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A Comprehensive Review on Nutraceuticals in Alzheimer's and Neurodegenerative Disease – A Cognitive Enhancement

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Abstract

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and related cognitive disorders, represent a significant and growing public health challenge, particularly in aging populations. Despite advances in pharmacological treatments, therapeutic options for cognitive decline and neurodegeneration remain limited. Recent interest has shifted towards nutraceuticals – bioactive compounds derived from food or natural sources – as promising adjuncts or alternatives in the management of these conditions. This review examines how nutraceuticals can help prevent and treat neurodegenerative illnesses, with a focus on their mechanisms of action, efficacy, and therapeutic potential. Numerous bioactive compounds found in natural foods and medicinal herbs have been shown to enhance cognitive function, including memory, attention, and learning. These substances affect cellular functions like neurogenesis, synaptogenesis, synaptic transmission, neuroinflammation, oxidative stress, and neuronal survival as well as brain metabolism. Furthermore, nutraceuticals can promote neuroplasticity, neuroprotection, and cognitive enhancement by modulating key pathways involved in brain function. The ability of nutraceuticals to influence these diverse biological processes underscores their potential as effective agents for brain health. As such, food-based strategies, including dietary supplements and functional foods enriched with nutraceuticals, represent a promising approach to improving cognitive function and potentially mitigating the impact of neurodegenerative diseases.

Keywords: Nutraceuticals, Alzheimer's disease (AD), Neurodegenerative diseases, Phosphatidylserine, Neuroprotective, Cognitive decline

INTRODUCTION

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Neurodegenerative diseases are becoming more common in aging populations, they pose a growing public health concern. These illnesses include various cognitive abnormalities, Parkinson's disease (PD), and Alzheimer's disease (AD). The prevalence of these illnesses throughout the world highlights how urgently effective treatments are needed. While traditional pharmacological therapies for cognitive decline and neurodegeneration have had limited success, there is a rising interest in nutraceuticals bioactive compounds derived from food or natural sources – as potential cognitive enhancers. The mechanisms of action, efficacy, and therapeutic potential of nutraceuticals in the management of Alzheimer's disease and other neurodegenerative illnesses are examined in this review [1]. The aging process and the development of neurological illnesses are

significantly influenced by nutrition. Many substances found in food and medicinal herbs have long been used to improve mental functions like motivation, memory, focus, and attention. One appealing strategy for managing cognitive impairment is thought to be altering these processes. Food-based nutraceutical compounds have been shown to have pharmacological effects on brain metabolism. Consuming whole foods or taking dietary supplements that contain purified compounds are two ways to get these natural compounds [2]. To improve brain health, nutraceuticals have been employed because they directly affect cellular processes, such as neurogenesis, synaptogenesis, synaptic transmission, neuro-inflammation, oxidative stress, cell death regulation, and neuronal survival. Similarly, complex brain processes, like memory, cognition, neuro-regeneration, neuroprotection, and neuroplasticity, are all influenced by nutraceuticals [3]. The potential to create food-based strategies, such as creating dietary supplements and foods containing nutraceuticals that have neurological activity, is revealed by the ability of nutraceuticals to alter all of these processes (Figure 1).

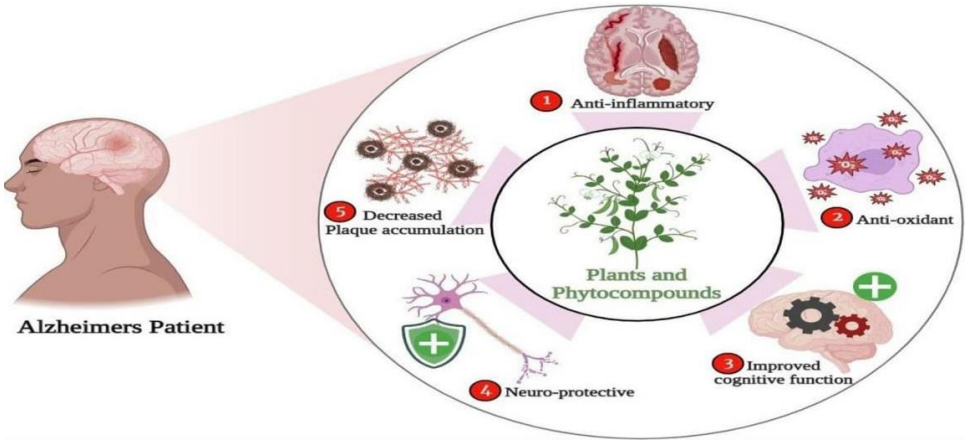

Figure 1. Alzheimer's Patient.

WHAT ARE NUTRACEUTICALS

Nutraceuticals refer to any food or its constituent ingredients that provide health benefits beyond basic nutrition. In the context of neurodegenerative diseases, nutraceuticals are considered to possess neuroprotective properties and may contribute to cognitive enhancement and slowing the progression of neurological diseases [4].

Key Characteristics of Nutraceuticals

Natural Origin

Derived from plants, animals, or marine organisms. Includes substances like herbs, fruits, vegetables, fish oils, and algae extracts.

Bioactive Compounds

Contain essential and non-essential components, such as:

- *Antioxidants:* Combat oxidative stress.
- *Polyphenols:* Found in foods like berries and tea.
- *Vitamins and Minerals:* Support overall health.
- *Fatty Acids:* Omega-3s, beneficial for cardiovascular and brain health.
- *Amino Acids:* Crucial for protein synthesis.
- *Herbal Extracts:* Used traditionally for health enhancement.

Non-Pharmacological

Viewed as safer alternatives to drugs. Associated with fewer side effects.

Multiple sclerosis, Parkinson's disease, and Huntington's disease are examples of neurodegenerative illnesses with similar pathophysiological pathways, while each has distinct traits and course. Given

these shared processes, nutraceuticals targeting these mechanisms have gained attention as potential therapeutic agents [5].

MECHANISMS OF ACTION OF NUTRACEUTICALS IN NEURODEGENERATIVE DISEASES: NUTRACEUTICALS EXERT THEIR NEUROPROTECTIVE EFFECTS THROUGH A VARIETY OF MECHANISMS

Antioxidant Activity

Oxidative stress is linked to a number of neurodegenerative diseases. Vitamin E, curcumin, and resveratrol are examples of antioxidants that lower inflammation and shield neuronal cells from damage caused by free radicals [6].

- *Anti-inflammatory Effects:* Neurodegeneration is accelerated in the brain by persistent inflammation. Strong anti-inflammatory qualities have been shown by nutraceuticals, such as curcumin, green tea polyphenols, and omega-3 fatty acids, which may stop or slow the progression of disease [7].
- *Acetylcholinesterase Inhibition:* In Alzheimer's, the degradation of acetylcholine contributes to cognitive impairment. Nutraceuticals, like *Ginkgo biloba*, *Huperzine A*, and *Bacopa monnieri*, have shown acetylcholinesterase inhibition, thereby increasing acetylcholine levels in the brain [8].
- *Neurogenesis and Neuroplasticity:* Some nutraceuticals, including *omega-3 fatty acids* and *ginseng*, have been shown to support neurogenesis and synaptic plasticity, crucial processes for learning and memory [9].
- *Metal Chelation:* Certain nutraceuticals, such as *green tea catechins* and *curcumin*, can chelate metals, like copper and iron, which accumulate in the brains of Alzheimer's patients and contribute to oxidative damage [10].
- *Mitochondrial Support:* Many neurodegenerative diseases involve mitochondrial dysfunction. Nutraceuticals, like *Coenzyme Q10*, *alpha-lipoic acid*, and *N-acetylcysteine*, help improve mitochondrial function and energy production in neurons [11].

PROMINENT NUTRACEUTICALS FOR COGNITIVE ENHANCEMENT

Curcumin (Turmeric Extract)

- *Mechanism of Action:* Curcumin, the active compound in turmeric, has demonstrated strong antioxidant, anti-inflammatory, and anti-amyloid properties.
- *Evidence:* Studies have shown curcumin can reduce amyloid plaque deposition in the brains of Alzheimer's patients and enhance cognitive function. One important component of its possible effectiveness is its capacity to penetrate the blood-brain barrier (with formulation improvements) [12].

Omega-3 Fatty Acids (DHA and EPA)

- *Mechanism of Action:* Omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA), play a vital role in preserving the fluidity of neuronal membranes and enhancing synaptic activity.
- *Evidence:* Research from clinical trials suggests that omega-3 supplementation could help delay cognitive decline and lower the likelihood of developing Alzheimer's disease, especially when introduced during the early stages of cognitive impairment.

Brahmi, or Bacopa Monnieri

- *Mode of Action*: Known for its ability to improve cognition, bacopa is a traditional Ayurvedic herb. It is thought to function by enhancing synaptic transmission, encouraging acetylcholine synthesis, and exerting antioxidant activity [13].
- *Evidence:* Studies have shown Bacopa improves memory, attention, and cognitive performance, particularly in individuals with age-related cognitive decline.

Ginkgo Biloba

- *Mechanism of Action:* Ginkgo Biloba has been widely studied for its ability to improve cerebral circulation and protect neurons from oxidative damage.
- *Evidence:* Some studies suggest that Ginkgo biloba may help in the symptomatic management of Alzheimer's and dementia, enhancing cognitive function, although findings have been mixed [14].

Huperzine A

- *Mechanism of Action:* Huperzine A is an acetylcholinesterase inhibitor that increases acetylcholine levels in the brain, aiding in memory and learning.
- *Evidence:* Clinical trials suggest Huperzine A can improve cognitive function in Alzheimer's patients, with minimal side effects [15].

Resveratrol

- *Mechanism of Action:* Resveratrol, a polyphenol found in red wine and grapes, has antioxidant, anti-inflammatory, and anti-amyloidogenic properties.
- *Evidence:* Resveratrol has been shown to inhibit the formation of amyloid plaques and reduce inflammation in the brain. However, more research is needed to confirm its efficacy in human clinical trials [16].

POTENTIAL OF NUTRACEUTICALS IN COMBINATION THERAPY

While individual nutraceuticals show promise, the potential benefits of *combination therapy* cannot be overlooked. A synergistic approach, combining multiple nutraceuticals that target different pathways involved in neurodegeneration, may provide superior benefits. For example:

- *Combination of Curcumin and Omega-3 Fatty Acids:* Both compounds reduce inflammation and oxidative stress, enhancing brain function and protecting against cognitive decline.
- *Bacopa Monnieri with Ginkgo Biloba:* Both improve memory and cognitive function, but through different mechanisms, offering a complementary effect [17].

CHALLENGES AND FUTURE DIRECTIONS

Despite the growing body of evidence support in the use of nutraceutical in neurodegenerative diseases, there are several challenges that remain:

- *Bioavailability:* Many bioactive compounds in nutraceuticals have poor bioavailability, limiting their effectiveness. Innovations in drug delivery systems (e.g., nanoformulations) are needed to enhance absorption and brain penetration [18].
- *Standardization and Quality Control:* The lack of standardization in the preparation of nutraceuticals raises concerns regarding the consistency of doses and effectiveness across products.
- *Clinical Evidence:* While preclinical studies and animal models are promising, more large- scale, well-designed human clinical trials are needed to establish the clinical efficacy of these compounds [19].
- *Alzheimer Disease:* The irreversible loss and damage of neuronal cells that occurs with aging is known as neurodegeneration, and it is made worse by neuropathological conditions. The biological process of aging is intricate and unavoidable, involving neurodegeneration mechanisms that lead to structural alterations in the brain. These alterations are among the primary risk factors for the development of chronic neurodegenerative diseases, despite the fact that they are a normal physiological process. As a result, the prevalence of neurodegenerative diseases, like AD, the primary cause of dementia in people over 60 worldwide, has increased due to longer life expectancies. AD is a complex illness, and risk factors include age, genetics, traumatic brain traumas, pre-existing disorders, infections, unhealthy lifestyles, and environmental variables. While the exact cause of the pathological alterations in AD is still unknown, these risk factors may weaken the blood-brain barrier (BBB), reduce cerebral blood flow, increase the deposition of amyloid beta (Aβ), induce neuro-inflammation and oxidative

stress, which could lead to the development of tau or Aβ pathology, and more. The accumulation of extracellular Aβ oligomers and intracellular neurofibrillary tangles of hyperphosphorylated tau protein are neuropathological features of AD that impact brain regions with high plastic capacities, like the cortex and the hippocampus, and are implicated in higher functions like memory and learning. Large numbers of neurons and synapses are lost as a result of these protein accumulations causing glial activation, neurotransmitter deficiencies, elevated neuro-inflammatory responses, and oxidative stress. Amyloid plaque is initiated by the successive hydrolysis of the amyloid precursor protein (APP) by the β- and γ-secretases. The amyloidogenic cleavage at the APP β-site is catalyzed by the transmembrane type I aspartyl protease β-site APP cleaving enzyme 1 (BACE1), which yields the membrane-associated carboxyl-terminal fragment of 99 amino acids. The β-C-terminal portion is then broken down by γ-secretase, a multimeric protein complex that includes presenilin-1 (PSEN1) and -2 (PSEN2), nicastrin, Aph-1, and Pen-. This γ-secretase cleavage facilitates the release of Aβ 37–43 peptides. On the other hand, neurofibrillary tangles are created by the large aggregation of insoluble paired helical filaments formed by the microtubule-associated protein tau. An early molecular event called aberrant tau phosphorylation causes the tau protein to undergo successive structural alterations, including truncations [20]. Tau hyperphosphorylation, which primarily takes place at Ser-Pro or Thr-Pro patterns, is mediated by proline-directed kinases, such as MAPK, GSK3β, and CDK-5, as well as perhaps additional kinases like CAMK, PKA, and PKC. When axonal microtubules disassemble, tau hyperphosphorylation and aggregation follow, affecting axonal transport (Figure 2).

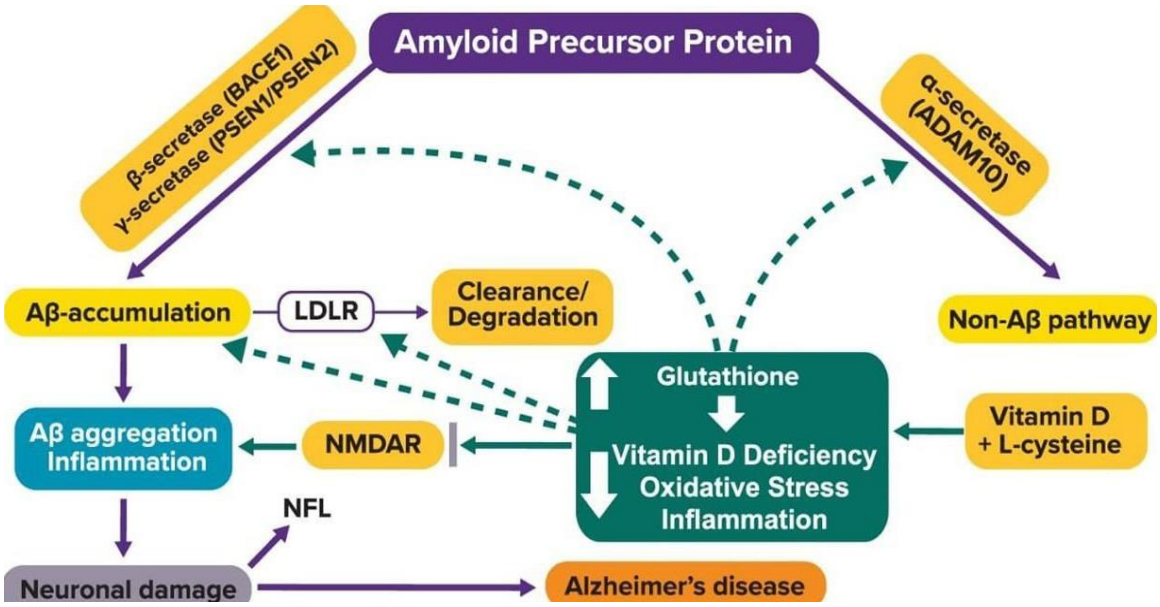

Figure 2. Alzheimer's disease.

The Typical Slowing Down of Learning and Memory Processes

Dysfunction in AD is usually explained by a decrease in synaptic cleft acetylcholine (Ach) levels, which leads to a loss of presynaptic cholinergic transmission. Reduced activity of the enzyme choline O-acetyltransferase, which is in charge of its synthesis, or increased catalytic activity of acetylcholinesterase (AchE), which is in charge of its degradation, could be the cause of the drop in ACh levels. Though much less frequently and with a lower affinity for ACh, butyrylcholinesterase also hydrolyzes Ach. One appealing treatment option to reduce AD symptoms was to inhibit these enzymes. In the hippocampus, the GABAergic system is essential for controlling, coordinating, and avoiding excessive neuronal signaling. Animal models of AD have demonstrated that hippocampus hyperactivity is caused by early GABAergic interneuron losses. Although GABAergic disruption may be an early marker of AD pathogenesis in animal models, there is no concrete evidence that changing GABA

neurotransmission might prevent age-related cognitive deterioration. 3. GABA has important roles in communication between neurons and microglia in addition to its role in signal transmission between neurons. It's interesting to note that GABA signaling appears to be necessary for microglia to activate Aβ uptake, which aids in amyloid removal. Furthermore, it has been demonstrated that the Aβ oligomers reduce synaptic plasticity by increasing LTD and suppressing LTP, the two main types of synaptic plasticity thought to be the neural underpinnings of learning and memory. By phosphorylating NDMAR and activating Fyn tyrosine kinase, the Aβ oligomers can result in neuritic dystrophy [21].

The disruption of NDMAR activity alters the availability of extracellular glutamate, which leads to reduced spinal density and synaptic loss. The Aβ aggregates also increase intracellular Ca2+ levels, which suppresses LTP and promotes neuronal death by modifying the structure and function of the membrane and intensifying the membrane lipid peroxidation response [22]. The pathogenesis of AD includes oxidative stress as a key early component because of worsening Aβ and hyperphosphorylated tau accumulation, which directly initiates ROS generation through mitochondrial stress and NADPH oxidase activation. The production of superoxide and this activation are necessary for oxidative stress and neurotoxicity [23]. Nuclear factor erythroid-related factor 2 (NRF2) is crucial for minimizing oxidative stress because it regulates the expression of almost 500 target genes that encode proteins that serve as redox balancing factors, detoxifying enzymes, stress response proteins, and metabolic enzymes [24]. The degenerative process of neuroinflammation is another important and inevitable aspect of AD. A common glial activation is one of the phenomena associated with AD. In neuroinflammation, active microglia may release an excess of pro-inflammatory and neurotoxic chemicals. In microglia, NRF2 increases the levels of several anti-inflammatory markers and controls the production of IL-6, cyclooxygenase 2 (COX2), nitric oxide synthase 2 (NOS2), and tumor necrosis factor alpha (TNFα) [25]. NRF2 functionality decreases with age, as evidenced by the lower NRF2 protein and mRNA expression, as well as the reduced NRF2 activation, in senile animals and older adults compared to younger people. Despite the fact that AD was initially identified in 1906, there are currently no preventative or treatment approaches that alter the disease. Research on disease-modifying therapies for AD is still ongoing today. Only symptomatic therapies are currently approved for mild to moderate types of AD [26]. Three cholinesterase inhibitors and memantine are among the treatments that attempt to balance the neurotransmitter disruption. The cholinergic hypothesis, which holds that memory and learning are greatly impacted by the progressive loss of the cholinergic system, served as the foundation for the development of AChE inhibitors [27]. AChE inhibitors, such as donepezil, rivastigmine, and galantamine, are advised for patients with mild to moderate AD, where the loss of cholinergic neurons is less severe than in end-stage AD. By preserving Ach levels in the synaptic cleft, AchE inhibitors improve central cholinergic neurotransmission and, at least during the first year of treatment, lessen cognitive decline [28]. For moderate to severe forms of AD, memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with low to moderate affinity, is the only neuroprotective therapy available. The NMDA-mediated ion flux is blocked, and the dangerously high glutamate levels that lead to neuronal dysfunction are decreased. A lot of work has gone into trying to find a disease-modifying treatment that works. The two main targets for disease-modifying therapies are tau and Aβ. The goal of many Aβ-directed treatments is to reduce the number of amyloid deposits and parenchymal Aβ in the AD brain. Antiamyloid monoclonal antibodies, for instance, are the first disease-modifying treatments for AD that slow the disease's clinical progression by interfering with its fundamental biological mechanisms. Lecanemab, a humanized monoclonal antibody that was recently approved by the FDA, binds with high affinity to an Aβ soluble protofibril, lowering amyloid indicators in moderate AD patients and causing a somewhat less severe decrease in cognitive tests. Its use was associated with adverse consequences, nevertheless. While there is no hard evidence linking the elimination of Aβ aggregates to less cognitive or functional decline, Aducanumab, another monoclonal antibody that targets aggregated soluble and insoluble forms of Aβ, promotes microglial phagocytosis, which helps to remove Aβ aggregates [29].

Assessment of Nutraceuticals' Neurological Effects Using Preclinical Models

The first step of the therapeutic drug discovery process is generally acknowledged to consist of the identification and confirmation of targets, the almost essential identification of biochemical processes,

and the identification of a macromolecule implicated in a particular signaling pathway [3–7]. Promising nutraceuticals are therefore chosen based on scientific data from in vitro and in vivo investigations. Basic neuroscience research for mechanistic determination has been further advanced by neuron culture, with a focus on cognitive improvement and neuroprotection evaluation. Neuron culture offers invaluable information, even though it cannot precisely imitate brain activity. They are commonly used to study cell death and neurotoxic damage because the PC12 cells, a rat adrenal pheochromocytoma cell line, can differentiate into sympathetic nerve-like cells under the induction of nerve growth factor (NGF), growing cell protrusions, forming synapse-like structures, and synthesizing acetylcholine. Because it expresses typical immature neural markers, like nestin, doublecortin (DCX), and beta III tubulin, SH-SY5Y is the most widely utilized human neuroblastoma cell line in neuronal cell biology research. Retinoids and other differentiation-inducing substances cause the cells to take on the structure of primary neurons. These cells exhibit excitable membranes, longer neurites, polarization, and smaller cell bodies. Other cell models include primary neuronal culture or neurons generated from human-induced pluripotent stem cells. These cell cultures are frequently used to study autophagy, cell death, oxidative stress, mitochondrial malfunction, alterations in neuritic length and synapsis, and disturbance of neurotransmitter homeostasis.

Through these in vitro models, it is possible to evaluate the molecular and cellular mechanisms of neuroplasticity phenomena that underpin cognitive enhancement, such as functional plasticity, which involves changing the efficiency of synaptic transmissions, including long-term potentiation (LTP), dendritic spine maturation, and synaptic activation. These models are useful for evaluating the processes of synaptogenesis, neurogenesis, axonal regeneration, dendritic branching, structural plasticity, and alterations in cell structure and neuroprotection. At the same time, rodent models have been crucial in helping us better understand a number of pathophysiological processes connected to the development of disease. Existing transgenic AD models provide important mechanistic insights into pathogenic mechanisms. To accurately model the neurodegeneration, familial AD mutations must be overexpressed. For example, the triple-transgenic mouse model of AD (3xTg-AD) expresses three transgenes linked to dementia: tauP301L, PS1M146V, and APPSWE. These transgenes promote synaptic dysfunction, neurofibrillary tangle disease, and amyloid beta plaque, all of which lead to learning and memory problems. This pathological recapitulation makes it a valuable model for developing treatments and understanding the basic mechanisms of AD. A variety of substances, including streptozotocin, amyloid beta peptides, colchicine, aluminum chloride, lipopolysaccharides, and D-galactose, can be infused into mice to create nontransgenic AD models. These models can be used to simulate pathological processes, such as oxidative stress, insulin resistance, synaptic dysfunction, and apoptosis [30].

CONCLUSIONS

Alzheimer's and other neurodegenerative diseases, nutraceuticals present a promising substitute or supplement to conventional pharmaceutical treatments. Their potential to enhance cognitive function, protect neurons from damage, and slow disease progression makes them an attractive area of research. However, continued research is needed to optimize their formulations, improve bioavailability, and establish robust clinical evidence. Given the complexities of neurodegenerative diseases, nutraceuticals may play an important role as part of a comprehensive approach to prevention and treatment, especially in the context of an aging population. Finding and creating new, promising compounds as well as investigating the ligand conformations used within the binding sites of macromolecular targets have greatly benefited from the integration of computational and experimental approaches. The chemicals' doses and effectiveness can be improved with the help of these analyses. Additionally, it is crucial to keep in mind that certain nutrients and nutraceuticals exhibit neuroprotective effects through synergistic mechanisms between food components.

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