

Nutraceuticals and the Microbiota–Gut–Brain Axis: A Pathway for Preventing Cognitive Decline

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With the global rise in aging populations, cognitive impairment and neurodegenerative diseases, such as Alzheimer's disease (AD), present a growing public health issue. Current pharmacological treatments primarily target symptoms rather than underlying causes, necessitating the exploration of alternative preventive strategies. Nutraceuticals have emerged as promising candidates for neuroprotection due to their ability to modulate oxidative stress, neuroinflammation, and mitochondrial function. This narrative review aimed to evaluate the neuroprotective potential of nutraceuticals and their interactions with the microbiota–gut–brain axis in preventing age-related cognitive decline. A comprehensive search of the scientific literature using the PubMed, Scopus, and Web of Science databases was undertaken, focusing on publications during the period 2010–2025. Nutraceuticals, including vitamins, omega-3 fatty acids, coenzyme Q10, polyphenols, and isothiocyanates, exhibit neuroprotective properties through antioxidant, anti-inflammatory, and mitochondrial-support mechanisms. The gut microbiota plays a crucial role in regulating the bioavailability and efficacy of these compounds. Microbiome-based interventions, such as prebiotics, probiotics, and fecal microbiota transplantation demonstrate potential in modulating neuroinflammatory responses and supporting cognitive function. Nutraceutical and microbiome-targeted interventions represent promising, low-risk strategies for preventing cognitive decline. Their ability to modulate neuroinflammation and oxidative stress underscores their potential for future clinical applications. Further large-scale studies are needed to validate their efficacy and explore personalized approaches adapted to individual microbiome profiles.

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INTRODUCTION

The Global Aging Population, Cognitive Decline, and the Search for Solutions

As the global population continues to age, the prevalence of neurodegenerative diseases is steadily increasing. Mild cognitive impairment (MCI), Alzheimer's disease (AD), and other types of dementia represent a significant burden for individuals, families, and the healthcare systems. Mild cognitive impairment is the transitional stage between a healthy cognitive state and the cognitive decline associated with aging and dementia, and it is one of the most usual conditions among the elderly.¹ Furthermore, it has been reported that 6% to 15% of patients with MCI tend to develop AD, the most common cause of dementia, which affects an estimated 55 million people globally, expected to rise to 139 million by 2050.² Dementia leads to the progressive deterioration of memory, thinking, behavior, and the ability to perform everyday activities, affecting patients' quality of life and placing emotional, physical, and financial burdens on caregivers and society.³

The economic impact of dementia is staggering, with global costs surpassing \$1 trillion annually in 2019, and expected to reach nearly \$3 trillion by 2030.² For all these reasons, there is an urgent need for strategies to prevent and treat cognitive decline.

Early detection, lifestyle interventions, and pharmacological treatments are critical in slowing down cognitive impairment progression. In this regard, the traditional aging hallmarks at molecular and cellular levels were defined in 2013 by Lopez-Otin et al,⁴ including genomic instability, telomere shortening, epigenetic changes, loss of protein homeostasis, disrupted nutrient sensing, mitochondrial dysfunction, cellular aging, stem cell depletion, and altered communication between cells, and recently expanded to also include impaired macroautophagy, chronic inflammation, and gut microbiota dysbiosis.⁵ These last findings open new doors for researchers to discover new treatments.

Although there are pharmacological treatments for AD that are commercialized or in an advanced phase of clinical trial, there is no cure for this condition. Up-to-date treatments primarily manage symptomatology and try to slow disease progression. Most pharmacological approved treatments are monotargeted and the benefits are often modest, taking into account both efficacy and side effects⁶ (Figure 1). These treatments aim to delay cognitive decline, although their long-term individual efficacy and safety remain subjects of ongoing research.⁷

Therefore, given the limitations of current pharmacological treatments, many experts advocate for greater emphasis on preventive strategies, including lifestyle modifications such as a healthy diet, regular physical activity, cognitive training, and management of cardiovascular risk factors, which have been shown to potentially reduce the risk of cognitive decline.⁸ Early detection and a comprehensive approach to brain health may help reduce the impact of these conditions. Nutraceuticals, combining pharmaceutical and nutritional approaches, are gaining interest in clinical trials for their potential in prevention and lower harmful side effects on the body (Figure 1).

This narrative review was conducted through a comprehensive search of the scientific literature using the PubMed, Scopus, and Web of Science databases with keywords including “nutraceuticals”, “microbiota–gut–brain axis”, “cognitive decline”, “neuroprotection”, “probiotics”, “prebiotics”, “polyphenols” and “Alzheimer's disease.” Articles published between 2010 and 2025 were prioritized, with a focus on peer-reviewed research, clinical trials, and systematic reviews. The review included both preclinical (animal models) and clinical studies demonstrating mechanistic or functional relationships between nutraceuticals, microbiota modulation, and cognitive outcomes. Non-English publications and articles without clear relevance to cognitive protection or the microbiota–gut–brain axis were excluded.

The term “nutraceuticals” was created by Dr Stephen DeFelice in 1989 and its definition differs between countries and regulatory systems. However, it is generally defined as food-derived products, or parts of foods, that provide health benefits beyond their basic nutritional value, including the prevention or management of disease risk.^{9–12} Regulatory frameworks differ across countries. In the United States, nutraceuticals are typically categorized as dietary supplements, whereas in Japan the concept overlaps with Foods for Specified Health Use (FOSHU); in the European Union, they are usually regulated as food supplements of functional foods, depending on their composition and permitted claims. Nutraceuticals are often regarded as lower-risk alternatives or as a support to pharmacological drugs, as they act through modulation of physiological processes rather than through direct pharmacological mechanisms. Consequently, they are generally associated with fewer side effects and a higher safety profile when used within recommended doses.

This narrative review aimed to analyze the neuroprotective benefits of nutraceutical approaches for the prevention of cognitive decline, describing the mechanisms of

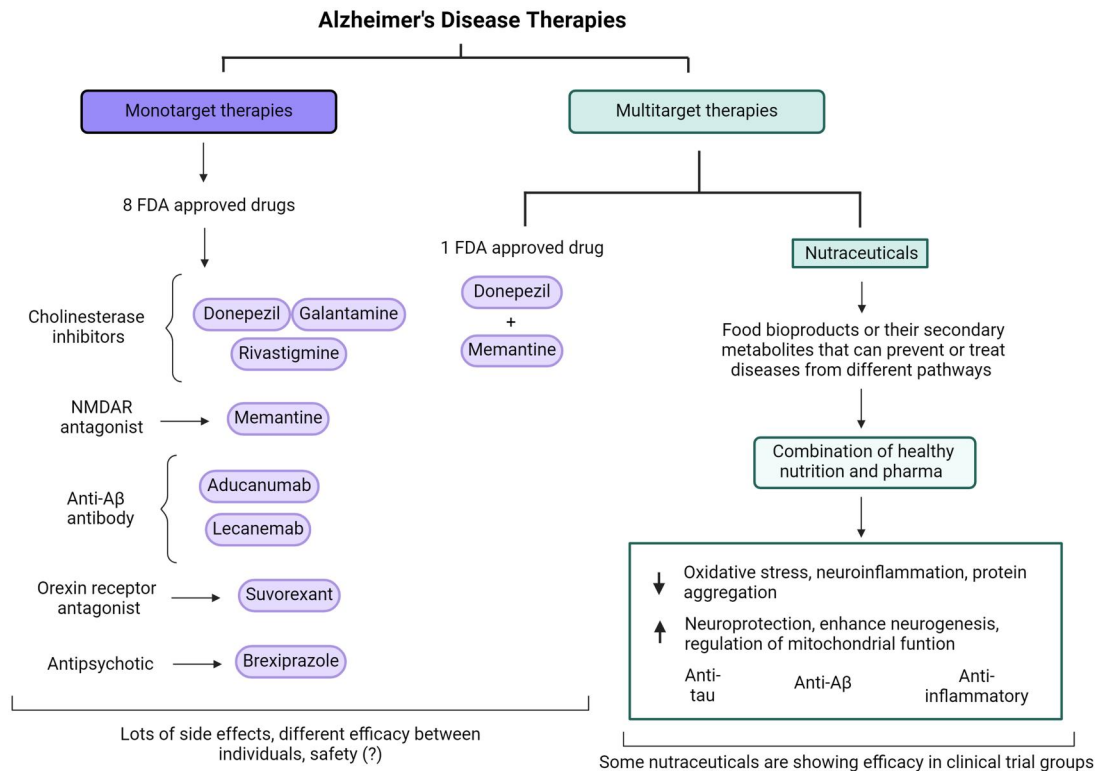


Figure 1. Alzheimer's Monotarget Pharmacological Therapies vs Multitarget Nutraceutical Therapies. Nowadays there are 9 Food and Drug Administration (FDA)-approved pharmacological therapies for Alzheimer's disease (AD). Most of them are monotargeted, such as cholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine) for memory and cognitive issues, and the N-methyl-D-aspartate receptor antagonist called memantine. The other monotargeted therapies, Suvorexant and Brexpiprazole, address non-cognitive symptoms; the former assesses sleep issues and the latter psychological problems. The FDA has recently approved disease-modifying therapies, Aducanumab and Lecanemab, which target amyloid-beta (A β) plaques. However, only one of them (Donepezil + Memantine) is focused on more than one target. The high rate of patients suffering from their side effects, the differences in the efficacy between individuals, and the fact that they are aimed to treat the disease and not to prevent it, makes it of vital importance to search for new multitargeted therapies, such as nutraceuticals, that are a combination of nutrition and pharma. The black arrow down means a decrease and the black arrow up an increase. Figure created with BioRender.com.

action and current knowledge of the potential of the various approaches. Nutraceuticals are found in functional foods and dietary products and offer bioactive compounds that could support enhanced physiological functioning, reduce inflammation, and boost well-being. Furthermore, the gut microbiota plays an essential role in the effectiveness of nutraceuticals, as it influences their absorption, bioavailability, and effectiveness. A homeostatic microbiota optimizes nutraceutical benefits, while microbiota dysbiosis—defined as an alteration in the microbial composition, diversity, or metabolic activity that alters host–microbe interactions—could weaken their efficacy, showing the complex relationship between the diet, the microbiota and gut health, and therapeutic outcomes.^{13,14}

Role of the Gut Microbiota in Cognitive Decline

The gut microbiome has key functions, including nutrient extraction from the diet, regulation of the immune system,

maintenance of the intestinal barrier integrity, cholesterol metabolism, bile acid transformation, and the production of antimicrobial peptides.¹⁵ Furthermore, growing evidence has demonstrated the bidirectional communication that occurs between the gut (and its microbiota) and the central nervous system (CNS) through various mechanisms, which is known as the “gut–brain axis” (GBA) (Figure 2). The main mechanisms involved in this connection are the vagus nerve, the enteric nervous system (an expansive network of neurons lodged in the gut wall), the immune system (through the production of cytokines and other mediators), and the microbial metabolites that can cross the blood–brain barrier (BBB) and modulate brain function.¹⁶

Gut dysbiosis has been described as an active aging process, shedding light on the critical role of the microbiome.¹⁷ Alterations in the gut microbiota have been observed in mood disorders such as depression and anxiety, which have been associated with an increased

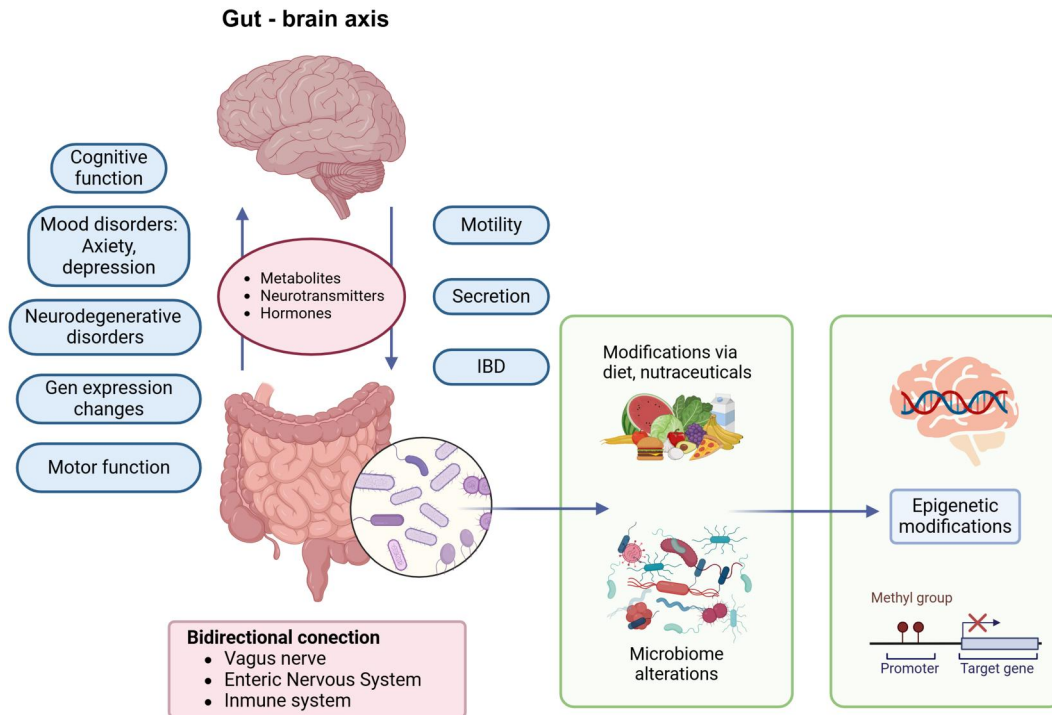


Figure 2. Microbiota–Gut–Brain Axis. Bi-directional interaction between gut (and its microbiota) and brain. The key components of this link are the vagus nerve, the enteric nervous system, and the immune system, and the communication is made through metabolites, neurotransmitters, and various hormones that play a role in the response to changes in the environment. Changes in the microbiome could affect the host positively or negatively, and states of stress or neurodegenerative disorders can alter the gut microbiota too. Adaptations in diet could help to prevent or ameliorate symptoms or the development of mental disorders such as AD, mild cognitive impairment (MCI), inflammatory bowel disease (IBD), or other age-related diseases by the modulation of signals from the gut microbiome that could make changes in the brain epigenetics. Figure created with BioRender.com.

proportion of proinflammatory bacterial species.¹⁸ In this scenario, pro- and prebiotic approaches can shift the balance of the gut microbiota and have been shown to alleviate symptoms of these diseases.¹⁹ The gut microbiome can also affect cognition through neuroactive compounds and modulation of neuroinflammatory responses.²⁰ Similarly, exposure to stress can influence the gut microbiota composition. Both physiological or psychological stressors (including environmental, emotional, and metabolic stress) can disrupt intestinal homeostasis and affect gut–brain communication by changing gut motility, secretion, and permeability, thereby contributing to or being associated with stress-related gastrointestinal disorders such as inflammatory bowel syndrome (IBS).^{21–23} In addition, the nervous system may modulate gut function by secreting neurotransmitters that influence gut motility and secretion.²⁴ Microglia, immune cells in the brain, are critical in neurodegeneration and influenced by the gut microbiota. Gut dysbiosis can trigger chronic microglial activation and inflammation (“*inflammaging*”) through metabolites and cytokines crossing the BBB, contributing to neurodegeneration.²⁵ For instance, isoamylamine (a metabolite produced by some gut bacterial families, such

as the Ruminococcaceae family) crosses the BBB, triggering microglial cell death; it is common to find higher abundance of this family in the gut of elderly individuals.²⁶ Thus, the association between brain and the microbiota is of critical importance for the regulation of microglial cell activity, which in turn plays a crucial role in the course of neurodegenerative diseases. At this point, probiotics, prebiotics, and even fecal microbiota transplantation (FMT) may reduce microglial activation and cognitive decline by restoring both the BBB and the intestinal barriers. However further research is needed to elucidate clinical treatments that may cover these aspects.²⁷

Furthermore, some studies into the epigenetic reprogramming mechanisms of the microbiota–gut–brain axis (MGBA) are beginning to emerge.²⁸ Thus, the gut microbiota can modify the host’s epigenome, leading to long-lasting consequences²⁹ (Figure 2). These changes in the epigenetic machinery modulate the gene expression involved in synaptic plasticity, neurotransmitter systems, and stress responses.²⁸ Some studies have demonstrated that DNA methylation follows a unique temporal pattern along the lifespan, slowing down with aging.³⁰ An aged

hippocampus shows a reduction in DNA methylation and hydroxy-methylation, and these effects similarly occur in the progression of AD.³¹ It is tempting to think that increasing methylation activity with methyl group donors might reverse hypomethylation and restore healthier patterns. Dietary intake of methionine, choline, betaine, folic acid, and vitamins B2, B6, and B12 supports methionine production and availability. In addition, aging and some neurodegenerative diseases involve the dysregulation of deacetylation.³² For example, short-chain fatty acids (SCFAs), such as butyric acid produced by the gut microbiota, may inhibit histone deacetylases (HDACs),³³ whereas both propionate and butyrate have been shown to activate acetyltransferases.³⁴ Interestingly, several studies have found reduced SCFAs and SCFA-producing bacteria in individuals with MCI and AD.³⁵

Therefore, understanding the interplay between the gut microbiota, neuroinflammation, epigenetic regulation, and dietary factors is key to formulating nutraceutical strategies to limit cognitive decline and promote healthy aging.

NUTRACEUTICALS—A WAY TO IMPROVE COGNITIVE IMPAIRMENT THROUGH THE MICROBIOTA–GUT–BRAIN AXIS

Hence, diet, the microbiota, metabolism, the immune system, and the CNS are interconnected, making bioactive food-derived compounds (molecules naturally occurring in food or plants) and probiotics potential tools for cognitive enhancement and prevention of age-related decline. Nutritional supplements such as vitamins, minerals, fatty acids, and other antioxidants support CNS function, especially in aging, when some nutritional deficiencies, due to poor or unbalanced diets, reduced nutrient absorption, or medication side effects are common, making supplementation important for cognitive health, memory, and sharpness. This section will emphasize the important contributions of nutritional supplements in maintaining or enhancing cognitive function among elderly subjects.

Impact of Vitamins in Neuroprotection

Vitamin B Group. This group of vitamins serves a vital function in preserving cognitive function as people age, including crucial cofactors in numerous neurological processes³⁶ (Table 1). With aging, the risk of vitamin B deficiencies increases, potentially leading to cognitive deterioration.³⁷ Vitamins B6 (pyridoxine), B9 (folate), and B12 (cobalamine) are of particular importance as they support normal brain function by participating in homocysteine metabolism. Elevated homocysteine levels are associated with neurodegenerative disorders and cerebrovascular issues.³⁸ Clinical evidence has been demonstrated,

showing that a higher intake of these B vitamins can significantly slow cognitive decline in older adults, especially in those with elevated homocysteine levels or MCI.^{36,37} For instance, supplementation with B vitamins has been proven to decrease homocysteine levels, thus diminishing the rate of brain atrophy in MCI patients and enhancing cognitive outcomes.³⁹ Research in preclinical studies has suggested that B vitamins are also involved in the synthesis of neurotransmitters and the maintenance of the myelin covering nerve fibers, which is essential for brain signaling.⁴⁰ These neuroprotective roles of B vitamins in preventing cognitive decline support the hypothesis that an adequate intake of these nutrients could be pivotal in preserving cognitive health in aging.

Notably, several B vitamins (such as folate, biotin and cobalamin analogs) are synthesized by members of the gut microbiota. This endogenous microbial production may complement dietary intake and contribute to host vitamin status, thereby influencing homocysteine metabolism and cognitive outcomes.^{41,42} However, the extent of absorption and the bioavailability of microbiota-derived B vitamins in humans remain under investigation, and microbial dysbiosis may reduce this contribution, potentially exacerbating deficiencies in aging populations.

Vitamin C. Vitamin C, or ascorbic acid, is an antioxidant vitamin that protects the brain from oxidative stress. It is one of the prominent neurotransmitter systems supporting dopamine and noradrenaline synthesis and function, enhancing brain function.⁴³ Various studies have associated vitamin C deficiency with mental health disorders in humans, such as cognitive decline, impaired attention, and memory deficits.⁴³ Other clinical studies indicate that low vitamin C levels are associated with increased risk of depression and cognitive decline, whereas higher levels are associated with a better mood and cognitive functioning,⁴⁴ attenuating depression-like symptoms.⁴⁵ In addition, there is emerging evidence that maintaining healthy levels of vitamin C may be protective against age-related cognitive decline, while supplementation may be beneficial in improving cognitive function.^{44,46,47} However, further research, particularly longitudinal studies conducted on large populations, is needed to firmly establish the protective role of vitamin C against the progression of cognitive decline and dementia.

Vitamin D. Vitamin D supports neurological development, fostering memory and cognitive function later in life.⁴⁸ Notably, vitamin D deficiency is associated with an increased risk of multiple sclerosis (MS), depression, Parkinson's disease (PD), and AD.⁴⁹ Studies involving over 1600 elderly individuals demonstrated that mild vitamin D deficiency raised dementia risk by over 50%, with even higher risk being associated with severe

Table 1. Vitamins, Minerals, and Other Key Compounds in Healthy Aging and Implicated in Cognitive Health

Group	Treatment	Adequate ranges	Effect	References
Vitamins	<u>Vitamin B6, B9, and B12</u>	B6 intake ≥ 1.7 mg/day, B9 ≥ 400 ($\mu\text{g}/\text{day}$), and B12 ≥ 2.4 ($\mu\text{g}/\text{day}$)	Slows cognitive decline, reduces homocysteine levels, decreases brain atrophy, and enhances cognitive outcomes	38
	<u>Vitamin C</u>	Deficiency takes levels below $11.4 \mu\text{mol}/\text{L}$	Acts as an antioxidant, enhances mood and cognitive performance, and may protect against cognitive decline	44
	<u>Vitamin D</u>	Inadequate serum concentrations $< 25 \text{ nmol}/\text{L}$	Supports brain health, neurotransmission, and cognitive function. Reduces risk of dementia	48
	<u>Vitamin E</u>	Recommended dietary allowance (RDA) is $15 \text{ mg}/\text{day}$	Protects brain cells from oxidative damage and reduces the risk of cognitive decline and dementia	53
	<u>Vitamin K</u>	Depending on comorbidities	May preserve memory, potentially protects nerve cells from A β toxicity, and is linked to reduced cognitive decline	55
Minerals	<u>Magnesium</u>	$350 \text{ mg}/\text{day}$ is associated with better results	Improves cognitive functions and reduces dementia risk by protecting nerve cells and impacting blood pressure	60
	<u>Iron</u>	Average adult stores should be about 1–3 g	Enhances cognitive function, improves IQ, and is linked to reduced dementia and AD prevalence	61
	<u>Selenium</u>	Serum concentration must be around $80 \mu\text{g}/\text{L}$	Protects the brain from oxidative stress, which reduces the risk of cognitive decline and neurodegenerative diseases	63
	<u>Zinc</u>	Neuroprotective at physiological concentrations ($82.7 \mu\text{g}/\text{dL}$). Neurotoxic at higher concentrations	Supports cognitive functions, mitigates depression, and aids in free radical elimination	65
Omega-3 PUFAs	<u>EPA, DHA</u>	Supplementation typically ranging from 500 to 2000 mg/day	Improves cognitive function, synaptic plasticity and neuronal signaling. Reduces neuroinflammation, with potential anti-depressive effects	77
CoQ10		No systematic pattern of adverse effects has been observed with high dosages in adults ($2400 \text{ mg}/\text{day}$)	Antioxidant properties that help repair oxidative DNA damage. Declines with age, leading to increased oxidative stress and mitochondrial dysfunction, contributing to aging and various diseases	69

Abbreviations: AD, Alzheimer's disease; Co-Q10, coenzyme Q10; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IQ, intelligence quotient; PUFA, polyunsaturated fatty acids.

deficiency.⁵⁰ These findings underscore the crucial role of maintaining adequate vitamin D levels in older adults, improving performance and benefiting those subjects with deficiencies.⁵¹ In addition, vitamin D supports brain blood flow and helps protect against the cognitive effects of cerebrovascular disease.⁴⁹ Moreover, preclinical research shows that it contributes to the production of neurotransmitters, such as dopamine and serotonin, which play an important role in regulating mood and emotions.⁵² The contribution of vitamin D to neuroprotection, neurotransmission, and brain plasticity reaffirms the possibility of being an essential nutrient in maintaining brain health with aging in older adults. However, although these associations appear promising, there is need for more large-scale clinical trials to establish definitive causal links of vitamin D supplementation with preservation of cognitive function.

Vitamin E. Vitamin E, a fat-soluble vitamin, protects cells from oxidative stress-induced damage, preserves neuronal integrity, and supports cognitive health, preventing lipid peroxidation and atherosclerosis.⁵³ As the levels of this vitamin decrease in elderly individuals with MCI and AD, numerous clinical studies have shown that the higher the intake or serum levels of vitamin E, the lower the risk of cognitive decline and dementia, including AD,^{53,54} but more research in the field of potential health benefits is needed for it to be approved as a treatment itself.

Vitamin K. Vitamin K is a fat-soluble vitamin and plays an indispensable role in essential physiological processes. The major function of vitamin K is to act as a co-factor for the synthesis of coagulation factors. Beyond this major action, vitamin K is integral to other processes such as cell growth, maturation, proliferation, and apoptosis, and it contributes to memory preservation within older adults, with low vitamin K serum levels being linked to cognitive decline in subjects aged over 65.⁵⁵ In addition, preclinical investigations hint at the potential of vitamin K to shield nerve cells from amyloid-beta ($A\beta$) peptides toxicity.⁵⁶

Similarly, to vitamin B production, the gut microbiota is an important source of vitamin K; in particular, vitamin K₂ (menaquinones) is produced by bacteria such as *Bacteroides* and members of the Enterobacteriaceae family.^{57,58} These microbial-derived forms may add to the host's vitamin K pool and exert specific neuroprotective effects. Interactions between dietary vitamin K and microbiota-derived menaquinones represent a promising but still underexplored area in the context of cognitive decline.⁵⁹

Minerals

Minerals are crucial for brain and cognitive function and must be obtained through diet or supplementation. Adequate mineral levels correlate with cognition improvement and reduced risks of dementia.

Higher magnesium serum levels are significantly associated with lower risks of dementia, while increased magnesium intake supports brain health by preventing neurodegeneration and modulating blood pressure in humans.⁶⁰

Iron plays an active role in several physiological functions, including cognitive function. Mild iron deficiency could interfere with cognition and impair immune function and has also been related to delayed neurological development and poor school performance. Iron supplementation has also been linked to improved intelligence quotient (IQ) scores, whereas iron-deficiency anemia in older adults has shown correlation with increased dementia and AD prevalence.^{61,62}

Selenium is an important co-factor for many antioxidant enzymes, including glutathione peroxidase (which protects the brain from oxidative damage implicated in the aging process) and in the etiology of neurodegenerative diseases such as AD and PD.⁶³

Finally, zinc is vital for growth, development, and immune function, and it also benefits the nervous system, potentially helping to mitigate depression due to its calming properties.⁶⁴ Indeed, zinc deficiency is seen in the course of ageing and in various diseases, and this might impair cognitive functioning as well as memory.⁶⁵ In addition, preclinical studies show that zinc also plays a crucial role in the operation of antioxidant enzymes, such as superoxide dismutase (SOD), which aid in the clearance of free radicals when they are elevated.⁶⁶

Taken together, any nutritional supplement proposed as a therapeutic approach for preventing cognitive decline should consider the inclusion of minerals in its composition.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a key player in the mitochondrial electron transport chain, thereby facilitating energy production and controlling the integrity of mitochondria. In its reduced form, CoQ10 acts as an antioxidant, inhibiting lipid peroxidation, protecting cells against oxidative stress, and supporting the function of DNA repair enzymes.^{67,68} The levels of CoQ10 decline with age, resulting in an increase in oxidative stress and mitochondrial dysfunction.⁶⁹ Furthermore, subjects with neurodegenerative diseases and metabolic syndrome exhibit lower levels of CoQ10, which may contribute to the progression of both conditions.⁶⁹ Experimental studies in

animal models of PD and AD have demonstrated that CoQ10 supplementation reduces oxidative stress, improves mitochondrial function, and prevents neuronal loss.^{70,71} In addition, CoQ10 has been shown to reduce (A β) accumulation and enhance synaptic plasticity, highlighting its potential neuroprotective properties.⁷¹ The results of clinical trials in the context of cognitive decline are still scarce and inconclusive, with small samples and heterogeneous methodologies. Nevertheless, given its safety profile and biological plausibility, CoQ10 continues to be considered a promising adjunct candidate, but further well-designed clinical studies are needed to validate its efficacy in this field.

Omega-3 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) are increasingly being identified as assisting in preserving cognitive functioning as age progresses. The benefits of PUFAs on memory, attention, learning, and general well-being are still under investigation. Particularly, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are 2 vital elements in the neuronal membranes.⁷² Docosahexaenoic acid, predominant among the omega-3 fatty acids, plays a major role in the brain and is vital for the integrity and function of neural cells.⁷³ Docosahexaenoic acid supplementation was shown to aid the synaptic plasticity and neuronal signaling that are critical for cognitive processes, learning, and memory in an animal study.⁷⁴ On the other hand, clinical studies have shown that EPA provides support for cognitive health by serving as an anti-inflammatory agent to reduce neuroinflammation.⁷⁵ Supplementation with high doses of omega-3 has been proposed in ameliorating symptoms of clinical depression and anxiety, thereby bolstering cognition.⁷⁶ Regular use of omega-3 supplements is linked to various cognitive and emotional benefits, including positive effects on cognitive development, reading skills, concentration, and cognitive abilities.⁷³ Additionally, clinical research has suggested that omega-3 PUFAs may lower the risk of neuro-degenerative disorders such as AD, possibly delaying its onset and progression, and improving cognitive abilities.⁷⁷ Future studies should delve deeper into the role of omega-3 derivatives (eg, pro-resolving lipid mediators such as resolvins, maresins, or protectins) in protecting against cognitive decline, given the potent effects observed in other contexts.

Polyphenols and Isothiocyanates

Polyphenols are natural compounds with antioxidant properties found in fruits, vegetables, and other plants, and they help reduce oxidative stress and neuronal damage⁷⁸ (Table 2). Polyphenols also enhance neuronal

function, regeneration, and proliferation.⁷⁹ Furthermore, polyphenols protect neurons from the toxic effects of A β neurotoxicity⁸⁰ and the neural damage caused by nitric oxide (NO),⁸¹ modulating neuronal signaling pathways.⁸² Next, we will detail some of the most well-known polyphenols with positive effects on neurodegeneration.

Luteolin is a flavonoid found mostly in leaves and also present in rinds, barks, pollen, and honey. Preclinical studies have shown that it enhances spatial working memory by preventing microglia-associated inflammation and neuronal death in the hippocampus.⁸³ Luteolin also improves and safeguards synaptic transmission in the hippocampus, helping to restore memory, while also protecting cortical neurons from A β toxicity in a rat model of AD.⁸⁴

Ferulic acid has been shown to present neuroprotection against oxidative stress after cerebral ischemia injury in rats.⁸⁵ Additionally, ferulic acid enhances synaptic plasticity in in vitro and in vivo models of AD.⁸⁶

Chlorogenic acid (CGA) protects against methyl mercury-induced apoptosis in in vitro cell cultures by reducing reactive oxygen species (ROS) and maintaining glutathione peroxidase and glutathione levels, attenuating apoptosis through caspase-3 inhibition.⁸⁷ In addition, in scopolamine (a drug that blocks the action of the acetylcholine)-induced dementia-like mice, CGA improves scopolamine-induced learning impairments by recovering acetylcholine action and reducing lipid peroxidation.⁸⁸

Hesperidin, a flavonoid predominantly found in citrus fruits, has shown notable neuroprotective properties. It reduces oxidative stress by enhancing antioxidant defenses, including increasing glutathione levels and SOD.⁸⁹ In vitro studies have confirmed these effects against neuroinflammation, showing that hesperidin reduces A β -induced oxidative stress, diminishing astrocyte and microglial activation.^{90,91} Hesperidin has also been shown to ameliorate the harmful neurobehavioral effects of emamectin benzoate on rats by reducing oxidative stress and inflammation and boosting hippocampal neurogenesis.⁹² Furthermore, a clinical study has shown that chronic daily consumption of a flavanone-rich (mainly hesperidin) orange juice over 8 weeks was beneficial for global cognitive function in healthy older adults.⁹³ These properties position hesperidin as a promising candidate for the prevention and management of neurodegenerative diseases.

Resveratrol and curcumin are non-flavonoid polyphenols with strong antioxidant and anti-inflammatory properties that are cardinal to cognitive health as individuals age. Resveratrol, found in grapes as well as in red wine, could afford neuronal protection, improve blood flow, and enhance cognition, with some clinical trials revealing such benefits in older adults in relation to

Table 2. Nutraceutical Treatments with Each Effect on Cognitive Health

Family	Nutraceutical	Model and dosage	Effect	References
Phenolic compounds and isothiocyanates	Resveratrol	In human clinical trials, up to 1000 mg/day ^a (Brown et al, 2024)	Enhances memory and cognitive performance, improves cerebral blood flow, and lowers neurodegenerative disease risk	91
	Quercetin	Administered to SAMP8 mice for 2 months 25 mg/kg/day	Reduces oxidative damage, improves memory and learning, is anti-inflammatory, decreases neuron apoptosis, promotes autophagy, inhibits aggregation of neurotoxic proteins (A β , tau), and selectively eliminates senescent cells in the brain of the murine model	104
		AD rat model, 100 mg	Improves cognitive memory, decreases A β 1-42, acts as an antioxidant, and increases expression of Nrf2/HO-1 in the rat brain	101
	Curcumin	In humans, daily intake of 50 mg for 24 weeks ^a In humans, up to 8 g/day in adults; doses varied between studies ^a	Reduces age-related cognitive decline, possibly by improving emotional conditions Exerts neuroprotective effects, may prevent age-related cognitive decline, and improves memory and mood	106 92
	Epigallocatechin gallate	Clinical trials using 5–7 mg/kg/day for 3 months ^a	Neuroprotective role, reduces amyloid plaque formation, and improves cognitive function	94
	Anthocyanins	0–0.5 mg/mL of blueberry extract added for 7 days to the growth medium of adult human neural progenitor cells ^a Middle-aged humans with overweight and subjective cognitive decline; daily dosage of 0.5 cup of the whole fruit for 12 weeks ^a	Improves neural signaling and memory by providing antioxidative and anti-inflammatory benefits	95
	Luteolin	Aged mice, 20 mg/day for 4 weeks	Improves lexical access, improves executive control, and decreases insulin resistance	97
	Ferulic acid	5 and 10 μ M 2 hours before A β treatment in primary neuron culture	Enhances memory and synaptic function, reduces neuroinflammation, and protects neurons from A β toxicity	83
	Chlorogenic acid	Cerebral ischemic injured rats APP/PS1 mice, 50 mg/kg/day for 4 months Apoptosis was induced in PC12 cells by methylmercury, 0.15, 0.45, and 1.35 μ M of CGA before MeHg	Reduces neuronal damage, protects against oxidative stress-induced apoptosis, and demonstrates anti-inflammatory properties during cerebral ischemia/reperfusion injury Neuroprotection against oxidative stress Prevents the increase of A β burden by modulating its production and clearance, improving neuroinflammation and enhancing plasticity Confers neuroprotection against methyl mercury-induced apoptosis by reducing ROS and maintaining glutathione peroxidase and glutathione levels; caspase-3 inhibition.	83 84
		Administered to mice with cognitive impairment induced by scopolamine, between 3 and 9 mg/kg	Protects against apoptosis induced by toxins, mitigates learning and memory impairments, and inhibits AChE activity, reducing oxidative stress in the brain	85

(continued)

Table 2. Continued

Family	Nutraceutical	Model and dosage	Effect	References
	Hesperidin	In clinical studies, different doses were used	Antioxidant, anti-inflammatory, neuroprotective, and cardioprotective. It also reduces A β -induced oxidative stress, diminishing astrocyte and microglial activation	87
		Mature Sprague-Dawley rats, 100 mg/kg via gavage for 8 weeks	Reduces astrocyte and microglial activation, reduces oxidative stress and inflammation, and boosts hippocampal neurogenesis.	89
		Healthy older adults, flavanone-rich (mainly hesperidin) orange juice over 8 weeks ^a	Shown to be beneficial for global cognitive function	90
	Sulforaphane	Different rodent models, dosed from 1 to 50 mg/kg, via oral, intraperitoneal, or gavage	Enhances antioxidant defenses, reduces neuroinflammation, promotes autophagy, decreases neuronal apoptosis, and mitigates neurotoxic protein aggregation (A β , tau), supporting neuroprotection and brain health	108
		Healthy older adults, daily intake of 30 mg of the sulforaphane precursor glucoraphanin ^a	Significantly improves processing speed and working memory performance	109
Prebiotics	GOS	APP/PS1 mice	Alleviates A β pathology and neuroinflammation, changes neurotransmitter concentrations, and modulates the gut microbiota	120
	MOS	Administered to 5xFAD mice for 8 weeks (0.12%)	Improves intestinal barrier integrity, reduces microglial activation and A β deposition, lowers oxidative stress, and alleviates cognitive deficits	111
	XOS	150 μ L/day, 10% XOS; APP/PS1 mice for 5 weeks	Restores intestinal and BBB integrity, reduces inflammation, and mitigates spatial memory deficits in cognitive dysfunction models	112
		600 mg/kg/day XOS, D-galactose aged mice	Enriches beneficial bacterial strains, improves cognitive function, inflammatory markers, and oxidative stress levels	119
	SCP-1	Administered to D-galactose-induced mice for 4 weeks	Restores SCFAs levels, reduces neuroinflammation and A β deposition, and alleviates chemically induced cognitive deficits	114
	β -glucan	APP/PS1 mice, 100 mg/kg/day for 1 month	Enhances SCFA levels, reduces intestinal and brain inflammation, decreases A β deposition, and alleviates cognitive impairment in Alzheimer's models	113
		Clinical trial in adults with ME/CFS, multivitamin with 250 mg beta-glucan, 12 weeks ^a	In patients with ME/CFS, enhances self-perception of the symptoms: Fatigue, anxiety, depression, sleep quality Enhances SCFA levels, reduces intestinal and brain inflammation, decreases A β deposition, and alleviates cognitive impairment in Alzheimer's models. In patients with ME/CFS, enhances self-perception of the symptoms: Fatigue, anxiety, depression, sleep quality.	121

(continued)

Table 2. Continued

Family	Nutraceutical	Model and dosage	Effect	References
	R13	5xFAD mice, doses of 21.8 and 43.6 mg/kg, for 5 months	Inhibits gut signaling pathways related to APP and Tau fragmentation, and reduces gut leakage, oxidative stress, and cognitive decline	128
	SCP-2	A β 25–35-induced AD rats, 0.545 g/kg/day for 8 weeks	Restores SCFA levels, improves intestinal barrier integrity, reduces systemic and microglial inflammation, and enhances learning and memory in AD models	115
	PSP-1	5xFAD mice, 3-month dosing period	Increases expression of TJPs, reduces A β deposition, prevents synaptic loss, and improves spatial memory in AD models	118
	DOP	Mice with CRD, 200 mg/kg for 4 weeks	Strengthens intestinal barrier, lowers serum LPS and pro-inflammatory cytokine levels, and prevents neuronal damage and memory deficits related to circadian rhythm disruption	116
Probiotics	<i>Bifidobacterium longum</i> BB68S	In healthy older adult humans, 5 x 10 ¹⁰ CFU/day for 8 weeks	Increases abundance of beneficial bacteria and decreases abundance of bacteria related to cognition impairment	136
	<i>B longum</i> NK46	Tested on 5xFAD mice for 8 weeks	Reduces NF- κ B activation, enhances TJP expression, diminishes A β plaque formation, and mitigates cognitive decline	125
	<i>B pseudocatenulatum</i>	HFD mouse model	Could contribute to attenuating obesity-associated depressive-like behavior	127
	<i>B brevis</i> HNX26M4	Administered daily for 12 weeks to APP/PS1 mice	Increases SCFA levels, reduces pro-inflammatory cytokines, improves tight junction integrity, lessens A β deposition, and alleviates cognitive deficits	126
	<i>B brevis</i> MCC1274	In humans from 65 to 88 years with MCI 2 x 10 ¹⁰ CFU/day for 24 weeks	Stops brain atrophy and cognitive decline related to "orientation" and "writing"	136
	<i>Lactobacillus salivarius</i>	Administered for 16 weeks to 5xFAD mice	Inhibits gut-brain signaling pathways, decreases gut permeability, reduces A β pathology, and lowers oxidative stress in the brain	117
	<i>L paracasei</i> PS23	Administered for 12 weeks in aged SAMP8 mice	Decreases intestinal permeability, lowers pro-inflammatory factors, and improves memory	129
	<i>L fermentum</i>	Middle-aged mice daily for 48 weeks	Improves cognitive performance, modulates the immune response, and alters the gut microbiota composition to increase beneficial bacteria	130
	<i>L rhamnosus</i> GR-1	Supplied to Pb-exposed rats daily for 2 months	Attenuates learning and memory deficits, increases gut microbiota diversity, reduces gut permeability, and modulates cytokine expression toward an anti-inflammatory profile	131
	<i>L rhamnosus</i> GG	In humans, middle-aged and older, 12 weeks treatment	Improves cognitive score and decreases the relative abundance of genes associated with MCI	138
<i>Akkermansia muciniphila</i>	Administered 10 ⁹ CFU/mL, 3 times a week to induced hepatic injury mouse model for 3 weeks	Significantly decreases tissue damage and improves cognitive dysfunction and expression of BDNF and serotonin	135	

(continued)

Table 2. Continued

Family	Nutraceutical	Model and dosage	Effect	References
	<i>A muciniphila</i> GP01	Administered daily for 6 months to APP/PS1 mice	Restores colonic mucus cell numbers, improves intestinal barrier function, corrects lipid metabolism, and reduces A β plaque accumulation, mitigating cognitive impairments	134
	<i>L plantarum</i> MA2	Administered for 12 weeks in mice with AD induced by D-galactose and AICl ₃	Enhances intestinal barrier integrity, reduces neuronal degeneration, and inhibits microglial activation, thus improving cognitive function and reducing anxiety	133
	ProBiotic-4	Aged SAMP8 mice with daily treatments for 12 weeks	Improves mucus layer health, reduces crypt loss and villus damage, lowers plasma pro-inflammatory cytokines, and protects against age-related cognitive impairments	133
	Multi-strain probiotic ^b	In humans with AD, 1 × 10 ¹⁰ CFU/day for 12 weeks of treatment	Patients show increased BDNF serum levels, as well as increased antioxidant SOD, and a reduction in IL-1 β . A trend toward less cognitive deterioration has been observed.	137
	Probiotic mix ^c	In humans over 60 years with MCI, administered >2 × 10 ¹⁰ CFU/day for 12 weeks	The treatment regulates the homeostasis of the gut microbiota, and enhances cognitive function and sleep quality.	138

^a Intake values shown in this table correspond to the highest doses tested in human clinical trials with acceptable safety or to the effective dose reported in the cited study. Official upper intake levels or safety cut-offs have not been established for most of these nutraceuticals.

^b Multi-strain probiotic composition: *Bifidobacterium longum* subsp. infantis BLI-02, *B. breve* Bv-889, *B. animalis* subsp. *lactis* CP-9, *B. bifidum* VDD088, and *Lactobacillus plantarum* PL-02.

^c Probiotic mix composition: *Lactobacillus plantarum* BioF-228, *Lactococcus lactis* BioF-224, *Bifidobacterium lactis* CP-9, *Lactobacillus rhamnosus* Bv-77, *Lactobacillus johnsonii* MH-68, *Lactobacillus paracasei* MP137, *Lactobacillus salivarius* AP-32, *Lactobacillus acidophilus* TYCA06, *Lactococcus lactis* LY-66, *Bifidobacterium lactis* HNO19, *Lactobacillus rhamnosus* HN001, *Lactobacillus paracasei* GL-156, *Bifidobacterium animalis* BB-115, *Lactobacillus casei* CS-773, *Lactobacillus reuteri* TS332, *Lactobacillus fermentum* TSF331, *Bifidobacterium infantis* BLI-02, and *Lactobacillus plantarum* CN2018. Abbreviations: A β , amyloid beta; AChE, acetylcholinesterase; AD, Alzheimer's disease; AICl₃, aluminum chloride; APP, amyloid precursor protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CFU, colony-forming units; CGA, chlorogenic acid; CRD, calorie-restricted diet; FAD, familial Alzheimer's disease; HFCD, high-fat diet; IL-1 β , interleukin-1 beta; LPS, lipopolysaccharide; MCI, mild cognitive impairment; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; NF- κ B, nuclear factor kappa B; Pb, lead; ROS, reactive oxygen species; SAMP8, senescence-accelerated mouse prone 8; SCFA, short-chain fatty acids; SOD, superoxide dismutase; TJP, tight junction protein; XOS, xylitol-oligosaccharides.

cognitive performance and memory.⁹⁴ Likewise, given its neuroprotective potential (obtained by crossing the BBB), curcumin, the active compound in turmeric, may allegedly hinder age-related cognitive decline. It is hypothesized that curcumin supplementation may potentially enhance memory and mood in persons suffering from mild age-related memory loss.⁹⁵

Flavonoids found in berries, teas, and cocoa are vital to cognitive health and are associated with reduced dementia risk along with improved memory and learning capabilities.⁹⁶ For instance, clinical studies with epigallocatechin gallate from green tea have shown its neuroprotective actions, such as reduction of $A\beta$ plaque formation and improvement of cognitive function.⁹⁷ Anthocyanins, present in dark-colored fruits, such as blueberries, have been shown to promote neuronal signaling and memory function in human neural progenitor cells.⁹⁸ Therefore, supplementation with these flavonoids may confer antioxidant and anti-inflammatory benefits and help ameliorate age-dependent cognitive decline.⁹⁹ A clinical trial assessed the effects of blueberry intake on middle-aged adults with subjective cognitive decline, and it showed that there exist neurocognitive benefits, suggesting that supplementation with anthocyanins has potential for protection against future cognitive decline in vulnerable individuals. However, more research is needed on such supplementation over long periods.¹⁰⁰

Quercetin is a flavonoid present in several fruits, vegetables, and nuts, and it is often highlighted due to its multiple health benefits. Quercetin may exert neuroprotective and anti-inflammatory actions, being a promising candidate for treating neurodegenerative disorders and protecting against neuroinflammatory toxicity from environmental contaminants.¹⁰¹ Quercetin has been shown to protect neuronal cells from oxidative stress and $A\beta$ -induced damage in culture.^{102,103} In an AD rat model, quercetin treatment could markedly reverse pathological processes, such as amyloidosis, tauopathies, astrogliosis, and microgliosis, along with enhancing memory and learning.¹⁰⁴ Additionally, *in silico* analysis shows azaleatin, a quercetin derivative, has a greater capacity to inhibit acetylcholinesterase (AChE) compared with conventional drugs used in AD, due to its stronger binding to the active site of AChE.¹⁰⁵ Quercetin also regulates several other essential transcription factors and enzymes, including nitric oxide synthase (NOS), nuclear factor kappa B (NF- κ B), AMP-activated protein kinase (AMPK), and nuclear factor erythroid 2-related factor 2 (Nrf2), which activate genes for detoxification and antioxidant protein synthesis.¹⁰⁶ Furthermore, quercetin has shown neuroprotective effects in an accelerated senescence mouse model (SAMP8)¹⁰⁷ and in a transgenic mouse model of AD, preventing $A\beta$, tau, and α -synuclein aggregation by stabilizing their oligomeric forms.¹⁰⁸ Overall, the evidence found from *in vitro* and

in vivo studies accentuates the potential of quercetin as a viable treatment strategy for managing and preventing cognitive decline associated with AD. A study conducted in a Japanese elderly cohort supplemented with quercetin-rich onions demonstrated a reduction in cognitive decline progression after 24 weeks.¹⁰⁹ These findings could also provide rational insights regarding treatment for neuroinflammation, providing neuroprotection in other neurodegenerative diseases.

Other natural compounds that have garnered attention for their potential neuroprotective effects are isothiocyanates. Their most studied example is sulforaphane, found in cruciferous vegetables such as broccoli. Sulforaphane is a potent activator of the Nrf2 signaling pathway, which enhances the expression of antioxidant enzymes and supports cellular detoxification processes, reducing oxidative stress, and protecting neurons from damage.¹¹⁰ Several studies have already tested and asserted these properties in various *in vivo* neurodegeneration models, supporting the role of sulforaphane in neuroprotection and brain health.¹¹¹ Furthermore, a clinical study has shown that the daily intake of 30 mg of the sulforaphane precursor glucoraphanin significantly improved processing speed and working memory performance in healthy older adults.¹¹²

Prebiotics, Probiotics, and Microbiota Transplantation

Gut microbiota-based treatments could be promising treatments for alleviating or preventing age-associated neurodegenerative diseases. By targeting the gut dysbiosis related to aging, it may be possible to restore a healthy balance in individuals who are obese or aging, which could improve symptoms, correct underlying metabolic issues, and address related health complications. Particularly focused on the GBA, various types of biotics—such as prebiotics, probiotics, synbiotics, and postbiotics—offer specific advantages to the body and could be harnessed to create new treatments for aging and associated diseases. The upcoming section will outline the key discoveries related to biotics and their impact on cognitive decline.

Prebiotics. Prebiotics represent a promising class of nutraceuticals acting within the MGBA. Prebiotics are non-digestible compounds that specifically encourage the growth of beneficial bacteria, and despite the diversity of the compounds described, most studies converge on a common set of mechanisms: Strengthening intestinal barrier integrity, restoring microbial metabolites (such as SCFAs), and reducing systemic and neuro-inflammation. The best-studied prebiotics include inulin, fructooligosaccharides, and galactooligosaccharides, which support the growth of bacteria such as *Lactobacillus* and *Bifidobacterium* species. However, with advances in technology, prebiotics

are now also being developed to target other beneficial gut microbes, such as *Roseburia*, *Eubacterium*, and *Faecalibacterium*. Emerging evidence highlights the potential of prebiotics in addressing neurodegenerative disorders through GBA modulation, and efficacy has been reported mainly in animal models of cognitive decline with galactooligosaccharides (GOSs), mannan oligosaccharides (MOSs), xylooligosaccharides (XOSs), β -glucans, SCP-1 and SCP-2, PSP-1, and DOP, which are polysaccharides, and R13 (pro-drug of 7,8-dihydroxyflavone).^{113–122} In addition, some clinical trials are starting to emerge.¹²³

Beyond these shared features, some studies emphasize additional or more specific outcomes. For instance, XOSs were reported to improve BBB integrity,¹¹⁴ PSP-1 to prevent synaptic loss,¹²⁰ and DOP to protect against circadian rhythm disruption-induced deficits.¹¹⁸ While these observations may not be unique to a single compound, they illustrate the breadth of potential pathways through which prebiotics can influence brain health.

From a translational perspective, most of the evidence remains preclinical. To date, β -glucans supplementation has provided the first human data, showing improvements in subjective neurocognitive symptoms such as fatigue, sleep quality, and mood in patients with myalgic encephalomyelitis or chronic fatigue syndrome.¹²³ These early results highlight the potential of prebiotics as adjunctive strategies for cognitive decline.

Nevertheless, translating these findings into consistent clinical benefits remains challenging, as predicting and controlling gut microbiota outcomes is complex due to their effects on various microbial species. Ongoing research aims to understand how different dietary fibers influence this.¹²⁴ Prebiotics are often more effective when beneficial bacteria populations are already present in the gut. If these strains are missing due to pathological conditions, it is essential to reintroduce them and restore a healthy gut microbiota.¹²⁵ Understanding how prebiotics are metabolized and absorbed will therefore be crucial for designing effective human interventions.

Probiotics. The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as live microorganisms that, when administered in adequate amounts, provide health benefit to the host.¹²⁶ Typically, probiotics are used to introduce specific microbial strains that activate health-promoting processes in the gut microbiota and boost the production of beneficial metabolites. Advances in our understanding of the human gut microbiota have allowed the development of next-generation probiotics with promising potential for neuroprotection. According to international Food and Agriculture Organization (FAO) guidelines, probiotics are selected for their ability to withstand gastric transit; however, persistent colonization of the host is not

required for their beneficial effects, which are often mediated through transient interactions and metabolic activity during passage through the gastrointestinal tract.¹²⁷ In this section, we will review some of these probiotics with reported effects, based on both preclinical and clinical studies. Numerous preclinical studies have investigated the impact of probiotics on models of AD, aging, or chemically induced cognitive decline. Several strains of *Bifidobacterium* have demonstrated neuroprotective properties in rodent models. For example, *B longum* NK46 reduced the activation of NF- κ B induced by lipopolysaccharides (LPSs) in 5xFAD mice,¹²⁸ while *B breve* HNX26M4 decreased neuroinflammation and amyloid burden in APP/PS1 mice.¹²⁹ Furthermore, *B pseudocatenuatum* alleviated high-fat-diet-induced memory impairment.¹³⁰ Similarly, strains of *B breve* reduced A β deposition and improved behavioral performance in AD mouse models.¹²⁹ *Lactobacillus* strains have also shown benefits in this field: *L paracasei* PS23 improved memory and reduced oxidative stress in aged SAMP8 mice,¹³¹ and similar effects were found when *L paracasei* PS117 was administered to naturally aged mice.¹³² *L fermentum* mitigated cognitive decline in middle-aged mice,¹³³ and *L salivarius* reduced intestinal permeability and neuroinflammation in 5xFAD mice.¹¹⁹ Other *Lactobacillus* strains, such as *L plantarum* MA2 and *L rhamnosus* GR-1, showed benefits in cognitive decline when administered to different chemically induced AD rats, respectively.^{134,135} Some multi-strain formulations combining *Bifidobacterium* and *Lactobacillus*, such as ProBiotic-4 (a combination of *B lactis*, *L casei*, *B bifidum*, and *L acidophilus*), have also shown reduced intestinal permeability, attenuation of neuroinflammation, and improvements in spatial learning and memory in SAMP8 mice.¹³⁶ The genera *Akkermansia* has also shown amelioration in cognitive decline in various animal models: *A muciniphila* GP01 showed improvement of the intestinal barrier function, and a reduction in brain A β plaques, helping alleviating cognitive impairments and anxiety in APP/PS1 mice.¹³⁷ Another study using *A muciniphila* treatment in mice showed an improvement in the cognitive state by regulating brain-derived neurotrophic factor (BDNF) and serotonin levels.¹³⁸

Although most of the available evidence derives from preclinical models, several clinical studies have reported promising effects. In elderly subjects with MCI, *B breve* MCC1274 (2×10^{10} colony-forming units (CFU)/day for 24 weeks) showed a reduction in cognitive decline and halted brain atrophy, particularly areas associated with orientation and writing skills.¹³⁹ A clinical trial in middle-aged and older adults showed improved memory performance and favorable shifts in the gut microbiota composition after supplementation with *L rhamnosus* GG.¹³⁵ In AD patients, a multi-strain formulation including *B longum* subsp. *infantis* BLI-02, *B breve* Bv-889, *B*

animalis subsp. *lactis* CP-9, *B bifidum* VDD088, and *L plan-tarum* PL-02 administered for 12 weeks, increased serum BDNF levels and antioxidant capacity, with trends toward slower cognitive decline.¹⁴⁰ The effect of a mixture of different strains of *Lactobacillus*, *Bifidobacterium*, and *Lactococcus* was evaluated in 60-year-old MCI subjects, and it showed an equilibrated gut microbiota, higher levels of serum BDNF, enhanced cognitive functions (Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment Scale [MoCA]) and sleep quality after the treatment.¹⁴¹

One major issue is that probiotics can lose their effectiveness due to their sensitivity to stomach acid and digestive enzymes, thus diminishing their beneficial effects. Additionally, they are limited by low adhesion to the intestinal lining and poor retention in the gut, making difficult effective transient “colonization.”¹⁴² To address these challenges, researchers are developing new strategies to improve the oral bioavailability and targeted delivery of probiotics to the intestines. These new approaches may include techniques like microencapsulation,¹⁴³ hydrogel encapsulation,¹⁴⁴ integration with nanozymes,¹⁴⁵ nanocoating,¹⁴⁶ mineral coating,¹⁴⁷ and the use of optogenetic probiotic systems.¹⁴⁸

Overall, these findings suggest that probiotics can modulate cognition through MGBA pathways. However, despite encouraging preclinical and early clinical results, no probiotic strain has yet been granted an authorized health claim related to cognitive or psychological benefits by regulatory authorities such as the European Food Safety Authority (EFSA) or the U.S. Food and Drug Administration (FDA). Although several formulations are marketed as “psychobiotics,” their claims rely mainly on preliminary evidence that does not yet meet regulatory standards for substantiation. According to international expert consensus¹²⁶ and EFSA guidance,¹⁴⁹ establishing such claims requires strain-specific, well-designed randomized controlled trials (RCTs) in target populations such as MCI or early AD, including standardized cognitive end points, validated biomarkers, and mechanistic data linking microbiota modulation to cognitive outcomes. Moreover, inter-individual variability in microbiota composition must be considered when evaluating probiotic efficacy, as it likely contributes to the heterogeneous responses observed in clinical trials.

Synbiotics. In addition to single-component interventions, synbiotics—combinations of probiotics with complementary prebiotics—have gained attention as a strategy for improving translational consistency. Numerous studies have demonstrated that synbiotic formulations often exert greater benefits than probiotics alone, increasing the survival of probiotics during passage through the gastrointestinal tract.^{150,151} Prebiotics not only promote the growth of commensal bacteria but also enhance the survival and metabolic activity of co-administered probiotic

strains, thereby increasing their chances of exerting functional effects on the host. Indeed, synbiotics have been shown to outperform probiotics in metabolic, gastrointestinal, and immune-related outcomes. This broader evidence further supports the rationale for testing synbiotic strategies in cognitive decline, as they may provide a more reliable means of harnessing the MGBA.^{150,151}

Preclinical evidence indicates that synbiotic formulations often outperform their individual components in models relevant to cognition: For example, synbiotics combining *Enterococcus faecium* with *Agave* inulin improved spatial memory and hippocampal plasticity in aged rats,¹⁵² while combinations such as *Lactobacillus paracasei* plus XOS reduced neuroinflammation and restored cognitive performance in obese-insulin resistant rats.¹⁵³ Synbiotic preparations have also shown efficacy in AD models and in ischemic stroke paradigms, reducing amyloid burden and inflammatory markers, and improving behavioral read-outs.^{154,155} Some reviews also highlight the theoretical potential of synbiotics to support mental health and mitigate neurodegenerative processes.^{156–158} Human data are much more limited, but there are emerging trials and early reports about which synbiotic formulations are being investigated for cognitive end points,^{159,160} and a recent preprint reported synbiotic-associated improvements in working memory measures in an adult cohort.¹⁶¹ Taken together, these results suggest that synbiotics are a promising approach for addressing 2 key translational issues: Probiotic survival during passage through the GI tract and consistency of functional activity in the host gut microbiota; rigorous RCTs in target populations are needed in order to establish efficacy and safety.

The use of both nutraceuticals and gut microbiota-based therapies should ideally follow a personalized approach, given the high inter-individual variability in the gut microbiota composition and function. Differences in baseline microbial diversity, metabolic capacity, diet, age, sex, and host genetics strongly influence the production of the bioactive metabolites (eg, SCFAs, tryptophan derivatives, polyphenol metabolites) that mediate MGB interactions. This variability likely contributes to the heterogeneous outcomes observed across clinical trials of probiotics, prebiotics, and polyphenols, in which some participants benefit markedly while others show no effect. Personalized strategies may therefore include selecting specific strains or nutraceuticals according to an individual’s microbial and metabolic profile, or combining gut microbiota-targeted interventions with dietary and lifestyle factors to optimize outcomes. Emerging tools such as gut microbiota sequencing, metabolomics, and machine learning-based prediction models offer opportunities to stratify individuals and design precision nutraceutical approaches for cognitive decline.^{162–164} Although these approaches are still in their early phases of

translation, they represent a promising avenue for translating gut microbiota–nutraceutical interactions into clinically meaningful cognitive benefits.

Fecal Microbiota Transplantation. Fecal microbiota transplantation, the transfer of a stool-derived microbial ecosystem from a healthy donor to the gastrointestinal tract of a recipient host, aims to modify the recipient host's gut environment to address conditions associated with gut dysbiosis. It has emerged as a powerful approach to demonstrating the causal roles of the gut microbiota in host physiology.¹⁶⁵ Although fecal microbiota is not a probiotic (its main component consists of the bacterial species present in the stool of the donors), FMT was originally developed as a therapy for recurrent *Clostridioides difficile* infection.¹⁶⁶ Its application in models of aging and neurodegeneration provides compelling evidence that microbiota-targeted interventions can influence cognitive function. In rodent studies, transplantation of microbiota from young or healthy donors into aged or disease-model hosts improved the BBB and cognition, restored synaptic plasticity markers, and reduced neuroinflammation.^{167–169} Conversely, FMT from AD patients into germ-free or antibiotic-treated rodents exacerbated amyloid pathology and cognitive impairment,¹⁶⁷ highlighting the causal contribution of an altered gut microbiota to neurodegenerative processes. Although FMT is not a nutraceutical intervention, it provides unique mechanistic insights relevant to dietary modulation of the MGBA. Unlike probiotics, which deliver selected microbial strains, FMT involves the transfer of an entire microbial assemblage. The demonstration that FMT can modulate cognitive outcomes reinforces the rationale for developing safer and more controlled strategies, including nutraceuticals, that aim to reproduce some of these beneficial effects.¹⁶⁸

A major limitation of donor-derived FMT is the lack of standardization and safety concerns, since there is no universally validated and adopted protocol for screening the donors.^{170,171} Inter-donor variability, batch heterogeneity, and the risk of transmitting pathogens complicate large-scale clinical translation.¹⁵¹ For this reason, there is growing interest in defined microbial therapeutics, particularly synthetic microbial consortia, which are rationally designed mixes of cultured strains intended to replicate the functional attributes of donor-derived material. These standardized preparations are considered more reproducible, controllable, and safer than raw fecal suspensions.^{172,173} From the perspective of cognitive decline, such defined therapeutics are attractive because they can be deliberately formulated to enrich for functions mechanistically linked to neuroprotection, such as SCFA biosynthesis, tryptophan metabolism, or reinforcement of the intestinal barrier. Furthermore, they enable the dose standardization and rigorous quality control

required for regulatory approval as live biotherapeutic products, while minimizing the risk of transferring unwanted microbial genes—such as antibiotic resistance—or opportunistic pathogens.^{142,174,175} Preclinical studies with synthetic microbial mixtures have already shown modulation of host metabolic and inflammatory pathways, and ongoing clinical programs for microbiota-based therapeutics in other conditions (eg, *C difficile* infection) demonstrate the feasibility of this strategy.^{142,175}

Age and sex are critical determinants of FMT outcomes. Aging reshapes the composition and metabolic output of the gut microbiota, and transplantation from young donors into aged hosts can partially restore microbial diversity and improve cognitive and synaptic endpoints.^{168,169} Moreover, there is increasing recognition of sex-specific responses: Males and females differ in baseline microbiota composition, immune signaling, and susceptibility to neuroinflammation, and some studies report sex-dependent efficacy of FMT interventions.^{176,177} Unfortunately, many preclinical reports fail to specify donor or recipient sex, limiting the interpretation and translational relevance. Future investigations should systematically incorporate age and sex as biological variables to improve the robustness and applicability of microbiota-targeted interventions, including nutraceuticals.

Overall, although neither donor-derived FMT nor synthetic microbial therapeutics qualify as nutraceuticals, they provide strong proof-of-concept that reconfiguring the gut microbiota can modulate cognitive trajectories. Insights from these approaches may inform the design of nutraceutical interventions that selectively enhance equivalent microbial functions, such as the production of neuroactive metabolites or the maintenance of intestinal barrier integrity, thereby converging on complementary pathways for cognitive protection.

It is important to note that the rationale for targeting the microbiota with nutraceuticals is supported by causal evidence (as outlined in the preceding paragraphs of this section): Experimental models using germ-free animals, antibiotic depletion, and FMT, which clearly demonstrate that microbial communities can shape cognitive outcomes and even transmit cognitive phenotypes between hosts.¹⁶⁷ These observations substantiate microbiota as more than an associative factor—rather as a mechanistic driver of cognition, thereby reinforcing its role as a therapeutic target in the context of cognitive decline.

CONCLUSIONS AND FUTURE PERSPECTIVES

The present review highlights the potential of nutraceuticals, such as vitamins, polyphenols, omega-3 fatty acids, and CoQ10, together with gut microbiota-targeted therapies, including prebiotics, probiotics, and synbiotics, to promote neuroprotection, reduce neuroinflammation,

and support cognitive health. Omega-3 PUFAs enhance neuronal integrity and reduce neuroinflammation, while vitamins like C, D, and K are crucial for neurotransmission, neuroprotection, and cognitive performance. Polyphenols and isothiocyanates such as resveratrol, quercetin, or sulforaphane exhibit potent antioxidant and anti-inflammatory properties, offering a promising approach to slowing or preventing cognitive decline. Further studies should focus on combining various nutraceuticals to explore potential synergistic effects of these bioactive compounds.

Gut microbiota-based interventions are particularly promising, because they act on central mechanisms of the GBA, including intestinal barrier integrity, immune modulation, and systemic inflammation, all of which are closely related to neurodegenerative diseases. Prebiotics and probiotics can enhance gut health and restore a healthy balance in the GBA, thus potentially contributing to better cognitive outcomes. Synbiotics, by combining probiotics with targeted prebiotics, may represent a more reliable approach than probiotics alone, enhancing microbial survival and functional activity.

Probiotics can also enhance the bioavailability of bioactive compounds. For example, sulforaphane, a compound found in cruciferous vegetables, is derived from glucoraphanin through the enzymatic action of myrosinase, which is naturally present in these plants. Since cooking significantly reduces endogenous plant myrosinase activity, sulforaphane formation and bioavailability are significantly diminished. In this sense, probiotics strains with demonstrated myrosinase-like activity could offer a promising approach to overcoming this limitation, potentially increasing the levels of sulforaphane that reach the circulatory system. By enhancing sulforaphane bioavailability, these probiotics could play a beneficial role in neuroprotection and cognitive health.

In conclusion, a comprehensive approach that combines dietary strategies, nutraceuticals, and gut microbiota-targeted therapies offers a promising low-risk avenue for preventing and mitigating cognitive decline. As the global population ages, such innovative and personalized interventions could play a key role in improving quality of life and reducing the burden of neurodegenerative diseases. Despite these promising prospects for nutraceutical and gut microbiota-based therapies, further research is needed to fully understand their long-term impacts and optimize therapeutic strategies. Large-scale clinical trials are crucial to confirm the effectiveness of these interventions and identify the most effective combinations for personalized treatments, and future research should explore synergistic effects of combining prebiotics with specific nutraceuticals such as polyphenols to optimize cognitive outcomes.

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Supplementary Material

[Supplementary Material](#) is available at *Nutrition Reviews* online.

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Conflicts of Interest

None declared.

Data Availability

The data underlying this article are available in the article and in its online [supplementary material](#).

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