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Review Article

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Nutraceuticals as therapeutic interventions in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a chronic neurodegenerative disease of the brain. Currently, approximately 55 million people have dementia across the globe and the number of AD patients is estimated by the WHO to reach about 78 million people by 2030 and nearly 139 million by 2050 globally. Amyloid β42, amyloid β oligomers, and tau proteins are the major biomarkers to understand the AD-like pathology. Therapies target β-amyloid (Aβ) for the modification of AD but poor permeability hampers the uses of drugs against AD. Other drugs including NMDA-receptor antagonists, cholinesterase inhibitors and their combination provide only temporary symptomatic relief. Meanwhile nutraceuticals are studied for mitigating the course of dementia. This study reviews therapeutic nutraceuticals which could be effective for treating AD.

KEYWORDS: Nutraceuticals; Alzheimer's disease; Phytochemicals; Flavonoids

1. Introduction

Neurological degenerative ailments such as Alzheimer's disease (AD) is one of the most common forms, accounting for 2/3 of all dementias. This condition includes a wide array of chronic diseases comprising a highly complicated origin[1,2]. Studies have shown that a nutrient-deficient diet may affect the central or peripheral nervous system that could lead to its disturbance[3]. The number of AD patients is predicted to increase in the aging societies and other related studies have reported that more than 10 million people globally are suffering from neurological disorders annually[1,3]. One of the main causes of disability in the old age is AD, which dramatically imposes great impact on the everyday life of the elderly. Several studies in the past decades showed increasing interests about possible interventions that might aid in the improvement of the cognitive performance of aging people or, at best, delay the onset of dementia.

The public health priority is now more focused on the prevention of cognitive decline rather than the cure against dementia and AD, due to the absence of a definitive cure for the said condition. According to Polidori *et al.*, the predisposing factors leading to the molecular cascade of neurodegeneration in AD are still unclear, but genetic and environmental factors play a crucial role in AD pathogenesis together with the vascular pathology and its risk factors[4]. Hence, current studies have shown that strategies on lifestyle modification with helpful and useful benefit on the development of cognitive decline, AD, and vascularity, including nutrients, dietary components, natural nourishments and supplement formulations, mental and social activity, and physical conditioning, have been recognized as probable target potentials for AD prevention[4]. Collectively these nutritional approaches and supplementation are

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commonly known as nutraceuticals. The potential and beneficial effects of nutraceuticals are challenged by numerous limitations such as poor brain permeability, metabolism, poor bio-availability, etc[5].

Several evidences reveal that these natural compounds-nutraceuticals are now emerging as an auspicious strategy in the management of quite a few chronic diseases, including neurodegenerative disorders, and the relationship between dietary, and balanced nutrition in lowering the risk of dementia and its commonest form—AD[6,7,8]. Briefly, as defined by Gupta *et al.*, nutraceuticals refer to functional food and dietary products (vitamins, minerals, herbal supplements etc.), which have reputable health benefits or preventive qualities in the treatment of diseases, and are used for enhancing the health and well-being of an individual aside from its nutritional properties[8,9] .The focus of the present study in the field of nutraceuticals lies in the search of metabolites and molecules isolated from the nutritional and dietary medicines and how they can be useful in debilitating and degenerative pathologies[10].

As stated in the articles of Van der Burg *et al.*, nutraceuticals used as adjunct in certain medications strengthen its therapeutic effects such as enhancement of re-uptake of inhibited monoamines through the augmentation of several pathways, resulting to an exceptional neurobiological effect when the individual is taking it[11]. Figure 1 shows the depletion of the neuronal energy uptake which is one of the biochemical hallmarks of AD. Hence, this article highlights the potential nutraceuticals that have been studied with great usability for the prevention and management of neurological disorders and brain health specifically for AD.

2. Nutraceuticals and its classifications

Nutraceuticals are used in nonspecific biological therapies for the prevention of mild symptoms of chronic disorders, health enhancement, and promoting the well-being of an individual. The neuroprotective role of nutraceuticals is highly acknowledged in the brain health enhancement and prevention of neurodegenerative disorders such as dementia and AD. Nutraceuticals are classified according to the following criteria. Mechanism of action of some nutraceuticals in AD was described in Table 1.

2.1. Nutrients: Dietary products (Vitamins)

Nutrients are defined as the principal metabolites of compounds like vitamins, minerals, amino acids, and fatty acids that play an important role in having nutritional properties in the metabolic pathways. These nutrients have well-established benefits in combination with plant and animal products in the treatment of neurological disorders including AD[12,13]. The prime impediment in the management of AD and in the formulation of therapeutic strategies is the problem of delaying neuronal loss in the disease and unhealthy brain once the pathogenesis of neuronal death has started. Thus, an auspicious alternative approach is to sustain a strong and healthy neuronal condition in the aging brain for as long as possible. A factor clearly significant for neuronal health and function is the optimum amount of nutrients essential for keeping the normal functioning of the brain. Several epidemiologic analyses, mechanistic studies, and randomized controlled intervention trials have manifested good insight into the encouraging positive benefits of docosahexaenoic acid (DHA) and micro-nutrients such as the

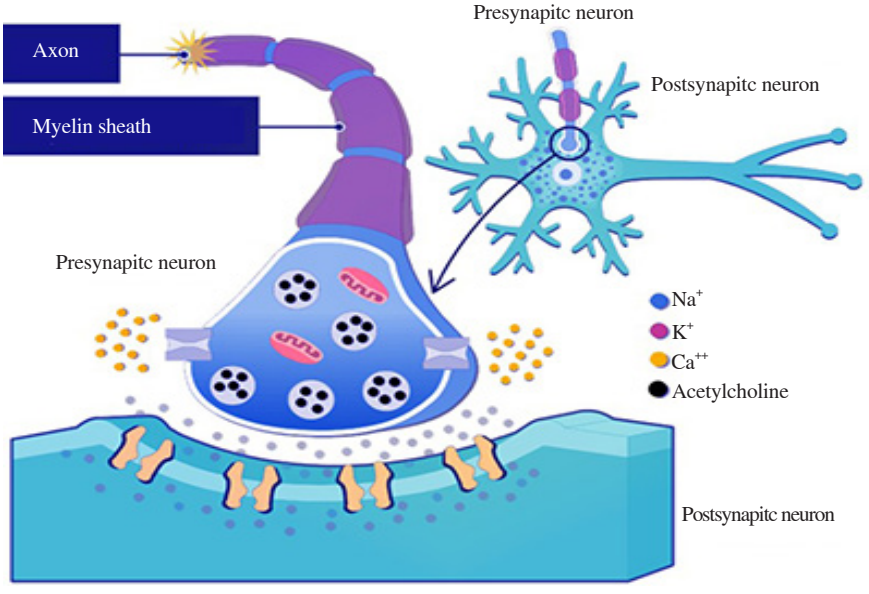

Figure 1. Acetylcholine transmission through synapse (cholinergic transmission) and action of acetylcholinesterase on acetylcholine.

Table 1. Mechanisms of action of some nutraceuticals in Alzheimer's disease

Nutraceuticals	Mechanisms of action	References
B vitamin Family: Vitamin B6, B12, B9	B6, B9 and B12 vitamins are involved in brain functions (controls thought, memory, emotion, motor skills, vision, and breathing). These vitamins are also helpful for DNA/RNA synthesis/repair, and the synthesis of numerous neurochemicals.	[15,16,19]
Antioxidant vitamins: C, and E	Vitamin C (Ascorbic acid) is vital for the formation of dopamine and noradrenaline, known neurotransmitters that take part in the modulation of tyrosine metabolism and Vitamin E is necessary as it plays the role of a potent antioxidant.	[24–26, 29, 30]
Gingko biloba	*Gingko biloba* decrease cell membrane lipid peroxidation and edema against bromethalin-induced cerebral lipid peroxidation which improve reduction of neuronal injury.	[38–44]
Garlic (*Allium sativum*)	Allicin, an organosulfur component of *Allium sativum*, inhibits cholinesterase enzymes and upregulate levels of acetylcholine in the brains	[45]
Isoflavones: soybeans	Isoflavones appear to improve cognitive function by mimicking the effects of estrogen through estrogen receptor β in the brain improving its antioxidant property.	[48,49]
Caffeine	Caffeine, a xanthine alkaloid has been shown to possess the ability to decrease amyloid-beta production via quenching of hydroxyl radicals	[52,53]
Flavanols: catechin, epicatechin, epigallocatechin, epigallocatechin gallate, isorhamnetin, kaempferol, myricetin and quercetin	The biochemical constituents of flavanols exert the ability to scavenge free radicals (oxidative stress) in the blood and the gut, suppress inflammation, and help prevent cellular damage	[63,64]
Polyphenols (non-flavonoid): curcumin and resveratrol	Resveratrol exerts decrease inflammation and minimize the neuronal toxicity.	[23,68–70]
Sesquiterpene alkaloid (Huperzine A)	Huperzine A is a sesquiterpene alkaloid may serve as reversible inhibitor of acetylcholinesterase .	[82,84]
Alpha-lipoic acid (ALA)	The anti-inflammatory and antioxidant property of alpha-lipoic acid assist production of cellular energy in CNS.	[86]
Carotenoids	Carotenoids has an antioxidant property which is accountable for neuroprotection.	[92,93]
Fish oil: omega-3 fatty acids	Fish oil: omega-3 fatty acids directly affect arachidonic acid metabolism by displacing arachidonic acid from membranes that catalyze the biosynthesis of thromboxane, prostaglandins and leukotrienes.	[101,102]
Cyanidine (anthocyanidins)	Cyanidine (anthocyanidins) inhibiting the stimulation of brain cell damage and pro-inflammatory cytokines in the body.	[104]
Flavonoids	Flavonoids as modulators of memory and learning: molecular interactions resulting in behavioral effects.	[63,66,107]

vitamins E, vitamin B family, C, and antioxidants, in boosting and aiding neurons to cope with aging. These nutrients are essential for life, inexpensive in use, practically safe with low rate of having side effects when used at recommended doses, and they can be easily used at instruction, hence a wide acceptance by the general population[13,14].

2.1.1. Vitamin B family (folate, cobalamin, pyridoxine)

Vitamin B is a diverse group in terms of structure and function. Folate also known as vitamin B9, is essential for DNA methylation by providing the methyl group component, and plays an important role in the pathogenesis of neurological diseases. Folate is absorbed from the diet and its reduction in the blood is highly dependent on malabsorption, alcoholism, and a poor diet[15,16]. The patients with AD, have shown a reduction in DNA methylation, thus poor nutrition can directly affect the regulation of gene expression which in turn can have an impact indirectly on the course of the disease. Vitamin B family are substances closely related to the methionine cycle[17]. This family of vitamin B has a beneficial effect on cognitive function that is associated with homocysteine metabolism, which contributes to heightened cardiovascular risk and intensified cognitive impairment[18]. Vitamin B12 (cyanocobalamin) is associated with the conversion of homocysteine to methionine, involving vitamin B6 and folic acid as co-factors for this reaction. The accumulation of homocysteine in the body is the result of the deficiencies of the above B vitamins, which also results in digestive disorders inleading to malabsorption that is frequently seen in older adults(≥age 60), bringing with it peripheral neuropathy, an irreversible neurological disorder[15,19,20]. Vitamin B6 (pyridoxine) includes three compounds with distinct chemical structures such as pyridoxal, pyridoxamine, and pyridoxine, which are all associated with function and mood regulation. In the vitamin B family, the most studied substances in the domain of cognitive decline and dementia are folate (vitamin B9), cobalamin (vitamin B12), and pyridoxine (vitamin B6)[5]. These compounds are vital for preserving the strength and integrity of the hematopoietic and nervous systems[21].

2.1.2. Antioxidant vitamins

Antioxidants are very vital in handling nearly all ailments, especially chronic diseases because they carry with them a boundless deal of oxidative stress. Neurodegenerative diseases such as AD, Huntington's disease, amyotrophic lateral sclerosis, and Parkinson's disease, are all affected by oxidative stress that can be accelerated by the aging process and also the lack of dietary antioxidants. Vitamins C and E are examples of vitamins that are likely to play antioxidant roles in the brain[15]. A contributory factor to the onset and

advancement of neurodegenerative processes is said to be caused by increased oxidative stress. Studies made by Cosín-Tomàs *et al.* have noted the presence of AD lymphoblastoid cell lines showing higher reactive oxygen species levels than those from healthy controls in response to H_2O_2 and $FeSO_4$ oxidative insults and impaired antioxidant processes on neurodegenerative disorders[22,23].

The brain has higher vitamin C content than any other organ next to the pituitary gland and leukocytes. Vitamin C(ascorbic acid) is vital for the formation of dopamine and noradrenaline, known neurotransmitters that take part in the modulation of tyrosine metabolism[24,25]. Furthermore, the alkaline form-ascorbate is also said to be an antioxidant in protecting neurons against oxidative stress, probably because it is also beneficial for reprocessing and converting vitamin E to its antioxidant form[26,27]. Related studies have shown that for proper neuronal functioning, Vitamin E is necessary as it is a potent antioxidant, a constituent of neuronal membranes, and a free radical scavenger, preventing the oxidation of lipids and polyunsaturated fatty acids[28,29].

In the study conducted by Lloret A *et al.*, patients were given 400 IU of vitamin E plus 1 000 mg of vitamin C, while other groups were given vitamin E and C alone and were given to AD patients for one month. The cerebral spinal fluid of AD patients has been examined and found reduced concentrations of vitamin C and vitamin E. The findings revealed that vitamin C and E significantly decreased oxidation susceptibility in the brain cells as well as strengthening the fact that vitamin C and vitamin E operate together, and that vitamin C regenerates vitamin E in the body. So, it was stipulated that intervention on the use of antioxidants for neurodegenerative disorders is best given before significant damage occurs since mild brain damage can still be reversed[30,31].

2.2. Herbal supplements: Extracts and concentrates of botanical products

2.2.1. Gingko (G.) biloba

G. biloba is probably considered to be the most studied herb with respect to its potential benefit for the improvement of memory, cognitive function, overall brain performance, activities of daily living, and global clinical assessment in patients with mild cognitive impairment or AD[32, 33].

Based on the study of Yang G *et al.*, patients of AD treated with 120 to 240 mg of *G. biloba* extract of objective measures of cognitive function were found to have a small but significant effect in the 3- to the 6-month period after being administered the herbal supplements. There were no significant adverse effects found in the drug in formal clinical trials but two cases of bleeding complications were reported[32,34]. There was no clear evidence in the case of Gingko that it increased bleeding. Bal Dit Sollier *et al.* conducted a double-blind placebo-controlled study to assess the effect of a daily treatment of Ginkgo (120, 240, or 480 mg per day) on the blood of 32 healthy men. The results showed that bleeding time was not increased, even at the high dose of 480 mg and there were no alterations of coagulation of platelet function. Therefore, he concluded that bleeding events were not related to the pharmacological properties of Ginkgo[34,35].

Currently, nutraceuticals such as *G. biloba* used for medicinal purposes are in the form of ginkgo extracts standardized to contain 24% ginkgo-flavone glycosides and 6% terpenoids[34]. Flavonoids, one of the major components of ginkgo extract was found in a considerable amount that contributes to ginkgo's antioxidant and free radical scavenger effects[36]. It has been shown that flavonoids are used already in neurogenerative disorders, mainly AD. Components such as catechin, epicatechin, epigallocatechin, and epigallocatechin gallate are polyphenolic compounds mainly extracted from the human diet that were also found in Ginkgo[37]. Ginkgo has been found to have the following beneficial effects, namely: 1) decrease cell membrane lipid peroxidation in experimental spinal cord injury found similarly to methylprednisolone[38]; 2) decrease edema and bromethalin-induced cerebral lipid peroxidation[39]; 3) guard and preserve brain neurons against oxidative stress induced by peroxidation[40–42]; 4) reduce neuronal injury following electroconvulsive shock or ischemia[43]; and 5) decrease sub-chronic cold stress effects on receptor desensitization[44]. As suggested by several related studies, additional research is warranted to explain which elements in the ginkgo extract are giving its possible result in individuals with AD.

2.2.2. Garlic (Allium sativum)

Garlic extracts containing Allicin and some of its constituents have been shown to have antioxidants and exert a protective property against neurotoxicity (amyloid-beta-induced) in cells and in experimental animals[45–47]. Allicin, an organosulfur component of *Allium(A.) sativum*, inhibits cholinesterase enzymes and upregulates levels of acetylcholine in the brains as shown in the study of Jeong *et al.*[45], suggestive of a likely usage in the treatment of AD. Another study, like the Doetinchem Cohort Study, have the following results when garlic extracts were administered to 2613 participants aged 43-70 years for cognitive function (in a 5-year interval and dietary assessment), it was found that higher consumption of allium (onion, garlic, and leek) was associated with worse scores on the speed of cognitive processes and cognitive flexibility in cross-sectional analyses. On the other hand, a similar study was performed, in longitudinal analyses, consumption of *A. sativum* was not associated with a decline in cognition[46].

2.2.3. Isoflavones in soybeans

Soybean is a rich source of phytoestrogens, especially isoflavones which have been studied as a potential alternative to estrogenic

treatment. Other constituents of soybean include several minerals, fibers, proteins, and oligosaccharides[48,49]. The isoflavones from soybean are shown to exert an agonistic effect on estrogen receptors, thus considered to be responsible for the observed memory-enhancing effects on patients with soybean supplementation upon examination. Isoflavones appear to improve cognitive function by mimicking the effects of estrogen, in particular through estrogen receptor β in the brain[48,49]. Estrogen replacement therapy as proven by studies conducted by Gabor *et al.*, was said to improve cholinergic function by increasing choline uptake and potassium-stimulated acetylcholine release[49–51]. Another study conducted by Bansal *et al.* on young and mature mice demonstrated that chronic dietary supplementation with soybean improves cognitive performance, decreases thiobarbituric acid reactive substances, and increases plasma glutathione peroxidase levels, suggesting that soy isoflavones have antioxidant properties[48, 50, 51].

2.2.4. Caffeine

A xanthine alkaloid has been shown to possess the ability to decrease amyloid-beta production in animal models of AD, and at the same time has an anti-oxidative property, via quenching of hydroxyl radicals[52,53] in caffeine. It is a non-selective antagonist of adenosine receptors (mainly A1 and A2A), demonstrating a structural similarity to adenosine, for which related studies often described caffeine's mechanism as somehow complex. Coffee and caffeine exert a short-term stimulating effect on the central nervous system, but the long-term impacts on cognition have been less clear. The decrease in amyloid plaques was linked with high levels of phosphor-CREB, low levels of phosphor-JNK and phosphor-ERK expression, and stimulation of protein kinase A activity, in an experimental mouse model of AD[53, 54]. Other related studies have shown that consumption of caffeine is associated with improved cognitive performance, alertness, healthy brain functioning, and a slower cognitive decline[53,55]. A case-control study conducted by Cao C *et al.* revealed that among the 124 older persons (≥age 60) investigated, high blood levels of caffeine (1 200 ng/mL) were linked with a lack of progression to dementia in patients with mild cognitive impairment, and another reported that 65% decrease in the incident of AD and dementia was found in persons who had a consumption of 3 to 5 cups of coffee per day[56–58]. Moreover, it is revealed from different studies conducted that intake or administration of coffee has been associated with less risk of dementia and cognitive decline in some while other studies would not confirm all of these claims. The variations and inconsistency of the available evidence (*i.e.*, confounding, survival bias owing to the cohort age, the timing of exposure) exclude final conclusions regarding the role and benefits of coffee in the prevention of neurodegenerative disorders such as dementia and AD. Recommendations for additional studies are warranted in order to elucidate the role of caffeine in the development of cognitive impairment, dementia, and AD[59–61].

2.3. Phytochemicals based on the chemical nature of the compounds: Phenolic compound derivatives that are neither vitamins nor minerals.

2.3.1. Flavanols

Nutraceuticals can also be categorized based on the chemical nature of the constituents present in each compound, known as the secondary metabolites they possess, such as flavonols, quercetin, amino acid-based compounds, carbohydrates, and fatty acids to name a few, and differs according to the origin depending on the natural source[62].

According to the study of Spencer *et al.*, flavonoid groups of secondary metabolites are subdivided into different types, and flavonols are the larger portion of the antioxidant class of flavonoids that are usually found in chocolate and cocoa as well as in grapes, green and black tea. Over the past decade, research has found flavanols display various beneficial physiological, biological, and antioxidant effects, predominantly in terms of vascular function. Flavanols, in the form of epicatechin and catechin, are richly found in Cocoa beans in particular. Chocolate is another source of flavonoids, though in a much lower concentration as mentioned in other studies. The biochemical constituents of flavanols exert the ability to scavenge free radicals (oxidative stress) in the blood and the gut, suppress inflammation, and help prevent cellular damage[63,64]. A recent article by Halland *et al.* has shown results of the risk reduction effects on neurodegenerative conditions of four flavonols surveyed: isorhamnetin, kaempferol, myricetin, and quercetin. About 38% risk reduction in people with Alzheimer's incidence who ingested the most isorhamnetin-rich foods—olive oil, wine, pears, and tomato sauce, was achieved as compared with the study members in the lowest quintile with the less intake of the said flavanols rich food. On the other hand, the highest sources of kaempferol-rich foods are Kale, tea, beans, broccoli, and spinach which supplied a 51% drop in risk. Myricetin, another flavanols subclass found in wine, kale, tea, tomatoes, and oranges is also considered as it showed a 38% reduction in Alzheimer's incidence[62]. Therefore, it can be stated that there is potential impact in regular flavonoid-rich fruit consumption on normal or abnormal deteriorations in cognitive performance[65].

2.3.2. Polyphenols(non–flavonoid): Curcumin and resveratrol

According to some studies, curcuminoids (curcumin and desmethoxycurcumin) and resveratrol, both plant-derived polyphenolic compounds, are found naturally in turmeric and have shown promising roles as anti-AD compounds[66,67]. The evidence showed that these non-flavonoid polyphenols have revealed favorable results and effects

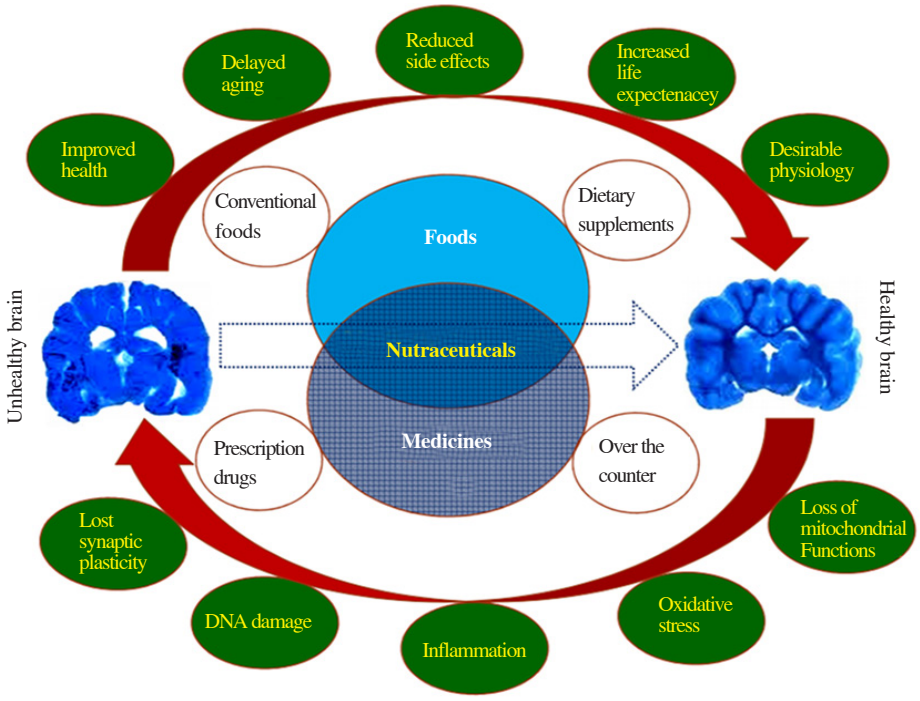

Figure 2. Bridging food and medicines towards a Healthy brain.

in the *in–vivo* models and the cell culture of neurodegeneration (dementia and AD) and neurotoxicity investigation[66].

Studies specified that resveratrol exerted the ability to keep neurons from death and decrease inflammation as shown in the *in vivo* experiments using animal models of oxidation-induced neuronal toxicity[67–69]; the protection of organotypic hippocampal slices from hydroperoxide insults was also observed[69,70]. Other probable mechanisms of resveratrol displaying its neuroprotective action are related to its capacity of modulation of Aβ processing and up-regulation of the longevity-linked gene sirtuin 1 and its antioxidant properties[71].

Curcumin is the most active element of turmeric (*Curcuma longa*), an herb of the ginger family that possesses an anti-inflammatory, antioxidant, neuroprotective, and lipophilic action that helps improve cognitive functions in patients with AD[72,73]. An expanse of growing evidence shows that the key risk factors point out principally to oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by toxicity to bio-metal, and abnormal inflammatory reactions that have contributed to AD pathology. The ingestion of curcumin resulted in various beneficial effects that have improved the neurogenerative conditions of the study group, such as reduction in beta-amyloid plaques, metal-chelation, delayed degradation of neurons, anti-inflammatory, antioxidant, and reduced microglia formation, thus leading to overall memory improvement in patients with AD[68,73]. The unique molecular structure of curcumin has received increased research interest due to its potential in targeting inflammation and antioxidant pathways as well as exerting positive results in amyloid aggregation, which is one of the major hallmarks of AD[73]. Figure 2 shows the benefits of phytochemical compounds working as neuro-nutraceuticals and provide benefits to the brain.

2.3.3. Sesquiterpene alkaloid

Sesquiterpene alkaloids (sesquiterpenoids) are the derivatives of a 15-C precursor called farnesyl pyrophosphate, and a group of various natural compounds that are mainly confined to specialized secretory cells and laticifers, and are also found in the vacuoles of other cells during the time of biotic stress[74,75]. These compounds are vital for the identity and protection of plants in response to allelopathic stimulation and exert many activities biologically such as anti-inflammatory and antimicrobial effects[76–82].

Huperzine alpha or huperzine A is a sesquiterpene alkaloid plant compound that is extracted from club moss/firmoss, *Huperzia serrata*, a potent but reversible inhibitor of acetylcholinesterase. Accordingly, this compound works similarly to that of the cholinesterase inhibitor drugs that are presently on the market. Concerning its safety and toxicity, the human and animal safety data attest to its nontoxic and safe properties. The pharmacokinetic nature of this compound has shown rapid penetration and absorption into the brain, very much similar to *G. biloba*. Huperzine A has a higher therapeutic index and a longer duration of activity compared to tacrine and donepezil, thus, it has the ability to decrease neuronal death by glutamate[83–86]. The cholinergic side effects are minimal and insignificant when compared to other anticholinesterase drugs. Furthermore, based on various related studies these compounds have shown the probability that they can be used to hit pharmacological targets in managing a neurodegenerative condition such as dementia and AD (Figure 2).

Additionally, Zhang *et al.*, conducted a study of 202 AD patients

in 15 centers as part of the study group. Huperzine A 400 μg were given each day for each participant or a placebo for 12 weeks. Remarkable results were generated on the improvements on several scales used, including the MMSE scale, the CIBIC-Plus (Clinician Interview-Based Impression of Change-Plus) scale, the ADAS cognitive scale, and the activities of daily living (ADL) scale. Huperzine A compound given orally was found to significantly improve the cognition, mood, behavior, and activity of daily life in each of the AD patients. Furthermore, it was also proven to be a safe and effective treatment for AD, with insignificant side effects as observed[78,79, 87].

2.3.4. Alpha–lipoic acid(ALA)

Lipoic acid(LA) is a natural, vitamin-like substance produced by the human body, while the synthetic version is known as ALA. ALA has the capacity to exert an anti-inflammatory effect and has shown antioxidant properties that is essential for the production of cellular energy[88]. Other benefits of ALA were revealed in the study of Packer *et al.* and Maczurek *et al.*, which showed that ALA had a variety of properties that can interfere with the pathogenesis or progression of AD as it plays an important role in brain functioning by delaying the onset or slowing down the progression of the disease[88–91]. Several reviews stressed that the biochemical hallmarks of AD were attributed to oxidative stress and energy depletion as characterized by mitochondrial failure[86,91]. The action mechanism of ALA appears to increase the acetylcholine (ACh) production in the body by activating choline acetyltransferase and thereby increasing glucose uptake, resulting in the supply of more acetyl-CoA for the production of ACh. Chelation of redox-active transition metals was another mechanism of action, preventing the development of hydroxyl radicals and scavenging reactive oxygen species in that way increasing reduced glutathione level[89,91]. Hager *et al.* stated in their article that ALA has shown varying results in patients with mild to moderate AD. An experimental study was conducted on nine patients with AD and related dementias, 600 mg of ALA daily was given to those who were already receiving also standard ACh inhibitors, for about 337 d in an open study, in which those who received ALA have shown stabilization of their cognitive function as demonstrated by the constant scores on the AD assessment scales and MMSE scale which he concluded a positive outcome for the said nutraceuticals[88]. ALA is said to be generally safe for healthy individuals based on the clinical trials performed, though it was reported that occasional minor stomach discomfort at high doses was seen in one clinical trial. Nausea and skin rash are shown to be additional minor side effects. Allergic reactions can occur as well as a potential lowering of blood sugar[88].

Broccoli, spinach, carrots, beets, potatoes, and red meat are the common sources of ALA though found to be in small amounts. It is also widely available as an OTC supplement. ALA supplements have no official recommended doses, but doses ranging from 600 to 900 mg/day for up to two years were used in clinical trials with Alzheimer's patients and reported without serious side effects[92]. Furthermore, ALA has received increased attention as a nutritional supplement with therapeutic potential in the treatment or prevention of different pathologies, such as neurodegenerative diseases[93].

2.3.5. Carotenoids

As mentioned in several review articles, they have identified over 700 various members of the carotenoid family to date, and 40 types are found in blood and human tissues. Lutein, lycopene, β-cryptoxanthin, and zeaxanthin, including α and β carotenes, are the major types of carotenoids present in humans. The known antioxidant activity of the carotenoids is identified based on their structural settings and experimental data. The common source of these compounds is from orange, deep-yellow and red-colored fruits and vegetables, and are fat-soluble pigments in nature[94–96]. A seafood-derived carotenoid known as astaxanthin has been widely studied for its antioxidant and anti-inflammatory potential in experimental animal models done *in–vivo* and *in–vitro*. Astaxanthin was also considered a potent neuroprotective compound as it showed microcirculatory protective and mitochondrial protective functions in the conducted experimentations. Results verified that patients with severe or moderate AD lack lutein and beta carotene, which are major carotenoids when compared with patients with mild AD or the control group[97–99]. From among the six carotenoids tested, lycopene stood as the only carotenoid that has shown an inverse association with the quality of cognitive performance and improvement assessed by both DemTect (Dementia Detection Test) and MMSE, in healthy subjects from 45 to 102 years of age that supported by the Clock Drawing Test performed to the study group[100].

2.4. Miscellaneous bioactive compounds

2.4.1. Fish oil (omega–3 fatty acids)

Another systematic review made by Hooijmans *et al.* showed that there was a reduction in the amount of amyloid-β in experimental animal models of AD when omega-3 fatty acids A supplementation was used for a long term, thus proven also to improve cognitive function like learning, thinking, reasoning, remembering, problem-solving, decision making; however, the effect appeared to be visible in larger rats compared to mice, in males compared to females. Furthermore, supplementation of omega-3 fatty acids in mild AD corroborates epidemiological observational studies that its effect may be beneficial in disease onset, with slight impairment of brain function such as AD, Parkinson's disease, and amyotrophic lateral sclerosis, amyotrophic lateral sclerosis, etc[101]. In addition, supplementation with omega-3 fatty acids lessened the amount of neuronal loss, especially in female animals. This systematic review's positive results indicate that performing new clinical trials is possible using omega-3 FA supplementation in AD patients for long-term use[102–103].

Another study showed the effect of omega-3 fatty acids when

administered for four years to a study group of 815 individuals aged 65 to 94 years to see if they would develop AD. Results presented a 60% less risk of AD for those who ate fish just once a week or more when compared to those who do not eat fish or have been eating rarely. The total intake of omega-3 and DHA was then associated with reduced AD risk. Therefore, it is concluded that supplementation or dietary intake of omega-3 fatty acids and consumption of fish weekly may help reduce the risk of AD[103].

2.4.2. Anthocyanidins (Cyanidine)

According to the article written by Zafra-Stone *et al.*, berry fruits such as bilberry, blueberry, cranberry, elderberry, raspberry seeds, and strawberry are the source of the major compounds known as cyanidine (anthocyanidins). These compounds exert a potent anti-inflammatory and neuroprotective action by repressing the stimulation of the proinflammatory cytokines that lead ultimately to brain cell damage. The primary function can be ascribed to the inhibition of phospholipase A2, which is primarily concerned with the signaling of proinflammatory cytokines and oxidative stress parameters, the inhibition of which presents notable neuroprotection[104,105]. Neuronal health and cognitive brain function, a potential treatment of age-related depression and cognitive decline as well as ocular health, and protection of the genomic DNA integrity are associated with berry fruits containing cyanidine (anthocyanidins) [106,107]. There are several bioactive constituents like flavanols, flavonols and other phenolic compounds that may validate the increasing benefits against AD[108].

Further experimentations and research have been done to confirm the effects of anthocyanidins in neurodegenerative disorders specifically, AD. Studies have recorded the following observations on experimental animals that have been fed blueberries. Found in the specific cerebral sites, including the hippocampus and neocortex are anthocyanidins which they associated with neurogenesis acting on the hippocampus, a mechanism by which blueberry flavonoids might improve memory. Thus, strong evidence suggests that blueberries can improve memory and learning in aged animals and these improvements seem to be in connection with the modulation of the important structure and synaptic plasticity markers[108–110].

Furthermore, it was demonstrated by an improvement in the performance in several memory maze tasks in aged rats' experimentation on a blueberry diet which seems to have a more significant effect on short-term memory than long-term memory by a suggested alteration of reactive oxygen species signalling through CREB and MAP-kinase[111–114]. Finally, another indication for anthocyanins has been documented in the study as these compounds have been found to contain insulin-like and glitazone-like properties which are linked to the improved metabolic function and lipid-lowering effects on the study group[115,116] as well as the improvement in memory and reduced depressive symptoms[116].

3. Conclusions

The elderly population is greatly susceptible to specific nutrient deficits that may aggravate and exacerbate the processes of cognitive decline. The changes in our lifestyle have weakened the body's defense mechanism against free oxygen radicals to scavenge and suppress antioxidant levels in the body, thus resulting in overloaded oxidative stress. Aging also leads to reduced levels of antioxidants in our body, thereby attracting chronic illnesses in humans. Consequently, for several years now, the focus has been directed to a variety of nutraceuticals for their preventive and therapeutic properties. Certainly, nature has provided us with benefits from several nutrients and bioactive compounds commonly found in our diet that could help in the prevention of cognitive impairment and other diseases, and cure lifestyle-related disorders including neurodegeneration through important herbal molecules. The role played by phytonutrients and phytochemicals in dealing with neurodegenerative conditions and cognition prevention has been described in various studies. The beneficial and curative effects of nutraceuticals are associated with brain health neuroprotection, anti-inflammatory, antioxidant, cellular protection, and healing properties, which target different ligand-binding receptors to enhance protein synthesis in the hippocampus and frontal cortex, which ultimately leads to neuroprotection.

Suggestions on how to combat and help prevent and treat AD were done by several anti-aging physicians and one of them is by encouraging the patients to take antioxidant supplementation, that includes antioxidant vitamins – vitamin A, C, and E preferably the natural E (d-alpha-tocopherol and mixed tocopherols) and carotenoids (natural beta-carotene). Systematic reviews and other related studies revealed various plant bioactive compounds and natural products have a significant role in both the treatment and prevention of AD, but the body's response varies from person to person. Through the years experts were able to establish therapeutic doses of some nutraceuticals which seem to be effective and resulted to improve cognition and brain health such as that *Ginkgo biloba* for AD, the recommended dose is 240 or 480 mg/day. For prevention of neurodegenerative condition 120 mg was advised. Huperzine A has a therapeutic dose of 200 to 400 μg for AD, and that of flavonols (Catechin, epicatechin, epigallocatechin gallate - EGCG) is 6–9 mL/kg of grape juice extract, cocoa flavanols are given at 720 mg, and for EGCG 300 mg[1,115]. It is also reported that higher intake of flavonoids, particularly from berries, appears to reduce rates of cognitive decline in older adults[116]. Taking DHA and fish oil (omega-3 FA) is also advised at three grams each day. Several reviewed studies have shown that practical activities such as reading, writing, doing a hobby to stimulate your brain to work, or learning new languages, are beneficial for the brain, and it reduces the risk of AD. Avoidance of chemical and pollutant exposures is also advised as much as possible. What is good in the reviews made, is the fact that AD is preventable and a lot of precautionary measures can be done to actually slow down the progression or even stop or reverse

the pathogenesis of this neurodegenerative disease.

The current study features the benefits, pros, and cons, the mechanism of actions of commonly used phytochemicals/ bioactive compounds (nutraceutical therapy), and its potentiality in preventing neurodegenerative conditions, particularly AD. However, though nutraceuticals have been shown and demonstrated in various research to display remarkable properties, their use, administration, and supplementation should still be regulated and patients are advised to seek the physician's approval prior to taking it. Thus, recommended dosages to promote good neurological health and prevent the progress of diseases will be at bay; however, nutraceuticals are still one of the best options as preventive measures for neurodegenerative conditions like AD.

4. Discussion

As of today, despite the numerous research and systematic reviews done on dietary approaches and herbal supplements for slowing down or preventing the progress of neurodegenerative diseases like AD, current scientific evidence is still incomplete. Investigations performed seeking potentials for nutraceutical interventions to either prevent or delay cognitive impairment, and slow down the development of AD have been still rapidly growing, with various clinical trials recently being accomplished or underway. Several considerable pieces of evidence suggest that other factors can help delay the progress and risk of brain deterioration in AD such as a combination of a healthful diet plan and regular physical exercise. Guidelines for the prevention and treatment of AD should be modified accordingly as investigations are still ongoing nowadays in finding the appropriate drugs whether it's from natural or synthetic sources.

The field of neuro-nutraceuticals is still exploratory and remains to capture the thoughts of many physicians, neuroscientists, and various researchers. Nowadays, with the stunning advances in neuroscience in the 21st century, remarkable growth in the identification of target molecules, pharmacophores, and phytochemicals is still in progress to find therapeutic benefits for degenerative conditions such as AD. Undoubtedly high throughput screenings are underway at identifying target molecules using modern technologies. The different nutraceuticals reported here in this review like the B vitamin family, antioxidant vitamins C, and E, *Gingko biloba*, garlic, isoflavones, flavanols, curcumin and resveratrol, Huperzine A, ALA, carotenoids, fish oil and Cyanidin represent important developments and indicate that naturally occurring bioactive compounds can be beneficial to the aged brain, and have potential actions that can be directed to aid in the enhancement of cognition and improvement of debilitating brain pathology. Therefore, the authors suggest that further research is needed to be carried out to explore the use of different neuro-nutraceuticals in larger aged populations to get a validated result of its effect whether it is preventive or cure for AD.

Conflict of interest statement

The authors claim there is no conflict of interest.

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Authors' contributions

Gargantiel MF and Faller E discussed the framework of this article. Gargantiel MF was responsible for the literature collection and manuscript writing. Kumar D and Tiwari P embellished the linguistic aspects.

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