition which is negatively involved in a complex network of signaling pathway slinking receptor agonists, oxidants, and pro inflammatory cytokines to the release of arachidonic acid and eicosanoid synthesis. Memory performance linked to the modulation of the expression of particular proteins. Inflammation pathways and modulation of the expression of inflammatory genes might also be involved. In humans, a prospective evaluation with a food frequency showed that a greater intake of blueberries and strawberries is associated with slower rates of cognitive decline in subjects older than seventy years, suggesting the potential protective role of berries on different cognitive functions. (Mecocci *et al*. 2014) [9].

B-Vitamins: Folate, Cobalamin, Pyridoxin

Folate (vitaminB_9), cobalamin (vitaminB_{12}), and pyridoxine (vitaminB_6) are the most important B-vitamins that prevent Alzheimer's disease. They are important to maintaining the integrity of the nervous and hematopoietic systems. B vitamins help to good brain function, it produces energy and it also helps to repairing damaged cells. B vitamins are good to body. Diet contain folate it absorbed by stomach. Decreased level of folate in blood is highly dependent on a poor diet, malabsorption, and alcoholism. It helps to falls the level of homocysteine level. High levels of homocysteine cause DNA damage in the brain cell. Folic acid enriched food such as breads, cereals, flours, corn meals, and rice. Cobalamin deficiency is also associated with homocysteine level. Malabsorption of cobalamin due to digestive disorders occurring in older adults and it can result in dementia. High level of homocysteine level also leads to Alzheimer's disease. Vitamin B_6 containing three compounds, pyridoxal, pyridoxamine, and pyridoxine is essential for the regulation of mental function and mood. It also acted as homocysteine re-methylation cofactor. Deficiency of B_6 increases blood homocysteine levels. The level of B6 is very low in older people. Folate and cobalamin deficiencies cause accumulation of homocysteine. Vitamin B_{12} is involved in the methylation of homocysteine to methionine for the synthesis of methyl acceptors such as membrane phospholipids, myelin and neurotransmitters. Homocysteine is potentially toxic to neurons; its high levels have been associated with changes in the brain. It is also used as a marker for low serum vitamin B_{12} and folate.

Supplementation with B vitamins including vitamin B_6 reduces the blood homocysteine levels. In addition, B6 vitamin concentration has been associated with the decrease in blood homocysteine levels. Although vitamin B_6 did not succeed in reducing atherosclerotic manifestations in hyper homocysteinemic patients, neuropsychiatric disorders-seizures, migraine, chronic pain, and depression have been linked to vitamin B_6 deficiency. There is no evidence for treatment of vitamin B_6 improves mood (depression, fatigue and tension symptoms) or cognition. Folate, vitaminB_{12} and vitamin B_6 supplementation have been performed in subjects with mild to moderate AD. These failed in showing any effect of supplementation in slowing cognitive decline. Prolonged treatment with B-vitamins can decreases the risk of dementia in later life. However, in a recent study high-dose B-vitamin treatment (folic acid, vitamin B_6 and vitamin B_{12}) not only slowed shrinkage of the whole brain volume over 2 years but it reduced for seven- fold to the AD process. (Ahmed *et al.*, 2011) [1].

Conclusion

Due to the low toxicity and high bioavailability of phytochemicals, treatments including phytochemicals for cognitive decline and depression could be moved into a stronger clinical trial level on humans. Short term or long term dietary intake of nutraceuticals can reduce the severity and incidence of neurodegenerative and other age related diseases in future. Recent research develops in nutraceuticals have led to a great public and scientific interest about the potential of nutraceuticals to prevent age related disease in general and cognitive decline in particular by counter acting deleterious neurodegenerative and pathological processes.

References

1. Ahmed HH, Shousha WG, Hussien RM, Farrag ARH. Potential role of some nutraceuticals in the regression of

Alzheimer's disease in an experimental animal model. Turkish Journal of Medical Sciences. 2011; 41(3):455-466.
2. Cristina Polidori M, Joachim Schlz R. Nutritional contributions to dementia prevention: main issues on antioxidant and micronutrients. Genes Nutr. 2014; 9(382).
3. Engel RR, Stzger W, Gunther W, Kathmann N, Bove D, Gerke S *et al*. Double-blind cross over study of phosphatidylserine vs. placebo in pateints with early dementia of Alzheimer type. *Eur Neuropsychopharmacol.* 1992; 2:149-155.
4. Falinska AM, Colmbo CB, Irina AG, Mark G, John LH. The role of omega 3- fatty acid in brain function and ameliorating Alzheimer's disease: opportunities for biotechnology in the development of nutraceuticals. Biocatalysis and Agricultural Biotechnology. 2011; 1:159-166.
5. Hager K, Marahrens A, Kenklies M, Riederer P, Munch G. Alpha-lipoic acid as a new treatment option for Alzheimer type dementia. Arch Gerontol Geriatr. 2001; 32:275-282.
6. Katsuno M, Sahashi K, Iguchi Y, Hashizume A. Preclinical progression of neurodegenerative diseases. Nagoya Journal of Medical Science. 2018; 80(3):289.
7. Khan RA, Elhassan GO, Qureshi KA. Nutraceutical: In the prevention and treatment of diseases an overview. The Pharma Innovation Journal. 2014; 3(10):47-50.
8. Marianna M, Giuseppe M, Gianandrea T, Pietro Bria, Salvatore Mazza. Primary cerebral blood flow deficiency and Alzheimer's disease: sadows and lights. Journal of Alzheimer's disease. 2010; 23:375-389.
9. Mecocci P, Tinarelli C, Schulz RJ, Polidori MC. Nutraceuticals in cognitive impairment and Alzheimer's disease. Frontiers in Pharmacology. 2014; 5(147):1-11.
10. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N *et al*. Dietary fats and the risk of incident Alzheimer disease. Archives of neurology. 2003; 60(2):194-200.
11. Vayeda DR, Mukh N, Universi DS, Bangalore K, Mukherjee N, Spoorthi BC *et al*. Nutraceuticals: The New Generation Therapeutics for Alzheimer's Disease. IJPMN. 2017; 4(2):1-8.
12. Zandi PP, Anthony JC, Khachaturian AS, Stone SV, Gustafson D, Tschanz JT *et al*. Reduced risk of Alzheimer disease in users of antioxidant vitamin suppliments. Arch Neurol. 2004; 62:82-88.