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REVIEW ARTICLE

A Thorough Analysis of The Neuropharmacological Potential of Nutraceuticals in the Treatment of Cognitive Disorders

Mohd. Shoeb Abdul Mukhtar[1]* , Mudabbirul Haque Muqueemul Haque[2], Renuka Umesh Balpande[3] , Mohan Gajanan Doijad[4] , Suvarna Manoj Kothule[5] , Rutuja Vijay Khatik[6] , Trupti M. Shirbhate[7] , Vaishnavi vaidya[8] , Sagar Vinod Thakre[9] , Zohra Firdous M.S.A[10]

[1]*Department of Pharmaceutical Science, Oriental University, Indore, Madhya Pradesh, India, 453 555
[2]Department of Pharmaceutical Science, New Montfort Institute of Pharmacy, Ashti, Wardha, 442 202
[3]Department of Pharmacology, Priyadarshini J.L. College of Pharmacy, Hingna, Nagpur, Maharashtra, India, 440 016
[4]Department of Pharmaceutics, Sant Gadge Baba Amravati University, Amravati, Maharashtra, 444602
[5]RSM N. N. Sattha College of Pharmacy, Ahilyanagar, Maharashtra, India, 414402
[6]SEF's Sarsam College of Pharmacy, Palashiwadi, Baramati, Maharashtra, India, 413102.
[7]Department of Pharmacology, Kamla Nehru College of Pharmacy,Nagpur 441108
[8]Department of Pharmaceutics, Tulsiramji Gaikwad-Patil College of Pharmacy, Nagpur, Maharashtra, India, 441108
[9]Department of Pharmacognosy, Kamla Nehru College of Pharmacy, Nagpur, Maharashtra, India , 441108
[10] Department of Pharmaceutics, Kamla Nehru College of Pharmacy, Nagpur, Maharashtra, India , 441108
Corresponding Author Email: mshoeb839@gmail.com

ABSTRACT

Age-associated Parkinson's disease, dementia, Alzheimer's disease, and cognitive decline are among the cognitive illnesses that are becoming more and more of a worldwide health problem. Despite providing symptomatic relief, synthetic medications frequently have negative side effects and little long-term effectiveness. Bioactive substances obtained from food sources, known as nutraceuticals, have shown promise as neuroprotective agents with low toxicity and wide-ranging therapeutic advantages. These substances alter a number of neuropharmacological processes, including the control of synaptic plasticity, cholinergic system augmentation, anti-inflammatory action, and oxidative stress reduction. The medicinal potential and molecular insights of significant nutraceuticals, including Ginkgo biloba, bacosides, flavonoids, Fatty acids with omega-3, resveratrol, and curcumin, in the treatment of cognitive impairment are well covered in this study. A careful analysis is conducted of their function in regulating neurotrophic factors, neurotransmitters, and neuronal signaling cascades. Furthermore, preclinical research and current clinical trials are assessed to support applications that are grounded on evidence. The paper also discusses the drawbacks, challenges with formulation, issues with bioavailability, and opportunities for incorporating nutraceuticals with traditional neuropharmacological treatments. This study offers a solid scientific basis for future research on the role of nutraceuticals in cognitive health, promoting their logical advancement as complementary or alternative treatments for cognitive and neurodegenerative diseases.

Keywords: *Natural neuroprotective agents, Alzheimer's disease, cognitive disorders, neuropharmacology, oxidative stress, and nutraceuticals.*

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INTRODUCTION

A group of mental and neurological disorders known as cognitive disorders mainly impact language, learning, memory, attention, and the ability to solve problems. These conditions range from mild cognitive impairment to brain disorders including Alzhkeimer's, Parkinson's, vascular, and

frontotemporal dementia. It is Alzheimer's disease that is the most prevalent, which causes between 60 and 70 percent of dementia cases globally [1]. Irreversible neural damage, major functional decline, emotional misery, and a large caring and financial burden are all consequences of these illnesses' progressive nature.

The frequency of dementia is progressively increasing worldwide. According to the WHO, there are already over 55 million people with dementia globally, and as the population ages and life expectancy increases, that number is predicted to increase to 139 million by 2050 [2]. About 7.4 million people in India alone were estimated to have dementia, and estimates indicate that number will double over the next 20 years [3]. Current pharmaceutical therapies, including as NMDA receptor antagonists' cholinesterase inhibitors mostly show symptoms and offer little help in changing the course of the disease, despite its rising occurrence. Furthermore, these medications are frequently linked to negative side effects as bradycardia, hepatotoxicity, nausea, and neuropsychiatric symptoms [4].

These drawbacks have increased interest in safer and more comprehensive substitutes. The neuroprotective, antioxidant, anti-inflammatory, and cognitive-enhancing qualities of nutraceuticals—naturally occurring bioactive substances included in foods and medicinal plants—have drawn a lot of interest [5]. These substances are thought to alter a number of important molecular processes implicated in cognitive impairment, such as neurotransmitters imbalance, dysfunction of mitochondria, inflammation of the brain, and oxidative damage. They are also widely regarded as safe for long-term usage.

Using the PICO model as a framework, this review is organized around the following research question: Do nutraceutical interventions improve cognitive function and slow the progression of cognitive decline in people with neurodegenerative diseases or cognitive impairment (Population) when compared to a placebo or traditional synthetic therapies (Comparison)?

consequently, this study's objective is to evaluate the neurological therapeutic capability of important nutraceuticals in the treatment and prevention of cognitive problems. Their modes of action, corroborating data from preclinical and clinical research, formulation techniques to improve efficacy, and the difficulties and potential paths forward for incorporating nutraceuticals into cognitive healthcare are all highlighted.

REVIEW METHODOLOGY

This narrative review covers modern and classical research on the use of nutraceuticals in cognitive disorders. The selection of studies was based on their clinical value, molecular discoveries, and pharmacological relevance. Earlier foundational research was included to offer historical and mechanistic context, but when possible, contemporary meta-analyses and randomized controlled trials were given priority.

COMPREHENDING COGNITIVE IMPAIRMENTS

MEANING AND CATEGORIZATION

Language, acquisition, perception, recall, focus, and making choices are the main mental functions that are impacted by cognitive disorders, a category of mental health issues. These illnesses, which frequently have neurodegenerative, vascular, traumatic, or psychiatric causes, are brought on by failure in certain brain regions that are in charge of processing and integrating information [6].

The cause and degree of impairment are usually used to categorize cognitive disorders:

• Neurodegenerative diseases, including frontotemporal dementia, Parkinson's disease dementia, and Alzheimer's disease.

• Vascular cognitive impairment: Deficits in cognition brought on by cerebrovascular insufficiency, frequently after a stroke.

• MCI: A stage that preserves functional independence between normal aging and dementia.

• Dementia and reversible cognitive disorders: These conditions may be curable and are brought on by infections, metabolic abnormalities, or drug toxicity [7].

The most prevalent type of dementia worldwide is Alzheimer's disease, which is followed by vascular dementia and Lewy body dementia.[8].

TYPICAL COGNITIVE DEFICITS

Based upon the root condition, the areas of the brain impacted, and the course of the disease, cognitive diseases can present in a variety of ways. The following are the main cognitive deficits noted:

- Memory loss: A significant and early symptom of Alzheimer's disease, memory loss impacts the formation of equally for the short as well as long term memories [9].

- Attention impairment: prior to depressive disorders, dementia, as well as delirium, patients frequently experience trouble focusing or maintaining their attention.
- Learning difficulties: A reduction in one's capacity to pick up new information or abilities, especially in neurodegenerative disorders involving the hippocampal region.
- Frontotemporal and vascular dementias are frequently associated with deficiencies in making decisions and executive function, that encompass simultaneous tasks, organizing, reasoning, and resolution of issues [10].

COGNITIVE IMPAIRMENT MECHANISMS

Neuroinflammation as well as Oxidative Damage

Oxidative damage is caused by a disparity among the production of ROS, or reactive oxygen species, and the antioxidant defense mechanisms in the cerebral cortex. The nervous system is particularly vulnerable to oxidative damage due to its substantial use of oxygen, elevated lipid amount, as well as relatively low levels of enzymes known as antioxidants [11]. Neurodegeneration may result from ROS's ability to harm proteins, DNA, as well as neuronal membranes. The development of Alzheimer's disease and other dementias is significantly influenced by chronic neuroinflammation [12].

Impairment of the Cholinergic as well as Dopaminergic Systems

Acetylcholine levels significantly drop in Alzheimer's condition due to Memory building and consolidation are hampered by the loss of cholinergic neurons in the basal forebrain [13]. This provides the pharmacological basis for using inhibitors of cholinesterase for treating AD.

Similarly, the cognitive impairment associated with Parkinson's disease is mostly caused by dopaminergic dysfunction. Executive processes, mood modulation, and motor control are all impacted Through the substantia nigra's dopaminergic cells dying off [14].

Mitochondrial Impairment

Calcium homeostasis, apoptosis control, and neural energy generation all depend on mitochondria. Mitochondrial malfunction causes apoptosis, elevated ROS generation, and decreased ATP synthesis in cognitive disorders. This leads to gradual loss of neurons and synaptic failure [15].

Tau Dysfunction as well as Amyloid Beta Aggregation

Amyloid-beta (Aβ) plaque accumulation outside of cells along with tau protein hyperphosphorylated accumulation within, which forms neurofibrillary tangles, are the hallmarks of Alzheimer's disease. Tau disease causes microtubule instability and neuronal death, whereas Aβ oligomers disrupt synaptic connection and start oxidative and inflammatory cascades [16].

The severity of cognitive impairment is correlated with the evolution of these pathological alterations, which start years before clinical symptoms manifest. Due to the intricacy of disease pathways, therapeutic treatments that target these proteins are now being investigated; nevertheless, their efficacy in clinical trials has been limited [.17].

NUTRACEUTICALS

MEANING AND CATEGORIZATION

The word "nutraceutical" is a compound of the words "pharmaceutical" and "nutrition." It encompasses a wide range of naturally occurring bioactive substances that have both medicinal and nutritional advantages. Usually present in food, plants, or dietary supplements, these compounds have potential use in the prevention and treatment of neurological and cognitive diseases [18].

The word "nutritraceutical" was first used in 1989 by Stephen DeFelice, who defined it as "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of disease" [19]. Instead of being chemically treated like traditional medications, nutraceuticals are derived from natural sources and are frequently included in a normal diet.

Classification of Nutraceuticals:

Based on its place of origin and functional characteristics, nutraceuticals may be divided into the following categories:

• Diet nutrients: They consist of amino acids and vitamins that lower oxidative stress and promote brain function.

• Herbal Items: herbal extracts with neuroprotective and cognitively boosting qualities from medicinal herbs

• antioxidants as well as phytochemicals, substances with anti-inflammatory and antioxidant properties that are present in tea, wine, and fruits [20].

• Functionality Meals: Foods enhanced with bioactive ingredients.

• Prebiotics and probiotics: They have been shown to have new functions in mental wellness and mental stabilization by regulating the relationship between the gut and the brain.

BENEFITS COMPARED TO TRADITIONAL MEDICINES

- Multi-targeted Mechanisms: Nutraceuticals frequently have pleiotropic effects, such as antioxidant, anti-inflammatory, neuroprotective, and mitochondrial-supporting properties, in contrast to traditional medications that target certain receptors or pathways [21].
- Better Tolerability and Low Toxicity: The majority of nutraceuticals are derived from natural sources and are easily absorbed by the body, resulting in fewer side effects than manufactured drugs [22].
- Long-term Suitability: Nutraceuticals are perfect for preventative and maintenance treatments due to their good safety profile, which allows for prolonged usage without risk.
- Synergistic Effects: Numerous nutraceuticals have the potential to be employed as an adjuvant treatment for neurodegenerative diseases when combined with traditional medications, improving therapeutic results without increasing toxicity [23].
- Public Preference: As natural and plant-based treatments gain popularity worldwide, nutraceutical-based interventions are becoming more widely accepted and adhered to, particularly among the elderly [24].

LIMITATIONS

Notwithstanding their encouraging advantages, a number of obstacles prevent nutraceuticals from being used as effectively as possible in cognitive therapies:

- Standardization and Quality Control: The potency and purity of nutraceutical formulations vary depending on plant sources, growth conditions, harvesting methods, and extraction procedures. Dosage recommendations and efficacy evaluation are made more difficult by a lack of uniformity [25].
- Low Bioavailability: A lot of nutraceuticals, particularly polyphenols like resveratrol and curcumin, have low systemic availability due to their quick metabolism, limited intestinal absorption, and low water solubility [26].
- Limited Clinical Evidence: Although there is a wealth of preclinical research, many nutraceuticals still lack high-quality, extensive randomized controlled trials (RCTs), which makes it difficult for mainstream medical practice to approve and accept them [27].
- Regulatory Difficulties: Nutraceuticals are subject to food or supplement rules in many nations rather than drug legislation, which leads to lax regulatory supervision, unclear labeling, and unsupported health claims [28].

Novel formulation approaches, such as solid lipid nanoparticles, liposomes, and nanoparticle delivery systems, are being investigated to improve stability and bioavailability in order to solve these issues.

NEUROPHARMACOLOGICAL MECHANISMS OF NUTRACEUTICALS

Numerous pharmacological mechanisms that are essential to preserving brain function are how nutraceuticals achieve their neuroprotective benefits. These bioactive substances affect neurodegenerative pathogenesis by modifying oxidative stress, inflammation, neurotransmitter systems, and synaptic integrity.

ANTIOXIDANT MECHANISMS

The antioxidant capacity of nutraceuticals is one of the main ways they shield brain tissue. One of the main causes of cognitive decline is oxidative damage, which is brought on by an imbalance between ROS as well as antioxidants. Nutraceuticals with strong free radical scavenging properties include flavonoids, curcumin, resveratrol, and vitamins C and E. These substances suppress ROS-mediated neuronal death, stabilize mitochondrial membranes, and lower lipid peroxidation [29]. Likewise, it has been demonstrated that resveratrol, which is present in berries and grapes, increases mitochondrial biogenesis and lessens oxidative neuronal damage [30].

REDUCED INFLAMMATORY ROUTES

Another important factor that contributes to the development of cognitive problems is chronic neuroinflammation. Numerous nutraceuticals work by inhibiting pro-inflammatory mediators such factors. Green tea's polyphenolic components, such as quercetin and EGCG, block the NF-κB pathway, a crucial transcription factor in the control of inflammation [31].

These substances help lessen neuronal damage by regulating microglial activity, a defining feature of brain inflammation. For instance, curcumin reduces the expression of COX-2 and iNOS in activated microglia, hence reducing neuroinflammatory reactions [32].

CHANGES IN NEUROTRANSMITTERS

Neurotransmitter dynamics have a profound impact on cognitive functions. By either inhibiting degradation or increasing receptor sensitivity, nutraceuticals help maintain neurotransmitter homeostasis. For example, the bacoside-rich plant *Bacopa monnieri* increases the levels of acetylcholine (ACh), which is necessary for memory and learning, by inhibiting acetylcholinesterase (AChE) [33].

Mucuna pruriens, a naturally occurring source of L-DOPA, improves dopaminergic transmission, which is advantageous for cognitive impairment associated with Parkinson's disease. Supplements high in tryptophan and 5-HTP promote the production of serotonin, which helps to regulate mood and lessen cognitive impairment linked to depression. Additionally, substances like Valeriana officinalis' valerenic acid increase GABAergic activity and have anxiolytic and relaxing effects [34].

NEURODEVELOPMENT AS WELL AS SYNAPTIC FLEXIBILITY

Numerous nutraceuticals promote synaptic plasticity and neurogenesis, which are essential for memory and learning. In the hippocampus, omega-3 fatty acids, particularly docosahexaenoic acid (DHA), stimulate synapse development, dendritic branching, and neurite outgrowth [35].

By upregulating synapsin-I along with PSD-95, two synaptic proteins essential for brain connection, ashwagandha as well as Panax ginseng demonstrated to improve Neurodevelopment as well as Synaptic Flexibility These activities promote cognitive resilience and memory consolidation [36].

CONTROL OF NEUROTROPHIC ELEMENTS

The survival, development, and synaptic regulation of neurons depend on brain-derived neurotrophic factor (BDNF). By activating signaling cascades like the PI3K/Akt and CREB pathways, nutraceuticals like as curcumin, resveratrol, and green tea catechins increase the expression of the BDNF gene [37]. In aging humans as well as animal models, physical exercise and dietary consumption of nutraceuticals, especially polyphenols as well as omega-3ss, have a synergistic impact on BDNF synthesis, improving hippocampus Flexibility and cognition [38].

IMPORTANT NUTRACEUTICALS AND HOW THEY AFFECT COGNITIVE IMPAIRMENTS

Through various neuropharmacological processes, a variety of nutraceuticals have demonstrated encouraging outcomes in enhancing cognitive performance and reducing neurodegeneration. The main substances, their origins, and their neuroprotective properties are highlighted in the section that follows.

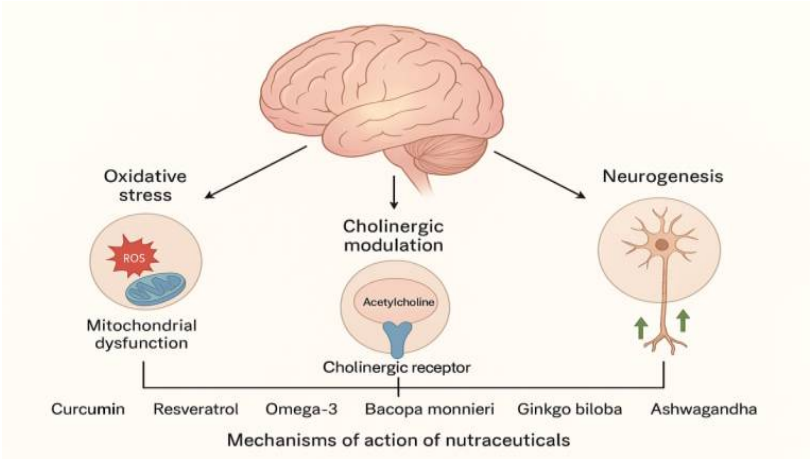

Figure 1: Mechanisms of action of nutraceuticals in cognitive disorders. Compounds act on major neural pathways including oxidative stress, cholinergic modulation, and neurogenesis.

CURCUMIN (*CURCUMA LONGA*)

Turmeric's main curcuminoid, curcumin, is well known for its anti-inflammatory, anti-amyloidogenic, and antioxidant qualities. Mechanistically, it inhibits acetylcholinesterase, scavenges reactive oxygen species (ROS), decreases β-amyloid plaque formation, and downregulates pro-inflammatory cytokines—all of which are important factors in cognitive loss in models of Alzheimer's disease [39].

The cognitive advantages of curcumin have been assessed in a number of randomized controlled studies (RCTs). For example, 40 nondemented older adults (aged 51–84) who received 90 mg of Theracurmin® twice daily for 18 months reported notable improvements in memory and attention, as well as a decrease in amyloid and tau accumulation on PET scans, according to a double-blind RCT by Small et al. (2018) [75]. Nevertheless, the limited population and small sample size constrain how broadly these results may be applied.

After reviewing six RCTs, Panahi et al. (2019) conducted a meta-analysis and came to the conclusion that curcumin had a minor positive impact on cognitive performance. However, significant heterogeneity and bias risk are introduced by inconsistent trial design, short trial lengths, limited formulation bioavailability, and a lack of standardized outcome measures [76].

Although early results are promising, longer-term follow-up and more thorough, multicenter RCTs using standardized curcumin formulations are necessary to validate its neuroprotective effectiveness. Given the limitations, it is necessary to evaluate the current evidence cautiously, since it indicates moderate strength.

RESVERATROL

The polyphenolic chemical resveratrol is mostly present in wine, cherries, and red grapes. Through sirtuin-1 (SIRT1) activation, oxidative stress reduction, pro-inflammatory cytokine inhibition, and mitochondrial biogenesis promotion, it has neuroprotective benefits. It has been linked to improved memory performance, synaptic plasticity, and neurogenesis in experimental models [40].

However, there is still conflicting clinical data in people. Witte et al. (2014) discovered that consuming 200 mg of resveratrol daily for 26 weeks improved memory performance in a randomized, double-blind, placebo-controlled research including 46 healthy older people (60–79 years old) [77]. Other trials, especially in persons with good cognitive function, found no discernible cognitive effect.

The results of a 2020 meta-analysis of seven RCTs looking at resveratrol's effects on cognitive function were inconsistent, showing no consistent benefits on global cognition but some improvements in working memory. Short duration, small sample numbers, low bioavailability, and variations in dose and formulations were among the limitations of these trials, all of which increased the risk of bias from moderate to high [78].

Overall, despite resveratrol's continued mechanistic promise, bigger, longer-term studies employing standardized, high-bioavailability formulations are required to confirm its therapeutic potential because its clinical effectiveness in cognitive disorders is still unclear.

OMEGA-3 FATTY ACIDS

The two major omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are essential for preserving the integrity of neuronal membranes, controlling inflammatory reactions, and promoting synaptic plasticity. Cognitive impairment, depression, and the advancement of neurodegenerative diseases have all been connected to omega-3 deficiency [41].

Higher omega-3 consumption has been linked in a number of observational studies to less cognitive deterioration, especially in older populations. Randomized controlled trials (RCTs) have more inconsistent results, though. Over 3,500 older persons were examined in the VITAL-Cog trial (2022), a large-scale RCT nested inside the larger VITAL investigation, after receiving omega-3 supplements (1 g/day) for two years. The study demonstrated no statistically significant improvement in cognitive outcomes when compared to a placebo [79].

Similar findings were made by the 485 individuals in the MIDAS study (2010), which found that DHA supplementation improved memory and learning somewhat but that the therapeutic relevance was short-lived. There is modest indication of benefit in people with moderate cognitive impairment (MCI), but no discernible effects in adults who are cognitively well, according to meta-analyses (Yurko-Mauro et al., 2020).

Variability in baseline omega-3 status, dose, trial duration, participant cognitive stage, and utilization of various cognitive endpoints may be the cause of these disparities. Adherence and bioavailability are also significant confounding factors.

All things considered, the data supporting omega-3 fatty acids' ability to improve cognition is conflicting, ranging from weak to moderate depending on the demographic. Longer trial lengths, tailored strategies, and focused at-risk recruiting should be the main focuses of future research.

GINKGO BILOBA

Bioactive flavonoids and terpenoids found in *Ginkgo biloba* extract (usually standardized as EGb 761) have anti-inflammatory, vasodilatory, and antioxidant properties. It is thought to assist memory and cognition in elderly populations by enhancing neurotransmitter activity, protecting neurons from oxidative damage, and improving cerebral blood flow [42].

Although it is widely used, there is still conflicting clinical data about its effectiveness. One of the biggest RCTs ever carried out, the Ginkgo Evaluation of Memory (GEM) trial, including 3,069 individuals who were 75 years of age or older and who received 240 mg/day of EGb 761 for a median of 6.1 years. Although there was a slight improvement in memory subsystems in certain secondary outcomes, there

was no discernible difference between the Ginkgo and placebo groups in terms of dementia incidence or cognitive deterioration [80].

Smaller RCTs and open-label trials, on the other hand, have shown moderate benefits in memory and attention, particularly in individuals with mild cognitive impairment (MCI). Small sample numbers, brief study periods, and the possibility of publication bias are common problems with these kinds of studies. Due in significant part to variations in extract formulations, dose, and demographic characteristics, meta-analyses reveal variability in results.

Overall, the data supporting *Ginkgo biloba*'s potential in early cognitive decline is only moderate, and it is unlikely to be successful when used alone to treat severe dementia.

BACOPA MONNIERI

By modifying cholinergic activity, improving cerebral blood flow, and strengthening antioxidant defenses, the ancient Ayurvedic herb *Bacopa monnieri* improves cognitive function [43]. Numerous clinical studies have demonstrated improvements in learning, attention, and memory retention.

After 12 weeks of standardized Bacopa extract, 98 healthy older individuals participated in a randomized, double-blind, placebo-controlled study by Stough et al. (2008) that revealed notable gains in verbal memory and anxiety reduction. However, the findings' strength is constrained by the small sample size and subjective objectives.

Although interpretation is complicated by variations in dose, duration, and cognitive tests, Pase et al. (2012)'s meta-analysis of six RCTs found moderate but statistically significant memory benefits. Placebo effects and inconsistent outcomes highlight the need for bigger, standardized studies, particularly in individuals with cognitive impairment.

FLAVONOIDS

A broad class of polyphenolic substances found in tea, cocoa, fruits, and vegetables are called flavonoids. By scavenging reactive oxygen species (ROS), lowering lipid peroxidation, and blocking pro-inflammatory cytokines including TNF-α and IL-1β, they have neuroprotective benefits. Additionally, these substances affect signaling cascades that are essential for synaptic plasticity, memory consolidation, and neuronal survival, including PI3K/Akt, ERK, and CREB.

In order to promote neurogenesis and prevent age-related cognitive decline, flavonoids such as epicatechin, luteolin, and quercetin have been shown to improve long-term potentiation (LTP), increase brain-derived neurotrophic factor (BDNF), and pass the blood–brain barrier [44].

Human trials are still few and far between, despite preclinical research continuously demonstrating their neuroprotective function. While certain small-scale RCTs, including those evaluating cocoa flavanols, have shown benefits in older individuals' executive function and processing speed, the results vary depending on the formulation and dosage. Furthermore, converting these advantages into practical application is complicated by issues with bioavailability, individual metabolic variability, and brief trial durations. Larger, longer-term clinical trials are necessary to confirm flavonoids' significance in neuroprotection and cognitive improvement because the data supporting them is generally encouraging but mild.

ASHWAGANDHA

The adaptogenic herb that has long been utilized in Ayurvedic medicine to support resilience and mental health is ashwagandha. Withanolides, its main bioactive component, have potent anti-inflammatory, neuroprotective, and antioxidant qualities. Ashwagandha lowers cortisol levels and improves stress tolerance via mechanistically inhibiting NF-κB signaling, reducing ROS generation, and modulating the hypothalamic–pituitary–adrenal (HPA) axis.

It has also been demonstrated to lower neuronal apoptosis, boost ATP synthesis, and improve mitochondrial function. Crucially, ashwagandha promotes the expression of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which promotes neurogenesis, synaptic plasticity, and cognitive improvement [45].

Following eight weeks of supplementation, 60 persons with moderate cognitive impairment participated in a randomized, double-blind, placebo-controlled study by Lopresti et al. (2019), which found substantial improvements in both immediate and general memory ratings. In a different RCT, healthy volunteers demonstrated enhanced cognitive and psychomotor performance [44].

These results are constrained, though, by small sample numbers, brief research periods, and possible bias brought on by different funding sources or formulations. Furthermore, dosage standardization among trials is made more difficult by the variety of ashwagandha extracts (KSM-66, Sensoril, etc.).

Larger, independent trials are required to prove Ashwagandha's long-term safety and efficacy, although overall, the evidence supporting its cognitive and stress-relieving benefits is modest.

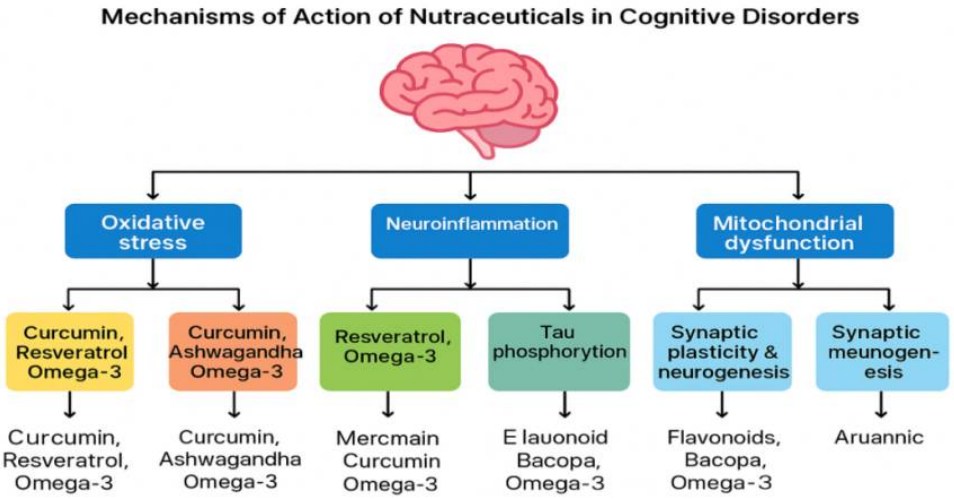

Figure 2: *Summary of the major mechanisms of action of key nutraceuticals relevant to cognitive function and neurodegeneration.*

EVIDENCE FROM PRECLINICAL AND CLINICAL STUDIES

Nutraceuticals' promise for treating cognitive impairments is highlighted by the expanding corpus of scientific research on the topic. Numerous nutraceuticals have been investigated for their effectiveness in enhancing cognitive abilities and reducing neurodegeneration in both preclinical (animal-based) and clinical (human-based) investigations.

ANIMAL MODEL STUDIES

Clarifying the neuroprotective effects of nutraceuticals has been made possible in large part by animal models. A number of rodent models, such as those triggered by lipopolysaccharide (LPS), β-amyloid, or scopolamine, mimic elements of cognitive diseases including Alzheimer's disease and age-related memory loss.

CLINICAL TRIAL

Numerous observational studies and randomized, placebo-controlled trials (RCTs) have evaluated the cognitive advantages of nutraceuticals in people, particularly in the elderly and in patients suffering from Alzheimer's disease or moderate cognitive impairment (MCI).

• Curcumin: Compared to a placebo, taking 90 mg of curcumin daily for 18 months enhanced memory and attention in 60 healthy older individuals, according to a double-blind RCT [52].

• Resveratrol: Clinical research showed that older persons who took 200 mg of resveratrol daily for 26 weeks had improved hippocampal functional connectivity and memory performance [53].

• Omega-3 Fatty Acids: Long-term DHA as well as EPA intake reduces cognitive decline in older populations with moderate cognitive impairment, according to multiple meta-analyses [54].

• *Ginkgo biloba*: Although the advantages were more pronounced in small-scale studies, the Ginkgo Evaluation of Memory (GEM) research indicated a little cognitive improvement in older persons without dementia [55].

• *Bacopa monnieri*: Research has demonstrated that taking 300–450 mg daily for 12 weeks greatly enhanced learning and memory retention in healthy persons [56].

• Ashwagandha: According to a randomized study, persons with MCI who took 300 mg twice a day for eight weeks saw a substantial improvement in their memory, executive function, and attention [57].

META ANALYSES AS WELL AS SYSTEMATIC REVIEW

A number of nutraceuticals have been shown to improve cognitive function, according to meta-analytical research.

• A meta-analysis of 18 RCTs conducted in 2020 found that *Bacopa monnieri* had few adverse effects and greatly enhanced memory function [58].

• A comprehensive analysis of 12 studies on omega-3 fatty acids revealed a steady improvement in cognitive function, especially in processing speed and episodic memory, in those over 60 [59].

• Meta-analyses have demonstrated that curcumin and resveratrol provide neurocognitive protection; nevertheless, findings from various trials continue to vary because of variations in formulation and bioavailability [60].

DEVELOPING TECHNIQUES TO INCREASE EFFECTIVENESS

In order to overcome constraints and maximize the therapeutic potential of nutraceuticals in cognitive disorders, recent developments in pharmaceuticals have investigated innovative formulation techniques.

DELIVERY USING LIPOSOMES AND NANO-FORMULATIONS

Among the most researched methods for enhancing the biological absorption as well as directed delivery of nutraceuticals are nano-formulations, including solid lipid nanoparticles, liposomes, nanoparticles, as well as nanoemulsions. These systems improve the transport of drugs like curcumin and resveratrol to the central nervous system (CNS) by increasing solubility, preventing degradation of bioactive chemicals, and facilitating blood-brain barrier (BBB) crossing. For instance, because of its improved brain permeability and prolonged release characteristics, nano-curcumin has shown increased neuroprotective and anti-inflammatory benefits in both in vitro and in vivo models of Alzheimer's disease [61].

Liposomal encapsulation is very useful for improving the stability and duration of systemic circulation of nutraceuticals. a mixture of omega-3 fatty acids with liposomal resveratrol have shown improved absorptions as well as cognitive function outcomes in both animal studies as well as young human interventions. [62]. These nanocarriers minimize possible side effects by improving pharmacokinetics and lowering necessary doses.

SYNERGISTIC COMBINATIONS

Synergistic therapeutic effects can be achieved by combining nutraceuticals with other bioactive substances or with traditional pharmaceutical drugs. Because of their multitargeted activity, polyherbal formulations that contain many plant-based chemicals have demonstrated better memory, learning, and neuroprotection results. For example, it has been demonstrated that formulations that combine *Ginkgo biloba* and *Bacopa monnieri* improve cholinergic neurotransmission and lower oxidative stress more successfully than when taken separately [63].

Furthermore, using nutraceuticals along with prescription medications (such donepezil or levodopa) may have synergistic or additive effects. According to some research, acetylcholinesterase inhibitors as well as omega-=3 fatty acids together improve cognition function scores more than when used alone. This might be because they alter both the neurotransmitter and inflammatory pathways [64].

ADJUVANTS' FUNCTION IN IMPROVING THE BIOLOGICAL AVAILABILITY

In nutraceutical formulations, concurrent use of adjuvants that improve a drug's bioavailability or therapeutic effect—has become a common practice. Black pepper contains piperine, a naturally occurring alkaloid It has been in use for a long time as a bioenhancer. It has been demonstrated to improve intestinal absorption and prevent curcumin's metabolic degradation, increasing its bioavailability by up to 2000% [65].

In order to increase the solubility and transport of hydrophobic nutraceuticals across the blood-brain barrier, additional adjuvants such phospholipids and cyclodextrins are also used to form inclusion complexes with them [66].

OBSTACLES AND RESTRICTIONS

Although nutraceuticals are becoming more popular for treating cognitive problems, a number of restrictions prevent their broad clinical use and evidence-based advice.

INSUFFICIENT STANDARDS

The absence of uniformity in the makeup, concentration, and purity of bioactive substances is one of the main issues facing the nutraceuticals industry. Nutraceuticals are frequently made from natural sources like plants, herbs, or food matrices, which are naturally variable because of variations in how they are grown, harvested, processed, and stored. Because of the batch-to-batch variability caused by this inconsistency, it is challenging to guarantee repeatable therapeutic effects [67].

CONFLICTING CLINICAL DATA

Clinical trials have shown variable or subpar results, despite preclinical research showing promise neuroprotective benefits of nutraceuticals. The lack of clear evidence is caused by changs in study design, sample size, length, dose, as well as outcome measurements. *Ginkgo biloba*, for example, has been shown in certain studies to improve memory, while in others, the effects are insignificant when compared to a placebo. The legitimacy of Using nutraceuticals in scientifically supported medicine is weakened by this discrepancy [68].

INDIVIDUAL DIFFERENCES IN REACTION

Nutraceuticals' efficacy, metabolism, & absorption can be impacted by individual variations in genetics, gut flora, metabolic rate, and co-existing medical disorders. Phytochemicals' bioavailability varies from

community to population and is frequently poor. Because of this, it is challenging to standardize treatment plans and forecast therapy outcomes for a variety of groups with cognitive problems [69].

ISSUES WITH REGULATION & QUALITY CONTROL

In contrast to traditional medications, nutraceuticals are frequently governed as dietary supplements in several nations, such as the US and India. They are thus not put through the same stringent testing for quality, safety, and efficacy before being made available to customers. Numerous issues about product adulteration, contamination with heavy metals, pesticides, or microorganisms, and fraudulent medicinal claims are brought up by this regulatory laxity.

Clinical usage is further complicated by the lack of standardized labeling and dose information. The use of non-standardized plant extracts and uneven Good Manufacturing Practices (GMP) can cause significant differences in quality and potency across producers.

The possibility of herb-drug interactions is a rising safety concern, particularly for older patients who often take many drugs. For example, curcumin may influence medication metabolism by cytochrome P450 enzyme regulation, and *Ginkgo biloba* may raise the risk of bleeding when taken with anticoagulants.

Global standardization is urgently needed since the absence of clear worldwide criteria makes it difficult to monitor and regulate nutraceutical goods effectively across national boundaries. In order to guarantee consumer safety and product dependability, it is imperative to strengthen regulatory monitoring, enforce more stringent GMP compliance, and require post-marketing surveillance [70].

VARIABILITY IN COMMERCIAL NUTRACEUTICAL PRODUCTS

The significant variation in product composition, purity, and potency across commercially available formulations is one of the main clinical obstacles in the application of nutraceutical treatment. Inconsistent doses and bioavailability are caused by variations in extraction techniques, source materials, production standards, and labeling procedures. For instance, the amount of curcumin in different brands might differ greatly, and some products might not include standardized active ingredients like EGb 761 in *Ginkgo biloba* or bacosides in *Bacopa monnieri*.

These disparities impede cross-study replication and make clinical interpretation of data more difficult. Furthermore, the absence of strict regulatory supervision and quality control raises the possibility of contamination, adulteration, or incorrect labeling, all of which might jeopardize patient safety and treatment effectiveness. Because of this unpredictability, standardized production procedures and certification processes must be put in place to guarantee uniformity, dependability, and safety in commercial

FUTURE DIRECTIONS

The increasing amount of data demonstrating the cognitive advantages of nutraceuticals necessitates concerted efforts to improve their creation, approval, and incorporation into traditional medicine. In order to fully realize their promise in neuroprotection and memory improvement, future research must solve the existing constraints.

THE NECESSITY OF EXTENSIVE CLINICAL TRIALS

Numerous small-scale studies indicate that nutraceuticals may have cognitive advantages, However, to demonstrate their efficacy and safety, massive, global, properly planned RCTs are required. To generate results that can be used broadly, these studies should concentrate on standardized formulations, precise dosage schedules, and consistent objectives. Assessing long-term cognitive outcomes at various phases of neurodegenerative illnesses should be a priority [71].

CUSTOMIZED NUTRACEUTICAL TREATMENT

The potential for individualized nutraceutical treatments, in which a person's genetic composition and metabolic profile inform the choice and dosage of nutraceuticals, is made possible by developments in nutrigenomics, metabolomics, and microbiome research. Clinical response variability may be reduced and therapeutic efficacy may be increased by customizing therapies according to genetic predisposition and biomarkers [72].

INTEGRATION WITH CONVENTIONAL PHARMACOTHERAPY

Nutraceuticals can be used as supplements to traditional therapy, improving results through synergistic processes, rather than as substitutes. For example, combining antioxidants with anti-inflammatory drugs or curcumin with cholinesterase inhibitors may lessen the need for high dosages and the negative effects of medications. To maximize such integrated regimens, future research should concentrate on drug-nutraceutical interaction investigations [73].

THE EXTENT OF PREVENTIVE HEALTHCARRE

Nutraceuticals have great potential as preventative measures, particularly for people at risk for moderate cognitive impairment (MCI). PD and AD may not develop or advance as quickly if neuroprotective foods are consumed early and consistently. The promotion of brain health throughout the lifetime should be emphasized in public health programs [74].

PERSPECTIVES AND FUTURE DIRECTIONS

• Standardization of Formulations: To guarantee repeatability and clinical dependability, future research must employ nutraceutical formulations that have been well described and standardized [75].
• Large-Scale Randomized Trials: To confirm cognitive advantages and reduce placebo effects shown in small-scale investigations, more thorough, multicenter randomized controlled trials are required [76,77].
• Personalized Approaches: Based on genetics, gut microbiota, metabolic state, and illness stage, research should examine how each person responds differently to nutraceuticals [78,79].
• Synergistic Combinations: For improved therapeutic efficacy, future studies should evaluate the synergistic effects of mixing nutraceuticals with other nutraceuticals or with traditional medications [75].
• Long-Term Safety and Regulatory Oversight: To encourage clinical adoption, safety profiles for prolonged use and improved regulatory frameworks for product quality control must be created [75].
• Mechanistic Exploration: To connect molecular targets with cognitive results, further in-depth mechanistic insights are still required, especially for chemicals that have received less attention [80].

CONCLUSION

The growing body of scientific research emphasizes the medicinal efficacy of nutraceuticals for the therapy of cognitive disorders, including memory impairment and neurodegenerative diseases. Several processes, including neuroprotective, anti-inflammatory, neurotransmitter-modulating, & antioxidant, are demonstrated by these naturally occurring chemicals, supporting their use in cognitive healthcare. The overall clinical data is still ambiguous, despite encouraging results from preclinical research and a few clinical trials. Small sample numbers, brief study periods, and inconsistent methodology are the main drawbacks of many human research. The kinds of nutraceuticals employed, their doses, formulations, treatment durations, and the populations under study all vary greatly. It is challenging to generalize the results across various clinical contexts due to this heterogeneity, which also adds to conflicting results.
Therefore, regular use of nutraceuticals in clinical practice should be supported by more robust, high-quality data, even if they may be useful adjuncts or preventative measures in cognitive health. Large-scale, well planned randomized controlled trials with validated outcome measures and uniform formulations are required. To allow for more individualized methods, these studies should also take individual variations in metabolism, gut microbiota, genetics, and illness development into account.
In conclusion, using nutraceuticals for preventing and treating of cognitive decline is a promising but still developing field. Better standardization and more thorough clinical validation might make them an important part of integrative approaches to managing neurodegenerative diseases.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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