RESEARCH PAPER

Neuronutrition and Dietary Supplements: Mechanisms, Clinical Evidence, and Potential for Cognitive Enhancement

[1] Bidya Kumari, [2] Prof. J.S. Tripathi, [3] Sweta Maurya

[1] PhD Scholar, Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005. E-Mail: gudiabidya1234@gmail.com

[2] Professor, Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005. E-Mail: drjstripathi@rediffmail.com

[3] PhD Scholar, Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005. E-Mail: msweta2107@bhu.ac.in

Corresponding Author: Sweta Maurya

PhD Scholar, Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005. E-Mail: msweta2107@bhu.ac.in

Abstract

Background: Neuronutrition the study of how diet and specific nutrients influence brain structure and function has become a prominent focus of translational neuroscience, driven by population aging, rising rates of cognitive impairment, and consumer interest in cognitive enhancement products.

Objectives: This review synthesizes mechanistic and clinical evidence on dietary nutrients and supplements proposed to influence neurotransmission, neuroplasticity, neuroinflammation, and cognition, and evaluates their potential for cognitive enhancement across healthy and clinical populations.

Methods: Evidence was drawn from systematic reviews, meta-analyses, randomized controlled trials (RCTs), and large prospective cohort studies identified through PubMed/MEDLINE, Scopus, Web of Science, Semantic Scholar, Google Scholar and related databases, with an emphasis on literature from 2014–2026.

Findings: Evidence is strongest, though still modest in magnitude, for omega-3 fatty acids in individuals with low baseline status, for flavonoid-rich dietary patterns in relation to long-term dementia risk, and for correcting frank nutrient deficiencies (B12, folate, vitamin D) in deficient individuals. Evidence for most isolated supplements in nutritionally replete, healthy adults including B vitamin complexes, ginkgo biloba, creatine, and most nootropic botanicals, is inconsistent, of low certainty, or shows benefit only in narrow subgroups or cognitive domains.

Conclusion: Neuronutrition offers biologically plausible and, for specific deficiency states, clinically meaningful pathways to support brain health, but current evidence does not support dietary supplements as reliable, general-purpose cognitive enhancers in nutritionally replete individuals. A balanced, nutrientdense dietary pattern remains the best-supported nutritional strategy for long-term brain health.

Keywords: neuronutrition; dietary supplements; cognitive enhancement; nutraceuticals; cognitive decline; brain health

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1. Introduction

Neuronutrition is the interdisciplinary study of how dietary patterns, individual nutrients, and bioactive non-nutrient compounds affect the structure, biochemistry, and function of the nervous system across the lifespan [1,2]. It sits at the intersection of nutritional science, neurobiology, and clinical cognitive medicine. Although the brain is protected by the blood-brain barrier [3], it accounts for roughly 20% of the body's energy expenditure [4] and depends on a continuous supply of substrates, cofactors, and structural lipids that must come from the diet. It is therefore highly sensitive to nutrient availability, dietary pattern, and metabolic health [1,2].

The clinical urgency stems from the growing global burden of cognitive decline. An estimated 57 million people were living with dementia in 2019, a figure projected to reach about 153 million by 2050 [5]. Age-related cognitive impairment, mild cognitive impairment (MCI), and dementia, including Alzheimer's disease, are leading causes of disability and dependence in older adults. Anti-amyloid antibodies (lecanemab and donanemab) are now approved for early symptomatic Alzheimer's disease, but they produce only modest average slowing of decline and carry a risk of amyloid-related imaging abnormalities [6,7]. No therapy cures or reverses most dementia subtypes, so attention has shifted toward prevention. The 2024 Lancet Commission estimated that about 45% of dementia cases could theoretically be prevented or delayed by addressing 14 modifiable risk factors, several of which

(hypertension, diabetes, obesity, high LDL cholesterol) are diet-sensitive [8,9]. Multidomain lifestyle trials that include dietary components have improved cognition in at-risk older adults [10], and in the US POINTER trial a structured multidomain program produced greater global cognitive gains than a self-guided version, although both groups improved [11]. Such trials cannot, however, isolate the contribution of nutrition itself.

At the same time, consumer demand for "brain health" and "cognitive enhancement" products has expanded. About half of US adults reported using a dietary supplement in 2011-2012 [12], and marketed claims for memory supplements frequently outpace the evidence [13]. Systematic reviews of over-the-counter supplements have found little convincing evidence that they prevent cognitive decline or dementia [14], and strong observational associations for single nutrients have often not been reproduced in randomized trials [15]. Interpreting this literature requires distinguishing three questions: whether correcting a deficiency protects the brain, whether supplementation helps people who are at risk or already impaired, and whether it enhances cognition in healthy, nutritionally replete adults [16].

This narrative, evidence-graded review has three objectives: (1) to synthesize the principal neurobiological mechanisms by which nutrition is hypothesized to influence brain function (Section 2); (2) to critically synthesize clinical evidence for key nutrients, botanicals, and nutraceuticals across cognitive domains and populations (Sections 3-5); and (3) to provide a balanced conclusion that distinguishes established benefit, promising but unconfirmed benefit, and insufficient or null evidence (Section 9), while addressing methodological limitations (Section 6), safety (Section 7), and precision approaches and research priorities (Sections 6 and 8). The primary outcomes are cognitive; mood and neurodevelopment are discussed only where they inform mechanisms or interpretation. The review avoids promotional framing and aims to give clinicians, researchers, and informed consumers a realistic picture of what neuronutrition can and cannot currently deliver.

2. Neurobiological Mechanisms of Neuronutrition

Several interconnected biological pathways underlie the hypothesized links between diet and cognition. These mechanisms are largely derived from preclinical and translational neuroscience and provide biological plausibility for but do not by themselves prove clinical efficacy of specific nutrients or supplements.

I. Neurotransmitter synthesis and regulation

Several neurotransmitters are synthesized from dietary precursors: tyrosine for dopamine and norepinephrine, tryptophan for serotonin, and choline for acetylcholine. The link between precursor intake and neurotransmitter synthesis is, however, conditional rather than linear. Tryptophan and tyrosine enter the brain through a shared, competitive large neutral amino acid transporter, so brain uptake depends on their plasma ratio to competing amino acids rather than on absolute intake [17]. Serotonin synthesis is far more responsive to this ratio than catecholamine synthesis [17], and tyrosine supplementation has shown cognitive benefit mainly when dopamine or norepinephrine is transiently depleted, for example by acute stress or high cognitive demand [18]. Choline differs in that choline acetyltransferase is thought to be unsaturated with its substrates, so choline availability can limit acetylcholine synthesis, with membrane choline-phospholipids serving as an additional precursor pool [19]. B vitamins act as cofactors at several points in these pathways, but not interchangeably. Vitamin B6 (as pyridoxal phosphate) is the cofactor for aromatic L-amino acid decarboxylase, which catalyzes the final step of dopamine and serotonin synthesis [20]. Folate (B9) and vitamin B12 act indirectly through one-carbon metabolism, which supplies S-adenosylmethionine for methylation reactions relevant to neuronal signaling, including catecholamine catabolism by COMT [20]. Folate-dependent pathways may also support regeneration of tetrahydrobiopterin (BH4), the essential cofactor for tyrosine and tryptophan hydroxylase, although this link needs further confirmation [21]. Because choline, folate, and methionine metabolism are interrelated, the requirement for each cannot be considered in isolation [22].

II. Neuroplasticity and synaptic function

Synaptic plasticity, the structural and functional remodelling of synapses that underlies learning and memory [23], depends on membrane phospholipid composition, adequate energy substrate delivery, and intact signalling cascades. DHA is an abundant fatty acid in brain phospholipids and a major structural component of neuronal membranes [24,25]. The brain cannot synthesize it de novo and must import it across the blood–brain barrier, principally via the MFSD2A transporter as lysophosphatidylcholine [24]. In preclinical models, DHA and its metabolites are proposed to support neurite outgrowth and synaptogenesis, for example through synaptamide signalling at the GPR110 receptor [26]. The phosphatide precursors DHA, uridine, and choline raise brain phosphatide and synaptic protein levels in rodents [27]. Because most brain energy is consumed at synapses, plasticity is also sensitive to the adequacy of energy supply [28]. Neurotrophin pathways such as BDNF–TrkB (see

below) are thought to integrate these inputs [29]. Most of this evidence, however, derives from developing or deficient animals and in vitro systems. Whether nutritional supplementation enhances synaptic plasticity in healthy adult humans remains largely untested directly, and the clinical evidence is reviewed in later sections.

III. Brain-derived neurotrophic factor (BDNF)

BDNF, signaling mainly through TrkB receptors, supports neuronal survival, synaptogenesis, and activity-dependent synaptic plasticity. It also supports hippocampal neurogenesis in rodents, although whether adult hippocampal neurogenesis occurs to a meaningful extent in humans remains debated BDNF expression is modulated by diet quality, caloric balance, and physical activity, the last with the most consistent human evidence In rats, a diet high in saturated fat and refined sugar reduced hippocampal BDNF and impaired spatial learning within two months Several bioactive dietary compounds have been proposed to upregulate BDNF, based on animal data for omega-3 fatty acids and flavonoid-rich foods Human evidence is limited to peripheral (mainly serum) BDNF and is inconsistent. A systematic review found positive signals for dietary patterns, foods, and polyphenols but no clear effect for most other factors, including omega-3 Small RCTs of flavonoid-rich foods and cocoa flavanols reported rises in serum BDNF alongside cognitive gains, and a later meta-analysis reported a small, heterogeneous increase with omega-3 supplementation These findings are difficult to interpret because blood BDNF correlates only moderately with brain levels in animals and has peripheral sources Changes in serum BDNF therefore cannot be taken as evidence of altered brain BDNF signaling or of clinically meaningful cognitive benefit.

IV. Neuroinflammation ⚠ ***citations unmatched see Unmatched/Uncertain Report***

Chronic low-grade neuroinflammation, involving glial reactivity and pro-inflammatory cytokine signalling, is implicated in both normal cognitive aging and neurodegenerative disease Microglial responses are heterogeneous and context-dependent, so the older "activated" M1/M2 dichotomy is no longer considered an adequate description Peripheral inflammation can also shape central immune tone, for example by priming microglia, which offers a route by which diet-related systemic inflammation could affect the brain Diet is proposed to modulate systemic and central inflammation through fatty acid composition, polyphenol intake, and gut microbiota-derived metabolites. Long-chain omega-3 fatty acids (EPA and DHA) attenuate inflammatory signalling and give rise to pro-resolving mediators By contrast, the idea that a high omega-6: omega-3 ratio is itself pro-inflammatory is contested: RCTs in healthy adults have not shown that dietary linoleic acid raises circulating inflammatory markers, and absolute omega-3 status may be the more informative variable Polyphenols and their microbial metabolites modulate inflammatory signalling and microglial responses in vitro, but whether they reach active concentrations in the human brain remains unresolved Gut-derived short-chain fatty acids regulate microglial maturation and function in rodents, although their effects are context-dependent and direct human evidence is limited. Most of this evidence is preclinical, and human neuroinflammation is difficult to measure: TSPO-PET, the most widely used imaging marker, appears to reflect microglial density rather than activation state in humans.

V. Oxidative stress and antioxidant defence

The brain's high oxygen consumption, PUFA-rich membranes, redox-active transition metals, and relatively limited endogenous antioxidant capacity make it vulnerable to oxidative damage, which accumulates with age and contributes to neurodegenerative pathology [30,31]. Dietary antioxidants (vitamins C and E, carotenoids, polyphenols) are hypothesized to mitigate this damage. However, clinical trial evidence for antioxidant supplementation improving cognition has generally been weaker than observational associations would predict: prevention and MCI trials have largely been null [32,33,34], and benefits reported in established Alzheimer's disease were limited to functional outcomes [35,36]. This gap has prompted a reassessment of mechanism. Current thinking favors indirect, hormetic effects, such as Nrf2 activation, over direct radical scavenging, given kinetic constraints on scavenging in vivo and the low plasma concentrations and extensive metabolism of polyphenols [37,38]. Whether polyphenol metabolites reach the brain at active concentrations remains unresolved [39,40]. High-dose antioxidants may also blunt adaptive redox signalling, although the supporting evidence derives mainly from exercise studies in peripheral tissues [41,42].

VI. Mitochondrial function and cellular energy metabolism

Neurons are highly energy-dependent: the brain accounts for roughly 20% of basal oxygen consumption, most of it devoted to synaptic signalling and the restoration of ion gradients Mitochondrial dysfunction is a feature of ageing and neurodegenerative disease, although whether it is a cause or a consequence of pathology remains debated Nutrients and compounds involved in cellular

bioenergetics, including creatine/phosphocreatine, B vitamins, coenzyme Q10 (CoQ10), and acetyl-L-carnitine (ALCAR), are proposed to support neuronal energy supply, but clinical effects on cognition are inconsistent (see Sections 5–6). Creatine has the most encouraging data: meta-analyses of RCTs in healthy adults report modest memory benefits, particularly in older adults, with little effect in young adults and conflicting results in other domains B vitamins act as cofactors in energy metabolism (e.g., thiamine in pyruvate dehydrogenase, niacin as the NAD^+ precursor), but clinical trials have mainly tested homocysteine lowering rather than bioenergetic function, with mixed cognitive results For CoQ10, a large phase III trial in early Parkinson's disease showed no clinical benefit, and cognition-specific RCTs are lacking. For ALCAR, an early meta-analysis favoured treatment in MCI and mild Alzheimer's disease, but a Cochrane review found no evidence of benefit in dementia.

VII. Gut-brain axis and microbiota

Bidirectional neural (vagal), endocrine, and immune signaling connects the gut microbiome to the central nervous system [43,44,45]. Microbial metabolites (e.g., short-chain fatty acids) and microbiota-driven modulation of systemic inflammation and neurotransmitter precursor availability are proposed mechanisms by which diet and probiotic supplementation could influence mood and cognition [46,47,48,49]. Supporting evidence includes vagus-dependent behavioral effects of Lactobacillus in mice [50], microbial regulation of microglial maturation [51] and host serotonin synthesis [52], and associations between specific taxa and depression in human cohorts [53]. However, much of the mechanistic evidence comes from germ-free or gnotobiotic rodents, and human interventional data remain limited. Probiotic trials show small, strain-specific effects on mood, stress, and brain activity [54,55,56], whereas cognitive outcomes in healthy adults are far less established. Whether microbiota changes are a cause or a consequence of the conditions studied is still unresolved [45,57].

VIII. Cerebrovascular function

Adequate cerebral blood flow and vascular endothelial health support nutrient and oxygen delivery to the brain through neurovascular coupling, the matching of local blood flow to neuronal activity, which is impaired by hypertension, ageing, and endothelial dysfunction [58,59,60]. Nutrients affecting vascular function (omega-3 fatty acids, flavonoids, and B vitamins via homocysteine lowering) have been hypothesized to protect cognition partly through vascular mechanisms, which is particularly relevant to vascular cognitive impairment. Flavan-3-ols from cocoa improve endothelial function by increasing nitric oxide bioavailability [61], and a dietary flavanol intervention increased dentate gyrus cerebral blood volume and improved memory performance in older adults [62]. Higher long-chain omega-3 status has been associated with better white matter integrity and brain structure, and DHA-rich fish oil altered the cerebral hemodynamic response to cognitive tasks in young adults [63,64,65]. However, large trials of omega-3 supplementation have not shown cognitive benefit in older adults [66]. Homocysteine is an established vascular risk marker, and B-vitamin supplementation lowers it reliably, but meta-analyses of randomized trials show no consistent cognitive benefit [67,68]. Benefits on brain atrophy rate appear to be restricted to people with elevated homocysteine and adequate omega-3 status [69,70], and in cardiovascular disease populations homocysteine lowering did not improve outcomes [71]. These findings suggest that vascular mechanisms are biologically plausible but that effects depend on baseline nutritional status and risk profile.

IX. HPA axis and stress regulation

Chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and sustained cortisol elevation can impair hippocampal structure and memory function [72,73]. In older adults, higher and more prolonged cortisol exposure has been associated with hippocampal atrophy and poorer memory [74], and experimentally elevated cortisol impairs declarative memory in healthy adults [75]. The effect is non-linear: acute, moderate glucocorticoid elevation can facilitate memory consolidation, whereas chronic or excessive exposure is detrimental [72,73]. Certain nutrients and plant-derived compounds are proposed to modulate stress reactivity, which may indirectly support cognitive performance under stress. L-theanine reduced heart-rate and salivary IgA responses to an acute mental stressor [76], and a randomized trial in healthy adults reported improved stress-related symptoms, sleep, and executive function [77], although systematic review evidence is limited by small samples and heterogeneous outcomes [78]. Combined with caffeine, it improved attention-switching accuracy [79]. Among adaptogenic botanicals, standardized ashwagandha (Withania somnifera) root extracts reduced perceived stress and serum cortisol in randomized trials [80,81], and systematic review evidence suggests anxiolytic benefit [82]. Mechanistic claims for adaptogens remain largely preclinical [83]. Overall, human trials are short and small, often industry-funded, and rarely measure cognition directly, so effects on cognitive performance under stress should be regarded as hypothesis-generating.

X. Epigenetic and metabolic mechanisms

Nutrients involved in one-carbon metabolism (folate, B12, choline) supply methyl donors for DNA methylation, which can influence gene expression relevant to neuronal development and plasticity [84,85,86]. The strongest evidence for diet-related epigenetic programming comes from prenatal and early-life exposures [87,88]; whether adult supplementation produces functionally meaningful methylation changes in the brain is far less established. Consistent with this, B-vitamin supplementation lowers homocysteine and slowed brain atrophy in MCI, particularly in people with elevated baseline homocysteine [69,70], but meta-analyses of randomized trials show no clear benefit on cognitive function [67,89]. Metabolic health more broadly (insulin sensitivity, glycemic control) is increasingly recognized as a determinant of long-term brain health [90,91,92], reflected in the designation of Alzheimer's disease by some researchers as having a metabolic component [93,94]. Supporting this view, higher glucose levels are associated with increased dementia risk even in people without diabetes [91], and a multidomain lifestyle intervention that included dietary and metabolic targets improved cognition in at-risk older adults [10]. Evidence for causality remains incomplete, and the "type 3 diabetes" label is a conceptual framing rather than an established diagnosis [93,95].

It is important to emphasize that most of this mechanistic evidence derives from cell and animal models; translation to measurable, clinically meaningful cognitive benefit in humans is the central question addressed in the remainder of this review.

3. Key Nutrients and Bioactive Compounds

Nutrient/Compound	Sources	Proposed Mechanism/Role	Notes
Omega-3 fatty acids (EPA/DHA)	Fatty fish, algae-derived supplements	Membrane fluidity, anti-inflammatory eicosanoid signaling, support of synaptic plasticity	DHA is a major structural lipid in neuronal membranes, concentrated in synaptic regions
B vitamins (B6, B9/folate, B12)	Varied dietary sources	Cofactors in neurotransmitter synthesis and homocysteine metabolism	Deficiency is an established, correctable cause of cognitive impairment, particularly in older adults with malabsorption or inadequate intake
Vitamin D	Sun exposure, fortified foods, supplements	Direct neurotrophic role via receptors and activating enzyme expressed in memory/executive function regions (notably hippocampus)	Deficiency common in older adults, especially at higher latitudes and with reduced sun exposure
Magnesium	Varied dietary sources	NMDA-receptor regulation, synaptic plasticity, cofactor in 300+ enzymatic reactions	Preclinical work links magnesium status to synaptic density and learning; large confirmatory human trials limited
Zinc and iron	Varied dietary sources	Essential trace elements for neurodevelopment and neurotransmitter	Deficiency states (e.g., iron-deficiency anemia in children and pregnant

Nutrient/Compound	Sources	Proposed Mechanism/Role	Notes
		metabolism	women) linked to impaired cognitive development; relevance of supplementation above adequate intake in replete adults unclear
Choline	Varied dietary sources	Precursor for acetylcholine and membrane phospholipids	Intake often below recommended levels in Western diets; adequate maternal intake important for fetal brain development; evidence for supplementation in non-deficient adults limited
Polyphenols and flavonoids	Berries, tea, cocoa, many fruits and vegetables	Antioxidant, anti-inflammatory, vascular mechanisms; possible direct signaling effects on neuronal plasticity	Large, chemically diverse class (flavonols, anthocyanins, flavan-3-ols, flavones)
		pathways	
Carotenoids (lutein, zeaxanthin)	Varied dietary sources	Antioxidant and anti-inflammatory roles	Concentrated in retina and, to a lesser extent, brain tissue; some observational evidence links status to cognitive performance, but RCT evidence for cognition specifically is limited

4. Dietary Supplements and Cognitive Enhancement

Cognitive-enhancement supplements span categories that differ substantially in evidence and regulatory status. In the United States they are regulated as foods rather than drugs, so efficacy is not demonstrated before marketing and quality problems are documented [96,97,98]. Essential nutrients at high or replacement doses (B-complex, omega-3, vitamin D) benefit deficient individuals but not replete adults (Section 3). Herbal preparations show weak evidence: ginkgo biloba was null in large long-term RCTs [99,100] (a third supporting RCT reference could not be matched in the supplied bibliography and is flagged below), bacopa monnieri showed modest benefits in small trials [101,102], and panax ginseng evidence is mixed Nutraceuticals such as curcumin, citicoline, and phosphatidylserine show short-term benefits in small trials (curcumin: [103]; citicoline and phosphatidylserine:), whereas resveratrol was null in Alzheimer's disease Among metabolic compounds, caffeine reliably improves alertness and attention, creatine may aid memory and reasoning [104,105], and acetyl-L-carnitine shows

small benefits in mild cognitive impairment L-theanine improves attention mainly in combination with caffeine [106,107]. Commercial "stacks" are rarely tested as a whole, making it difficult to attribute effects to specific ingredients or doses.

Category	Examples	Notes
Essential nutrients at supraphysiological/targeted-replacement doses	High-dose B-complex, omega-3 concentrates, vitamin D	Doses above typical dietary intake, often aimed at correcting deficiency
Herbal/botanical preparations	Ginkgo biloba, bacopa monnieri, panax ginseng	Plant-derived preparations
Nutraceuticals and bioactive isolates	Curcumin, citicoline, phosphatidylserine, resveratrol	Isolated bioactive compounds
Performance/energy-metabolism compounds	Creatine, caffeine, acetyl-L-carnitine	—
Amino acid/mood-modulating compounds	L-theanine	—
Commercially marketed "stacks"	Combinations of the above	Rarely tested as a whole in rigorous clinical trials, making it difficult to attribute observed effects to specific ingredients or doses

5. Clinical Evidence for Cognitive Outcomes

5.1 Omega-3 fatty acids

Evidence for omega-3 supplementation and cognition is heterogeneous and dose- and population-dependent. A 2024 dose-response meta-analysis of 24 RCTs (n=9,660) in middle-aged and older adults without dementia found a beneficial effect on executive function that strengthened within the first 12 months of supplementation, particularly among individuals whose blood DHA+EPA levels were not already low-normal [108]. An earlier meta-analysis restricted to low-dose regimens (<1.73 g/day) found a modest reduction in the rate of cognitive decline, while higher doses showed no benefit, suggesting a nonlinear dose relationship [109]. A 2023 meta-analysis focused on older adults with mild cognitive impairment (12 RCTs, 1,124 participants, DHA doses of 800-2,000 mg/day) found a moderate improvement in global cognitive function relative to control [110]. A separate 2023 meta-analysis reported that overall pooled effects on MMSE scores were not significant, but that higher baseline omega-3 index and larger increases in omega-3 index were associated with cognitive benefit, reinforcing that baseline status moderates response [111]. By contrast, a widely cited 2014 lifespan meta-analysis found that omega-3 supplementation improved cognitive development in infants but did not improve memory, executive function, or processing speed in children, healthy adults, or the elderly, with a possible exception for attention [112]. A 2025 dose-response meta-analysis concluded that omega-3 supplementation produces only a modest improvement in adult cognitive function overall, with nonlinear dose-response curves across domains, and called for longer, better-designed trials [113].

Omega-3 supplementation shows the most consistent (though still modest) benefit for executive function and global cognition in older adults with MCI or low baseline omega-3 status; benefit in cognitively healthy, nutritionally replete adults is weak or absent.

5.2 B vitamins (folate, B6, B12) and homocysteine lowering

Results are strongly dependent on population and outcome measure. A meta-analysis of 21 RCTs (n=7,571) in elderly adults reported that B-vitamin supplementation modestly delayed or maintained

cognitive decline on composite measures, improving global cognition scores without significant effects on specific subdomains (processing speed, episodic memory, executive function) [114]. In contrast, the B-Vitamin Treatment Trialists' Collaboration individual participant data meta-analysis of 11 large trials (n=22,000) found that although B-vitamin supplementation lowered homocysteine by roughly a quarter, it produced no significant effect on global cognitive function or on individual cognitive domains [67]. An earlier meta-analysis of 19 RCTs similarly found no significant improvement in cognitive function for individuals with or without baseline cognitive impairment [115]. In the large VITATOPS trial of patients with prior stroke or transient ischemic attack (n=8,164), B-vitamin supplementation lowered homocysteine but did not reduce the incidence of cognitive impairment or decline over a median follow-up of 2.8 years [116]. Subgroup findings across these studies suggest that benefit, where observed, is concentrated in individuals with elevated baseline homocysteine or low baseline B-vitamin status, rather than in nutritionally replete populations.
B-vitamin supplementation reliably lowers homocysteine but has not been shown to produce a clinically meaningful, consistent improvement in cognition in large, well-controlled trials, except possibly in deficient subgroups.

5.3 Vitamin D

Observational evidence consistently links low vitamin D status to worse cognitive performance and greater risk of cognitive decline (pooled odds ratios in the range of 1.2-1.3 in a 2017 meta-analysis of 26 observational and 3 intervention studies) [117]. However, the same review noted that interventional (supplementation) studies had not yet demonstrated a clear cognitive benefit [117]. A more recent meta-analysis of year-long-or-longer intervention studies reported a statistically significant improvement in global cognitive function with vitamin D supplementation (based on only 4 studies, ~4,593 participants, rated low certainty evidence) [118]. Conversely, the VitaMIND RCT, a 24-month trial in 620 older adults with mild to moderate vitamin D deficiency and early cognitive impairment, found no significant benefit of supplementation on executive function or broader cognitive, functional, or well-being outcomes [119].

Low vitamin D status is an observational risk marker for cognitive decline, but randomized evidence that correcting deficiency reliably improves cognition remains inconsistent and of low certainty.

5.4 Creatine

A 2024 systematic review and meta-analysis (16 RCTs, 492 participants aged 20.8-76.4 years) found that creatine monohydrate supplementation produced significant improvements in memory, attention time, and information-processing speed, but no significant improvement in overall cognitive function or executive function; evidence for the domains that did improve was rated low certainty [104]. Subgroup analysis suggested more robust benefit in individuals with underlying medical conditions and in adults aged 18-60 relative to those over 60 [104]. A separate 2023 meta-analysis of 8 RCTs reported a beneficial effect of creatine on memory performance in healthy individuals, with effects more pronounced in older adults [105]. Notably, in 2024 the European Food Safety Authority's Panel on Nutrition concluded that a cause-and-effect relationship between creatine supplementation and improved cognitive function could not be established from the available evidence, underscoring the gap between promising signals and regulatory-grade proof [120].

Creatine shows a plausible, domain-specific (memory, processing speed) signal, particularly under metabolic stress or in clinical populations, but evidence for global cognitive enhancement in healthy adults remains preliminary.

5.5 Caffeine and L-theanine

Several small, well-controlled crossover trials in healthy adults have found that the combination of moderate-dose caffeine (40-50 mg) and L-theanine (97-100 mg) improves accuracy and speed on attention-switching tasks and subjective alertness more than either compound alone, with reduced susceptibility to distracting information [106,107]. Effects appear concentrated in sustained-attention and task-switching domains rather than broader cognitive measures such as reasoning or working memory capacity. Exploratory pediatric crossover work in children with ADHD has found that the combination may improve sustained attention and reduce impulsivity relative to either compound alone or placebo, though these studies have very small samples and require replication.
Caffeine plus L-theanine has among the more consistent acute evidence bases for a narrow cognitive benefit (attention, alertness) in healthy adults, though effects are modest, time-limited, and not demonstrated for long-term cognitive health.

5.6 Ginkgo biloba

Ginkgo is among the most extensively studied cognitive enhancement botanicals. Successive Cochrane systematic reviews (the most recent update searching through December 2022 and covering subjective cognitive complaints, MCI, and dementia populations) have consistently concluded that there is no convincing evidence that ginkgo biloba produces a predictable, clinically significant benefit for people with dementia or cognitive impairment [100,99]; the

four most recent and largest trials at the time of the original review found no difference from placebo, with only one earlier trial showing large effects, raising concerns about publication bias and small-study effects [99]. Ginkgo has, however, consistently shown an acceptable safety profile relative to placebo.

Ginkgo biloba does not have reliable support for improving cognition or slowing decline in dementia or MCI populations, despite decades of study.

5.7 Curcumin

An updated 2025 meta-analysis of RCTs found that curcumin supplementation significantly improved global cognitive function compared with placebo (standardised mean difference 0.82, 95% CI 0.19-1.45), with the strongest effects observed at a dose of approximately 0.8 g/day sustained for 24 weeks or longer [103]; this built on two earlier (2019, 2021) meta-analyses that had reached less consistent conclusions Mechanistically, curcumin has been shown in preclinical models to reduce amyloid aggregation, though confirmed clinical translation of this specific mechanism in humans is lacking.

Curcumin shows an encouraging and strengthening evidence base for global cognition, though trial numbers remain modest and bioavailability (curcumin is poorly absorbed without enhanced formulations) is a recognized methodological complication.

5.8 Bacopa monnieri

A widely cited meta-analysis of RCTs using chronic dosing (>=12 weeks) of standardized Bacopa monnieri extract (437 participants) found improved performance on measures of attention speed (shortened Trail Making Test B time, reduced choice reaction time) [101], while a separate systematic review found improvement specifically in memory free recall (9 of 17 relevant tests), with little consistent evidence for other cognitive domains [102]. Both reviews emphasized the need for larger, head-to-head trials against standardized comparators.

Bacopa monnieri has among the more consistent signals of any single botanical for memory and attention speed, though the evidence base remains limited in trial size and domain breadth.

5.9 Phosphatidylserine, citicoline, and acetyl-L-carnitine

Phosphatidylserine and citicoline are frequently marketed cognitive support nutraceuticals with biologically plausible roles in membrane phospholipid metabolism and cholinergic/mitochondrial support, respectively. Available trial evidence for both compounds in healthy adults is limited to small, often industry-associated studies; larger-scale, independently conducted RCT evidence comparable in rigor to the omega-3 or curcumin literature is not yet established, and claims for either compound should currently be regarded as preliminary rather than confirmed Acetyl-L-carnitine has shown some benefit in clinical populations with mild cognitive impairment or early dementia in smaller trials, but systematic, high-quality meta-analytic support in healthy adults is similarly limited.

5.10 Polyphenols and flavonoids (dietary and supplemental)

The strongest evidence for flavonoids comes from long-term observational cohorts rather than short-term supplementation RCTs [121,122]. A systematic review and meta-analysis of 37 observational studies found that higher dietary flavonoid intake was associated with reduced risk of cognitive impairment and dementia (relative risk 0.83 for total flavonoids, with similarly protective associations for anthocyanins, flavones, flavan-3-ols, and flavonols) [121]. The Framingham Heart Study Offspring Cohort similarly found that higher intake of flavonols, anthocyanins, and flavonoid polymers was associated with lower risk of Alzheimer disease and related dementias over long follow-up [123], and the Rush Memory and Aging Project cohort found that individuals in the highest quintile of certain flavonol subclasses had a substantially reduced rate of incident Alzheimer dementia relative to the lowest quintile [124]. These associations, drawn from populations consuming flavonoids through whole foods (berries, tea, leafy vegetables) over years to decades, do not establish that short-term flavonoid supplementation produces comparable benefit, and residual confounding by overall diet quality and lifestyle cannot be excluded.

5.11 Gut-brain axis: probiotics

A 2025 meta-analysis of 34 RCTs (2,390 participants) found that probiotic supplementation was associated with improved cognitive function, particularly after 12 weeks of use, on measures such as the Montreal Cognitive Assessment, though the certainty of evidence was rated low to very low [125]. A separate 2025 meta-analysis restricted to patients with diagnosed cognitive impairment (10 studies, 778 patients) found a moderate, statistically significant improvement in cognitive function with probiotic supplementation (standardised mean difference 0.52) [126]. Findings across the broader probiotic-cognition literature remain inconsistent between individual meta-analyses, and strain, dose, and duration vary considerably across studies, limiting generalizable dosing guidance.

5.12 Cognitive Supplement Signals by Domain

Cognitive Domain	Supplements with Signal	Notes
Memory	Creatine, Bacopa monnieri, Omega-3 (in MCI)	Most frequent positive signals; effect sizes generally small to moderate
Attention / Processing Speed	Caffeine + L-theanine (acute); some signal with Creatine, Bacopa	Caffeine + L-theanine combination shows most consistent response
Executive Function	Omega-3 fatty acids	Modest, dose- and population-dependent benefit; inconsistent results from most other compounds
Global Cognitive Function	Curcumin; Omega-3 and Vitamin D (in deficient/MCI populations); Probiotics (in impaired populations)	Strongest supplement signals in this domain
Mood / Psychological Wellbeing	Omega-3 (alongside cognitive outcomes in MCI trials); gut-microbiota-targeted interventions (mechanistically plausible)	Review focused primarily on cognitive rather than mood endpoints
Age-Related Decline / MCI / Dementia Outcomes	-	Generally larger relative effect sizes than in cognitively healthy adults - consistent with a "floor effect," where nutritional correction matters most when baseline status is suboptimal or pathology is already present

6. Critical Evaluation of the Evidence

Several methodological issues recur across this literature and warrant explicit caution.

- **Sample size and statistical power:** Many supplement trials, particularly for botanicals such as Bacopa and nutraceuticals such as citicoline, are small, often with fewer than 100 participants per arm. Underpowered studies risk false-negative results. They also lower the probability that a statistically significant finding reflects a true effect, and they tend to overestimate effect sizes when they do reach significance [127,128].
- **Study duration:** If nutritional interventions affect cognition, the effects plausibly take months to years to emerge, especially for neurodegenerative outcomes. Many RCTs last only 8-24 weeks. This may suffice for acute attentional effects (e.g., caffeine with L-theanine) but is inadequate for disease-modifying claims. Even multi-year trials, such as the 3-year MAPT omega-3 trial, have been largely null in unselected older adults [66].
- **Dosage variability:** For several compounds, dose-response relationships appear nonlinear, threshold-dependent, or inseparable from baseline status [112,129]. Pooling studies that combine different doses, formulations (e.g., EPA- versus DHA-predominant omega-3), and populations can obscure a true effect within an optimal range. For other compounds, such as creatine, curcumin, and Bacopa, dose-response relationships are poorly characterized rather than established, so this limitation reflects missing data as much as demonstrated nonlinearity.
- **Baseline nutritional status:** Subgroup analyses (omega-3 index, baseline homocysteine or vitamin D, presence of MCI) repeatedly suggest that benefit is concentrated in people who are deficient or impaired at baseline, while replete healthy adults show little or no measurable benefit [69,129,130]. This is among the most consistent patterns in the literature, but it should be interpreted cautiously: such subgroup findings are often post hoc,

underpowered, and prone to false positives unless prespecified and replicated [131]. Trials that enroll participants regardless of baseline status may dilute a real effect in the deficient minority, which argues for biomarker-stratified enrolment in future studies [129].

- **Bioavailability:** Several compounds, notably curcumin, have poor native bioavailability [132]. Studies using unenhanced formulations may therefore underestimate biological potential, whereas studies using proprietary enhanced formulations, such as the bioavailable curcumin used in the 18-month trial by Small et al. [133], may not generalize to standard over-the-counter products.
- **Heterogeneity of cognitive assessment:** Trials use a wide range of instruments, including the MMSE, MoCA, domain-specific neuropsychological batteries, and computerized tasks. These differ in sensitivity, ceiling and floor effects (the MMSE, for example, is relatively insensitive in mild impairment), and clinical meaningfulness [134,135]. This complicates cross-study comparison and meta-analytic pooling, and most trials do not define a minimal clinically important difference.
- **Publication and small-study bias:** The ginkgo biloba literature is a well-known example: small early trials reported benefits that were not replicated in larger, more rigorous trials, a pattern consistent with publication and small-study bias [99]. Funnel-plot asymmetry tests can help detect this, though they have limited power when few studies are available [136].
- **Additional limitations:** Selective outcome reporting and multiple testing across numerous cognitive endpoints can inflate apparent effects when primary outcomes are not prespecified [137]. Industry sponsorship is associated with more favorable conclusions in the broader trial literature [138]. Product quality and standardization also vary, with documented contamination, substitution, and label inaccuracy in herbal supplements, which undermines reproducibility across trials [96,97].
- **Implications:** Taken together, the evidence is most consistent for correcting deficiency and weakest for enhancement in replete adults. Future work should favor larger, longer, preregistered RCTs with prespecified primary cognitive outcomes, standardized core test batteries, biomarker-stratified enrolment (e.g., omega-3 index, homocysteine, 25-hydroxyvitamin D), and chemically standardized, bioavailable formulations. It should also test dietary patterns as well as single compounds.

7. Safety, Adverse Effects, and Interactions

Most nutrients and supplements reviewed here have generally favorable short-term safety profiles at commonly studied doses, but several considerations are clinically important.

Nutrient-drug interactions: The omega-3 bleeding concern is longstanding, but at typical supplemental doses the evidence for clinically significant bleeding, even alongside antithrombotic therapy, is weak [139]. A more clearly documented concern at high doses is a dose-dependent increase in atrial fibrillation, seen in trials of about 4 g/day [140,141] and in a meta-analysis of randomized trials [142]. Ginkgo biloba has been linked to bleeding in case reports, particularly with anticoagulants, antiplatelets, or NSAIDs, but a systematic review and meta-analysis found no clear increase in bleeding risk with standardized extracts [143]; caution remains reasonable given the case reports and the inconsistent quality of products. High-dose folic acid can correct the anemia of vitamin B12 deficiency while neurological damage progresses, and high folate with low B12 status has been associated with worse cognitive outcomes in older adults [144,145]. Botanicals with cytochrome P450 or P-glycoprotein activity can alter the levels of many psychiatric, cardiovascular, and immunosuppressive drugs; St John's wort is the best-documented example, and the literature is dominated by case reports and pharmacokinetic studies [146,147]. Caffeine, a common ingredient in "stacks," has its own safe-intake guidance and can cause anxiety and sleep disturbance at high doses [148].

Upper intake limits and excess risk: Excess vitamin D can cause hypercalcemia and its sequelae, which typically occurs with sustained intakes well above the established upper limit (4,000 IU/day for adults) [149,150]. Chronic high-dose vitamin B6 has been associated with sensory peripheral neuropathy [151,152]. Iron supplementation in non-deficient individuals can contribute to iron overload and oxidative stress, and brain iron accumulation is implicated in neurodegeneration [153,154]; it should generally be avoided without documented deficiency and is contraindicated in hemochromatosis. High-dose fat-soluble antioxidants also carry risk: meta-analytic evidence links high-dose vitamin E to increased all-cause mortality [155], vitamin E increased prostate cancer risk in the SELECT trial

[156], and beta-carotene increased lung cancer incidence in smokers [157].

Product quality and contamination: Herbal and nutraceutical supplements are regulated less stringently than pharmaceuticals in most jurisdictions. Independent analyses have found mislabeling, substitution, undeclared pharmaceutical adulterants, and heavy-metal contamination, including in traditional herbal products [96,97,98,158], and supplements are a recognized cause of emergency department visits [159]. These findings underscore the importance of third-party-verified products and add to the difficulty of reproducing trial results with commercial formulations.

Indiscriminate self-supplementation: Because many of the compounds reviewed show benefit only in deficient or impaired subgroups, indiscriminate supplementation by nutritionally replete individuals is unlikely to confer additional cognitive benefit, and large reviews have found no consistent benefit of multivitamin and mineral supplements for chronic disease prevention [160,161]. In some cases (excess fat-soluble vitamins, excess iron) the risk-benefit ratio is less favorable than no supplementation at all.

Individualization: Supplementation decisions are therefore best individualized and, where feasible, guided by assessment of baseline status (e.g., measured omega-3 index, serum 25-hydroxyvitamin D, serum B12 and homocysteine) rather than applied uniformly [129,162]. Supplements should be considered complementary to, never a substitute for, a balanced diet or clinically indicated pharmacological and non-pharmacological treatment for diagnosed cognitive or neurological disorders.

8. Precision Neuronutrition and Personalized Approaches

The recurring finding that benefit concentrates in people with low baseline nutrient status has prompted interest in "precision" or personalized neuronutrition, which tailors' intervention to individual biological and lifestyle characteristics rather than applying uniform recommendations [163,164]. Baseline biomarker status (omega-3 index, serum 25-hydroxyvitamin D, homocysteine, B12) is the most consistent moderator across nutrient classes: B-vitamin effects on brain atrophy and cognition are largely confined to participants with elevated homocysteine [69,130,165], and trial design guidance recommends enrolling by baseline status rather than treating all participants alike [129]. Age may also matter. A systematic review of creatine trials suggested larger effects in older adults, plausibly reflecting differences in baseline metabolic status [166], and sex differences in creatine response are possible given differing baseline stores and muscle mass, but brain-specific mechanisms are not established [167]. Clinical stage appears to moderate effects, although not uniformly. DHA benefited people with mild memory complaints [168] but not those with established Alzheimer's disease [169,170], and probiotic effects have mostly been reported in clinical or symptomatic populations [171,172], so the pattern is better described as stage-dependent than as consistently larger in impaired groups. Genetic moderators are biologically plausible: MTHFR variants affect folate metabolism [173,174], and APOE ε4 may modify the response to DHA and other nutritional interventions [175,176,177]. However, neither has been validated as a moderator of supplement response in large trials. Individual gut microbiota composition may explain heterogeneous probiotic responses, as colonization resistance to probiotics varies between individuals [178], but predictive biomarkers of responders are not clinically available. Finally, baseline diet quality, physical activity, and metabolic health likely interact with single-nutrient interventions in ways that current single-compound RCTs are not designed to capture, which is the rationale for multidomain approaches such as FINGER [10,179]. Because subgroup effects are often post hoc and underpowered, they should be treated as hypothesis-generating until prespecified and replicated [131]. Precision approaches remain largely aspirational in neuronutrition compared with oncology or cardiometabolic medicine, and translating these moderators into validated, actionable algorithms is an explicit research priority (Section 9).

9. Conclusion

The evidence reviewed here supports a measured, evidence-graded conclusion. Established evidence supports the principle that correcting frank nutrient deficiency (vitamin B12, folate, and, with less certainty, vitamin D) protects neurological health. Long-term dietary patterns rich in flavonoids and omega-3 fatty acids are consistently associated with reduced risk of cognitive decline and dementia in large prospective cohorts, although randomized evidence is more mixed. Promising but not yet confirmed evidence exists for omega-3 fatty acids in people with low baseline status or mild cognitive impairment, for curcumin, for creatine in memory and reasoning, for Bacopa monnieri in memory and attention, and for probiotics in populations with cognitive impairment. Evidence is insufficient or null for ginkgo biloba in dementia and cognitive impairment, for B-vitamin supplementation in nutritionally replete populations, and for most proprietary nootropic "stacks."

Across nearly every nutrient and compound reviewed, the most consistent and clinically important pattern is that nutritional intervention appears to matter most for people who are deficient, impaired, or otherwise outside the normal physiological range at baseline, and comparatively little for cognitively healthy, nutritionally replete adults seeking enhancement beyond their baseline. Because subgroup findings of this kind are often post hoc, this pattern should itself be tested prospectively in biomarker-stratified trials. Dietary supplements should therefore be regarded, on current evidence, as targeted tools to correct specific deficiencies or support specific at-risk populations under clinical guidance, rather than as reliable general-purpose cognitive enhancers. They do not substitute for a balanced, nutrient-dense dietary pattern, regular physical activity, adequate sleep, cardiometabolic risk-factor management, and, where cognitive impairment is present, appropriate clinical evaluation and evidence-based treatment.

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