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Magnesium and Brain Health across the Lifespan: A Multilevel Review of Nutritional Sources and Molecular Mechanisms Underlying Cognitive Resilience

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ABSTRACT: Aging, neurodegenerative disorders, metabolic disorders, and chronic inflammation are all conditions that are linked to cognitive dysfunction, making it a major health problem worldwide. The mineral magnesium, Mg^{2+} , is essential for a variety of enzymatic processes and is known to be crucial in neuronal functions, synaptic plasticity, energy metabolism, and cognitive processes. This review aims to provide a summary of the current evidence on dietary, marine and microbial, as well as supplemental sources of magnesium, focusing on magnesium bioavailability, brain magnesium homeostasis and molecular mechanisms involved in cognitive resilience. There are several ways in which magnesium supports brain health, such as regulating the activity of the N-methyl-D-aspartate (NMDA) receptor, supporting calcium homeostasis, supporting mitochondrial ATP production, and regulating oxidative stress and neuroinflammation. It also affects intracellular signaling, specifically ERK–CREB–BDNF signaling, that are crucial for the processes of neurogenesis, synaptic remodeling and memory formation. Evidence also continues to grow of interactions between magnesium, gut–brain axis and neuroimmune regulation. The specific importance of magnesium deficiency is supported by consistent preclinical findings of impaired synaptic function, neuroinflammation and cognitive dysfunction, while magnesium supplementation has been demonstrated to be supportive of learning and memory in experimental models. Evidence from human observational studies and intervention trials, however, is limited and variable, in study design, magnesium formulations, dosage regimen, and cognitive outcome measures. In addition, difficulty in evaluation of magnesium status makes the results of clinical assessments hard to interpret. In conclusion, the existing evidence highlights the significance of magnesium in brain health and cognition. The use of magnesium as a potentially beneficial nutritional factor for cognitive resilience is recommended but further well-designed randomized controlled trials are required to confirm its clinical efficacy, optimum supplementation protocols and long-term cognitive outcomes.

1. INTRODUCTION

One of the major problems responsible for a decline in mental abilities such as memory, learning, reasoning, attention, and decision-making is cognitive dysfunction [1]. It is one of the main conditions in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and metabolic, vascular, and psychiatric conditions. Its symptoms include memory loss, confusion, difficulty concentrating, poor problem-solving ability, reduced processing speed, language disturbances, poor judgment, and

disorientation [2], [3]. The number of cases of cognitive impairment continues to rise with increasing age, with an estimated 150 million dementia cases worldwide until 2050. If left untreated, it affects quality of life, which highlights the urgent need for treatment [4]. In India, the incidence of cognitive disorders increases sharply due to various factors, such as aging, stress, the environment, poor diet, nutrient deficiency, and many other diseases. Recent studies have shown that 7–8% of Indians aged 60 years show measurable cognitive impairment and Alzheimer’s disease in nearly 4 million cases [5], [6], [7], [8]. Magnesium (Mg^{2+}) plays a very important role in maintaining neuronal and synaptic health and is the fourth most abundant nutrient in the human body. Natural magnesium is widely distributed in green leafy vegetables (spinach, kale), nuts, legumes, seeds (pumpkin seeds), seafood (mackerel, seaweed), and dairy products [9]. It is also present in drinking water, particularly in “hard water” regions. Recent studies have shown sources to include microbial and fermented foods enriched with magnesium complexes. Despite the various sources, over half of the global population, including large segments of the Indian population, has failed to meet the recommended daily magnesium intake, resulting in various conditions, such as cognitive dysfunction [10], [11], [12]. It has various pharmacological activities, such as neuroprotective [13], cardioprotective [14], antidiabetic [15], anti-inflammatory, antioxidant, muscle relaxant, anxiolytic [16], bone-strengthening [17] and anticancer effects [18]. It stabilizes the cardiac rhythm, reduces hypertension, and improves insulin sensitivity and glucose homeostasis. The anti-inflammatory and antioxidant properties of magnesium inhibit NF- κ B signaling and support mitochondrial function. Magnesium is a crucial regulator of cell and neurological functions and defines the connection between mineral balance and neurocognitive outcomes [19], [20]. Magnesium enhances cognitive neurotrophic factors and controls NMDA receptors, calcium signals, and ATP synthesis. Mg deficiency induces oxidative stress, microglial inflammation, NMDA receptor overactivation, and poor synaptic plasticity, which results in cognitive impairment. In preclinical and clinical models, magnesium supplementation was able to reduce neuroinflammatory markers, improve learning and memory, and regenerate synaptic function [21], [22], [23]. The process by which magnesium affects cognitive processes remains ambiguous regardless of the data provided by the clinical, biological, and nutritional sectors. Therefore, the primary objective of this review is to examine how magnesium availability, absorption, and brain bioavailability influence cognitive resilience across the lifespan. We focus on the relationships among dietary, marine, microbial, and supplemental sources of magnesium; their ability to modulate brain magnesium concentrations; and the molecular mechanisms through which magnesium regulates synaptic plasticity, neuroinflammation, mitochondrial function, neurogenesis, and cognitive performance. Particular emphasis is placed on evidence linking magnesium status with age-related cognitive decline and neurodegenerative disorders while critically evaluating the translational potential and current limitations of magnesium-based interventions in humans.

2. SOURCES AND BIOAVAILABILITY OF MAGNESIUM

2.1 Dietary sources: plants, seafood, dairy, and water

Magnesium is found in a variety of foods. Plant sources are particularly rich, because of the part magnesium plays in the chlorophyll. Foods high in magnesium includes whole grains, Leafy greens (Spinach, Kale), Legumes, Nuts (Almond, Cashew), Seeds (Pumpkin, Flax, Sunflower). Dark chocolate and cocoa are other good sources of magnesium. The mean amounts of magnesium in these foods vary from 100–500 mg/100 g [24]. Seafoods such as mackerel [25], tuna [26], salmon, and shellfish [27] contribute moderate amounts (30–150 mg/100 g). Although dairy products are low in Mg, the milk’s lactose and casein peptides increase the absorption of minerals. Additionally, the mineral composition of drinking water can provide 5-50 mg/L of magnesium, with “hard water” areas generally having relatively high bioavailability of magnesium. The jejunum and ileum are the two main sites of dietary magnesium absorption, via passive paracellular diffusion and active transport in the ileum through TRPM6/7 channels. Only ~30-50% of the magnesium that is ingested is absorbed, however, fiber, phytates and calcium/phosphorus ratios affect bioavailability [28], [29]. The various sources of magnesium are given in Table 1.

Table 1. Dietary, marine, and microbial sources of magnesium

Source	Food/Species Example	Mg ²⁺ Content (mg/100 g)	Form (organic/inorganic)	Bioavailability Notes	Ref
Plant-based	Spinach (<i>Spinacia oleracea</i>)	79	Organic (Mg-chlorophyll complex)	High absorption (~40%); reduced by oxalates	[30]

	Pumpkin seeds (<i>Cucurbita pepo</i>)	535	Organic	Excellent bioavailability; lipid co-factors enhance uptake	[31]
	Almonds (<i>Prunus dulcis</i>)	270	Organic	Fat-rich matrix improves Mg absorption	[32]
	Legumes (lentils, beans)	120–160	Organic	Phytates reduce absorption; soaking/fermentation improves it	[33]
Marine/seafood	Atlantic mackerel	97	Inorganic (MgCl ₂ , MgSO ₄)	Moderate; enhanced by omega-3 s	[34]
	Brown seaweed (<i>Sargassum muticum</i>)	550	Mg–alginate complex	Highly bioavailable; synergistic polyphenols	[35]
	Green algae (<i>Ulva lactuca</i>)	410	Mg-sulfate	Promotes SCFA production; gut–brain benefits	[36]
Microbial/Fermentation	<i>Lactobacillus plantarum</i> –fermented soy	—	Mg-lactate complex	Enhanced intestinal Mg uptake; probiotic benefit	[37]
	<i>Saccharomyces cerevisiae</i> –enriched kefir	—	Mg-organic salts	Improved Mg bioavailability and cognitive biomarkers	[38]
Water (hard water regions)	Mineral water	5–50 mg/L	MgCO ₃ + MgSO ₄	Easily absorbed; consistent intake source	[39]

2.2 Marine and seaweed-derived magnesium

Marine and seaweed-derived magnesium represents one of the most bioavailable and nutritionally dense natural sources of magnesium because of its unique chemical forms and synergistic bioactive compounds [40]. Seeds such as *Sargassum*, *Ulva lactuca*, *Gracilaria*, and brown algae accumulate magnesium as Mg–alginate, Mg–sulfate, and other organic complexes that dissolve easily and are absorbed more efficiently than many inorganic magnesium salts. These marine sources are particularly rich because seawater itself contains abundant dissolved minerals that algae concentrate within their cellular matrix [41]. In addition to simply supplying magnesium, seaweed delivers additional bioactive components such as polyphenols, sulfated polysaccharides, carotenoids, and omega-3 precursors that enhance antioxidant, anti-inflammatory, and gut-supportive functions. Together, these compounds help reduce oxidative stress, modulate cytokine activity, and improve gut barrier integrity, ultimately supporting cognitive and metabolic health [42]. Recent studies have shown that seaweed-derived magnesium can promote beneficial microbiome changes and increase the production of short-chain fatty acids, which influence the gut–brain axis and neuroplasticity [43]. Marine magnesium therefore offers a multifunctional approach: improving mineral status, enhancing neuroprotective pathways, and supporting immune balance. Given its high solubility, natural origin, and additional therapeutic components, marine and seaweed-derived magnesium has become an emerging nutritional candidate for cognitive enhancement and overall neurological health [44].

2.3 Microbial sources and fermentation-based magnesium

Microbial and fermentation-based sources of magnesium represent an emerging and highly promising approach for enhancing magnesium bioavailability and supporting brain health [45]. Certain probiotic bacteria, such as *Lactobacillus plantarum*, *Bifidobacterium longum* [46], and specific *Saccharomyces* yeast strains, have the natural ability to accumulate, chelate, or convert magnesium into organic, highly absorbable complexes during fermentation. When foods such as soy, kefir [47], tempeh [48], or fermented grains undergo microbial processing, these microbes enrich the food matrix with magnesium-lactate, magnesium-organic salt complexes, and other biologically active forms. These forms are better absorbed in the intestine because of their high solubility and ability to bypass inhibitors such as phytates. Moreover, microbial fermentation improves gut colonization

by beneficial bacteria, which further enhances magnesium uptake through improved intestinal barrier function and increased expression of magnesium transport channels such as TRPM6/7 [49], [50].

In addition to mineral absorption, magnesium-enriched fermented foods influence the microbiota–gut–brain axis. Studies have shown that probiotics associated with magnesium-enriched fermentation modulate tryptophan metabolism, serotonin pathways, and short-chain fatty acid production factors crucial for cognition, the stress response, and neuroinflammation control [51], [52]. Mahboobi *et al.* investigated whether nine weeks of combined probiotic (LGG®, BB-12®) and magnesium chloride supplementation could improve mood, cognition, intestinal barrier markers, and inflammation in adults with obesity and a depressed mood. Compared with the placebo, the intervention did not significantly affect mood, cognitive score, zonulin, or LPS. However, supplementation led to a significant reduction in CRP, indicating decreased systemic inflammation [53]. Early research demonstrated that these foods can improve cognitive biomarkers, reduce systemic inflammation, and support healthy neurotransmission. Although human data are still limited, fermentation-derived magnesium represents a sustainable and biologically potent strategy for improving cognitive function and overall neurological health.

2.4 Chemical forms and bioavailability

Magnesium exists in different chemical forms, which differ in their solubility, absorption and capacity to reach their target tissues, such as the brain (Table 2) [54]. Commonly used inorganic forms include magnesium oxide (MgO) and magnesium chloride (MgCl₂); however, their bioavailability varies greatly. MgO is insoluble, whereas MgCl₂ is highly soluble and offers intermediate systemic bioavailability [53]. Organic magnesium salts such as magnesium citrate, glycinate, malate and taurinate are well absorbed, as they are conveniently soluble complexes that are stable and successfully cross through the intestinal lining. Among the various magnesium formulations, magnesium L-threonate (MgT) has attracted considerable attention because preclinical studies suggest enhanced brain magnesium delivery compared with several conventional magnesium salts. Experimental evidence indicates that MgT may improve synaptic plasticity, BDNF expression, and long-term potentiation in animal models; however, robust clinical evidence demonstrating consistent cognitive benefits in humans remains limited [55]. These findings suggest that MgT is a good cognitive-enhancing therapy. Formulations made with nanoparticles (e.g., MgO nanoparticles) have higher solubility and could be delivered to the brain more effectively, albeit in preliminary research [56]. On the whole, bioavailability is determined by solubility and transport pathways (TRPM6/7 channels) and chemical ligands that are bound to magnesium. The choice of the form is also important because variations in the formulas assist various physiological processes, such as gut absorption and metabolic balance, specific neuroprotection and cognitive enhancement [57].

MgT has been demonstrated in preclinical trials to cross the blood–brain barrier (BBB), where it elevates hippocampal Mg²⁺ concentrations and long-term potentiation (LTP). Xiong *et al.* reported that MgT promoted memory, stimulated BrdU/doublecortin-positive newborn neurons, elevated the expression of doublecortin, and activated ERK/CREB signaling, all of which were counteracted by the ERK blocker PD0325901. In general, MgT reversed neurogenesis and impaired cognitive decline, which was suggested to be mediated by ERK/CREB-involved pathways [58]. Wang *et al.* reported that the changes in the gut microbial composition induced by MgT included a reduction in *Allobaculum* and an increase in *Bifidobacterium* and *Turicibacter* species, changes in serum metabolites associated with neurodegeneration networks, and recovery of tight junction proteins in the intestine [59]. Chronic MgT supplementation in rodents increased spatial learning, working memory, and synaptic density. These results confirm that MgT can enhance cognition. Despite encouraging findings, the current evidence supporting magnesium L-threonates remains predominantly preclinical. Most studies have been conducted in rodent models, which may not fully reproduce the complexity of human cognitive disorders. Although several human studies have reported improvements in memory and cognitive performance, these trials generally involved small sample sizes and relatively short intervention periods. Furthermore, the optimal dosage, duration of treatment, and long-term safety profile remain incompletely understood. Therefore, magnesium L-threonate should currently be considered a promising therapeutic candidate rather than an established cognitive intervention.

Table 2. Chemical forms of magnesium used in research and supplements: properties and BBB penetration.

Magnesium Form	Solubility/Absorption (%)	Brain Bioavailability/BBB Penetration	Key Mechanistic
Magnesium oxide (MgO)	Low (~4%)	Minimal	Common supplement; poor GI absorption
Magnesium chloride (MgCl₂)	Moderate (~30%)	Limited	Improves serum Mg; little CNS penetration
Magnesium citrate	High (~45%)	Low–moderate	Organic acid enhances solubility
Magnesium glycinate	High (~60%)	Moderate	Chelate form; gentle on GI tract
Magnesium malate	Moderate	Moderate	Aids ATP synthesis; mitochondrial support
Magnesium-L-threonate (MgT)	~45–50%	High (crosses BBB)	Elevates hippocampal Mg ²⁺ , enhances LTP, BDNF
Magnesium nanoparticles (MgO NPs)	Variable; high at nanoscale	Potentially high	Enhanced BBB transport, antioxidant capacity

3. BRAIN MAGNESIUM HOMEOSTASIS AND BLOOD–BRAIN BARRIER TRANSPORT

Brain magnesium homeostasis depends on controlled uptake from the blood (mainly via the choroid plexus into the CSF) and regulated cycling among neurons, astrocytes and endothelial cells. Tight junctions at the BBB (claudins-1/3/5/12) probably block passive Mg²⁺ leakage, whereas TRPM- family channels (TRPM7/TRPM6) and other transporters (MagT1, SLC41, CNNM, NIPA) on endothelial membranes mediate active transcellular uptake [60]. For example, Castiglioni *et al.* (2023) used TRPM7-silenced human endothelial (HUVEC) cells and reported that the loss of TRPM7 did not alter total intracellular Mg²⁺ but triggered the upregulation of the MagT1 transporter (with unchanged SLC41A1 or mitochondrial Mrs2 levels), suggesting that MagT1 compensates to preserve Mg²⁺ [61]. CNNM2 (cyclin M) has been implicated in neural Mg²⁺ uptake. Arjona *et al.* (2014) identified CNNM2 mutations in human patients with hypomagnesemia, seizures and brain malformations and reported that CNNM2 enhances Mg²⁺ uptake via TRPM7 in cells, whereas zebrafish *cnm2* knockdown caused low brain Mg and developmental defects rescued by wild-type CNNM2 [62]. Similarly, Liu *et al.* (2023) reported that chronic hypomagnesemia in mice caused seizures and brain inflammation, but TRPM7 kinase-deficient mice were protected from seizure-related death, highlighting the role of TRPM7 in modulating the effects of neuronal Mg²⁺ [63]. These studies (mouse/rat vs. human) illustrate parallels: rodent models allow gene manipulation and monitoring of brain Mg, whereas human data come from genetic syndromes (e.g., CNNM2) or CSF measurements. Notably, animal studies of TBI benefit from Mg infusion, whereas a human TBI trial (Temkin *et al.*, 2007) failed, suggesting species differences or compromised BBB/BCSFB Mg transport in disease [64]. In summary, brain Mg²⁺ requires transcellular transport at the BBB (via TRPM7/MagT1, etc.), intracellular buffering (mitochondrial Mrs2 and binding proteins), and possibly astrocytic regulation (the details of which are unclear). Outstanding questions include whether any brain capillary claudins permit Mg²⁺ flux and how well animal findings translate to humans (e.g., MRI of brain Mg is still emerging).

4. ASSESSMENT OF MAGNESIUM IN THE CNS

4.1 Serum Magnesium

The most commonly used indicator of magnesium status is serum magnesium, which is cheap, accessible in many laboratories and routinely sampled. However, it is not a useful measure of total body magnesium stores, as only about 0.3–1% of total body magnesium is found in the extracellular compartment and most is stored in bone and soft tissues [65]. Even in magnesium deficiency, the serum level of magnesium is tightly controlled by the kidneys, gastrointestinal tract and endocrine systems. Therefore, normal levels of serum magnesium can occur along with a very low level of magnesium in the cells. The REGARDS cohort provides additional support of the role of magnesium in cognitive health. The results of this prospective study of 2,063 US adults showed that hypomagnesemia (<0.75 mmol/L) was significantly associated with the development of cognitive impairment compared with serum magnesium levels within normal range [66]. The implications of these findings are that keeping magnesium in balance could be crucial to maintaining cognitive function as age increases. However, the serum magnesium levels do not necessarily reflect the intracellular or CNS levels of magnesium and, therefore, cannot be used as a surrogate marker.

4.2 Cerebrospinal Fluid Magnesium

The concentration of magnesium in the cerebrospinal fluid (CSF) is a more direct measurement of magnesium status in the CNS than the concentration in serum, since it provides information about the ionic environment around neurons and glial cells. The studies have confirmed that the concentration of magnesium in CSF is usually higher than in blood and it is preserved independently through selective transport mechanisms across blood–brain and blood–CSF barrier. McKee et al showed that variation in plasma magnesium does not necessarily reflect that in CSF, suggesting the concept of autonomous CNS magnesium homeostasis [67]. This physiological compartmentalization is especially important for neurodegenerative disorders as abnormal magnesium transport can lead to dysfunction of the neurons. Experimental research has indicated that decreased brain Mg levels cause deficits in synaptic plasticity, LTP and memory formation. Routine CSF magnesium measurement is impractical, however, due to the invasiveness of lumbar puncture and the fact that this is not suitable for large population studies [68]. Therefore, although clinically relevant, CSF magnesium use is largely limited to specialized clinical studies and mechanistic research and is not routinely used for nutritional assessment.

4.3 Erythrocyte and Intracellular Magnesium

Since magnesium is largely intracellular, the measurement of erythrocyte magnesium and other intracellular magnesium pools might better represent magnesium status than serum levels. In the erythrocytes, magnesium is present in much greater amount than in plasma, and may have a better relationship to long-term magnesium availability. In a ground-breaking research, Xiong et al. demonstrated that the ICME and hippocampus were positively correlated with brain Mg levels as well as memory performance, indicating ICME as a potential biomarker for brain Mg status [69]. Before erythrocyte magnesium can be used as a reliable biomarker in clinical or research settings, there is a need to standardize procedures and methods for sampling and analysis.

4.4 Neuroimaging-Based Assessment

Neuroimaging technology has been developed in recent years, allowing a noninvasive assessment of magnesium metabolism in the living human brain. One of these methods, in particular, is of great promise: phosphorus magnetic resonance spectroscopy (^{31}P -MRS) estimates the concentration of free magnesium ions in the intracellular space by measuring the signals of magnesium-bound adenosine triphosphate (ATP). ^{31}P -MRS was employed in a cross-sectional study to measure the magnesium (Mg^{2+}) level in the cerebrum in women with preeclampsia, normal pregnancies, and healthy nonpregnant women [70]. Recently, there has been an interest in neuroimaging research aimed at examining the links between cerebral magnesium status, mitochondrial function and cognition. The present observations support the notion that brain magnesium contributes to the regulation of neuronal energy metabolism, synaptic activity and neuroprotection [71].

4.5 Current Challenges and Future Perspectives

Correctly assessing the magnesium status continues to be one of the most difficult challenges in nutritional neuroscience and neurodegenerative disease research. Currently none of the biomarkers fully represents whole body magnesium stores, intracellular availability of magnesium, and brain magnesium homeostasis [72]. But these techniques are still technically complex,

expensive and only applicable to specialized research environments. Overall, current evidence indicates that none of these biomarkers will be able to measure the whole body/brain level of magnesium. Multimodal approaches including serum, intracellular and new neuroimaging assessment instruments should be pursued in future studies to enhance the evaluation of magnesium homeostasis and to better delineate its relationship with cognitive resilience and progression of neurodegenerative disease.

5. CELLULAR AND MOLECULAR MECHANISMS OF MAGNESIUM IN THE BRAIN

5.1 NMDA receptor modulation and synaptic plasticity

Magnesium is a pivotal part of NMDA receptor regulation and the healthy plasticity of synapses and is pivotal to learning and memory [73]. Mg^{2+} is a natural voltage-dependent block of the NMDA receptor channel at rest membrane potentials and eliminates the excessive influx of Ca^{2+} and neuronal excitotoxicity [74]. Mg^{2+} is released through the receptor channel when the neuron depolarizes in relation to synaptic activity to permit the regulated entry of Ca^{2+} necessary to strengthen synapses and induce long-term potentiation (LTP) (Figure 1). Dehydration of magnesium disturbs this troponym and causes overactivation of NMDA receptors, ultimately increasing intracellular Ca^{2+} , oxidative stress and dysfunctional synaptic messages [75].

Supplementation replenishes normal NMDA receptor gating, stabilizes postsynaptic responses and improves the LTP core during the process of memory consolidation. Preclinical research has demonstrated that an increase in the amount of magnesium in the brain increases the rates of phosphorylation of NMDA receptor subunits, enhances the likelihood of release of presynaptic neurotransmitters and strengthens synaptic connectivity. These transformations cause improvements in behavioral activities that focus on spatial and working memory.

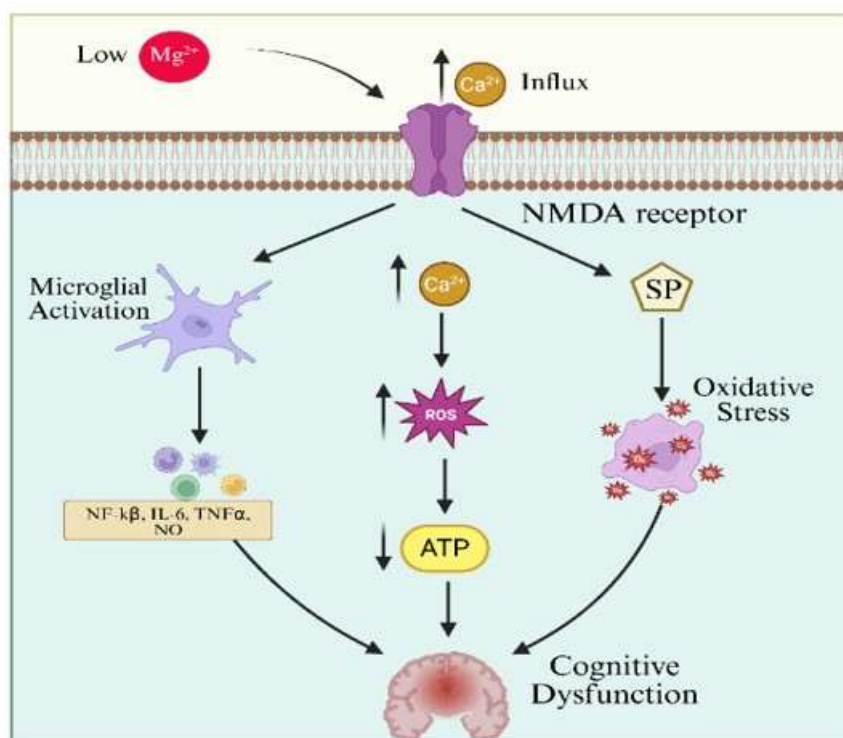


Figure 1: Role of magnesium in cognitive dysfunction

5.2 Intracellular signaling: Ca^{2+} , ERK/CREB, and neurotrophins

Magnesium plays a crucial intracellular regulatory role by modulating calcium dynamics and activating key signaling pathways that support neuronal survival, plasticity, and memory formation [76]. As a natural calcium antagonist, Mg^{2+} helps maintain Ca^{2+} homeostasis by regulating voltage-gated calcium channels and ATP-dependent calcium pumps. Adequate intracellular magnesium may help prevent calcium overload, which is a major trigger for mitochondrial dysfunction, ROS production, and

neuronal injury. By stabilizing Ca^{2+} levels, magnesium creates a favorable environment for controlled synaptic signaling (**Figure 1**) [77], [78].

In addition to calcium regulation, Mg^{2+} activates the ERK/CREB signaling cascade, a central pathway that drives the expression of genes related to learning and memory. The activation of ERK leads to the phosphorylation of CREB, a transcription factor required for the synthesis of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [79]. BDNF supports synaptic growth, dendritic spine formation, and long-term potentiation. Preclinical studies have consistently shown that magnesium supplementation may increase hippocampal BDNF mRNA and protein levels, which are correlated with enhanced cognitive performance. Through these mechanisms of calcium stabilization, ERK/CREB activation, and neurotrophin upregulation, magnesium strengthens the molecular framework that underlies synaptic plasticity and neural resilience [80].

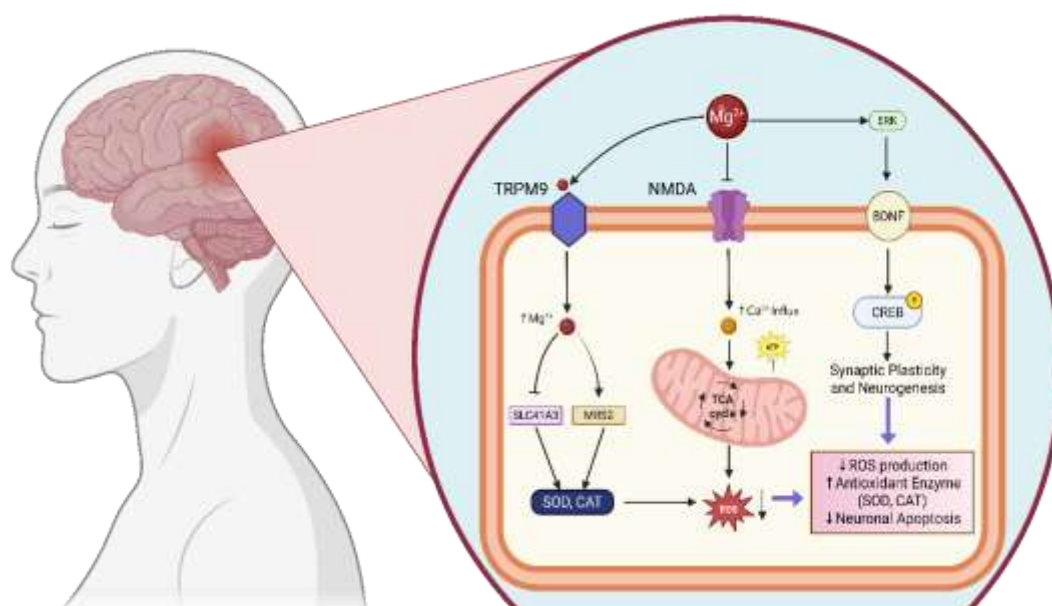


Figure 2: Magnesium-mediated neuroprotection and synaptic plasticity. NMDA (N-methyl-D-aspartate), CREB (cAMP response element-binding protein), SOD (superoxide dimerization), MRS2 (mitochondrial RNA splicing 2), SLC43A1 (solute carrier family 41, member 3), BDNF (brain-derived neurotrophic factor), TRPM9 (transient receptor potential melastatin 9), CAT (catalase), ROS (reactive oxygen species), ERK (extracellular signal-regulated kinases)

5.3 Neuroinflammation and immune modulation

A reduced level of magnesium promotes the activity of microglia and astrocytes, the main immune cells in the brain, and the release of proinflammatory cytokines, which include IL-1, TNF- α , and nitric oxide [81]. This inflammatory condition interferes with synaptic plasticity and neurotransmission and accelerates neuronal injury. Similarly, magnesium deficiency promotes the activation of NF- κ B, a major controller of the expression of inflammatory genes that further increase neuroinflammatory reactions [82].

Magnesium supplementation reportedly attenuates these pathological processes, inhibits NF- κ B signaling, slows the expression of inducible nitric oxide synthase (iNOS) and inhibits the release of inflammatory mediators [83]. Moreover, magnesium elevates the levels of anti-inflammatory cytokines, such as IL-10, to restore immunity. The results of preclinical studies have demonstrated that the use of magnesium decreases the expression of microglial activation markers (Iba1 and GFAP) and enhances cognitive performance. Furthermore, magnesium is an antioxidant that acts by stabilizing the work of the mitochondria and decreasing the level of ROS and, additionally, neural tissue protection against mitochondrial-induced injury caused by inflammation [84].

5.4 Mitochondrial function, oxidative stress, and energy metabolism

The importance of magnesium as a regulator of mitochondrial activity and cellular energy metabolism is hard to exaggerate, and this nutrient is needed to maintain the health of neurons [85]. As a necessary cofactor for ATP synthase, Mg^{2+} enables the

generation of ATP in the mitochondria, which is a biologically active complex, Mg-ATP, that drives most neuronal functions. A low concentration of magnesium causes inefficiency in mitochondrial respiration and a subsequent decrease in ATP production and destabilization of the mitochondrial membrane. This triggers a chain of deficiencies, such as the inability of electrons to be transported properly, a greater number of electrons leaking out, and the excessive formation of reactive oxygen species (ROS) [86], [87].

Thus, magnesium deficiency facilitates oxidative stress, lipid peroxidation and mitochondrial DNA damage, which leads to neurodegeneration [71]. On the other hand, magnesium supplementation reinstates the stability of the mitochondrial membrane, improves ATP production, and maximizes the ideal activity of antioxidative enzymes such as superoxide dismutase (SOD) and glutathione peroxidase. Preclinical trials have shown that supplementation with magnesium strongly reduces the accumulation of ROS and neuronal apoptosis and enhances cognitive function in aging, Alzheimer's, and ischemic injury models [88], [89].

5.5 Gut–brain axis and microbiome links

The role of magnesium in the control of the gut–brain axis is becoming increasingly recognized, mainly because of the effects of this element on the microbial composition, intestinal integrity, and metabolite synthesis [74]. Magnesium deficiency alters the diversity and stability of the gut microbiota, increasing the abundance of proinflammatory bacterial species and limiting the abundance of suitable taxa, including *Akkermansia muciniphila* and *Bifidobacterium adolescentis*. This dysbiosis enhances gut permeability or leaky gut, which permits the entry of endotoxins such as LPS into the bloodstream and induces systemic neuroinflammation, which ultimately damages cognitive ability [90].

In most of these studies, magnesium supplementation reversed these effects. Sufficient Mg^{2+} increases gut protective functions by improving tight junction protein synthesis and decreasing intestinal inflammation [91]. It also enhances the development of commendable microorganisms that synthesize short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which are also known to regulate immune activity, serotonin synthesis, and neurofunction. SCFAs are able to enter the blood brain and can affect neurotrophic pathways, such as BDNF release and the maturation of microglia [92].

Marine sources of magnesium, especially seaweed-based Mg complexes, demonstrate even better symbiotic effects when mineral supplementation is added in combination with prebiotic polysaccharides, which in turn increases the diversity of gut microbes. Magnesium has pronounced indirect effects on brain function through the gut–brain axis via microbiome regulation, SCFA improvement, gastrointestinal barrier repair and decreased systemic inflammation [93], [94]. Despite growing interest in the relationships among magnesium, the gut microbiome, and cognitive function, current evidence remains largely preclinical. Most studies demonstrating microbiota-mediated neuroprotective effects have been conducted in animal models, whereas studies investigating human intervention are limited. Moreover, the causal mechanisms linking magnesium-induced microbial alterations to improvements in cognition have not been fully established. Further longitudinal and randomized clinical studies are needed to clarify the contribution of the gut–brain axis to the cognitive benefits associated with magnesium supplementation.

5.6 Adult hippocampal neurogenesis and structural plasticity

Magnesium has been shown to stimulate neurogenesis and structural plasticity in the adult hippocampus, which are crucial for supporting learning, forming memories and resisting the brain from aging-induced cognitive impairment. In the dentate gyrus, the main location of adult neurogenesis, Mg^{2+} levels are conducive to proliferation, partialization, and differentiation of neural antecedents [95]. A lack of magnesium affects these processes, resulting in the inability to form new neurons and a poor circuit in the hippocampus.

Among the most promising results are that an ingestible form of magnesium, magnesium-L-threonate (MgT), can substantially increase the extent of synaptic perplexity and the number of dendritic spines in the hippocampus. Compared with other forms, MgT effectively increases the levels of Mg^{2+} in the hippocampus, which leads to the expression of synaptic proteins, including synaptophysin and PSD-95 [96]. Close to these structural variations are positive results in memory performance, such as augmentations of long-term potentiation (LTP), spatial navigation and working memory.

Moreover, magnesium enhances the assembly and stabilization of tiny dendritic spine neuronal protrusions, which are essential for communication through synapses. The added density and maturation onto the spine provide a structural advantage to better

neural networks. Magnesium also directly increases the activity of neurotrophic pathways, especially BDNF-CREB signaling, to support neurogenesis and synaptic remodeling, as shown in **Figure 2**.

6. IN VIVO AND IN VITRO EVIDENCE

The findings of rodent models of cognitive impairment in scopolamine, amyloid, diabetes, aging, and ischemia-induced and in vivo studies have demonstrated that magnesium supplementation is a reliable method for increasing behavioral performance in the Morris water maze, Y maze, radius arm maze, passive avoidance, and novel object recognition tests (**Table 3**). These results suggest advantages similar to those of spatial learning, working memory, and recognition memory. The mechanism has been mechanistically confirmed in in vitro studies utilizing neuronal and glial cell cultures. Magnesium improves neuronal survival by inhibiting A β -induced toxicity and increasing mitochondrial activity, augmenting the phosphorylation of CREB in addition to modulating APP processing in favor of the nonamyloidogenic pathway (**Table 4**). The typical mechanistic correlates include those observed in magnesium preparations such as chloride, sulfate, glycinate, malate and MgO nanoparticles: hippocampal LTP restoration, synaptic protein-encoding gene (PSD-95, synapsin-1) upregulation, and BDNF-CREB activation. In vivo experiments revealed a decrease in microglial (Iba1) and astrocytic (GFAP) activation, but in vitro models revealed a decrease in NF- κ B signaling and reduced levels of proinflammatory cytokines (TNF- α and IL-1), oxidative stress, and lipid peroxidation. These findings collectively suggest common neuroprotective mechanisms across experimental systems but emphasize the importance of standard dosing, protocols, and assays to enhance comparisons across studies and enhance translation to humans.

Table 3. In vivo studies of magnesium and cognition

Author (Year)	Model/Species	Mg form/Dose (as reported)	Experimental Test	Main findings	mechanism	Ref
Xiong <i>et al.</i> , 2025	APP/PS1 transgenic mice (AD model)	Mg-L-threonate (MgT), dose as reported in paper	Novel Object Recognition; other memory assays	↑ recognition memory and ↓ AD-like pathology ↑ hippocampal neurogenesis	ERK/CREB activation; neurogenesis promotion.	[97]
Zhang <i>et al.</i> , 2024	Rat cerebral ischemia–reperfusion model (in vivo implants)	Mg-based biodegradable implants/local Mg ²⁺ delivery	Infarct size, neurological score, histology	↓ infarct volume and neuronal loss ↑ neurological outcomes	Local Mg ²⁺ release → mitochondrial protection, reduced ROS/excitotoxicity	[98]
Kim <i>et al.</i> , 2020	Hypoxic zebrafish (in vivo)	Mg-L-threonate (MgT), experimental exposures	Behavioral assays relevant to cognition/locomotion	↑ neuroprotection against hypoxia-induced deficits	Upregulation of glutamate transporters; decreased excitotoxicity.	[99]
Gangoda <i>et al.</i> , 2023	Rat model of Alzheimer's-like	Magnesium L-threonate (coadministered)	Behavioral memory tests (MWM/NOR)	↑ memory and ↓ AD markers vs control	Synaptic protection, antioxidant and	[100]

	neurotoxicity (AlCl ₃ -induced)	d with atorvastatin in study)			anti-inflammatory effects.	
Nabaee <i>et al.</i> , 2022	Sleep-deprived rats (in vivo)	MgO nanoparticles (administration per paper)	Learning & memory tasks (animal behavioral tests)	↓ oxidative markers in some assays	Antioxidant effects, mitochondrial protection (dose-dependent).	[101]
Hosseini-Sharifabadi <i>et al.</i> , 2020	Mice memory impairment models	Magnesium (coadministered oral or i.p. as reported)	Passive avoidance, MWM, other memory assays	↓ memory impairment in models tested	Anti-inflammatory, antioxidant, cholinergic modulation.	[102]

Table 4. In vitro studies of magnesium and cognition

Study	Cell Model	Magnesium Type	Main Finding (Simple)	Ref
Hou <i>et al.</i> , 2020	Rat cortical neurons	Mg ²⁺ (extracellular)	↑ CREB signaling	[74]
Xiong <i>et al.</i> , 2022	HT22 hippocampal neurons + Aβ _(25–35)	Magnesium L-threonate	↓ oxidative stress, apoptosis, and ↑ neuronal survival.	[103]
Babylon <i>et al.</i> , 2022	SH-SY5Y human neuroblastoma (APP-overexpressing)	Magnesium orotate	↓ Aβ levels and ↑ APP processing.	[104]
Fujita <i>et al.</i> , 2023	Human cells (oxidative stress assay)	Intracellular Mg ²⁺	↓ oxidative damage.	[105]
Zhou <i>et al.</i> , 2024	Primary hippocampal neurons	Intracellular Mg ²⁺	↑ synaptic plasticity and connectivity	[106]

7. CLINICAL EVIDENCE

7.1 Observational Evidence

Epidemiological studies have shown mixed associations between magnesium status and cognition. For example, the Rotterdam prospective cohort (N≈9569, mean age 65) revealed a U-shaped risk for dementia: both low (≤0.79 mmol/L) and high (≥0.90 mmol/L) serum Mg were linked to increased all-cause dementia risk (HR≈1.30 for high vs mid-Mg; HR≈1.32 for low vs mid-Mg) [107]. A recent meta-analysis of 12 cohort studies similarly reported a U-shaped pattern: compared with an optimal level (~0.85 mmol/L), low (<0.75) or high (>0.95) serum Mg was associated with ~30–40% greater dementia risk [22]. In cross-sectional data, low Mg is also related to poorer cognition. In a Chinese study of 1006 adults ≥55 years, higher whole-blood Mg was inversely associated with mild cognitive impairment (MCI) and positively correlated with attention, executive and language test scores (highest vs lowest quartile OR for MCI ≈0.53) [108]. Similarly, a Qatari cross-sectional sample (N=1000) revealed that lower serum Mg (<0.85 mmol/L) was associated with a slower computerized reaction time: adjusted β≈−31.9 ms in the highest vs lowest Mg quartile [109]. However, other cohorts report weaker or inconsistent links (some cohorts of older women or diverse US samples found null or small effects). Overall, observational evidence suggests a nonlinear association of blood Mg with cognitive health but is limited by single-time biomarkers, dietary recall error, and confounding factors (e.g., vascular risk factors).

7.2 Intervention studies

There are few and diverse randomized trials of magnesium supplementation for cognition. The largest RCT to date in young adults involved 100 participants aged 18–45 years with sleep complaints who were treated with 2 grams/day of magnesium L threonate (Magtein®) for six weeks. In this trial, there were significant benefits with Mag-L-thr on cognition, with greater improvement on the NIH cognition composite ($p=0.043$) and reaction time ($p=0.031$) compared to placebo group [110]. One month of 2 g/day Mg-L-threonate (MagteinPS, a formula containing phosphatidylserine and vitamins) was found to significantly enhance the performance of healthy Chinese adults ($N=109$, aged 18–65) on the memory test scores and overall memory quotients, compared to a placebo group [110]. The results indicate that brain bioavailable Mg (threonate) could improve cognitive function. Smaller studies of other forms of Mg (oxide, citrate, or bisglycinate) and of standard populations have tended to have a more mixed result with regard to cognition. However, in older adults, a 16-week MgO intervention did not yield any changes to the MoCA score. The paucity of data from RCTs has led to a systematic review that concluded that there is “insufficient data” to draw conclusions regarding the effect of magnesium supplements. Interestingly, lower levels of serum Mg were observed in dementia cases compared to controls in case–control meta-analyses, and some small trials in AD/MCI patients showed trends towards benefit, albeit less conclusive [111]. To summarise, the few intervention trials that do exist suggest limited benefits of cognitive enhancement with certain formulations, including Mg L threonate, but with diverse doses, durations (weeks–months), end points, and with limited replication.

7.3 Systematic Reviews and Meta-Analyses

A recently published systematic review and meta-analysis by Chen et al. (2024) showed new but still ambiguous evidence regarding the connection between magnesium status and cognitive function, including three randomized controlled trials and 12 cohort studies. The authors noted that based on available RCTs, there was inadequate evidence for any definite cognitive benefits of magnesium supplementation. A few preliminary associations between magnesium status and cognitive outcomes were observed in cohort studies, but there was significant heterogeneity in study populations and outcome measures. In particular, the results showed U-shaped relationships between the serum magnesium concentration and the prevalence of cognitive impairment or dementia risk, indicating that both low and high serum magnesium concentrations are related to poor cognitive effects. The authors came to the conclusion that further, well-designed, longitudinal studies and randomized controlled trials are needed to better elucidate the role of magnesium in cognitive health [22]. In a systematic review by Veronese et al. (2016) that examined magnesium levels in AD, the researchers found significantly decreased levels in CSF and hair from individuals with AD versus healthy controls [112]. There were no consistent differences of serum magnesium levels, however. These results further demonstrate the lack of usefulness of serum magnesium as a marker of brain magnesium status and the need to develop more sensitive methods to evaluate magnesium homeostasis in neurodegenerative diseases.

7.4 Current Limitations of Human Evidence

Although promising results have been reported, there are some areas in which current clinical data does not allow definite conclusions. Moreover, serum magnesium is the most common biomarker used, even though it is not necessarily reflecting the magnesium status in the brain. Advanced neuroimaging methods (such as ^{31}P -magnetic resonance spectroscopy), or direct assessments based on measurements in the cerebrospinal fluid or in erythrocytes, are not commonly included in clinical trials. Also, baseline magnesium levels, food intake, age, comorbidities, and different magnesium supplement formulations have a tendency to have inconsistent results. Intervention trials often have small numbers of participants, limited treatment duration and varied magnesium formulations, complicating comparisons. In addition, the majority of studies use serum magnesium levels as a indicator that may not reflect levels of magnesium in the brain. Therefore, more well-designed randomized controlled trials with carefully selected cognitive outcomes and brain-relevant magnesium markers are required to elucidate the therapeutic effects of magnesium supplementation in cognitively impaired subjects and patients suffering from neurodegenerative diseases [10], [22], [113], [114].

Table 5. Clinical trials of magnesium for cognitive outcomes

Study	Type	Sample Size (N)	Inclusion Criteria	Exclusion Criteria	Mg Form/Dose	Duration	Cognitive Outcome	Limitation	Ref
Kieboom <i>et al.</i> , 2017	prospective population-based Rotterdam Study	9,569	Community-dwelling adults from Rotterdam cohort	Prevalent dementia at baseline	Baseline serum Mg assessment	Median 8 years	Incident dementia risk	Observational design; single Mg measurement	[107]
Lu <i>et al.</i> , 2023	Cross-sectional study	1,006	Adults ≥55 years	Missing cognitive or Mg data	Whole-blood Mg exposure	9 months	MCI prevalence; executive/language function	Cannot establish causality	[108]
Al-Ghazali <i>et al.</i> , 2020	Cross-sectional	1,000	Adult Qatari population	Incomplete biochemical/cognitive data	Serum Mg quartiles	5years	Mean reaction time	Single cognitive domain assessed	[109]
Zhang <i>et al.</i> , 2022	double-blind, placebo-controlled study	109	Healthy adults aged 18–65 years	Cardiovascular disease, diabetes, cancer, Parkinson's disease, Alzheimer's disease	Magtein® PS, 2 g/day	30 days	Memory quotient and memory subscales	Combined formulation; short duration	[115]
Lopresti <i>et al.</i> , 2025	Randomised, Double Blind placebo controlled trial	100	Adults aged 18–45 years with self-reported sleep complaints	Neurological disorders, major psychiatric illness, medications affecting sleep/cognition	Mg-L-threonate, 2 g/day	6 weeks	NIH cognition composite; reaction time	Healthy population; short follow-up	[110]
NCT04196023	Randomized Trial	~250	Adults aged 40–85 years enrolled in parent study	Inability to provide biological samples; major protocol violations	Magnesium glycinate	Several months	MoCA and cognitive measures	Cognition secondary outcome	[116]
NCT02210286	Interventional	~60–80 planned	Adults >60 years with	Active heart and severe comorbidities	Mg-L-threonate	6–12 weeks	Learning and memory measures	Limited published results	[117]

			mild-to-moderate dementia						
Hausenblas <i>et al.</i> , 2024	randomized, double-blind, placebo-controlled, parallel-arm study	80	35-55 age who self-reported poor sleep	sleep-affecting disorders, use of calcium channel blockers	1 g/day MgT	21 days,	Sleep quality, daytime functioning	Conducted in relatively healthy adults rather than cognitively impaired populations; short duration.	[118]

8. ROLE OF MAGNESIUM IN NEURODEGENERATIVE DISORDERS

Alzheimer's disease: Alzheimer's disease is a neurodegenerative condition that impacts cognitive functions and accounts for 60–70% of all dementia cases [119]. Although disease pathogenesis is complicated and partially unknown, we can assume that the deposition of the amyloid β (Ab) peptide as the residue of the β -amyloid precursor protein (APP) breakdown process by the action of α - and β -secretases plays a role. In contrast, soluble fragments are set free when cleavage by α and β secretases takes place on the APP [120]. Amyloid plaques are formed from Ab peptide aggregates in the extracellular environment, and neurofibrillary tangles are abnormal accumulations of phosphorylated tau protein in neurons. Aggregated proteins stimulate microglia and initiate neuroinflammation, which is also involved in the severity of the disease. Lower levels of Mg have been observed in patients, and the likelihood of BBB dysfunction to change Mg transport has not been demonstrated thus far [121]. A recent meta-analysis of 21 studies published in the previous 20 years indicated that the circulating levels of Mg in patients with Alzheimer's disease were very low compared with those in healthy individuals [122]. Although numerous studies have reported reduced magnesium levels in patients with Alzheimer's disease, the causal relationship remains unclear. It is uncertain whether magnesium deficiency contributes directly to disease progression or occurs secondary to neurodegenerative processes. Moreover, most mechanistic evidence originates from experimental models, while well-designed randomized clinical trials remain limited. Additional longitudinal and intervention studies are needed to determine whether magnesium supplementation can meaningfully modify disease progression or cognitive outcomes in patients with Alzheimer's disease.

Parkinsonism Disease: The second most prevalent neurodegenerative disorder is Parkinson's disease, but its prevalence has increased at an alarming rate over the past 2 decades [123]. Postural motor instability with cardinal motor activity may improve, rigidity, involuntary body movements, bradykinesia, and nonmotor symptoms such as cognitive impairment, depression, autonomic dysfunction, and sleeping disorders [124]. Many pathological events, such as abnormal protein aggregation, lysosome dysfunction, mitochondrial dysfunction, endoplasmic stress, glutamatergic excitotoxicity, oxidative stress, and neuroinflammation, cause Parkinson's disease. Magnesium may exert neuroprotective effects through the attenuation of oxidative stress, neuroinflammation, and NMDA receptor overactivation [125]. Moreover, Mg enhances BDNF, a trophic factor of dopaminergic neurons, including degenerating neurons, during disease. Furthermore, by interfering with the mTOR pathway, Mg inhibits the aggregation of α -synuclein, the principal protein involved in the pathogenesis of Parkinson's disease. A study revealed that MgT is associated with an increase in Mg in the CSF. MgT, rather than MgSO₄, can significantly attenuate MPTP-induced motor deficits and dopamine (DA) neuron loss and provide a protective effect against Parkinson's disease [126]. Current evidence suggests that magnesium may exert neuroprotective effects through the modulation of oxidative stress, neuroinflammation, excitotoxicity, and dopaminergic neuronal survival. However, much of the supporting evidence is derived from experimental Parkinson's disease models, and human studies remain relatively scarce. The extent to which magnesium

supplementation can improve motor symptoms, cognitive dysfunction, or disease progression in patients with Parkinson's disease remains unclear. Future clinical investigations are needed to determine optimal dosing strategies and identify patient populations most likely to benefit from magnesium-based interventions.

9. MAGNESIUM-BASED NANO FORMULATIONS

The traditional supplements are not well absorbed in the blood–brain barrier (BBB) and (Mg^{2+}) is essential for synaptic function. The use of nanoscale Mg carriers, such as polymeric or lipid-based NPs, can increase the uptake into the CNS by stability and by applying strategies that open the BBB. For instance, Wang et al. (2026) reported that the use of Mg–phosphate nanoparticles with the “orifice-opening” agents (borneol, muscone) was observed to increase brain targeting both in vitro and in vivo in a significant manner, as an example of this general concept [127]. There are a number of studies that have used animal models of cognitive deficits for the testing of Mg nanoformulations. Rajkumar et al. (2022) prepared a nanocomposite of gelatin/polyvinyl alcohol with magnesium hydroxide $[\text{Mg}(\text{OH})_2]$ which decreased the expression of β -amyloid, increased the antioxidant enzymes and decreased the MDA, AChE activity in an intracerebroventricular STZ induced rat model of Alzheimer's disease, and improved memory/synaptic function [128]. Likewise, Habib Ullah et al. (2022) synthesized MgO NPs from *Datura alba* extract, which in PTZ kindled mice robustly improved cognitive functions (Morris water maze, NOR tests) and maintained BBB integrity (reduction of Evans blue leakage) when compared to PTZ untreated epilepsy controls [129]. These formulations raise brain Mg levels and provide neuroprotection, but they are rodent models and there is a lack of long term and dose–response data. In addition, Mathew et al. developed magnesium sulfate nanoparticles and found that MGSN had a higher BBB permeability than the marketed i.v. MgSO_4 injection [130].

In preclinical tests, these NPs seem to be effective; however, safety and pharmacokinetics are problematic. In a rat study, repeated doses of i.p. 10–15 nm MgO NPs was well-tolerated at doses up to 250 $\mu\text{g}/\text{mL}$ (no significant organ damage), and higher doses increased liver enzymes and blood counts [126]. But its toxicity to humans has not been tested: accumulation of nanoparticles, chronic inflammation or neurotoxicity still remains a concern. The PK of Mg NPs (circulation time, clearance, and brain half-life) is not well defined. The reproducible formulation and large-scale production are also not straightforward; clinical grade nanomedicines have to be produced in a batch consistent manner. To sum up, the benefits of nano-Mg systems are demonstrated (proof-of-concept: higher delivery of Mg to the brain and cognitive/neuroprotective action), but still remain to be addressed the toxicity, biodistribution, and regulatory issues before its introduction to human use.

10. CONCLUSION

As an element, magnesium is necessary for controlling cognitive functions because of its pivotal and complex nature of integrating metabolism and synaptic, inflammatory, and redox networks in the brain. The evidence of the adequacy of magnesium presented in this review shows that it is important to keep neurons alive and sustain synaptic plasticity and neurogenesis, especially by regulating the activity of NMDA receptors, calcium signaling, mitochondrial bioenergetics and ERK/CREB-dependent transcriptional programs. Deficiencies in magnesium interfere with such well-regulated mechanisms, resulting in excitotoxicity, oxidative stress, neuroinflammation, impaired learning and memory and increased susceptibility to neurodegenerative and cognitive pathology. Notably, new information is evolving around the concept that not every source of magnesium could be equal; bioavailability, chemical form and blood–brain barrier penetration play crucial roles in determining therapeutic efficacy. Magnesium L-threonate has shown promise in increasing brain magnesium concentrations and improving cognitive performance in preclinical and early clinical studies. Furthermore, food-based interventions, micronutrient enrichment with fermentation, and connections between the gut microbiome are other untapped but potential opportunities for long-term cognitive therapy. Instead of depending only on serum measures, future research should focus on developing brain-specific magnesium indicators that more accurately reflect neuronal magnesium levels. Magnesium-sensitive molecular probes, cerebrospinal fluid profiling, and advanced neuroimaging methods may provide better translational accuracy. To find the best magnesium formulations, dosage schedules, and intervention durations for various cognitive phenotypes, such as aging-related cognitive decline, mild cognitive impairment, and neurodegenerative diseases, extensive randomized controlled trials are also necessary.

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DECLARATION

The authors declare that all the data were generated in-house and that no paper mill was used.

COMPETING INTERESTS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This review article does not involve any studies with human participants or animals performed by any of the authors; therefore, ethical approval and consent to participate are not applicable.

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Graphical Abstract

