



## REVIEW ARTICLE

# Exploring the potential of neuronutraceuticals as alternatives in the prevention of Alzheimer's disease

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### ABSTRACT

Various chemical compounds with natural dietary origins have been shown to protect against age-related disorders, such as neurodegenerative diseases such as Alzheimer's disease (AD). Such substances are known as nutraceuticals, and they differ structurally, function at distinct biochemical and metabolic levels, and have various neuroprotective characteristics. In this review, we analyzed the evidence from explanatory studies on the effects of selected nutritional supplements on age-related cognitive decline and dementia in humans, randomized clinical trials, and clinical trials. We provide findings from research on vitamins, flavonoids, and other natural compounds that have been researched in AD and may be useful for maintaining excellent cognitive function. In dementia-related therapy, nutraceuticals are not a choice due to a severe absence of high-quality research studies. Despite this, the significant potential for their neuroprotective effects discourages future research.

**KEY WORDS:** Alzheimer's disease, Cognitive impairment, Dementia, Dietary natural substances, Neurodegeneration, Nutraceuticals, Vitamins and minerals

### INTRODUCTION

Neurological disorders are one of the major healthcare issues worldwide.<sup>[1-3]</sup> Lifestyle changes are associated with the risk of chronic illness. Nowadays, Alzheimer's is becoming a major puzzle in medicine. Alzheimer's disease (AD) is regarded as a neurodegenerative disease with a progressive loss of the basal forebrain with the characteristics of loss of memory, dementia, and impairment in memory.<sup>[3,4]</sup> Aging is the most common factor of AD. Alois Alzheimer, a German psychiatrist, was the first to notice this disease in 1906. Auguste, a patient with growing cognitive impairment, was diagnosed by Dr. Alzheimer.<sup>[4,5]</sup> Auguste's brain was investigated using histology after his death, and Dr. Alzheimer discovered many military clusters of brain tissue in the cortex.<sup>[5,6]</sup> These military clusters are neurofibril deposits, which are well-known nowadays.<sup>[7,8]</sup> The aggregation and deposition of ubiquitinated and phosphorylated neurofibrillary tangles (NFTs) as tau proteins are responsible for the pathogenic response of AD.<sup>[8,9]</sup> Miliary foci are also caused by the

deposition of neurotoxic amyloid- $\beta$  precursor protein peptides (APP-A $\beta$ ).<sup>[9,10]</sup> It is distinguished by a progressive loss of cognitive abilities. In AD, the inflammation of the brain is distinguished by increasing microglia and astrocyte activation is the key feature of the neurodegenerative disease.<sup>[10,11]</sup> The etiology of AD is still not known, the several studies confirm the change in the brain affected by AD.<sup>[5,6]</sup> The expensive and epidemic behavior of AD concerns public and medical opinion while focusing efforts on its treatment and prevention.<sup>[6,7]</sup> The production of NFTs and senile plaques (SPs), predominantly due to the accumulation of plaques (A $\beta$ ) and higher presence of tau protein, is the most significant alterations.<sup>[7,8]</sup> These multipotent preventive natural substances can impact the generation and accumulation of A $\beta$  peptides.<sup>[8,9]</sup> These natural substances were also discovered to modulate

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certain intracellular signaling molecules and enzymes such as  $\gamma$ -secretase and  $\beta$ -secretase.<sup>[10,11]</sup> The focus of this review is to highlight the therapeutic benefits and modulation of molecular targets of several nutraceutical substances derived from natural products, as well as their potential to fight AD. The pathophysiology of neurodegenerative disorders is related to mutant protein aggregation development, accumulation in particular brain areas, and the consequent cellular stress response, neurotransmitter release disruption, neuroinflammation, excessive reactive oxygen species (ROS) production, and neuronal cell death.<sup>[12,13]</sup> The importance of nutraceuticals as a preventative therapy for neurological treatments has been demonstrated by a link between eating habits and individual lifestyle with neurodegeneration.<sup>[13,14]</sup> In general, nutraceutical products are often supplied in dosages derived from natural products. Nowadays, functional foods are increasingly being studied for their physiological advantages as well as their capacity to minimize chronic disease risk factors.<sup>[15,16]</sup>

### FACTORS AFFECTING BRAIN AGING AND COGNITIVE IMPAIRMENT

Exploring the causes of cognitive decline associated with regular aging may provide hope for the prevention and treatment of neurodegenerative diseases.<sup>[16]</sup> Multiple factors influence cognitive aging, such as diet, lifestyle, endocrine and genetic parameters, neurotoxic exposures, oxidative damage, and surgical and medical disease interventions. These variables compromise bioenergetics, neural network activity, neuronal plasticity, anti-inflammatory, and antioxidant systems, and calcium homeostasis, ultimately influencing brain functioning and cognitive processes.<sup>[16]</sup> With aging, the cortical lining thins, the cerebral ventricles enlarge, and the permeability of blood–brain barrier (BBB) rises. Changes in the levels of dopaminergic, cholinergic, noradrenergic, serotonergic, enzymes, hormones, glutamatergic neurotransmitters, and metabolites accompany brain aging. Sex hormones have been linked to faster structural and functional brain aging, as well as an increased risk of dementia.<sup>[17,18]</sup> The neuroprotective impact of estrogenic signaling including estrogenic receptors (ER $\beta$  and ER $\alpha$ ) and their coregulators in memory dysfunctions throughout aging and pathological situations have been extensively demonstrated.<sup>[18]</sup> Genetic and epigenetic factors that act as neurochemical, cellular regulatory switches, and psychological variables are largely responsible for multidimensional brain aging. From the perspective of memory problems and brain aging, Candia *et al.* have widely examined synaptic plasticity genes and chromatin remodeling factors such as histone methyltransferase, DNA methyltransferases, CREB-binding protein, and histone deacetylases,<sup>[19]</sup> as well as an APP and apolipoprotein E, two AD candidate genes, were also altered during normal brain aging.

### NUTRITION AS A POSSIBLE COGNITIVE AGE MODULATOR

The brain has a high dietary requirement, and growing research shows that nutritional imbalances compromise the anatomical and the brain's functional integrity is compromised, compromising our cognitive abilities. Malnutrition in the elderly community-dwelling population and the elderly hospital has been linked to the cognitive deterioration.<sup>[19]</sup> Micronutrient deficits are more common among the elderly due to a range of causes such as physical, social, emotional, and economic barriers to eating. Gastrointestinal discomfort and pain, loss of appetite, and rapid loss of weight are all signs of a dietary deficiency. To detect persons at risk of nutrition deficiencies, several assessment techniques such as the Mini-Nutritional Assessment and Malnutrition Universal Screening Tool (MUST) are being used to screen for malnutrition. Nutrition and food are thought to be possible moderators of age-related cognitive impairment, and the discovery of effectual dietary therapies for promoting healthy aging is developing as a new and complex area of scientific study. In cognitive aging, vitamins, minerals, dietary fatty acids, and micronutrients with anti-inflammatory and antioxidant characteristics have been studied. Because of the relevance of food and nutrient combinations, varied nutritional habits were also researched in the context of cognitive aging.<sup>[20]</sup>

### NUTRACEUTICALS

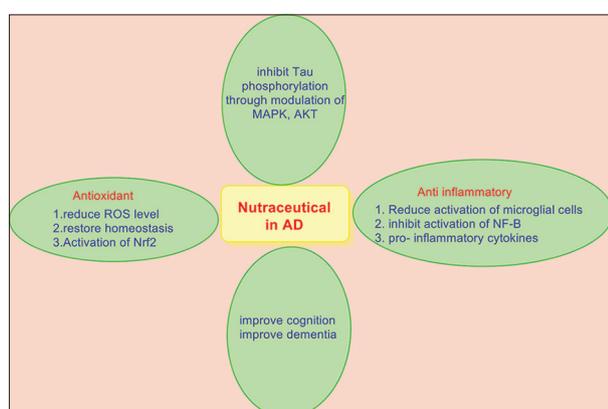
Dr. Stephen De Felice firstly invented the word nutraceuticals in 1979. Nutraceuticals are foods or products that provide health advantages. Dietary nutritional supplements genetically modified foods, herbal remedies, drinks, soups, vegetables, and processed meats such as cereals are all possibilities. According to Merriam-Webster Online Dictionary 2014, the current meaning of nutraceuticals is, “(1) a carefully prepared food, vitamin, mineral, herb, or other substance that you eat or drink to recover your health and (2) a food that gives health advantages in addition to basic nutrition (as a fortified food or dietary supplement).”<sup>[20,21]</sup> Vitamins, minerals, and amino acids are the most common and over 1000 probiotic components have been found too far. It's a human diet bioactive component that can help with illness prevention and treatment. Many compounds that become accessible after digestion have additional nutritional benefits.<sup>[22]</sup> The nutraceuticals market has risen in the recent decade as consumer awareness of these compounds has grown, as has their importance in the treatment and prevention of numerous diseases. The study of nutraceuticals with molecular effects is based on the idea that traditional remedies or tribal customs provide nutritional agents that can help treat sickness.<sup>[22]</sup> There is a growing interest in cognitive augmentation not only elderly but also among the young and cognitively healthy, according to new findings, is a modifiable component in cognitive disorders,

and appropriate dietary intake is required to sustain cognitive health, as shown in Figure 1. The significance of nutraceuticals in reducing cognitive impairments in elderly persons and protecting against age-related illnesses such as dementia and AD has gotten a lot of attention.

Polyphenols such as anthocyanins, flavonoids, flavanones, isoflavones, coumarins, lignin, and tannins are classed based on chemical components. The carotenoids, saponins, tocopherols, terpenoids, terpenes, and tocotrienols are all isoprenoid derivatives. There are about 500 plants from Ayurvedic medicine that has been studied, and access to a large collection of herbs that have been traditionally cultivated and used for daily treatments for various conditions has been made available.<sup>[23]</sup>

### INSIGHTS INTO THE ACTIVITY OF NUTRACEUTICALS

Several of the goals of this special issue have been to draw attention to current breakthroughs in natural product research where active principles have been established, especially when researchers were aiming to characterize activities at specified aims related to the healthy brain and devastating diseases.<sup>[24]</sup> Creatinine intake has, therefore, been studied in numerous adult neurodegenerative disorders since it protects mitochondrial activity directly, and its increasing consumption can enhance brain creatinine and sustain cognitive performance under pressure. Creatinine appears to protect against oxidative and nitrosative stress generated by L-glutamate in SH-SY5Y cells and appears to have comparable positive effects *in vivo* in the brain when continuously but not abruptly supplied.<sup>[25]</sup> Furthermore, dietary creatinine supplements throughout pregnancy may be a beneficial prophylactic for protecting the baby from the multiorgan repercussions of severe hypoxia after delivery, where newborn brain impairment occurs as a result of mitochondrial energy failure and decreased ATP synthesis. Eugenol (found in *Syzygium aromaticum*, leaves, and clove oil) improved the survival of the SH-SY5Y cells under experimental hyperglycemia by reducing oxidative stress. Moreover, eugenol treatment in diabetic



**Figure 1:** Mechanism of nutraceuticals in Alzheimer's disease

rats reduced oxidative indicators and protein carbonyls across both cytosolic and mitochondrial fractions, as well as restored the action of mitochondrial complexes I, II, and III. This naturally produced polyphenol has a long history of application as an antibacterial, analgesic, and carminative, for tooth issues in Ayurvedic medicine, and hence looks to be a promising adjuvant therapy molecule for diabetes complications. Curcumin, the most common phenolic ingredient in turmeric (*Curcuma longa*), has long been utilized for its health-promoting properties in Asian countries. Its incorporation into lactoferrin nanoparticles increases the effective concentration of curcumin reached, resulting in much higher enhancements in viability and decreases in  $\alpha$ -synuclein in the neuroblastoma SK-N-SH dopaminergic cell line compared to soluble curcumin. These findings support our first volume's assertion that new medication delivery methods boost curcumin bioavailability and efficacy.<sup>[26]</sup>

### INTERVENTION WITH NUTRACEUTICALS IN COGNITIVE DECLINE AND DISORDERS

Mental enhancement is gaining popularity among people of all ages, not just the elderly. Emerging evidence suggests that diet is a modifiable risk factor for cognitive impairments and that adequate nutritional intake is required to maintain cognitive health and lower the risk of neurodegenerative diseases later in life. In this context, the significance of nutraceuticals in mitigating cognitive deficiencies in older persons and protecting against age-related cognitive illnesses such as AD and other types of dementia has attracted substantial attention.<sup>[27]</sup> Nutraceutical is a phrase coined from nutrition and pharmaceutical that refers to a wide variety of nutritional items that are physiologically helpful and have established effects on illnesses. Nutraceuticals such as dietary supplements, phytochemicals, medical foods, functional foods, and specific dietary patterns. Those are categorized chemically as polyphenols (anthocyanins, flavonoids, flavanones, isoflavones, coumarins, lignins, and tannins), isoprenoid derivatives (terpenoids, carotenoids, saponins, terpenes, and tocotrienols), carbohydrate derivatives (oligosaccharides, ascorbic acid, and non-starch polysaccharides), and structural lipid (prebiotics and probiotics).<sup>[28,29]</sup>

### AMELIORATING EFFECTS OF SEVERAL NUTRACEUTICALS ON THE ETIOLOGY OF AD.

#### Taurine

It is a sulfur-containing amino acid produced as a by-product of cysteine metabolism. It also is founded that after methionine is transformed into cysteine with the aid of cysteine dioxygenase, cysteine is transformed into cysteine sulfinic acid. The enzyme cysteine sulfinic

acid decarboxylase decarboxylates cysteine sulfinic acid to produce hypotaurine that is then transformed into taurine. *Taurine* is mostly created in the kidney and liver, but it is also formed in the heart, brain, blood, and muscles, particularly leukocytes. In certain organ pathophysiological situations, *taurine* has antioxidant and anti-inflammatory capabilities. Tauroursodeoxycholic acid (TUDCA) is a bile acid that is neuroprotective in a mouse model of AD. TUDCA administration decreased tau phosphorylation, A $\beta$  deposition, and synaptic function loss in APP/PS1 mice. It also reduced glial cell activation and neuroinflammation in APP/PS1 mice by downregulating interleukin (IL)-1b, tumor necrosis factor alpha (TNF-a), and IL-6 protein expression. TUDCA's-positive function is due to the stimulation of the Akt/GSK3 signaling pathway. TUDCA also altered apoptosis in neuroblastoma cell lines with high levels of Ab synthesis and aggregation through the E2F-1/p53/Bax pathway. TUDCA inhibited caspase 2 and 6, downregulated the expression of Bax and bcl2, and decreased nuclear fragmentation. In ICV-STZ-treated rats, pre-treatment with taurine at a dosage of 50 mg/kg body weight delivered orally increased the activity of antioxidant enzymes such as glutathione (GSH) peroxidase, catalase, superoxide dismutase (SOD), GSH reductase (GR), and GSH-S-transferase. It also enhanced the amount of GSH. Taurine inhibited acetylcholine esterase activity while improving the architecture of hippocampal pyramidal neurons.<sup>[30]</sup> It acted as a neuroprotective agent against STZ-induced cognitive deficits in rats. Jang *et al.* confirmed that by directly binding to oligomeric A $\beta$ , oral taurine treatment alleviated A $\beta$ -induced cognitive impairments in an oligomeric A $\beta$ -infusion mouse paradigm. Surface plasmon resonance was used to demonstrate this binding. *Taurine* alleviated cognitive impairment in rats with ICV-STZ-induced cognitive dysfunction by modulating oxidative stress parameters and the release of pro-inflammatory cytokines TNF-a and IL-1b in the hippocampus area and cortex. *Taurine* also inhibited choline-esterase activity. These studies show that taurine is a viable medicinal agent.<sup>[31]</sup>

### Curcumin

Curcumin is a phytochemical and polyphenol derived from the herb *C. longa*, from which turmeric is derived. Turmeric is used to color cuisine throughout India and most of South Asia. Curcumin has been utilized for many years in Indian Ayurvedic medicine to treat different organ pathologies.<sup>[32-35]</sup> Curcumin is found in two tautomeric forms: Enol and keto. In acidic and neutral environments, it is mostly found in keto forms. Curcumin is a powerful antioxidant, and its antioxidant and anti-inflammatory properties have been studied in disorders such as cancer, diabetes, and drug-induced organ dysfunction. The antioxidant characteristic of this polyphenol is due to the phenolic OH groups' ability to lose protons, resulting in a phenoxy diradical that is stabilized by electron delocalization. Curcumin's

antioxidant capabilities are due to its resonance-stabilized structure, which assists it in scavenging free radicals. In AD, the formation of the oligomeric A $\beta$  plaques is associated with dementia and memory loss.<sup>[4,9,36,37]</sup> Curcumin was found to be beneficial in lowering A $\beta$  plaque development in a murine model. It inhibited the BACE-1 enzyme, which transforms APP to Ab through APP cleavage. Curcumin was demonstrated to attach to cerebral amyloid angiopathy, tau proteins, and SPs in the aging brains of numerous animal models as well as AD patient. Curcumin treatment increased the production of BAG2, an endogenous protein that assists in the clearance of neuronal tau tangles in cortical neurons of the primary rat. It also lowered the amount of phosphorylated tau in the body. Curcumin encapsulated in carefully engineered exosomes increased bioavailability, solubility, and blood-brain barrier bridging in AD models through receptor-mediated endocytosis. In the brain, curcumin stimulated the AKT/GSK-3b pathway, reducing tau phosphorylation, and death of a neuronal cell *in vivo* in AD.<sup>[8]</sup> Neuroinflammation is a defining feature of AD. Activated microglial cells are primarily responsible for the inflammatory response. The pro-inflammatory cytokines including TNF-a, IL-1b, and IL-6 are released by activated microglial cells in the brain. The composition of ROS follows the accumulation of these cytokines (ROS). IL-1b is essential in the biological process of AD. IL-1b triggers the (MAPK)-p38 signaling cascade, which, in turn, activates the BACE-1 protease. This BACE-1 causes proteolytic cleavage of APP, which results in A $\beta$  deposition. Through p38 activation, IL-1b also promotes tau protein phosphorylation and NFT aggregation, thereby enhancing AD pathology. Tau hyperphosphorylation and NFT deposition result in axonal and synaptic connection loss between neurons. By activating nuclear factor kappa B (NF-kB), IL-1 cytokines also enhance inflammation. By regulating IL-1 family cytokines, curcumin has been found to attenuate inflammatory reactions.<sup>[3,8,38]</sup>

### Vitamin C

*Vitamin C* shows the well-known antioxidant activity, also known as ascorbic acid that has been shown to improve a wide range of physiological processes. It is a vitamin that dissolves in water. Glucose may be used to produce *Vitamin C*. Humans are still unable to produce *Vitamin C* in the body due to a lack of the enzyme L-gulonolactone oxidase, which is required for the metabolic transformation of *Vitamin C* from glucose. Vitamin C works as an antioxidant by neutralizing free radicals and ROS directly. Ascorbate is formed when one hydrogen is lost. After losing one hydrogen, the resultant ascorbate is transformed into ascorbate free radical (AFR). Through electron rearrangement, AFR is transformed into dehydroascorbic acid (DHA). This DHA can then be dissimulated to produce ascorbate. With the help of NADPH thioredoxin reductase and oxidase, DHA may be transformed into ascorbate through GSH-dependent reduction.<sup>[39]</sup>

*Vitamin C*, in addition to its antioxidant effect, helps to recycle other antioxidants such as tetrahydrobiopterin and  $\alpha$ -tocopherol. Oxidative stress and ROS are inextricably connected to AD. Because of its high polyunsaturated fatty acid content and fast oxygen turnover, brain tissue is extremely sensitive to redox-mediated injury. The brain has the most ascorbic acid, and *Vitamin C* is abundant in the cortical neurons and hippocampus. Furthermore, the quantity of *Vitamin C* in the brain is decreased in people with AD, indicating the role of this antioxidant molecule in AD. In AD patients, the plasma level of *Vitamin C* is similarly lowered. Acute systemic *Vitamin C* infusion alleviated cognitive impairment in APP/PSEN1 mice. Mitochondrial dysfunction is a characteristic of AD caused by the build-up of ROS and the development of oxidative stress. *Vitamin C* supplementation decreased mitochondrial damage in 5XFAD mice (an AD model). In the brains of 5XFAD mice, it also decreased a plaque development and disruption of the BBB. A modest *Vitamin C* dosage administration in KO-Tg mice may lead to mitochondrial dysfunction because of disruption in the equilibrium of mitochondrial fusion and fission. A high dosage of *Vitamin C* treatment in 5XFAD animals also reduced astrocyte accumulation, lowering neuroinflammation in the brain. Endogenous ascorbate deficiency results in decreased mitochondrial respiration, mitochondrial transmembrane potential, mitochondrial power generation, and increased mitochondrial ROS production in mitochondria isolated from the brain of mice with both APP/PSEN1 and SVCT2 mutations compared to wild-type isolates. When ascorbate was administered to isolated mitochondria, it enhanced oxygen consumption while decreasing ROS production. *Vitamin C* supplementation was shown to be effective in clinical trial findings. For 1 year, *Vitamin E* (400 IU/day) and *Vitamin C* (1000 mg/day) treatments raised *Vitamin C* concentrations in plasma of AD patients and cerebrospinal fluid (CSF). Furthermore, the *Vitamins C* and E cosupplementation decreased lipid peroxidation in the CSF. *Vitamin* supplementation did not affect the progression of AD. In research including 276 elderly AD patients, a 16-week cosupplementation of *Vitamins C, E*, and carotene dramatically improved cognitive behavior and lowered plasma A $\beta$  levels. For 16 weeks,  $\alpha$ -lipoic acid and *Vitamins E and C*, and supplementation to AD patients lowered an oxidative stress marker, F2-isoprostane levels, but had no effect on A $\beta$ 42 and tau levels in the CSF.<sup>[40]</sup>

### Catechins

*Catechins* are a key class of flavonoids found in tea. Epicatechin (EC), (-)-epigallocatechin (EGC), (-)-EC gallate, and (-)-EGC gallate (EGCG) are the most common catechins found in tea, and their chemical structures reveal a lot about their biological activity. The position of the -OH group in the B and C rings of the structure of flavone differs between these catechins. The B-ortho-dihydroxyl ring's group adds to its radical neutralizing

action. The gallate moiety present in the 3<sup>rd</sup> position of the ring C boosts radical neutralizing activity. *Catechins* are digested relatively quickly, and there are chemical changes that occur throughout this process. *Catechins* are glucuronidated, O-methylated, and sulfated in Phase II by the enzymes catechol-O-methyltransferase, UDP-glucuronosyltransferases, and phenol sulfotransferases. The metabolites produced by catechin metabolism offer a wide range of biologically beneficial properties. *Catechins* were shown to have anti-inflammatory, anti-cancer, and antidiabetic properties. In rats, 0.5% catechins green tea treatment reduced A $\beta$ -induced cognitive deficits. For 6 weeks, intraperitoneal injection and oral EGCG at doses of 20 and 50 mg/kg decreased tau protein phosphorylation in an APPSw transgenic AD mouse model. Catechins are potent against ROS-induced neuronal injury and decrease NF- $\kappa$ B activation. In APP/PS-1 animals, a double mutant transgenic mouse model, EGCG restored mitochondrial respiratory rates, ROS generation, membrane potential, and ATP levels in mitochondria isolated from the striatum, cortex, and hippocampus. *Catechins'* anti-inflammatory activity is ascribed to the hydroxyl and galloyl moieties at the 30 locations on EGCG. Furthermore, catechins have a positive effect on AD pathogenesis through modulating the PKC, MAPK, and AKT pathways.<sup>[41]</sup>

### Resveratrol

It is a polyphenolic substance that originates in red wine, grapes, jackfruit, and mulberries. It is a stilbene family phytoalexin that is produced in response to environmental stress. *Resveratrol* can be found in two forms: Trans and cis. The transform is more stable as compared to the cis version and has biological properties. The *trans-resveratrol* undergoes methoxylation, glycosylation, isoprenylation, and oligomerization to create pterostilbene, trans-piceid, arachidic-3, and trans-V-viniferin. *Resveratrol's* oral bioavailability is <1% due to its weak water solubility, low chemical stability, and increased rate of digestion. It has been demonstrated that the coadministration of resveratrol with alkaloids such as piperidine improves its pharmacokinetic properties by inhibiting glucuronidation, hence boosting resveratrol bioavailability. Liposomes, colloidal carriers, and *resveratrol* protein complexes have been employed in delivery methods to improve the bioavailability and effectiveness of this molecule. Resveratrol is useful in the treatment of AD. It has been shown that it inhibits Ab plaque formation by binding to A $\beta$  in the cortical area. BACE1 and g-secretase have been discovered to be inhibited by resveratrol. It has also been found to reduce neuroinflammation by inhibiting Ab-mediated microglial cell cycle progression in APP/PS1 mice.<sup>[32]</sup> Neuroinflammation is inhibited in the AD animal model by downregulating the pro-inflammatory transcription factor NF- $\kappa$ B that lowering the release of cytokines IL-1b, IL-6, TNF-a, chemoattractants like NO generation, MCP-1, and prostaglandin E2 (PGE2) synthesis. The development of

A $\beta$  plaques and initiation of microglial cells frequently results in mitochondrial dysfunction, ROS generation, and oxidative stress. *Resveratrol* fights oxidative stress by lowering ROS levels through activating GSH, which scavenges ROS. In H<sub>2</sub>O<sub>2</sub>-induced neurotoxicity, it has also been demonstrated to activate heme-oxygenase 1, a redox-sensitive transcription factor (HO-1). Autophagy activation through AMPK is another protective mechanism of resveratrol in AD. Autophagy induction has been demonstrated to improve mitochondrial dysfunction in the brain. *Resveratrol* inhibits brain cell death by altering the Bax/bcl2 ratio through JNK activation. Furthermore, enhancing memory, cognitive function, and tauopathy are all aspects of AD treatment. According to the literature, resveratrol has a significant impact on these pathological symptoms of AD.<sup>[42]</sup>

### SIRT3 ACTIVATORS IN AD

In AD, several natural compounds are employed to affect SIRT3 activity. The following sections go through the many SIRT3 positive activators and modulators that have been discovered.

#### Honokiol

*Honokiol* is a SIRT3 activator that increases SIRT3 expression and deacetylation activity and has been studied extensively. Honokiol, chemically 2-(4-hydroxy-3-prop-2-enyl-phenyl)-4-prop-2-enyl-phenol, is a bioactive chemical derived from *Magnolia grandiflora* that has a wide range of characteristics such as anti-inflammatory, antioxidative, anti-tumor, anti-thrombolytic, anti-arrhythmic, anxiolytic, and anti-angiogenic activities. *Honokiol* penetrates the blood-brain barrier, making it a possible therapeutic agent with improved bioavailability for neurological illnesses. Several studies have demonstrated that honokiol is useful for the treatment of stroke, neurodegenerative illnesses such as Parkinson's and Alzheimer's, and brain tumors. The crystal structure of human SIRT3 (3GLS) was acquired from the protein databank and integrated into the computational tool Schrodinger.<sup>[43]</sup>

#### Dihydromyricetin (DHM)

DHM, chemically (2R,3R)-3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydrochromen-4-one, also known as Ampelopsis, is a flavanone that is the principal bioactive constituent of the Chinese medicinal plant *Ampelopsis grossedentata* (Hand-Mazz). DHM possesses antioxidant, anti-cancer, anti-inflammatory, and anti-alcohol intoxication properties. Interestingly, DHM has been demonstrated to have neuroprotective benefits through increasing SIRT3 levels, demonstrating that it is a powerful SIRT3 agonist.<sup>[44]</sup>

#### Trans $\epsilon$ -viniferin

*Trans  $\epsilon$ -Viniferin* remains a polyphenol stilbenoid found naturally in grape stems and other woody vine parts. This stilbenoid is a dehydrodimer of resveratrol and has characteristics that are superior to those seen with resveratrol. *Vitis vinifera* produces it in reaction to various stressors. SIRT3 is a NAD-dependent deacetylase sirtuin-3 that is located mostly in mitochondria and is abundantly expressed in the brain. The loss of SIRT3 in mice results in significant hyperacetylation of proteins and antioxidant enzyme failure, ultimately leading to mitochondrial malfunction. As a result, drugs that boost mitochondrial SIRT3 would increase mitochondrial function. Surprisingly, the study was conducted. In Huntington's disease cell models, viniferin was found to influence mitochondrial SIRT3, and research was carried out. Viniferin was shown to have an effect on mitochondrial SIRT3 in Huntington's disease cell models. Time-course research was conducted, and while SIRT3 levels were found to decrease with continuous mitochondrial dysfunction, viniferin is found to sustain levels of SIRT3 protein. Viniferin was discovered to be effective in reversing mutant Htt-induced SIRT3 decrease. Viniferin used this approach to improve the reduction of PGC-1. In HD molecules, the transcription occurs. Viniferin, interestingly, powered up AMPK, which drives ATP-generating catabolic pathways such as cellular glucose absorption and fatty acid oxidation. To maintain intracellular energy balance, AMPK activation also suppresses ATP-consuming activities. This demonstrated that the increase in SIRT3 is upstream and necessary for viniferin-mediated AMPK activation. This indicates modest SIRT3 activity. Furthermore, viniferin contains anti-inflammatory, antioxidant, platelet anti-aggregatory, and anticarcinogenic activities.<sup>[45]</sup>

#### Adjudin

*Adjudin* chemically also recognized as 1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydrazide. *Adjudin* has been initially developed as a lonidamine analog for non-hormonal treatable male contraception besides exfoliating undeveloped sperms from the seminiferous tubules. Multifunctional *adjudin* is being investigated as an anti-inflammatory and anti-cancer drug that might also help in neuroprotection. *Adjudin* has the unusual ability to activate SIRT3 in the mitochondrion. Computational analysis was used to identify *adjudin* binding to SIRT3. *Adjudin* has a glide ligand docking score of 6.415, indicating that it has only little SIRT3 activity. Neuroinflammation is a significant contributor to neurodegeneration, which is aided by the activation of microglia and invasion of the BBB. *Adjudin* was studied for its role in reducing neuroinflammation. Many researchers have focused on microglial cells due to their function in CNS immunity, restoration, and development. Once activated, microglia can produce massive amounts of pro-inflammatory mediators such as chemokines, cytokines, ROS, PGE<sub>2</sub>,

and nitric oxide (NO). In pathological situations, they are to blame for the neurotoxic effects. Chronic inflammation caused by microglial activation has been reported in Parkinson's disease, AD, and multiple sclerosis. An *in vitro* experiment was conducted; the impact of adjuvins on BV2 microglia viability was investigated. Adjuvins reduced IL-6 production by approximately 40% in BV2 cells pre-treated with adjuvins and subsequently activated with LPS. Furthermore, *adjuvins* influenced the expression of many neuroinflammation-related cytokines by reducing mRNA levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  induced by LPS in a dose-dependent manner. Exploring the potential of neuro-nutraceuticals as alternatives in the prevention of AD inhibited DNA-binding activity and NF- $\kappa$ B p65 nuclear translocation, as well as ERK MAPK activation, which gave it anti-inflammatory characteristics. In a mouse model of permanent middle cerebral artery occlusion (MCAO), the effects of adjuvins on microglial activation were studied *in vivo*. *Adjuvins* was shown to diminish ischemia-induced CD11b expression, which is a hallmark of microglial activation, in the research. Neurological deficiency improved as a result of this.<sup>[46]</sup>

### Trilobatin (TLB)

TLB will be known as the glycosylated dihydrochalcone bioactive chemical discovered in the traditional Chinese folk medicine *Lithocarpus polystachyus* Rehd. TLB has been demonstrated to have a wide range of pharmacological effects, such as antioxidative activity, anti-diabetes mellitus action, anti-inflammation, and anti-HIV-1 activity. Computational analysis was used to assess TLB binding to SIRT3. TLB got a glide ligand docking score of 6.29, indicating only little SIRT3 activity. TLB was found to inhibit mitochondrial ROS generation and death in PC12 neuronal cells injured by hydrogen peroxide. Furthermore, TLB's protective properties were ascribed to AMPK/nuclear factor erythroid 2-related factor 2 (Nrf2)/SIRT3 signaling activation. TLB was also shown to protect HT22 cells against A $\beta$ -induced toxicity by suppressing both the caspase-3-dependent apoptotic pathway and oxidative stress through the p38/SIRT3 pathway. Mechanically, TLB reduced A $\beta$ -induced ROS generation while increasing antioxidant enzyme activity. In addition, TLB also reversed the A $\beta$ -induced reduction in SIRT3 expression and activity. TLB inhibited A-induced tau hyperphosphorylation in HT22 cells, which was surprising. After blockage of the middle cerebral artery in rats, TLB inhibited neuroinflammation and decreased pro-inflammatory cytokines and oxidative stress damage. The suppression of the toll-like receptor 4 upregulating and activation of the Nrf2 signal transduction system were attributed to the neuroprotective effects. Although TLB looks to be a viable option for AD, further mechanistic research is needed to investigate the neuroprotective benefits of TLB in attenuating the pathologies of AD.<sup>[47]</sup>

### Salidroside

*Salidroside*, the main active constituent derived from *Rhodiola Rosea*, is extensively utilized in old-style Chinese medicine. It has been demonstrated to have anti-autophagic, anti-oxidative, and anti-inflammatory properties. *Salidroside* promotes SIRT3 expression and has been demonstrated to slow cellular aging. In various *in vitro* neuronal cell lines, *salidroside* reduces A $\beta$ -induced oxidative damage. In primary neuronal cultures exposed to A $\beta$ , *salidroside* was demonstrated to activate PI3K/Akt/mTOR signaling and reduce A $\beta$ . Similarly, it reduced cytochrome-C and apoptosis release in PC12 cells treated with H<sub>2</sub>O<sub>2</sub>, preventing apoptosis. In PC12 cells, *salidroside* therapy reduced glutamate excitotoxicity and elevated intracellular calcium. *Salidroside* prevented cognitive deficits and NF- $\kappa$ B-mediated inflammation in D-gal-treated rats. In streptozotocin-treated rats, *salidroside* increased neurogenesis while decreasing oxidative stress and cellular activity. Finally, in mouse model APP<sup>swe</sup>/PS1 $\Delta$ E9 of AD, *Salidroside* treatment reduced memory and learning deficits, inflammatory cytokines, lowered oxidative stress indicators, death of hippocampal neurons, and increased antioxidant enzyme expression. A recent study found that *salidroside* had neuroprotective benefits in APP/PS1 mice, a model of AD. *Salidroside* reduced the levels of both insoluble and soluble A $\beta$  while increasing the expression of calmodulin-dependent protein kinase II, NMDAR1, and PSD9. These benefits were related to phosphoinositide PI3K/Akt/mTOR signaling, which protected injured synapses in APP/PS1 animals. However, the activity of *salidroside* on particular target protein complexes is unknown, and more research is required to explore the molecular processes and value of *salidroside*.<sup>[48]</sup>

### Silybin

*Silybin* is one of the bioactive components in silymarin, a combination of lignin-derived flavanols extracted from *Silybum marianum* (L.) Gaertn seeds. *Silybin* was found to increase mitochondrial activity by regulating the production of SIRT3. *Silybin* was found to decrease the polymerization of A $\beta$  and to protect neurons from oxidative stress caused by A $\beta$ . In addition, through lowering ERK and JNK phosphorylation, *silybin* shielded glial cells from ROS damage and lowered astrocyte activation, reducing neuroinflammatory responses.<sup>[49]</sup>

### Polydatin

*Polydatin*, a resveratrol derivative and a significant constituent of the Chinese plant *Polygonum cuspidatum*, was demonstrated to stimulate SIRT3 and prevent A $\beta$ -induced neuron cell death through autophagy and mitochondrial clearance. In addition, *polydatin* restored memory and learning deficits because of its antioxidant and direct neuroprotective effects on rats suffering from

chronic cerebral hypoperfusion. Similarly, *polydatin* therapy decreased infarction volume, and neurobehavioral impairments, and reversed neuronal death in a permanent MCAO rat model. In a mechanism, *polydatin* inhibited the activation of c-Jun N-terminal kinase and p38 mitogen-activated protein kinase. *Polydatin* also increased the activity of the endogenous antioxidant nuclear factor heme-oxygenase-1, erythroid 2-related factor 2, and the thioredoxin pathway, reducing inflammation and ROS production in the brain. *Polydatin's* various effects suggest that it might be a viable neuroprotective drug in the treatment of AD pathology.<sup>[50]</sup>

### Pyrroloquinoline quinone (PQQ)

PQQ is an amine oxidase and dehydrogenase cofactor which act as an effective antioxidant. PQQ promotes mitochondrial biogenesis by increasing the expression and activity of SIRT3. It has been demonstrated to reduce lipid peroxidation and ameliorate oxidative stress-induced cognitive impairments. Similarly, in Wistar rats, PQQ therapy reduced cognitive impairments produced by oxidative stress. In an AD mouse model, PQQ therapy enhanced memory and learning deficits, lowered phosphorylated tau, reduced A $\beta$  deposition, and enhanced mitochondrial function. Another study found that a PQQ analog termed tri-lithium PQQ improved memory and learning in APP/PS1 transgenic mice by enhancing hippocampus long-term potentiation and decreasing phosphorylated tau and cerebral amyloid levels. In addition, PQQ was demonstrated to protect against glutamate-induced neurotoxicity both *in vivo* and *in vitro* studies.<sup>[51]</sup>

### 7-hydroxy-3-(4'-methoxyphenyl) coumarin

It is a new activator of SIRT3 that was demonstrated to bind to SIRT3 with high affinity while also promoting activation and deacetylation of manganese SOD (MnSOD), a key superoxide scavenger in mitochondria. The beneficial effects of C12 on the pathology of AD have yet to be discovered. A structural and theoretical foundation is required for the development of SIRT3 catalysts that attenuate the degree of SIRT3 catalytic activity through some precise method. The development of activators of the small molecule which target SIRT3 will be aided by a better knowledge of its structure and biological function.<sup>[52]</sup>

## BENEFITS OF MULTITARGET APPROACHES TO DIETARY SUPPLEMENTS

The hypothesis is that interactions among distinct kinds of substances found in food products could contribute to their robust "nutraceutical activities," according to the literature. Sinha *et al.* presented highly relevant proof of the efficacy of a nutraceutical "cocktail" in their study. Long-term nutritional treatment of rats with a mixture of tocopherol,

$\alpha$ -lipoic acid, and N-acetylcysteine from 18 months to mortality at 22–24 months reduced age-related changes in  $\beta$ -amyloid metabolism. This food regimen significantly reduced age-related impairments in spatial memory and learning in rats. Furthermore, the dosages used in this study were determined by established dietary requirements. While this is not a medicinal herb, one could help but be impressed by the efficacy of this carefully picked neuronutraceutical blend, which also harkens back to the oft-quoted phrase "the whole is greater than the sum of its parts." Solanki *et al.* expanded on this idea by discussing herbal medications and focusing on the therapeutic qualities of flavonoids (e.g., 7,8-dihydroxyflavone, quercetin, and fisetin). Their applicability for intervention and damage mitigation in several neurodegenerative illnesses is particularly significant. Their multitarget capabilities may be effective in the prevention and treatment of age-related neurodegenerative disorders as possible dietary supplements. The first volume of this Special Issue contains neurobiological insights on specific individual flavonoids. Wadhwa *et al.* also put the holistic, multitarget/multifunctional drug strategy into context, arguing that it has the potential to relieve the wide range of pathological outcomes caused by the multifactorial nature of brain illnesses. These authors examine the effects of Ashwagandha (*Withania somnifera*), a plant widely used in traditional medicine that boosts the body's stress resistance.<sup>[53]</sup>

## MINERALS AND VITAMINS: BENEFITS AND SOURCES OF NEUROCOGNITIVE

Minerals and vitamins are found in animal sources and dietary plants and also found in food supplements. The most researched vitamins in the subject of dementia and cognition include pyridoxin (Vitamin B6), cobalamin (Vitamin B12), and folate (Vitamin B9). Iron, magnesium, and zinc are minerals that are thought to be beneficial to cognitive function. In 70 male patients with a mean age of 66 years, higher levels or low levels of homocysteine and Vitamins B9 and B12 were linked to poor outcomes in a spatial copying test. In dementia ( $n = 92$ , mean age 80 years), plasma concentrations of Vitamin B9 were found to be lower and concentrations of homocysteine were found to be higher. In comparison to the control group ( $n = 55$ , mean age 76 years), the results in the normal aging population and MCI group ( $n = 81$ , mean age 76 years) were similar. Tucker *et al.* reported that on these older ( $n = 321$ ) men performed better in spatial copying and verbal fluency tests after consuming Vitamin B (B9, B12, and B6) for 3 years. Simple supplements of either 75 mg Vitamin B6, 750 g Vitamin B9, or 15 g Vitamin B12, daily for 35 days increased memory function such as recall, recognition, and linguistic ability in 211 middle-aged, healthy younger, and older women, but did not affect other cognitive functions such as mood. Stott *et al.* found that dietary Vitamin B (B9 (2.5 mg) + B12 (0.5 mg) reduced homocysteine levels

but had no effect on cognitive functioning in vascular disease patients ( $n = 185$ , age  $>65$  years old) as compared to the placebo condition. Pathansali *et al.* reported that in comparison to the placebo-controlled group, daily dietary consumption of Vitamin B9 (5 mg) by healthy older participants ( $n = 24$ , mean age 73 years) showed no influence on psychomotor performance during 4 weeks. These findings revealed that Vitamin B's effect on memory and other cognitive processes varied depending on the individual's physiological state, illness, dose, gender, duration, age, and treatment combination. Vitamin E intake has been connected to both healthy persons and Alzheimer's patients' cognitive ability. In AD plasma samples, the presence of Vitamin E content (tocopherols, tocotrienols, 5-nitrotocopherol, and tocopherylquinone,) was shown to be lower ( $n = 168$ ) and MCI ( $n = 166$ ) in participants as compared to the cognitively normal group ( $n = 187$ ). Epidemiological research revealed that Vitamin E supplementation may lessen the long-term risk of dementia, however, diets high in Vitamin C, beta-carotene, and flavonoids have not been associated with the risk of dementia. Randomized clinical trials, on the other hand, had contradictory results. According to Petersen *et al.*, daily consumption of 2000 IU of 3 years of Vitamin E therapy failed to prevent the progression from MCI to AD. Furthermore, a clinical investigation (The TEAM-AD VA Cooperative Randomized Trial) on 613 mild-to-moderate AD patients found that supplementation of tocopherol (2000 IU/day) slowed cognitive deterioration, even when used with the AD treatment memantine. In the double-blind study, it was shown that Vitamin E alone (400 IU/d) or in conjunction with selenium did not provide cognitive advantages in the older population ( $n = 7540$ ). High levels of Vitamin E in plasma have been linked to improved cognitive abilities as an antioxidant, yet the capacity of Vitamin E to postpone or prevent AD is still unknown.<sup>[54]</sup>

## MECHANISM OF ACTION

A basic metabolic pathway that supports brain functioning and translates into cognitive functions requires minerals and vitamins. The involvement of Vitamins B<sub>6</sub>, B<sub>9</sub>, and B<sub>12</sub> in particular has been connected to the metabolism of homocysteine. Vitamin B<sub>6</sub> is a cofactor in homocysteine metabolism, while B<sub>9</sub> is a methyl donor and B<sub>12</sub> is needed for homocysteine to methionine methylation. Homocysteine accumulation is thought to be a risk factor for dementia; thus, increased homocysteine metabolism with vitamin supplementation is linked to cognitive decline prevention. Because methionine is a precursor to S-adenosyl-L-methionine, Vitamins B<sub>12</sub>, B<sub>9</sub>, B<sub>6</sub>, B<sub>5</sub>, and B<sub>1</sub> have a comparable effect on neurotransmitter synthesis. Vitamin E is essentially an antioxidant that protects against oxidative stress, which is a common hallmark of neurodegenerative diseases. Iron is thought to be crucial for maintaining the electrophysiological characteristics

of brain circuits and neurotransmitter systems, whereas magnesium is thought to be important for nerve impulse transmission. Iron deficiency impairs cognition, but iron supplementation enhances cognition.<sup>[55]</sup>

## NATURAL MEMORY-ENHANCING CRUDE DRUGS

### Brahmi

Brahmi, or *Bacopa monnieri* (Bm), is a perennial creeper medicinal plant found in the damp and marshy wetlands of South and East India, Australia, Europe, Africa, Asia, and North and South America. In the Ayurvedic system of medicine, Bm is recommended for mental stress, memory loss, epilepsy, insomnia, and asthma. The bioactive phytochemicals present in this plant include saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A, B, C, D, E, and F, alkaloids, sterols, betulinic acid, polyphenols, and sulfhydryl compounds, which may be responsible for the neuroprotective roles of the plant. Both *in vitro* and *in vivo* studies show that these phytochemicals have an antioxidant and free radical scavenging action by blocking lipid peroxidation in several areas of the brain. Bm acts by reducing divalent metals, scavenging ROS, decreasing the formation of lipid peroxides, and inhibiting lipoxigenase activity.<sup>[56]</sup>

### Ginkgo biloba (Gb)

Gb has been in the spotlight primarily for its potential role in treating AD. Gb also appears promising as a therapeutic agent for several other chronic and acute forms of diseases. The main pharmacologically active groups of compounds are flavonoids and terpenoids. Almost all clinical studies use Gb extract that contains a combination of flavonoid glycosides, terpene lactones, and ginkgolic acids. Gb extract has shown beneficial effects in treating Alzheimer's, cardiovascular diseases, cancer, tinnitus, and other age-associated conditions. The suggested mechanisms of the Gb extract are its antioxidant effect, antiplatelet activating factor activity for vascular diseases, inhibition of  $\beta$ -amyloid peptide aggregation in AD, and decreased expression of peripheral benzodiazepine receptor for stress alleviation. Gb is popular as a treatment for early-stage AD and vascular dementia. Gb extract reverses  $\beta$ -amyloid and NO-induced toxicity *in vitro* and reduces apoptosis both *in vitro* and *in vivo*.<sup>[57]</sup>

### Gotu kola (Gk)

Considered both a nutraceutical and cognitive, Gk is a staple in Chinese, Indonesian, and Ayurvedic medicine. This medicinal plant is used to strengthen the brain, heal skin issues, and promote liver and kidney health. Gk is considered a rejuvenating herb for nerve and brain cells as it is believed

to promote intelligence and improve memory. *In vitro* studies using various Gk plant derivatives (asiaticosides, asiatic acid, madecassoside, and madasiatic acid) showed that these compounds were capable of blocking H<sub>2</sub>O<sub>2</sub>-induced cell death, decreasing free radical concentration, and inhibiting  $\beta$ -amyloid cell death, suggesting a potential role for Gk in the treatment and prevention of AD.<sup>[58]</sup>

## NUTRACEUTICALS AND THEIR PROMISE

The publications in “Nutraceuticals: Molecular and Functional Insights into How Natural Products Nourish the Brain” reflect the topic's dynamic nature as well as the writers' passion for this quickly emerging discipline.<sup>[33]</sup> For decades, several natural items used in traditional medicine were recognized to have therapeutic effects on various brain processes, and the active principles are frequently discovered. As a result, under suitably controlled settings, their application to help in the management of severe neurological and mental disorders might occur in the not-too-distant future.<sup>[59]</sup>

## CONCLUSION AND FUTURE PROSPECTIVE

In the prevention of age-related cognitive impairment and treatment of neurodegenerative disorders, nutraceuticals provide both potential and obstacles. Multiple neurocognitive advantages and a broad range of biological processes, such as anti-inflammation, antioxidant defense, metabolic homeostasis, and neuronal differentiation and proliferation provide a holistic cognitive gain when nutraceutical intervention is used. Nutraceutical supplementation to cure cognitive aging, on the other hand, faces a slew of hurdles, including dosage and optimization timing, adequate control equivalents, diagnosis, and individual variances as a result of genetic make-up and environmental exposures. Besides this, most nutraceutical active ingredients have disadvantages such as non-specific targeting, rapid metabolism, the inability of BBB permeability, low solubility, and low bioavailability. Novel drug delivery technologies, such as nanofibers, nanoparticles, chitosan, nanoencapsulation, and micelle-based delivery, are, therefore, being developed and should be widely exploited in nutraceutical treatments. Other barriers to the endorsement of nutraceuticals include poor quality control, a lack of understanding of the mechanism of action, gaps in toxicity evaluation, and insufficient clinical investigations. Furthermore, because the clinical study is mostly epidemiological and observational, comprehensive experimental and interventional techniques are required to validate nutraceuticals as therapeutic targets for age-related dementia and MCI. This is an interesting opportunity for cognitive health and nutraceutical research, and more studies integrating nutrition with developments in neuroscience, genetics, and epigenomics are needed to create innovative techniques for the treatment and prevention of cognitive problems. Given the benefits

and drawbacks of currently employed nutraceuticals, phytochemicals (plant-derived secondary metabolites) that provide physiological and cognitive benefits while having low side effects should be pursued for age-related dementia and MCI research. Furthermore, research should be focused on complete plant meals rather than single phytochemicals, with strict scientific scrutiny on the individual and additive impacts of each bioactive as a dietary element. Combinatorial techniques combining phytochemicals and pharmacological treatments may also be effective in the prevention and treatment of dementia, but clinicians must be aware of the value of each ingredient and their reciprocal interactions.

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## CONFLICTS OF INTEREST

All authors declare conflicts of interest as none.

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