Review article

Neuroprotective Properties of Nutraceuticals in Regulating Neurodegenerative Dementia

Nurul Ashikin Mazlan[1], Nurul Aqmar Mohd Nor Hazalin[1,2], Gurmeet Kaur Surindar Singh[1,3]

[1]Department of Pharmaceutical Life Sciences, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Selangor, Malaysia
[2]Integrative Pharmacogenomics Institute (iPROMiSE), Universiti Teknologi MARA, Selangor, Malaysia
[3]Brain Degeneration and Therapeutics Group, Universiti Teknologi MARA (UiTM), Selangor, Shah Alam, 40450, Malaysia

Abstract

Dementia is a syndrome marked by a loss of mental abilities due to damage to at least one cognitive function, resulting in poor brain performance that compromises daily life activities. The multiple pathologic pathways underlying neurodegenerative dementia include protein misfolding, oxidative stress, neuro-inflammation, mitochondrial dysfunction, and calcium overload. The syndrome is a major concern to the healthcare system since the therapeutic options are limited and it has multiple adverse effects. Such therapeutic options function particularly to alleviate signs and symptoms. Recently, nutraceuticals have attracted significant attention due to their neuroprotective properties against dementia. However, few studies have focused on the mechanisms mediating the neuroprotective effects of nutraceuticals or their effectiveness against dementia, particularly in regulating neurodegeneration. Therefore, this review underlines the nutraceuticals used against dementia that includes omega-3 (PUFA), flavonoid, curcumin, resveratrol, and vitamins and to establish their neuroprotective mechanisms. The review covers relevant clinical trials demonstrating the effectiveness of nutraceuticals in supporting the possible treatment in neurodegenerative dementia. In conclusion, it is evident that certain nutraceuticals showed neuroprotective properties such as antioxidant, anti-inflammatory and anti-amyloidogenic. The findings will be useful when employing nutraceuticals in the management or treatment of dementia.

Keywords: dementia, neurodegeneration, nutraceuticals, neuroprotective properties

Corresponding author
Gurmeet Kaur Surindar Singh,
Level 11, FF1 Building, Faculty of Pharmacy,
Universiti Teknologi MARA, Puncak Alam Campus,
42300 Bandar Puncak Alam,
gurmeet9952@uitm.edu.my

Received 15 Aug 2022; accepted 20 Dec 2022
Available online 1 Jan 2023 https://doi.org/10.24191/IJPNaCS.v5i2.03

1.0 Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, dementia can be defined as a decline in mental abilities due to the impairment of at least one cognitive function (1). It occurs in a gradual, persistent, and progressive manner that can greatly compromise daily activities. Symptoms of dementia often exhibit changes in daily function and behavior such as loss of memory, understanding, calculation, language and judgment (2).

Neurons are the main component of the nervous system that are primarily affected in all neurodegenerative diseases including dementia. Loss of neuron structure or function is known as neurodegeneration. This can be mediated by several mechanisms, such as protein misfolding (or aggregation), neuro-oxidative stress, neuro-inflammation, mitochondrial dysfunction, calcium overload and altered autophagy or apoptosis (3). Reactive oxygen species (ROS) are the main by-products derived from the cellular metabolism. This toxic chemical compound is attributed by the alteration of electron transport chains and the reactions of unpaired electrons with molecular oxygen, generating superoxide radicals (4). Over-expression of ROS may lead to the development of the condition known as neuro-oxidative stress which underlies many types of neurodegenerative diseases, including dementia. Meanwhile, mitochondrial dysfunction also can result in neuronal damage. A single neuron or a particular part of the brain may be affected by the impairment of mitochondrial function (5). Several studies suggest that this pathological condition primarily triggers toxicant induced neurotoxicity and various neurodegenerative diseases. Moreover, incidents of neuro-inflammation associated with excessive activation of the phagocytic and cytotoxic substances in the brain have been identified to cause neuronal deterioration (6). Fundamentally, neuro-inflammation is mainly triggered by the production of pro-inflammatory agents such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), which mediate neuronal injuries. Otherwise, neuronal damage can be mediated by the overload of intracellular Ca2+ ions. A sudden rise in the number of these particular compounds leads to the cascade of neurotoxic events, impairing neuronal function and causing neuronal death (7). Figure 1 shows how overexpression of ROS mediates neurodegeneration pathways.

Dementia is a serious public health issue that causes considerable concern to the worldwide healthcare system. Its therapeutic options are limited by its multiple adverse effects and functions, but such options focus particularly on the relief of signs and symptoms. Currently, approximately 44 million people worldwide have been diagnosed with dementia (8). The treatment of dementia alleviates symptoms while delaying progressive cognitive decline. Pharmacological approaches to the treatment of dementia, for example, using acetylcholinesterase inhibitors (AChEI) or memantine, are often limited by their side effects, especially in the long term (9). Major disadvantages arise with the use of both drugs; for instance, AChEI has several side effects such as nausea, vomiting, dizziness, insomnia, and diarrhea. Meanwhile, memantine, despite being known as a neuroprotective and disease-modifying agent, has been linked with headaches, dizziness, somnolence, dyspnea, constipation, and hypertension (10). In addition, the multiple pathways of neuronal damage contribute to the

development of dementia. For one drug to target a particular cause of disease is clinically impractical, so safer effective therapies - such as nutraceuticals that can act on the multiple mechanisms involved in neurodegeneration - are warranted to combat the disease effectively. Nutraceuticals are food-based compounds or their by-products that provide health benefits and treatments for many types of diseases. In the management of neurological disorders, they offer an affordable, all-in-one essential intervention that has the fewest adverse effects (5). Moreover, this food-based approach can be further divided into various types of nutraceuticals, such as dietary fiber, vitamins, polyunsaturated fatty acids, polyphenol, spices, and probiotics. In general, these are easily obtained, convenient, and inexpensive.

Although many reviews have revealed the health and medical benefits of nutraceuticals in the treatment of neurodegenerative diseases, limited focus has been directed to the mechanisms mediating the neuroprotective effects of nutraceuticals or their effectiveness against dementia, particularly in regulating neurodegeneration. A more advanced understanding of the neuroprotective mechanisms of nutraceuticals and their effectiveness, especially in regulating the neurodegeneration of dementia, may contribute by enabling a recommendation of nutraceuticals as a potent auxiliary treatment. It may also allow the optimum use of this food-based approach in the treatment of various neurodegenerative diseases.

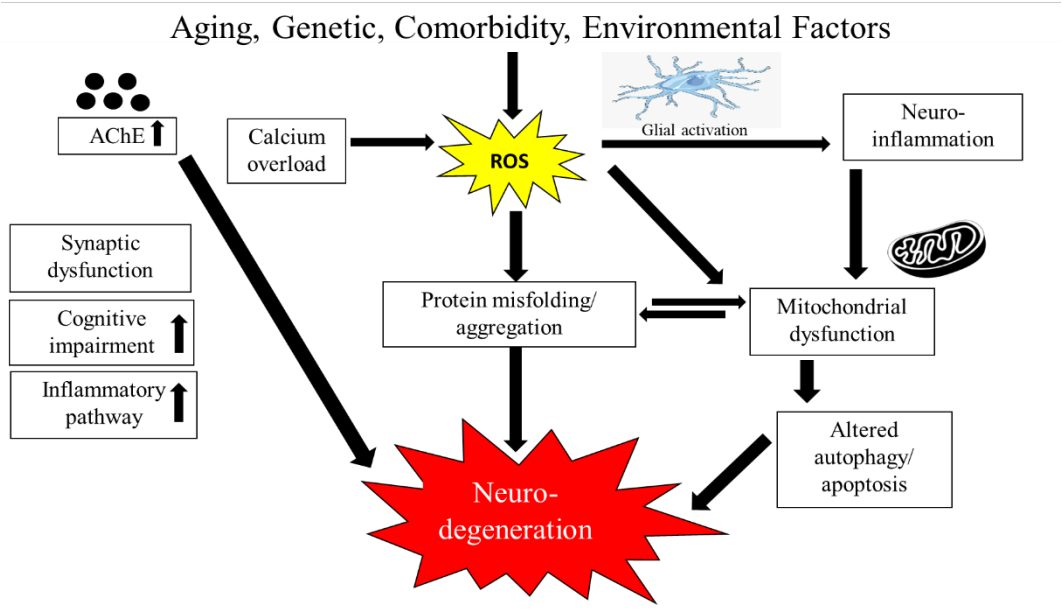

Figure 1 Over-expression of ROS mediates multiple neurodegeneration pathways include protein misfolding, neuro-inflammation and mitochondrial dysfunction. Increase activity of AChE also upregulate several pathologic events causing neurodegeneration. Abbreviations: ROS: Reactive oxidative species; AChE: Acetylcholinesterase

2.0 Methodology

Using PubMed and Science Direct, database searches were conducted that included the information in the present review. For data mining, a total of 559 articles were obtained using specific keywords that included dementia, neuronal damage, nutraceutical, and neuroprotective mechanisms. The search resulted in 417 articles that were published in English between 2016 and 2021. Upon screening, 348 articles were inaccessible, duplicates, or unavailable in a full-text version; these were excluded. Finally, 38 articles remained that discussed topics related to this review. All the selected articles were further reviewed, together with the remaining manually searched articles. These were used based on the main articles chosen.

3.0 Types of Nutraceuticals

Nutraceuticals is a universal term applied to any products in the form of food that offer health or medical benefits in addition to the basic nutritional value of the food. These compounds are known as special bioactive molecules and can be found in regular human diets. After being ingested into the human physiological system, nutraceuticals are presented as bioactive molecules that beneficially elicit an array of ameliorative effects on the body system. They can be classified according to the source of food, mechanism of action, and chemical nature. Nutraceuticals in the form of dietary fiber, vitamins, polyunsaturated fatty acids, polyphenol, spices, and probiotics, as shown in Table 1 can be categorized as traditional food sources. This type of nutraceutical is best described as food that has been naturally obtained from nature without any modification to its original constituents.

3.1 Dietary Fibers

Dietary fiber is a non-digestible component of plant cells due to its resistance to digestive enzymes; however, it can be broken down by the gut microflora (11). Examples of dietary fiber include celluloses, hemicelluloses, β-glucans, mucilage, gums, and pectins. Fiber is mainly divided into soluble and insoluble. Most fruits and vegetables contain great amounts of soluble fiber, for example, citrus fruits, apples, peas, beans, and carrots. These have been found to be beneficial in lowering serum cholesterol levels (11) and controlling the blood glucose levels of diabetic patients (12). There has been a link between the brain and gut, where the microbiome in the gut affects brain plasticity and cognitive function. Soluble high fiber diet was shown to enhance the presence of butyrate-producing bacteria that attenuate neuroinflammation associated with ageing (13). Much scientific evidence supports the effect of insoluble dietary fiber on gut motility and the prevention of constipation (14). The main sources of insoluble fiber include whole-wheat flour, wheat bran, nuts, cauliflower, green beans, and potatoes.

3.2 Vitamins

Vitamins are organic compounds involved in facilitating the effective working of the body. These functional micronutrients, however, are only needed in small amounts. They are mainly acquired from foods as the body is unable to make vitamins. They are divided into fat-soluble and water-soluble vitamins, which act in a broad array of ways to support and maintain bodily functions (15). Essential nutraceuticals such as vitamin E are categorized as fat-soluble vitamins, with this vitamin being well

known for its potent antioxidant properties. Many studies have discovered that vitamin E supplementation effectively reduces oxidative stress in experimental models. In addition, these compounds participate significantly in the development of tissues and organs, such as the brain (16). Abundant amounts of vitamin E can be obtained from foods like almonds, peanuts, olives, palm oil, canola, corn, and soybean. Water-soluble vitamins, specifically vitamin C, have been widely studied for their pleiotropic function, which contributes to human health (17). They are associated with maintaining the redox balance and supporting the immune system (18). Commonly, fruits and vegetables such as citrus fruits, tomatoes, and potatoes are rich in vitamin C content.

Table 1 Nutraceuticals' classification, function and source.

Classification of nutraceuticals	Functions	Sources	Ref.
Dietary Fibre	Lowering serum cholesterol level, control blood glucose, function in gut motility and prevent constipation.	Citrus fruits, apples, peas, beans and carrots, whole-wheat flour, wheat bran, nuts, cauliflower, green beans and potatoes	(11, 12, 14)
Vitamins	Antioxidant, immune booster	Almond, peanuts, olive, palm oil, canola, corn, and soybean, citrus fruits, tomatoes, and potatoes	(16-18)
Polyunsaturated Fatty Acids (PUFA)	Antioxidant, anti-inflammatory	Omega 3: Mackerel, salmon, blue fin tuna, fish oils, flaxseeds, soybean, canola, red/black current seeds, walnuts Omega 6: Corn, safflower and sunflower oil, soybeans as well as animal products such as meat, poultry and eggs	(19, 20)
Polyphenols	Antioxidant, anti-inflammatory, antimicrobial, cardioprotective agents, neuroprotective agents	Cocoa, chocolate, green tea, grapes, apples, broccoli, celery, parsley, soy, citrus fruits, tomatoes, berry fruits, red wine and Camellia sinensis tea	(21-23)
Spices	Antioxidative, chemo-preventive, antimutagenic, anti-inflammatory and immune-modulatory	Cloves, saffron, cinnamon, ginger, turmeric, chili, black pepper and cumin	(24, 25)
Probiotics	Anti-microbial, anti-toxin, neuroprotective, neurodevelopment, lactose intolerance, maintenance of gastrointestinal	Lactobacilli and bifidobacterial	(26-29)

3.3 Polyunsaturated fatty acids (PUFAs)

Polyunsaturated fatty acids (PUFAs) are characterized by fat molecules having more than one double bond. The omega-3-(n-3) and omega-6-(n-6) fatty acids are the main PUFA subdivisions, and both have distinct effects on metabolic function. A diet rich in omega-3-(n-3) fatty acids has been shown to be important for brain health and development (30), as well as for their antioxidant and anti-inflammatory effects through the suppression of neuronal apoptosis and other neurodegenerative pathways (19). In contrast, omega-6-(n-6) fatty acids are associated with pro-inflammatory properties that are essential to protect the host against infection and injury. Alpha-linoleic acid, eicosapentaenoic acid (EPA), docosapentaenic acid, and docosahexaenoic acid (DHA) are examples of omega-3-(n-3) fatty acids that can be found abundantly in marine products such as mackerel and salmon, as well as in flaxseed, soybeans, canola oil, and walnuts. Meanwhile, omega-6-(n-6) fatty acids comprised of linoleic acid, γ-linolenic acid, and arachidonic acid are found in corn, safflower and sunflower oil, soybeans, as well as animal products like meat, poultry, and eggs (20).

3.4 Polyphenols

The large group of phytochemical compounds called polyphenols are described as substances derived from a plant's secondary metabolites. Flavonoids, which are comprised of flavanols, flavones, isoflavones, flavanones, and anthocyanins, are the main type of polyphenols, followed by phenolic acids, phenolic amides, and other polyphenols (31). Resveratrol and curcumin are notable examples of nutraceuticals that are non-flavonoid polyphenols (4). Overall, polyphenols are beneficial in maintaining the cardiometabolic system and preventing neurodegenerative disease due to their potent antioxidant, anti-inflammatory, anti-microbial, and cardioprotective activities (21, 22). Studies also suggest that dietary polyphenols play a role in intestinal health by maintaining the gut microbial balance by stimulating the growth of beneficial bacteria and inhibiting pathogenic bacteria, thus mimicking the prebiotic effects (32). High flavonoid content can be obtained from foods such as cocoa, chocolate, green tea, grapes, apples, broccoli, celery, parsley, soy, citrus fruits, tomatoes, berry fruits, red wine, and *Camellia sinensis* tea. In the non-flavonoids group, rich levels of resveratrol have been found in the seeds and skin of some fruits, such as grapes used for red wine, whereas curcumin is the most prominent element of turmeric, a herb of the ginger family (23).

3.5 Spices

Spices can be characterized as the dried and typically pleasant aromatic parts of plants. Referring to the definition of the term by the Food and Drug Administration (FDA), spices are aromatic vegetable substances in whole, broken, or ground form. Their significant function in food is seasoning rather than nutrition (33). Spices such as cloves, saffron, cinnamon, ginger, turmeric, chili, black pepper, and cumin are functional foods that contain volatile oils, aromatic scents, and flavors. These are widely used in the food industry to enhance the sensory quality of foods.

Studies reveal that certain quantities of dietary spices emit antioxidative, chemo-preventive, antimutagenic, anti-inflammatory, and immune-modulatory effects on cells, thus contributing to human health (24, 25). Dietary ginger has been used as a natural medicine for its therapeutic effects: it can control blood glucose levels over a long period of time in

type 2 diabetes mellitus (T2DM) patients (34). Besides, a combination of garlic and fish oil has a synergistic effect on lowering LDL, cholesterol, and triglyceride levels (35).

3.6 Probiotics

Probiotics, or so-called 'healthy bacteria', can be defined as live, non-pathogenic and microbial. They are incorporated into food ingredients that offer health benefits to the host when used in appropriate amounts in foods or as dietary supplements (36). Interactions between the host and healthy bacteria in the intestinal environment have undeniably useful effects, especially on human health (37). In addition, the consumption of probiotics is reported to beneficially elicit a wide range of good biological effects (38). Probiotics are mostly taken as a part of fermented food products such as yogurt and curd. Moreover, due to the widespread recognition of the benefits of probiotics, food industries have been inspired to develop food products fortified with probiotics, such as ice-cream (39). As nutraceuticals, probiotics offer higher value as they mimic the activity of real drugs. Primarily, Lactobacilli and Bifidobacterium are the most common probiotic strains used in the maintenance of gastrointestinal, genitourinary, and oral health by promoting balance in these ecosystems (40). Examples of probiotic microorganisms are *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, bifidobacterial, certain strains of Lactobacillus casei, Lactobacillus acidophilus, and *Bacillus coagulans* (29). Every strain has distinct health benefits when used individually or in combination since probiotics have strain-specific effects (41).

4.0 Neuroprotective properties of nutraceuticals and their proposed mechanisms

A number of nutraceuticals from various sources of food have recently been discovered to alleviate the adverse effects of dementia. These compounds have also been reported to have anti-cancer, anti-diabetic, anti-hypertensive, antioxidant, and anti-inflammatory properties, as well as many other cytoprotective or pro-survival effects in a variety of pathophysiological situations (42). Nutraceuticals have demonstrated their potential medicinal value, especially in protecting the neuronal cells against oxidative damage, controlling acetylcholinesterase (AChE) activity, and blocking the multiple neurodegeneration pathways at all stages (43).

The proper consumption of functional compounds like PUFAs, flavonoids, resveratrol, curcumin, vitamins, and probiotics exhibit some prophylactic effects and has multipotent actions against neurodegeneration of dementia. These bioactive molecules elicit potential action mechanisms that regulate intracellular and extracellular molecular signaling cascades (44). The prophylactic role of some potent nutraceutical compounds exhibits significant protective action against the development and progression of neurodegeneration in dementia such as neuroinflammation, calcium overload, oxidative stress, and mitochondrial dysfunction. In this review, the author focuses on the specific nutraceuticals and mechanisms that mediate the neuroprotective properties, as shown in Table 2. These include omega-3 (PUFA), flavonoids, curcumin, resveratrol, and vitamins, which can effectively target and prevent neurodegeneration while serving as an affordable supplementary therapy that offers all-in-one intervention in the treatment of neurological disorders with the fewest side effects.

4.1 Omega-3

Essential fatty acids, referred to as PUFAs, must be obtained from the diet because they cannot be produced by the body. Long-chain fatty acids such as omega-3 play an important role in the human body system and are abundant in marine foods such as salmon and sardines, as well as flaxseed and walnuts. DHA and EPA are the common omega-3 fatty acids that have been shown to have a wide range of pharmacological activities, including anti-inflammatory, immunomodulatory, antioxidant, anti-obesity, anti-hyperlipidaemic, anti-diabetic, cardioprotective, and neuroprotective properties (20).

The consumption of omega-3 in nutraceutical form can boost brain activity owing to its antioxidant and anti-inflammatory properties. This pathway is mediated through the inactivation of microglia or astrocytes via c-Jun N-terminal kinase (JNK) and the peroxisome proliferator-activated receptor-γ (PPAR-γ) signaling pathway (45). Theoretically, the chronic activation of microglia and astrocytes can trigger the release of harmful cytotoxic molecules, such as a series of inflammatory chemokines and cytokines like interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α), as well as reactive oxygen intermediates, proteinases, and complement proteins. Hence, this event can have detrimental effects on neurons, including neuronal damage due to glial-mediated inflammation (46). Omega-3 molecules also function to diminish the amyloid β plaque and aggregation of tau protein, which are known as the pathological hallmarks of Alzheimer's disease (AD), through the amplification of α-β 42 phagocytosis. Omega-3 supplementation enhances neurological recovery while reducing white matter injury by eliciting protection against behavioral dysfunction, hippocampal damage, neuronal loss, inflammation, loss of myelination, and impulse conductivity (47). However, despite the utilization of omega-3 in nutraceutical form, which is useful in regulating neurodegeneration, recent studies have reported that long-term intervention with this compound may have several adverse effects, especially when combined with other oxidation products and vitamin E which have been linked to carcinogenesis (48).

4.2 Flavonoid

Epigallocatechin-3-gallate (EGCG), a major catechin found in green tea, belongs to the flavonoid family. Because its biological activities include antioxidant, anti-inflammatory, anti-microbial, antiplatelet aggregation, pro-autophagy, and anti-proliferative behavior, this compound contributes to various beneficial functions, particularly cardioprotective, hepatoprotective, and neuroprotective properties (49). EGCG, with a molecular weight of 458.37, is able to pass through the blood-brain barrier (BBB), and it significantly and effectively lowers the risk of neurological disorders. However, this compound has poor bio-availability due to its high water-soluble properties. Hence, EGCG - when complexed with liposomes or in nanoparticles, or when esterified with piperine or DHA or EPA - enhances the absorption of the compound (3). The major neuroprotective function of EGCG is demonstrated by its anti-amyloidogenic properties, which inhibit the agglomeration or production of amyloid β (Aβ) and suppress the peptide misfolding via modulation of the apoptosis and autophagy pathways (50). Furthermore, by inactivating the microglial cells, this functional compound increases the neuronal growth factor and improves the antioxidant status by modulating various signaling pathways, including the nuclear factor erythroid 2-related factor 2/ heme oxygenase 1 (Nrf2/HO-1), and the nuclear factor kappa

light chain enhancer of activated B cells (NF-kB) /JNK/ mitogen-activated protein kinase (MAPK); anti-inflammatory effects are produced (51).

4.3 Curcumin

Curcumin, an important component of turmeric (Curcuma longa L), has been used since ancient times as a seasoning and coloring agent in various cuisines as well as a cure for numerous diseases and ailments. This agent is the major contributing factor to diverse biological processes, so it is widely used as a nutraceutical. Curcumin has a great number of therapeutic benefits, including anti-inflammation, antioxidant, anti-obesity, anti-cancer, anti-diabetic, anti-microbial, neuroprotective, and cardioprotective properties (52). This compound is relatively cheap, well-tolerated, and capable of passing through the BBB, resulting in strong neuroprotection properties. However, curcumin has poor absorption and rapid metabolism; therefore, the compound has limited bioavailability (53).

Curcumin has been shown to have neuroprotective properties, mostly through its antioxidant activity via the Nrf2 signaling pathway, as well as anti-inflammatory properties through the inhibition of neuronal damage by suppressing the microglial and astrocyte activation as a result of inhibition in the NF-kB, toll-like receptors 4/ receptor for advanced glycation end products (TLR4/RAGE), JNK, extracellular-signal-regulated kinase (ERK), and MAPK signaling pathway (54, 55). Besides, curcumin was reported to reduce AD and neuro-inflammatory symptoms through the modulation of PPAR-γ, resulting in the restoration of the innate immune system, autophagy machinery, and the ubiquitin-proteasome system (3). Antidepression activity was also reported with curcumin, which lowered the cortisol level, inhibited monoamine oxidase A and B, and enhanced the neurotrophic factors. Moreover, curcumin is capable of inhibiting acetyl or butyryl choline esterase (AChE/ca) and mitigating mitochondrial dysfunction by reducing calcium overload to improve mitochondrial dynamics or membrane potential (56). Curcumin is also useful for detecting amyloid plaques in AD models to help in early diagnosis and the initiation of effective treatment. Alternatively, a study used an approach with magnetic nanoparticles (MNPs) made of superparamagnetic iron oxide (SPIO) conjugated with curcumin, which specifically binds to amyloid plaques in different regions of the molecule. Curcumin naturally binds to the SPIO surface by intermolecular hydrogen bonds, without the need for chemical linkers. Therefore, curcumin magnetic nanoparticles are good candidates for locating amyloid plaques in AD brains (57).

4.4 Resveratrol

Resveratrol can be classified as a polyphenol and is found in red grapes, red cherries, peanuts, pomegranates, and berries. It belongs to the phytoalexin family. Resveratrol is a popular nutraceutical due to its numerous health-promoting properties, including anti-inflammatory, anti-diabetic, anti-cancer, antioxidant, anti-hyperlipidaemic, cardio-protective, and neuroprotective properties (58). In addition, the amount of resveratrol found in food is likely to be safe to take and it is widely tolerated by all ages, including children, as well as pregnant and breast-feeding mother (59, 60). One of the major limitations of resveratrol, like curcumin, is that the compound has low bioavailability due to its high metabolizing rate and poor lipophilic properties. To address this, resveratrol is combined with piperine or quercetin to form a complex compound, which improves its bioavailability (61).

Resveratrol notably improves the antioxidant system through the upregulation of

the Nrf2/HO-1 and phosphatidylinositol 3-kinase /protein kinase B (PI3K/Akt) signaling pathways. It also beneficially diminishes the inflammatory response via the regulation of the NF-kB and JNK/MAPK signaling pathways. Studies have also mentioned that resveratrol could positively regulate the neurodegeneration process by controlling various signaling pathways, resulting in restored mitochondrial function and an improved neuronal survival rate (62). The major neuroprotective properties of resveratrol are derived because it acts as anti-amyloidogenic and displays anti-protein aggregation by eliminating Aβ protein formation and deposition. It diminishes the neurofibrillary tau protein tangles, resulting in improved cognition function (63, 64).

4.5 Vitamins

Foods such as nuts and seeds are some of the richest sources of unsaturated fats, and these are conveniently packaged with vitamin E as a protective compound. Vitamin E is commonly known for its role as a potent antioxidant agent that effectively preserves these fats from oxidation. Neurons in the central nervous system are cells that are largely made of cholesterol and polyunsaturated fats, which are highly susceptible to oxidative damage. Studies have reported that vitamin E can protect the neurons from oxidative damage by disrupting the propagation of lipid radicals to prevent lipid peroxidation chain reactions in cellular membranes (65). Patients with AD, for example, have been discovered to have insufficient amounts of vitamin E in the cerebrospinal fluid that nourishes and protects the brain, resulting in elevated levels of oxidative stress that contribute to the neuronal damage of dementia. Hence, vitamin E supplementation for AD patients may aid in protecting the neurons from further damage (16). Vitamin E supplementation reduced neuroinflammation and neuronal degeneration in the brains of rats with kainic acid-induced status epilepticus. This was achieved by decreasing the levels of astrocytic and microglial antigens, as well as the pro-inflammatory cytokines such as IL-1β and TNF-α (66). Moreover, vitamin C is a water-soluble vitamin that can act as an antioxidant, in addition to having an immune booster function. This compound interacts directly with free radicals, thus preventing oxidative damage (66). Overall, consuming foods rich in vitamins is evidently associated with a lower risk of a developing neurological disorder. Therefore, proper supplementation and a good diet are encouraged since this helps people to acquire a sufficient amount of vitamins.

4.6 Probiotics

Gut microbiota are highly functional in neurodevelopment and cognitive function, whereby an imbalance of gut microbiota is associated with several brain diseases, especially cognitive dysfunction (26, 27). For example, adjunct therapy using probiotic Bifidobacterium in a randomized controlled trial showed significant optimization of the composition of gut microbiota, while it also improved cognitive function and mood in the elderly (28). The Lactobacillus and Bifidobacterium strains demonstrate a variety of neuroprotective properties and fulfil the criteria of probiotics, which are to be non-pathogenic, non-toxic, resistant to gastric acid, and genetically stable, as well as possessing antibacterial effects (67, 68). A study on Parkinson disease mouse model, oral probiotic *Clostridium butyricum* supplementation was able to reduce the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on synaptic dysfunction, microglia activation, dopaminergic neuron loss, and motor impairments (69).

Table 2 Neuroprotective Properties of Nutraceuticals and its Proposed Mechanisms

Nutraceuticals	Neuroprotective properties	Proposed Mechanisms	Ref.
Omega-3 (PUFA)	Antioxidant and anti-inflammatory	• Inactivate the microglia or astrocytes via JNK signaling pathway and proliferate the (PPAR-γ) signaling pathway.	(45)
	Anti-amyloidogenic and anti-protein aggregation	• Amplify the α-β 42 phagocytosis.	(47)
Epigallocatechin-3-gallate (EGCG) flavonoid	Anti-amyloidogenic	• Inhibition of Aβ aggregation or production and suppression of peptide misfolding via modulation of apoptosis and autophagy pathway.	(50)
	Neurogenesis	• Enhances the neuronal growth factor by inactivating the microglial cells and improve antioxidant status via modulating various of signaling pathways such as Nrf2/HO-1.	(51)
	Anti-inflammatory	• Modulate the NF-kB/ JNK/ MAPK signaling pathway.	(51)
Curcumin	Antioxidant and anti-inflammatory	• Modulating Nrf2 signaling pathway and prevent neuronal damage by suppressing the microglial and astrocytes activation via inhibition of NF-kB, TLR4/RAGE, JNK, ERK and MAPK signaling pathways. • Modulate the PPAR-γ signaling pathway resulting in restoration of innate immune system, autophagy machinery and the ubiquitin-proteasome system.	(3, 54, 55)
	Antidepression	• Lowering the cortisol and inhibit monoamine oxidase A and B as well as enhance the neurotrophic factors.	(56)
	Neuroprotective	• Inhibit the acetyl or butyryl choline esterase and mitigate the mitochondrial dysfunction by reducing calcium overload to improve mitochondrial dynamics or membrane potential.	(56)
Resveratrol	Antioxidant	• Upregulating the Nrf2/HO-1 and PI3K/Akt signaling pathways.	(62)
	Anti-inflammatory	• Regulate the NF-kB and JNK/MAPK signaling pathways.	(62)

	Neuroprotective	• Control various signaling pathways and thus result in restored mitochondrial function and improve neuronal survival rate.	(62)
	Anti-amyloidogenic and anti-protein aggregation	• Eliminate the Aβ protein formation and deposition, and diminished the neurofibrillary tau protein tangles, thus, result in improve cognition functions.	(63, 64)
Vitamin C and E	Antioxidant	• Vitamin E disrupt the propagation of lipid radicals to prevent lipid peroxidation chain reactions in cellular membranes. • Vitamin C interact directly with free radicals, thus preventing oxidative damage in brain.	(65)
	Neuroprotective	• Reduced the neuroinflammation and neuronal degeneration in brain by decreasing the levels of astrocytic and microglial antigens as well as the pro-inflammatory cytokines such as IL-1β and TNF-α.	(66)
Probiotics	Synaptic plasticity	• Increased level of synapsin I in the PD model mice post probiotic *Clostridium butyricum* treatment	(69)
	Neuroprotective	• inhibiting the expression of TNF, IL-6, IL-1 β, PTGS2, and NOS2 genes by increasing the level of glucagon-like peptide-1	(69, 70)

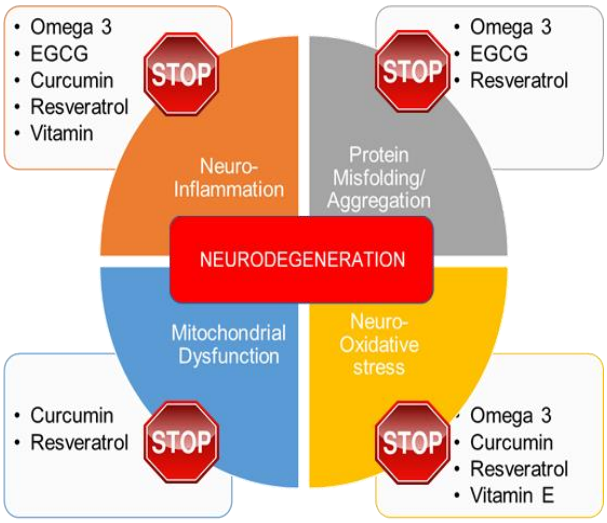

Figure 2 Major pathways involved in neurodegeneration and common nutraceuticals which provide neuroprotection.
Abbreviation: EGCG: Epigallocatechin-3-gallate.

5.0 Effectiveness of nutraceutical in regulating neurodegenerative dementia

A number of articles have reported that the supply of nutraceuticals in experimental animals can slow or stop the downfall in cognitive and behavioral activities. A growing body of research genuinely contends that a regular diet is important in the progression and treatment of various pathophysiological states, particularly cardiovascular disorders such as diabetes, obesity, hypercholesterolemia, and hypertension, which have been strongly linked to the development of dementia (71). A cohort study among older Japanese people revealed that the consumption of green tea catechins high in EGCG potentially increased the brain function and memory of the subjects (72). This was supported by another study, which found that a high intake of EGCG-rich green tea correlated with improved cognitive abilities in an elderly Japanese population (73). In addition, significant improvements in cognitive function and calmness were found in healthy subjects compared to the placebo group (74). However, a systematic review of 21 studies found that no single component of EGCG, theanine, or caffeine in green or black tea had a beneficial effect on cognition; this only occurred when they were used in combination. This approach showcased a potential cognitive or neuroprotective effect (75). Furthermore, a review conducted by Kakutani *et al*. (2019), used three cohorts and five cross-sectional studies. This revealed that green tea has a positive neuroprotective activity that lowers the risk of dementia, AD, and cognitive impairment. Overall, the consumption of green tea polyphenols or catechins has been shown to improve brain activity compared to the consumption of single components such as EGCG or caffeine (76)

A well-conducted and proper design of cohort studies with good randomized controlled trials are required in future findings to draw an empirical and substantial evidence of the benefit of polyphenols compound in the treatment of dementia as well as the other neurological disorders. Result from ecological study investigating the association between consumption of green tea and the incidence of AD and/or dementia worldwide can be helpful. In addition, more research supporting the profile of EGCG as nutraceuticals is required, for example, study of minimal dose required for green tea or its components to effectively exhibit their potential effects, as well as the shortest time taken to produce the long-term effects of green tea. Besides, studies related to the effects of green tea consumption on different types of dementia and their performance in combination with caffeine on cognitive activities also can be beneficial for future

use. Apart from water, tea is the most prominent beverages consumed worldwide, hence, future studies investigating the effects of EGCG supplementation in dose-ranging in comparison with actual green tea consumption are essential to find out which of the regimen is beneficial for short- and long-term mental functioning.

A placebo-controlled pilot clinical trial administered 1-4 g of curcumin to Chinese AD patients for six months, which resulted in slightly improved cognitive function due to the decline of neuronal atrophy, in comparison with the placebo group. Moreover, the utilization of curcumin in another clinical trial carried out for four to eight weeks resulted in considerable anti-depressant effects on patients with major depression disorders (77). A systemic review supported the positive effects of curcumin against various neurodegenerative disorders (NDDs), particularly AD and depression in humans (78). Nonetheless, more clinical trials are needed to validate and highlight curcumin's neuroprotective properties against various types of NDDs. Future reference might benefit from research with larger samples, conducted over an extended treatment period, and using a wide range of curcumin dosages. In addition, focusing on the levels of crucial inflammatory and antioxidant biomarkers, optimal curcumin dosages, food interactions, and treatment duration might enable a better understanding of curcumin's promising cognitive effects.

Supplementation with resveratrol in healthy adults for 26 weeks therapeutically resulted in enhanced cognitive abilities, including good cerebral blood flow (79). Meanwhile, in a randomized, placebo-controlled trial, Evans *et al*. (2017) showed that a regular intake of 150 mg of trans-resveratrol for 14 weeks resulted in a 17 percent increase in cerebrovascular responsiveness (CVR), verbal memory, and mood in postmenopausal women, compared to the placebo (80). However, a recent systematic review and meta-analysis, which included 10 studies, found that treatment with resveratrol did not result in a substantial increase in overall cognitive performance, but it did modestly improve several cognitive parameters (81). Based on studies and clinical trials, resveratrol evidently promotes cognitive performance in healthy individuals and people with NDDs. However, limited sample sizes can cause biased results that can impact the reliability of a study. To demonstrate resveratrol's neuroprotective effects on people, a large-scale study involving individuals of different ages and health statuses is preferable. Human research, on the other hand, is limited and the results are inconsistent, which makes interpretation difficult. These discrepancies could be due to differences in methodology and the population studied. Besides, studies should expand on the discussion of resveratrol's safety and efficacy profile, in addition to the efficacy for this compound in the treatment and prevention of AD.

Morris *et al*. (2003) conducted clinical research using 131 AD patients and found that fish oil high in DHA could reduce the incidence of AD by roughly 60 percent when compared to AD subjects who did not take the fish oil (82). A meta-analysis study also showed that a higher intake of fish oil was linked to a 36 percent reduction in the risk of AD. Moreover, a further 11 percent decrease in the risk of developing AD was associated with a 100-gram increase in the consumption of fish oil (83). According to a randomized, double-blind, placebo-controlled trial undertaken by Lee *et al*. (2013), supplementation with fish oil containing a high level of DHA may help patients with mild cognitive impairment to enhance their working and verbal memory (84). The majority of the clinical trials were conducted using small samples; therefore, future clinical studies should be equipped

with large-scale experiments to determine the beneficial effects of omega-3 fatty acids in the treatment of various neurological diseases and disorders. In addition, among the common nutraceuticals, vitamin deficiency has been strongly associated with the pathogenesis of AD. Although the benefits of vitamin supplementation have been widely observed in animal models, it is also important to focus on clinical trials investigating the human benefits of vitamin intake. This approach may help to ascertain the effectiveness of vitamins and their influence on the molecular mechanisms of the disease. This would contribute to the evaluation of vitamins as potent nutraceuticals for the prevention and therapy of neurological disorders.

Clinical trials are not only required to investigate the efficacy and safety of nutraceuticals; they must also be thoroughly conducted to understand the mechanism of action and the bioavailability of nutraceuticals. Production of nutraceuticals should also be monitored to avoid contamination of the nutraceuticals with toxic compounds such as heavy metals pesticides and mycotoxins that could pose serious health problems to consumers with long-term exposure. It may occur that certain nutraceuticals are well tolerated and non-toxic; however, there are also concerns about their interactions with other medications, especially when the information is withheld from healthcare providers. Most of the nutraceuticals' safety and effectiveness lack scientific evidence with regards to the mechanism of action and limited randomised clinical trials that support their beneficial neuroprotective effects on conditions related to neurodegenerative dementia. Meanwhile, most of the nutraceutical compounds are lipophilic, which makes them susceptible to degradation and needs to be formulated in a delivery system that could improve the stability and bioavailability of the nutraceutical bioactive compounds.

6.0 Conclusion

The current review highlighted various nutraceuticals that have been used against dementia, such as omega-3 (PUFA), flavonoids, curcumin, resveratrol, and vitamins. The review have evidently demonstrated several neuroprotective properties, such as antioxidant, anti-inflammatory, and anti-amyloidogenic properties, and been found to be anti-protein aggregation, antidepression, neurogenesis, and neuroprotective agents. Supplementation with these food-based approaches therapeutically showcases potential improvements in cognitive function and the modulation of various neurotrophic signaling pathways. However, most of the clinical trials presented in this review were interpreted based on small samples, as well as limited treatment regimens and durations. Hence, future researchers should conduct large-scale clinical trials involving larger samples and suitable treatment durations. Experimenting with the effects synergistically with other potent nutraceuticals may expand the roles of nutraceuticals in regulating neurodegeneration of dementia.

Acknowledgement

The authors would like to thank Faculty of Pharmacy, Universiti Teknologi MARA, Malaysia for providing the opportunity to conduct the study.

References

1. Gale SA, Acar D, Daffner KR. Dementia. Am J Med. 2018;131(10):1161-9.

2. Duong S, Patel T, Chang F. Dementia: What pharmacists need to know. Can Pharm J. 2017;150(2):118-29.

3. Chiu H-F, Venkatakrishnan K, Wang C-K. The role of nutraceuticals as a complementary therapy against various neurodegenerative diseases: A mini-review. J Tradit Complement Med. 2020;10(5):434-9.

4. Sadhukhan P, Saha S, Dutta S, Mahalanobish S, Sil PC. Nutraceuticals: An emerging therapeutic approach against the pathogenesis of Alzheimer's disease. Pharmacol Res. 2018;129:100-14.

5. Dadhania VP, Trivedi PP, Vikram A, Nand Tripathi D. Nutraceuticals against neurodegeneration: a mechanistic insight. Curr Neuropharmacol. 2016;14(6):627-40.

6. Gendelman HE. Neural immunity: Friend or foe? J Neurovirol. 2002;8(6):474-9.

7. Celsi F, Pizzo P, Brini M, Leo S, Fotino C, Pinton P, et al. Mitochondria, calcium and cell death: a deadly triad in neurodegeneration. Biochim Biophys Acta Bioenerg. 2009;1787(5):335-44.

8. Dening T, Sandilyan MB. Dementia: definitions and types. Nurs Stand 2015;29(37):37.

9. Zhu CW, Livote EE, Scarmeas N, Albert M, Brandt J, Blacker D, et al. Long-term associations between cholinesterase inhibitors and memantine use and health outcomes among patients with Alzheimer's disease. Alzheimers Dement. 2013;9(6):733-40.

10. Schwarz S, Froelich L, Burns A. Pharmacological treatment of dementia. Curr Opin Psychiatry. 2012;25(6):542-50.

11. Soliman GA. Dietary fiber, atherosclerosis, and cardiovascular disease. Nutrients. 2019;11(5):1155.

12. Weickert MO, Pfeiffer AF. Impact of dietary fiber consumption on insulin resistance and the prevention of type 2 diabetes. J Nutr. 2018;148(1):7-12.

13. Matt SM, Allen JM, Lawson MA, Mailing LJ, Woods JA, Johnson RW. Butyrate and dietary soluble fiber improve neuroinflammation associated with aging in mice. Front Immunol. 2018;9:1832.

14. Barber T, Kabisch S, Pfeiffer A, Weickert M. The health benefits of dietary fibre. Nutrients. 2020;12(10):3209.

15. Zhang FF, Barr SI, McNulty H, Li D, Blumberg JB. Health effects of vitamin and mineral supplements. Br Med J. 2020;369:m2511.

16. Gugliandolo A, Bramanti P, Mazzon E. Role of vitamin E in the treatment of Alzheimer's disease: Evidence from animal models. Int J Mol Sci. 2017;18(12):2504.

17. Brzezińska O, Styrzyński F, Makowska J, Walczak K. Role of Vitamin C in Prophylaxis and Treatment of Gout—A Literature Review. Nutrients. 2021;13(2):701.

18. Figueroa-Méndez R, Rivas-Arancibia S. Vitamin C in health and disease: its role in the metabolism of cells and redox state in the brain. Front Physiol. 2015;6:397.

19. Chen X, Pan Z, Fang Z, Lin W, Wu S, Yang F, et al. Omega-3 polyunsaturated fatty acid attenuates traumatic brain injury-induced neuronal apoptosis by inducing autophagy through the upregulation of SIRT1-mediated deacetylation of Beclin-1. J Neuroinflam. 2018;15(1):1-15.

20. Saini RK, Keum Y-S. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance—A review. Life Sci. 2018;203:255-67.

21. Liu Z, Ren Z, Zhang J, Chuang C-C, Kandaswamy E, Zhou T, et al. Role of ROS and nutritional antioxidants in human diseases. Front Physiol. 2018;9:477.

22. Durazzo A, Lucarini M, Souto EB, Cicala C, Caiazzo E, Izzo AA, et al. Polyphenols: A concise overview on the chemistry, occurrence, and human health. Phytother Res. 2019;33(9):2221-43.

23. Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food Funct. 2019;10(2):514-28.

24. Bi X, Lim J, Henry CJ. Spices in the management of diabetes mellitus. Food Chem. 2017;217:281-93.

25. Faria FR, Gomes AC, Antunes A, Rezende KR, Pimentel GD, Oliveira CLP, et al. Effects of turmeric extract supplementation on inflammation and muscle damage after a half-marathon race: a randomized, double-blind, placebo-controlled trial. Eur J Appl Physiol. 2020;120(7):1531-40.

26. Chu C, Murdock MH, Jing D, Won TH, Chung H, Kressel AM, et al. The microbiota regulate neuronal function and fear extinction learning. Nature. 2019;574(7779):543-8.

27. Erny D, de Angelis ALH, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nature Neurosci. 2015;18(7):965-77.

28. Kim C-S, Cha L, Sim M, Jung S, Chun WY, Baik HW, et al. Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling older adults: a randomized, double-blind, placebo-controlled, multicenter trial. J Gerontol. 2021;76(1):32-40.

29. Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics-a review. J Food Sci Technol. 2015;52(12):7577-87.

30. Ajith TA. A recent update on the effects of omega-3 fatty acids in Alzheimer's disease. Curr Clin Pharmacol. 2018;13(4):252-60.

31. Zhou Y, Zheng J, Li Y, Xu D-P, Li S, Chen Y-M, et al. Natural polyphenols for prevention and treatment of cancer. Nutrients. 2016;8(8):515.

32. Lu Q-Y, Rasmussen AM, Yang J, Lee R-P, Huang J, Shao P, et al. Mixed spices at culinary doses have prebiotic effects in healthy adults: a pilot study. Nutrients. 2019;11(6):1425.

33. Vázquez-Fresno R, Rosana ARR, Sajed T, Onookome-Okome T, Wishart NA, Wishart DS. Herbs and spices-biomarkers of intake based on human intervention studies–a systematic review. Genes Nutr. 2019;14(1):1-27.

34. Huang F-y, Deng T, Meng L-x, Ma X-l. Dietary ginger as a traditional therapy for blood sugar control in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Med (Baltimore). 2019;98(13):e15054.

35. Natarajan TD, Ramasamy JR, Palanisamy K. Nutraceutical potentials of synergic foods: a systematic review. J Eth Foods. 2019;6(1):1-7.

36. Bhaskarachary K, Vemula SR, Gavaravarapu S, Joshi AKR. Traditional foods, functional foods and nutraceuticals. Proceedings of the Ind Nat Sci Acad. 2016;82(5):1565-77.

37. Zhang Y-J, Li S, Gan R-Y, Zhou T, Xu D-P, Li H-B. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015;16(4):7493-519.

38. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017;9(9):1021.

39. Cruz AG, Antunes AE, Sousa ALO, Faria JA, Saad SM. Ice-cream as a probiotic food carrier. Food Res Int. 2009;42(9):1233-9.

40. Seminario-Amez M, López-López J, Estrugo-Devesa A, Ayuso-Montero R, Jané-Salas E. Probiotics and oral health: A systematic review. Medicina Oral, Patologia Oral y Cirugia Bucal. 2017;22(3):e282.

41. Chapman C, Gibson GR, Rowland I. Health benefits of probiotics: are mixtures more effective than single strains? Eur J Nutr. 2011;50(1):1-17.

42. AlAli M, Alqubaisy M, Aljaafari MN, AlAli AO, Baqais L, Molouki A, et al. Nutraceuticals: Transformation of Conventional Foods into Health Promoters/Disease Preventers and Safety Considerations. Molecules. 2021;26(9):2540.

43. Chen X, Drew J, Berney W, Lei W. Neuroprotective Natural Products for Alzheimer's Disease. Cells. 2021;10(6):1309.

44. Mendiola-Precoma J, Berumen L, Padilla K, Garcia-Alcocer G. Therapies for prevention and treatment of Alzheimer's disease. BioMed Res Int. 2016;2016:1-17.

45. Dong Y, Xu M, Kalueff AV, Song C. Dietary eicosapentaenoic acid normalizes hippocampal omega-3 and 6 polyunsaturated fatty acid profile, attenuates glial activation and regulates BDNF function in a rodent

model of neuroinflammation induced by central interleukin-1β administration. Eur J Nutr. 2018;57(5):1781-91.

46. Fakhoury M. Microglia and astrocytes in Alzheimer's disease: implications for therapy. Curr Neuropharmacol. 2018;16(5):508-18.

47. Pu H, Guo Y, Zhang W, Huang L, Wang G, Liou AK, et al. Omega-3 polyunsaturated fatty acid supplementation improves neurologic recovery and attenuates white matter injury after experimental traumatic brain injury. J Cereb Blood Flow Metab. 2013;33(9):1474-84.

48. Lange KW, Nakamura Y, Gosslau AM, Li S. Are there serious adverse effects of omega-3 polyunsaturated fatty acid supplements? J Food Bioact. 2019;7.

49. Venkatakrishnan K, Chiu H-F, Cheng J-C, Chang Y-H, Lu Y-Y, Han Y-C, et al. Comparative studies on the hypolipidemic, antioxidant and hepatoprotective activities of catechin-enriched green and oolong tea in a double-blind clinical trial. Food Funct. 2018;9(2):1205-13.

50. Prasanth MI, Sivamaruthi BS, Chaiyasut C, Tencomnao T. A review of the role of green tea (Camellia sinensis) in antiphotoaging, stress resistance, neuroprotection, and autophagy. Nutrients. 2019;11(2):474.

51. Pervin M, Unno K, Ohishi T, Tanabe H, Miyoshi N, Nakamura Y. Beneficial effects of green tea catechins on neurodegenerative diseases. Molecules. 2018;23(6):1297.

52. Mantzorou M, Pavlidou E, Vasios G, Tsagalioti E, Giaginis C. Effects of curcumin consumption on human chronic diseases: A narrative review of the most recent clinical data. Phytother Res. 2018;32(6):957-75.

53. Tiwari SK, Agarwal S, Seth B, Yadav A, Nair S, Bhatnagar P, et al. Curcumin-loaded nanoparticles potently induce adult neurogenesis and reverse cognitive deficits in Alzheimer's disease model via canonical Wnt/β-catenin pathway. ACS nano. 2014;8(1):76-103.

54. Limanaqi F, Biagioni F, Busceti CL, Ryskalin L, Polzella M, Frati A, et al. Phytochemicals bridging autophagy induction and alpha-synuclein degradation in parkinsonism. Int J Mol Sci. 2019;20(13):3274.

55. Teter B, Morihara T, Lim G, Chu T, Jones M, Zuo X, et al. Curcumin restores innate immune Alzheimer's disease risk gene expression to ameliorate Alzheimer pathogenesis. Neurobiol Dis. 2019;127:432-48.

56. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: involvement of serotonin and dopamine system. Psychopharmacol. 2008;201(3):435-42.

57. Cheng KK, Chan PS, Fan S, Kwan SM, Yeung KL, Wang Y-XJ, et al. Curcumin-conjugated magnetic nanoparticles for detecting amyloid plaques in Alzheimer's disease mice using magnetic resonance imaging (MRI). Biomaterials. 2015;44:155-72.

58. Pourhanifeh MH, Shafabakhsh R, Reiter RJ, Asemi Z. The effect of resveratrol on neurodegenerative disorders: possible protective actions against autophagy, apoptosis, inflammation and oxidative stress. Curr Pharmaceut Des. 2019;25(19):2178-91.

59. Zheng S, Feng Q, Cheng J, Zheng J. Maternal resveratrol consumption and its programming effects on metabolic health in offspring mechanisms and potential implications. Biosci Rep. 2018;38(2).

60. Ros P, Diaz F, Freire-Regatillo A, Argente-Arizon P, Barrios V, Argente J, et al. Resveratrol intake during pregnancy and lactation modulates the early metabolic effects of maternal nutrition differently in male and female offspring. Endocrinol. 2018;159(2):810-25.

61. Coimbra M, Isacchi B, van Bloois L, Torano JS, Ket A, Wu X, et al. Improving solubility and chemical stability of natural compounds for medicinal use by incorporation into liposomes. Int J Pharm. 2011;416(2):433-42.

62. Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, Aisen PS, et al. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J Neuroinflam. 2017;14(1):1-10.

63. Gomes BAQ, Silva JPB, Romeiro CFR, Dos Santos SM, Rodrigues CA, Gonçalves PR, et

al. Neuroprotective mechanisms of resveratrol in Alzheimer's disease: role of SIRT1. Oxid Med Cell Longev. 2018;2018.

64. Pasinetti GM, Wang J, Ho L, Zhao W, Dubner L. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. Biochim Biophys Acta Mol Basis Dis. 2015;1852(6):1202-8.

65. Ryan MJ, Dudash HJ, Docherty M, Geronilla KB, Baker BA, Haff GG, et al. Vitamin E and C supplementation reduces oxidative stress, improves antioxidant enzymes and positive muscle work in chronically loaded muscles of aged rats. Exp Gerontol. 2010;45(11):882-95.

66. Betti M, Minelli A, Ambrogini P, Ciuffoli S, Viola V, Galli F, et al. Dietary supplementation with α-tocopherol reduces neuroinflammation and neuronal degeneration in the rat brain after kainic acid-induced status epilepticus. Free Rad Res. 2011;45(10):1136-42.

67. Messaoudi M, Violle N, Bisson J-F, Desor D, Javelot H, Rougeot C. Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. Gut Microbes. 2011;2(4):256-61.

68. Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of nutraceuticals in human health. J Food Sci Technol. 2012;49(2):173-83.

69. Sun J, Li H, Jin Y, Yu J, Mao S, Su K-P, et al. Probiotic Clostridium butyricum ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. Brain Behav Immun. 2021;91:703-15.

70. Yoon G, Kim Y-K, Song J. Glucagon-like peptide-1 suppresses neuroinflammation and improves neural structure. Pharmacol Res. 2020;152:104615.

71. Edwards GA, Gamez N, Escobedo Jr G, Calderon O, Moreno-Gonzalez I. Modifiable risk factors for Alzheimer's disease. Front Aging Neurosci. 2019:146.

72. Tomata Y, Kakizaki M, Nakaya N, Tsuboya T, Sone T, Kuriyama S, et al. Green tea consumption and the risk of incident functional disability in elderly Japanese: the Ohsaki Cohort 2006 Study. Am J Clin Nutr. 2012;95(3):732-9.

73. Noguchi-Shinohara M, Yuki S, Dohmoto C, Ikeda Y, Samuraki M, Iwasa K, et al. Consumption of green tea, but not black tea or coffee, is associated with reduced risk of cognitive decline. PLoS One. 2014;9(5):e96013.

74. Scholey A, Downey LA, Ciorciari J, Pipingas A, Nolidin K, Finn M, et al. Acute neurocognitive effects of epigallocatechin gallate (EGCG). Appetite. 2012;58(2):767-70.

75. Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: A systematic review. Phytomedicine. 2017;34:26-37.

76. Kakutani S, Watanabe H, Murayama N. Green tea intake and risks for dementia, Alzheimer's disease, mild cognitive impairment, and cognitive impairment: a systematic review. Nutrients. 2019;11(5):1165.

77. Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD. Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. J Affect Disd. 2014;167:368-75.

78. Voulgaropoulou S, Van Amelsvoort T, Prickaerts J, Vingerhoets C. The effect of curcumin on cognition in Alzheimer's disease and healthy aging: A systematic review of pre-clinical and clinical studies. Brain Res. 2019;1725:146476.

79. Witte AV, Kerti L, Margulies DS, Flöel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. J Neurosci. 2014;34(23):7862-70.

80. Evans HM, Howe PR, Wong RH. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised placebo-controlled intervention trial. Nutrients. 2017;9(1):27.

81. Marx W, Kelly JT, Marshall S, Cutajar J, Annois B, Pipingas A, et al. Effect of resveratrol supplementation on cognitive performance and mood in adults: a systematic

literature review and meta-analysis of randomized controlled trials. Nutr Rev. 2018;76(6):432-43.

82. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003;60(7):940-6.

83. Wu S, Ding Y, Wu F, Li R, Hou J, Mao P. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. Neurosci Biobehav Rev. 2015;48:1-9.

84. Lee LK, Shahar S, Chin A-V, Yusoff NAM. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. Psychopharmacol. 2013;225(3):605-12.