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SHORT REVIEW

The Role of Phytochemicals as Nutraceuticals in the Therapy of Cognitive Impairment: A Comprehensive Review

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Abstract

Cognitive impairment comprises issues with memory, learning, attention, and cognitive processing is a significant concern, particularly in older populations. The primary causes of cognitive decline include oxidative stress, neuroinflammation and the formation of tau tangles and Amyloid-Beta (Aβ) plaques. These factors compromise neuronal function, leading to memory deficits and behavioural issues. Current pharmacological treatments for MCI (Mild Cognitive Impairment) and AD (Alzheimer's Disease), such as acetylcholinesterase inhibitors, often show limited effectiveness and are sometimes used off-label due to insufficient clinical evidence. Nutraceuticals derived from plant and food sources have emerged as promising alternatives for preventing and managing cognitive decline. These bioactive compounds, which include polyphenols, flavonoids, alkaloids and omega-3 fatty acids, demonstrate neuroprotective properties through mechanisms that are antioxidant, anti-inflammatory, and anti-apoptotic. For instance, flavonoids like Epigallocatechin Gallate (EGCG) and hesperidin have been shown to reduce Aβ plaque accumulation, decrease neuroinflammation and boost blood flow to the brain. Numerous polyphenols, such as resveratrol and curcumin, have proven effective in enhancing memory and reducing Aβ-induced tau phosphorylation. Alkaloids, including galantamine and berberine, work by inhibiting acetylcholinesterase, thereby improving cholinergic neurotransmission. In AD models, caffeine has been reported to enhance cognitive function and decrease Aβ levels. Docosahexaenoic Acid (DHA) is an essential omega-3 fatty acid for preserving the integrity of neuronal membranes and encouraging the development of new neurons. Despite their potential benefits, challenges such as bioavailability, dosage optimisation, and individual differences must be addressed. Researchers are exploring innovative drug delivery systems, including nanoparticles, to enhance the effectiveness of nutraceuticals. Further research, particularly large-scale clinical trials, is essential to confirm these compounds as effective treatments for cognitive impairment and neurodegenerative disease.

Major Findings- Phytochemicals such as polyphenols, flavonoids, alkaloids, and omega-3 fatty acids found in nutraceuticals have shown neuroprotective effects against cognitive impairment by lowering amyloid-beta buildup, oxidative stress, and neuroinflammation.

Keywords: Alkaloids, DHA, Flavonoids, Mild Cognitive Impairment, Neuroinflammation, Nutraceuticals, Polyphenols

1. Introduction

Cognitive impairment denotes challenges associated with learning, memory retention, concentration, cognitive processing and visuospatial abilities. This phenomenon encompasses various dimensions of cognitive function, including perception, interpretation, inferential reasoning, and alertness, all of which are crucial for facilitating memory and intelligence. The realm of cognitive functioning is susceptible to many influencing factors, including oxidative stress and an array of physiological and pathological states. These elements can trigger the onset of neurological disorders such as AD, Parkinson's disease and schizophrenia[1,2].

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As people get older, they may find that their memory issues get worse[3]. The approximate demographic of the geriatric population exhibits cognitive deficits that align with a formal clinical diagnosis of dementia[4]. MCI is conceptualised as a pivotal stage of transition between normative cognitive ageing and the onset of dementia[5]. MCI is delineated into two principal categories: amnestic and non-amnestic. Amnestic MCI predominantly encompasses deficits in memory functioning and is deemed a considerable risk factor for the formation of AD[6]. Individuals diagnosed with amnestic MCI frequently encounter memory-related challenges, such as the inability to recall recent occurrences or difficulties in remembering names. Conversely, non-amnestic mild cognitive impairment influences other cognitive domains, including attention and language, thereby potentially heightening the susceptibility to various forms of dementia, notably frontotemporal and vascular dementia. Each year, about 10-15% of individuals with MCI progress to dementia, with amnestic MCI showing the highest likelihood of this transition[7].The formation of tau tangles and amyloid plaques are two neurological irregularities associated with AD. These irregularities significantly contribute to the pathophysiological mechanisms underlying mild cognitive impairment. The primary factor in AD is memory loss, which results from the accumulation of beta-amyloid. This buildup is also a critical factor in the cognitive decline observed in the elderly population. Memory deficits arise from neuronal degeneration in key brain areas essential for memory consolidation, including the entorhinal cortex and hippocampus[8,9]. Cognitive decline, including memory loss, often leads to behavioural dysfunction and neuropsychiatric symptoms like depression, restlessness, delusions and perceptual issues[10,11].

Neurological illnesses are marked by the gradual deterioration of the nervous system. Together, these conditions afflict about 8% of people with cognitive impairment/AD and 1% of people having Parkinson's disease[12]. A range of causes, including a foundational genetic tendency that is present from birth or early in life and possible consequences from trauma, can cause a decline in cognitive performance[13]. Extending the human lifespan is a significant challenge in medical research, especially given its association with higher susceptibility to disability, mortality, and conditions that involve the progressive degradation of the nervous system. Key factors such as oxidative stress, excitotoxicity, the amyloid cascade, apoptosis, and sodium nitrite-mediated neurodegeneration are crucial for understanding neurodegenerative processes[14]. This study aims to emphasise data about the potential advantages of nutraceuticals, a class of plant and food-based substances. Gradually, several compounds have proven to have the capacity—or strong potential—to delay cognitive decline and/or function as neuroprotectants.

The current pharmacologic treatment strategy for MCI is similar to that for AD, however, it is not advised because there is not enough clinical data to support its advantages over hazards[15]. Acetylcholinesterase Inhibitors (AChEIs), memantine and its combinations are still used off-label[16]. In addition to traditional Aβ or tau interventions, there is increasing interest in alternative nutrition strategies. Nutraceuticals and bioactive compounds from foods and supplements are gaining significance. Enzymes, hormones, and metabolites, as well as cholinergic, serotonergic, dopaminergic, noradrenergic, and glutamatergic neurotransmitter levels, are all linked to the ageing of the brain[17]. These substances, which include antioxidant and homocysteine-related vitamins, come from ethnomedical sources[18]. Furthermore, flavonoids, including polyphenols, flavonols, flavones, isoflavones, flavonones, anthocyanidins, non-flavonoid polyphenols, carotenoids, and diterpenes, are suggested to offer preventive or therapeutic benefits for cognitive impairment[19].

2. Aspects Impacting Cognitive Decline and Brain Ageing

Understanding the factors that contribute to cognitive decline during normal aging could be used to treat neurological diseases and prevent pathological aging. Genetics, oxidative damage, exposure to neurotoxins, lifestyle, nutrition, and medical procedures all affect cognitive ageing. These factors affect brain structure, neurochemistry, and gene expression, compromising brain functions and cognitive processes[20,21]. Sex hormones, especially estrogen, significantly influence the risk of dementia and brain ageing. The neuroprotective effects of estrogen signalling through

the receptor ERα and ERβ are well established, particularly when treating memory impairments associated with age and pathological diseases[22,23]. Neurotransmitters such as cholinergic, serotonergic, dopaminergic, noradrenergic, as well as enzymes, hormones, and metabolites, are linked to changes in brain ageing[24].

3. Nutraceutical Intervention for Diseases and Ageing-Related Cognitive Impairment

The concept of cognitive enhancement is gaining popularity among people of all ages, even those who are young and intellectually intact. New research indicates that nutrition is a risk factor that can be changed for cognitive impairments and that maintaining proper nutritional intake is crucial to maintaining cognitive health[25,26] and lowering the chance of developing neurodegenerative diseases later in life[27]. In this regard, Nutraceuticals have drawn in a lot of attention because of their potential to treat older people with cognitive impairments and to guard against cognitive disease[28]. The word "Nutraceutical", which combines the terms «nutrition» and «pharmaceutical», refers to nutritional products that are known for their effects on specific diseases and health benefits[29]. Medicinal foods, functional foods, dietary supplements, phytochemicals, and particular dietary patterns are all considered nutraceuticals.

3.1 Polyphenols

Plants produce secondary metabolites called polyphenols, which are present across multiple foods and drinks, such as fruits, vegetables, and whole grains. These substances are thought to have the ability to enhance cognitive performance. In general, polyphenols fall into one of two groups: Non-flavonoids as well as flavonoids[30].

3.2 Flavonoids

Cognitive functions are positively impacted by flavonoids such as epicatechin, pelargonidins, anthocyanins, and EGCG. The cognitive advantage of EGCG and other catechins, which are plentiful in the grapevine (*Vitis vinifera*) and tea plant (*Camellia sinensis*), has been shown in both *in vivo* and cell culture models of AD. In ageing rats, intragastric EGCG treatment dramatically decreased cognitive decline as measured by the water maze paradigm and also decreased the development of Aβ1-42 plaques in their brains[31]. Consuming EGCG and catechin-rich green tea has been linked in epidemiological studies to improvements in cognitive performance among healthy individuals, a slower rate of cognitive ageing and a reduced risk of dementia[32-34]. Citrus fruits include the bioflavonoid flavonone glycoside hesperidin, which has been shown in animal and clinical research to have neuroprotective and cognitive advantages[35].

Flavonoids are potent substances that help protect cells from damage because of their anti-apoptotic and antioxidant qualities and prevent programmed cell death[36]. They also play a role in regulating genes that control how cells grow and divide. One well-studied flavonoid, EGCG (found in green tea), acts as a scavenger of harmful Reactive Oxygen Species (ROS), which can disrupt DNA and cell membranes. EGCG protects brain cells by boosting the activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase and inhibiting oxidative stress-promoting enzymes like nitric oxide synthase and monoamine oxidase B[37]. According to *in vitro* research, hesperidin and naringenin[38], and Studies conducted *in vivo* have revealed quercetin and rutin[39,40], are instances of flavonoids that can enhance cerebral blood flow and angiogenesis in elderly people by overcoming the blood-brain barrier. Consequently, the brain receives more oxygen, energy, and essential nutrients, potentially affecting memory and cognitive function[41]. Flavonoids may be able to reduce neuroinflammation by lowering pro-inflammatory cytokines and microglial activation, which is a significant factor in cognitive impairment in ageing and AD, and reducing BBB permeability[42,43]. Isoflavones, which resemble the neuroprotective properties of estrogen, are a rich source of phytoestrogens that may improve cognition[44].

3.3 Non-Flavonoids

Resveratrol, which is mostly contained in peanuts, blueberries, and grapes, has been connected to improved memory and learning. Male Wistar rats were administered resveratrol for 12 weeks in the study. This therapy successfully decreased the activity of neuroinflammatory signalling molecules and averted

deficiencies in spatial and emotional memory[45]. According to randomised controlled research, in AD patients, resveratrol consumption also reduced Aβ40 levels in plasma and cerebral fluid and enhanced specific cognitive abilities in older people[46,47].

Turmeric (*Curcuma longa*) contains curcuminoids used as a spice, colouring, and additive. They belong to a class of phenolic chemicals that could be used as nutraceuticals for cognitive function. Research using a range of animal models, such as dementia with cognitive decline and accelerated and normal ageing, has demonstrated the beneficial effects of curcumin and its effects. Both oral and intraperitoneal curcumin administration enhanced cognitive performance in naturally aged 14-month-old mice. In 15-month-old rats, oral curcumin therapy for 12 weeks improved their identification and spatial memory[32,48,49].

Curcuminoids and resveratrol have demonstrated anti-Aβ properties by lowering tau phosphorylation produced by Aβ *in vivo*, reducing Aβ42 aggregation and β-secretase activity and stopping the *in vitro* production of Aβ oligomers[32,50,51].

Additionally, they decreased oxidative stress and neuroinflammation by reducing astrocyte and microglial activation, which inhibited the brain's NF-κB, TNF-α, and COX-2 signalling pathways as well as the production of IL-8, IL-6, IL-1β, and IL-1α[52-54].

4. Alkaloids

More than 20% of plant species include alkaloids, a broad family of more than 12,000 cyclic chemicals that incorporate nitrogen[55]. Alkaloids have been used medicinally for almost 5,000 years[56]. The plant *Atropa belladonna* produces a variety of poisons, neurotoxins, and traditional psychedelics, such as atropine, scopolamine, and hyoscyamine. Furthermore, alkaloids are the cause of several social drugs, including cocaine, opiates, nicotine, caffeine and methamphetamine (ephedrine)[57]. When given orally to APP/PS1 AD transgenic mice, WS (*Withania somnifera*) root extract, which is high in withanolides, for 30 days, prevented the buildup of Aβ peptides, prevented plaque development, and corrected cognitive impairments[58].

Apart from its natural anti-inflammatory and antioxidant qualities, sominone and withanolides can repair damaged neurites, encourage neurite outgrowth, and rebuild synapses following neurological injury in animal models of AD and amnesia. According to molecular studies, extracts high in withanolides increase the expression of genes like BDNF, KLK8, and GAP43 that are involved in synaptic plasticity. Additionally, by attaching to muscarinic acetylcholine receptors, these extracts enhance cholinergic neurotransmission[59-61].

4.1 Galantamine

Galantamine, also known as galanthamine, is part of the isoquinoline alkaloid family. In the 1950s, it was initially identified and separated from *Galanthus woronowii* and the common snowdrop (*Galanthus nivalis*). Galantamine works in the cholinergic system by inhibiting acetylcholinesterase and allosterically modifying nicotinic acetylcholine receptor (nAChR) activation[62]. In the brain, galantamine binds to AChE, increasing the amount of ACh in the synaptic cleft while reducing acetylcholine (ACh) breakdown. The selectivity of galantamine for human AChE is notably 53 times higher than that of butyrylcholinesterase (BChE), a distinct cholinesterase type present in a variety of non-neuronal tissues. In contrast to this selectivity, non-selective substances that block both AChE and BChE activity include tacrine and physostigmine[63-65].

4.2 Berberine

Berberine, an isoquinoline alkaloid found in plants, is widely used in traditional Chinese and Indian medicine. Many medicinal plants' stems, roots, and bark contain the majority of berberine, such as *Hydrastis canadensis, Coptidis rhizome, and Berberis sp*[66]. Both AChE and BChE are inhibited by berberine, although AChE is more selectively inhibited than BChE. These findings suggest that berberine can be relied on to alleviate cognitive impairment in AD because it increases cholinergic stimulation[67,68].

4.3 Caffeine

The short-term central nervous system stimulation caused by caffeine's blockage of adenosine A2A receptors is widely established. It can enhance cognitive processes and promote mood, arousal, focus, and alertness[69,70]. Caffeine improves cognitive performance in mice with amyloid-beta (Aβ)-induced AD. Caffeine reduces Aβ levels in neuroblastoma-2a cells that have the human Swedish mutant Amyloid Precursor Protein (APP)[71].

5. Omega (Ω) – 3 Fatty Acids

The fluidity, stability, and synaptic connectivity of cell membranes depend on fatty acids[72], and one of the reasons for AD processes is oxidative stress on fatty acids[73]. Humans get 71% of their Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) from fish. Additionally, these acids can be present in other foods, such as meat (20%), eggs (6%), and some plant-based diets. In healthy rats, fatty acids improve cognition. DHA is a vital structural element of neuronal membranes and the brain's main source of omega-3 fatty acids. Learning and memory functions are influenced by the promotion of neurogenesis, neuronal differentiation, neuritogenesis, and synaptogenesis, as well as the maintenance of membrane homeostasis[74-76]. Furthermore, DHA decreases the synthesis of pro-inflammatory genes and strengthens antioxidant defence signalling pathways[77].

6. Terpenoids

Terpenoids are naturally occurring substances derived from plants that have a major effect on cognitive decline, especially in AD. Their biological responses, which include cholinesterase inhibition and inflammation modulation, are all essential for regulating cognitive impairment in AD, which may ease symptoms and reduce the onset of neurodegeneration. Effective cholinesterase inhibitors, which are essential in treating AD by increasing cholinergic activity in the brain, have been found in terpenoids, including diterpenoids, triterpenoids, and sesquiterpenoids[78]. Monoterpenoids derived from essential oils exhibit acetylcholinesterase inhibitory activity, potentially improving AD patients' cognitive function[79]. Terpenoids also regulate various signalling pathways, including those related to neurotrophins, which are crucial for neuronal survival and Functionality[80]. As shown in Table 1, various phytochemicals have demonstrated pharmacological effects relevant to cognitive impairment. Table 1 enlist the pharmacological effects of several phytochemicals that are significant to cognitive impairment.

7. Future Perspective

There are advantages and disadvantages to using nutraceuticals to treat neurodegenerative diseases and stop age-related cognitive decline. They provide a range of neurocognitive advantages via mechanisms such as anti-inflammatory and antioxidant defence, which may result in comprehensive cognitive enhancements. However, challenges include optimising dosage, accurate diagnosis, individual response differences and limitations such as rapid metabolism and poor bioavailability of active ingredients. Innovative drug delivery systems—like nanoparticles and nanoencapsulation—are being developed to overcome these obstacles. Despite promising benefits, many studies are observational, highlighting the need for experimental research to establish nutraceuticals as effective treatments for MCI and dementia. Furthermore, integrating nutrition with advancements in neuroscience, exploring synergistic combinations, and conducting large-scale clinical studies are essential steps forward. Additionally, developing biomarkers for cognitive impairment, promoting public awareness, and creating clear regulatory frameworks will further advance the field of nutraceuticals in cognitive therapy.

Table 1. Key phytochemicals used in cognitive impairment, with their pharmacological effect

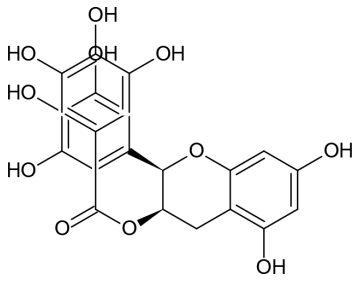
Bioactive Constituent	Class of PG	Herbal Sources	Structure	Mode of Action	References
EGCG	Flavonols	*Camellia sinensis*		It inhibits acetylcholinesterase, lowers the neuroinflammatory response of microglia to amyloid-beta, and has anti-inflammatory effects via a variety of pathways.	34

Table 1. Continued...

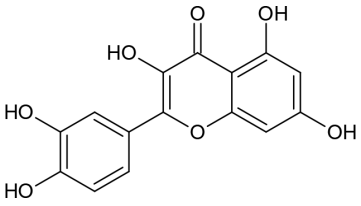
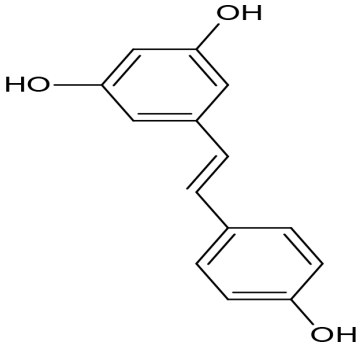
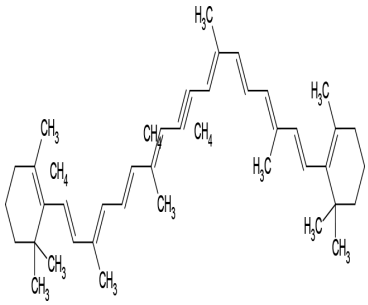
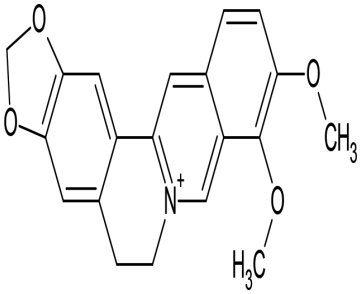
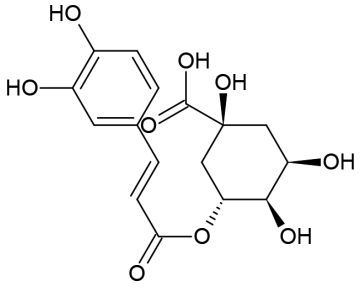
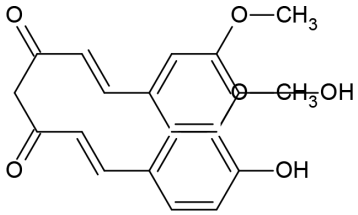
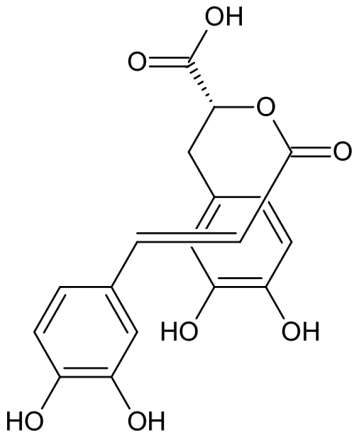
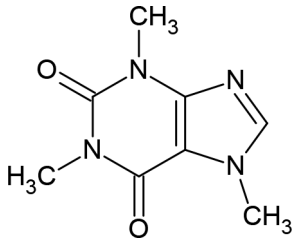
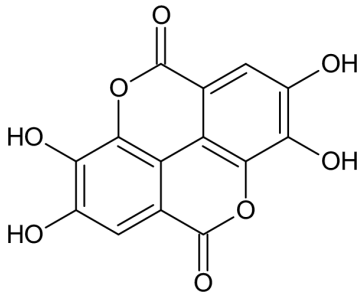
Bioactive Constituent	Class of PG	Herbal Sources	Structure	Mode of Action	References
Quercetin	Flavonols	Onions, broccoli, *Ginkgo folium, Euphorbia hirta*		Quercetin dampens the inflammatory response by lowering the release of proinflammatory cytokines and chemokines, which prevents microglia, and brain immune cells involved in neuroinflammation, including activating and proliferating.	81
Resveratrol	Anthocynidine	*Vitis thunbergii,* grapes and wine		It is said to reduce Aβ peptides by modulating the proteasome, thereby enhancing cognition through the targeting of SIRT1.	82,83
Beta carotene	Carotenoids	Carrot (*Dacus carota*), *Cucurbita moschata, Brassica juncea,* apricot (*Pruns armeniaca*)		In traumatic brain injury, beta-carotene decreases oxidative stress and brain oedema via promoting antioxidant enzymes such as quinone oxidoreductase 1 and activating the Nrf2-ARE pathway. It enhances cognitive by inhibiting acetylcholinesterase activity and reducing amyloid β-protein fragments.	84,85
Berberine	Alkaloid	*Tinospora cordifolia, Berberis aristata,*		Tau hyperphosphorylation and Aβ buildup are two characteristics of AD that are lessened by berberine. It accomplishes this by preventing Aβ from oligomerizing and aggregating and by encouraging tau's autophagic removal.	86,87
Chlorogenic acid	Phenolic acid	Coffee, *Cynara scolymus, Arctium lappa, Malus domestica*		CGA treatment enhanced mTOR/TFEB signalling pathway activation, which decreased cognitive impairments. and restored autophagic flow within mice brains.	88

Table 1. Continued...

Bioactive Constituent	Class of PG	Herbal Sources	Structure	Mode of Action	References
Curcumin	Polyphenol	*Curcuma longa*		Decreases Aβ *in vivo*, binds to pre-existing plaques, inhibits β-secretase, prevents the development of Aβ oligomers, and prevents tau phosphorylation brought on by Aβ to lessen microglial activation.	32,50
Rosmarinic acid	Polyphenols	Peppermint (*Mentha piperita*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*)		The JNK signalling pathway is inhibited by RA, which results in decreased hippocampal inflammation and tau phosphorylation, two factors that are critical to the development of AD.	89
Caffeine	Alkaloid	Coffee, tea (*Camellia sinensis*)		Neuroprotective by inhibiting glutamate release and reducing Aβ levels.	90
Ellagic acid	Polyphenol	Pomegranate (*Punica granatum*), raspberries (*Rubus* spp.), walnut (*Juglans regia*)		It safeguards the brain by inhibiting pro-inflammatory cytokine expression, including TNF-α.	91

8. Conclusion

Cognitive dysfunction is a developing issue, particularly among the senior population, as it affects memory retention, information acquisition, and focus. The formation of amyloid plaques, oxidative stress, and neuroinflammation are some of the underlying causes of neurodegenerative disorders like AD and dementia. Existing pharmacological treatments for mild cognitive impairment (MCI) and AD often show limited effectiveness and may have undesirable side effects, underscoring the need for alternative strategies. Nutraceuticals, natural compounds derived from plants and food sources, are emerging as potential agents to address cognitive decline and promote brain health. Polyphenols, particularly flavonoids like

EGCG and hesperidin, offer strong antioxidant and anti-inflammatory benefits, protecting neurons and improving blood flow to the brain. Non-flavonoid polyphenols such as resveratrol and curcumin can inhibit the formation of harmful amyloid-beta plaques. Alkaloids, like galantamine and berberine, also show promise by enhancing neurotransmission and inhibiting enzymes linked to cognitive impairment. Additionally, Omega-3 fatty acids are essential for maintaining brain function. Nutraceuticals appear to be promising neuroprotective agents that may help delay cognitive decline. Further research, including clinical trials, is crucial to understand their effects fully. Incorporating these compounds into dietary and lifestyle changes may enhance cognitive health.

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10. Author Contribution

Shalini Raghuvanshi: Conceptualisation, Writing and Literature Search; Dr. Avijit Mazumder: Reviewing and Verification; Dr. Saumya Das: Editing and literature review. All authors have read and agreed to the published version of the manuscript.

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