Neuropsychiatric Disease and Treatment

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REVIEW

L-α-GPC in Cognitive Decline: Mechanisms and Clinical Evidence in Neurodegenerative Disorders

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Abstract: Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia are characterized by progressive neuronal loss, synaptic dysfunction, and cognitive decline. Despite the widespread use of symptomatic treatments, including acetylcholinesterase inhibitors and dopaminergic agents, these disorders remain incurable and lack disease-modifying therapies. L-α-Glycerylphosphorylcholine (L-α-GPC), a naturally occurring choline-containing phospholipid, has attracted interest for its dual roles as a precursor to acetylcholine biosynthesis and a modulator of neuroprotective signaling pathways. This narrative review summarizes current preclinical and clinical evidence regarding the mechanistic and clinical relevance of L-α-GPC in neurodegenerative disorders associated with cognitive impairment. Preclinical studies suggest that L-α-GPC can cross the blood–brain barrier, enhance cholinergic neurotransmission, upregulate neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and modulate inflammatory responses, including those involving the α7 nicotinic acetylcholine receptor pathway. In animal models, L-α-GPC has been associated with improved cognitive performance, reduced neuroinflammation, and attenuation of amyloid-β and tau-related pathological features. Clinical studies have reported potential benefits of L-α-GPC, either as monotherapy or in combination with agents such as donepezil, in patients with AD, vascular dementia, mild cognitive impairment (MCI), and PD-related cognitive decline. However, the interpretation of these findings should be cautious because the available evidence remains heterogeneous, with notable variability in study design, dosage regimens, treatment duration, and outcome measures. Further well-designed, large-scale randomized controlled trials, together with biomarker-based assessments, are needed to clarify the therapeutic relevance and optimal clinical application of L-α-GPC in cognitive decline and neurodegenerative disorders. Overall, current evidence indicates that L-α-GPC may represent a promising adjunctive approach, although more robust validation is still required.

Keywords: L-α-GPC, acetylcholine, neurodegeneration, Alzheimer's disease, cognitive decline, neuroprotection, mild cognitive impairment

Introduction

Neurodegeneration involves the progressive loss of neuronal structure and function, leading to cognitive and motor impairments. Hallmarks of these disorders include beta-amyloid aggregation, hyperphosphorylated tau, neuroinflammation, and neuronal death, all of which contribute to symptoms such as memory loss, executive dysfunction, and motor dysfunction.[1,2] These disorders predominantly affect the elderly, and their prevalence is increasing with global aging, compounding health and economic burdens.

In 2019, neurological disorders affected 349.2 million people and caused 10 million deaths.[3,4] Alzheimer's disease and Parkinson's disease are the most prevalent forms, with neurological diseases now leading as causes of physical and cognitive disability worldwide.[5,6] Their incidence continues to rise, with an estimated 60 million individuals affected by ADRD and PD in 2019, driven by age, lifestyle factors, and complex genetic–environmental interactions.[3,7–9] Because

https://doi.org/10.2147/NDT.S579603
Received: 15 November 2025
Accepted: 6 May 2026
Published: 19 May 2026

cognitive decline is one of the most disabling manifestations of these disorders, identifying interventions that may preserve cognitive function remains a major clinical priority.

Nowadays, only symptomatic treatments exist for Alzheimer's disease, primarily targeting neurotransmitter disturbances through three cholinesterase inhibitors and memantine.[10] Acetylcholinesterase inhibitors (AChEIs), donepezil, rivastigmine, and galantamine, are approved for mild-to-moderate Alzheimer's disease, as well as Parkinson's disease dementia (PDD) in the case of rivastigmine.[10,11] These agents increase acetylcholine levels and offer temporary symptomatic relief, yet they do not alter the underlying disease progression.[12–14] To effectively halt or slow disease progression, therapeutic strategies must interfere with the pathogenic mechanisms responsible for neurodegeneration. Therefore, there is an urgent need for early intervention and the development of disease-modifying treatments. In this context, neuroprotective adjuvants and multi-target agents are increasingly being explored.[10] Compared to AChEIs, which primarily prevent acetylcholine degradation, L-α-GPC enhances both synthesis and release of acetylcholine, potentially offering complementary and longer-lasting benefits.[10,11] Combined therapy of L-α-GPC with AChEIs has shown potential synergistic benefits in certain trials,[15] and its safety profile is favorable, with most reported adverse events being mild and transient.[16]

Given that neurodegenerative diseases are chronic and complex processes, early intervention is essential to mitigate disease progression. Recently, there has been a resurgence of interest in L-α-GPC as evidenced by a spike in patent filings and scientific studies focused on its benefits and applications.[17] One such promising agent is L-α-GPC, also known as α-GPC. L-α-GPC is a choline-rich compound (41% by weight) capable of crossing the blood–brain barrier and metabolizing into phosphatidylcholine, enhancing acetylcholine and BDNF levels.[18–20] It has shown cognitive benefits in neurodegenerative and vascular disorders[21] and exhibits synergistic effects with AChEIs.[22,23] Clinical and animal studies have demonstrated its efficacy in improving memory and cognitive functions, with potential benefits in conditions such as Alzheimer's disease and dementia. L-α-GPC has considerable value in the pharmaceutical and medical industries, particularly for its role in enhancing cholinergic function and synaptic integrity.[17]

Although L-α-GPC has been discussed in both neurodegenerative and vascular-related cognitive disorders, the available evidence remains heterogeneous. Differences in study populations, diagnostic criteria, disease stage, treatment duration, dosage regimens, co-interventions, and outcome measures may all influence the reported findings and their clinical interpretation. Therefore, a careful and contextualized interpretation of the literature is necessary, particularly when comparing evidence across Alzheimer's disease, Parkinson's disease-related cognitive decline, and cognitive impairment associated with cerebrovascular conditions.

Given this background, the present narrative review focuses primarily on the mechanistic and clinical evidence regarding L-α-GPC in cognitive decline associated with neurodegenerative disorders, while also acknowledging relevant findings from studies of vascular- or cerebrovascular-related cognitive impairment where appropriate. Specifically, this review summarizes the biological mechanisms of L-α-GPC, reviews key preclinical and clinical findings, and discusses its possible role as an adjunctive therapeutic approach. In addition, this review highlights the heterogeneity and limitations of the current evidence base, which should be considered when interpreting the potential clinical relevance of L-α-GPC in neurodegenerative disorders.

Methods

This study was a review that critically evaluated the experimental and clinical evidence, focusing on the underlying mechanisms of action of L-α-GPC in neurodegenerative diseases and cognitive impairment. A structured literature search was conducted using the PubMed database from inception to May 2025, employing seven keyword combinations that included terms such as "L-α-Glycerylphosphorylcholine", "choline alphoscerate", "cognitive dysfunction", "Alzheimer's disease", "dementia", and "Parkinson's disease", as illustrated in Figure 1. All included studies were qualitatively synthesized and thematically analyzed to explore molecular mechanisms, therapeutic outcomes, and the potential role of L-α-GPC as an adjuvant in the treatment of neurodegenerative disorders.

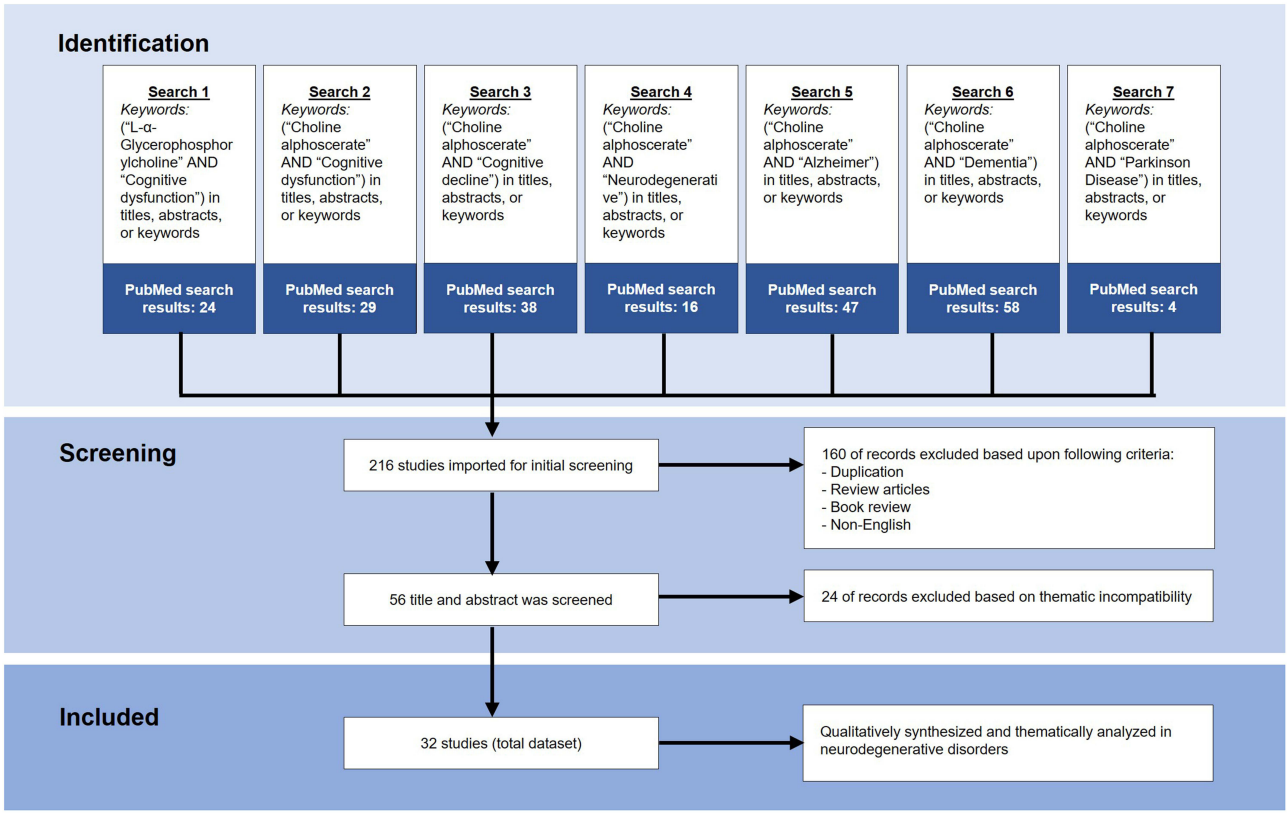

Figure 1 Flow diagram of the literature selection process for the review. Seven keyword combinations were used to search PubMed, resulting in a total of 216 records. After applying exclusion criteria and screening for thematic relevance, 32 original research articles were included in the final review dataset.

Results

Pharmacological Profile of L-α-GPC

L-α-GPC, also known as Choline alfoscerate, is a cholinergic compound and a biosynthetic precursor of acetylcholine (ACh) that is widely used as a dietary supplement. The structure L-α-GPC shown in Figure 2, with the molecular formula $C_8H_{20}NO_6P$ and a molecular weight of 257.22 g/mol, L-α-GPC contains approximately 41% choline by weight and is known for its efficient penetration across the blood–brain barrier.[21,24] Following oral administration, L-α-GPC is wholly and rapidly absorbed, with an elimination half-life of 0.5 to 6.2 hours. Due to its highly hygroscopic nature, its powdered form becomes sticky when exposed to humidity.[25]

After absorption in the small intestine via facilitated transport, L-α-GPC is hydrolyzed by glycerylphosphorylcholine diesterase into glycerophosphate and free choline. Plasma choline concentrations typically peak a few hours after intake

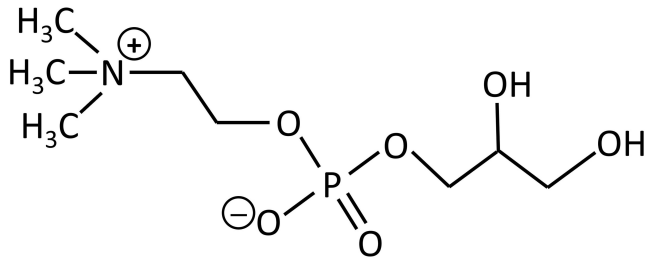

Figure 2 Structure of L-alpha-Glycerophosphorylcholine.[24]
Notes: Reproduced from: PubChem. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Choline-Alfoscerate#section=Structures. Accessed November 4, 2025.

and return to baseline within 6 to 10 hours.[26] Free choline in the body originates both from dietary intake and endogenous synthesis through the phosphatidylcholine-dependent de novo pathway.[25]

Pharmacologically, L-α-GPC functions as a parasympathomimetic agent, consistent with the cholinergic hypothesis, which posits that cognitive decline in disorders such as Alzheimer's disease (AD) and vascular dementia (VaD) is linked to reduced acetylcholine levels resulting from degeneration of cholinergic neurons in the basal forebrain. Like acetylcholinesterase inhibitors (AChEIs), L-α-GPC enhances ACh availability, supports its synthesis, and helps maintain cognitive function.[26] Clinically, L-α-GPC is well tolerated and has been evaluated both as monotherapy and in combination with other agents for cognitive enhancement in conditions such as mild cognitive impairment (MCI), dementia, AD, acute stroke, and transient ischemic attacks.[27]

Although generally safe, excessive choline intake from L-α-GPC or other sources may cause side effects, including fishy body odor, vomiting, hypersalivation, hypotension, excessive sweating, and potential hepatotoxicity.[28] L-α-GPC has been approved as a pharmaceutical drug in several countries, including Poland and Russia, and is widely used in South Korea for managing cognitive and behavioral symptoms related to cerebrovascular insufficiency, neurodegenerative disorders, and age-related cognitive decline.[29] Accumulating evidence from preclinical and clinical studies suggests potential neuroprotective properties of L-α-GPC, although its clinical effects on cognitive decline remain heterogeneous across study designs and populations. Figure 3 shows the Pharmacological profile of L-α-GPC.

Molecular Mechanism of L-α-GPC Action Against Cognitive Impairment

L-α-GPC has been reported to influence multiple neurobiological pathways relevant to cognition. As a direct precursor of acetylcholine (ACh), it enhances central cholinergic neurotransmission by supporting ACh synthesis and availability in cortical and hippocampal regions. This effect extends to the regulation of cholinergic enzymes and receptors, which are essential for sustaining synaptic activity and memory processes.[30–33] Beyond the cholinergic system, L-α-GPC also modulates inhibitory neurotransmission. By facilitating γ-aminobutyric acid (GABA) release, it helps restore the balance between excitatory and inhibitory signaling, thereby protecting neurons from hyperexcitability and excitotoxic

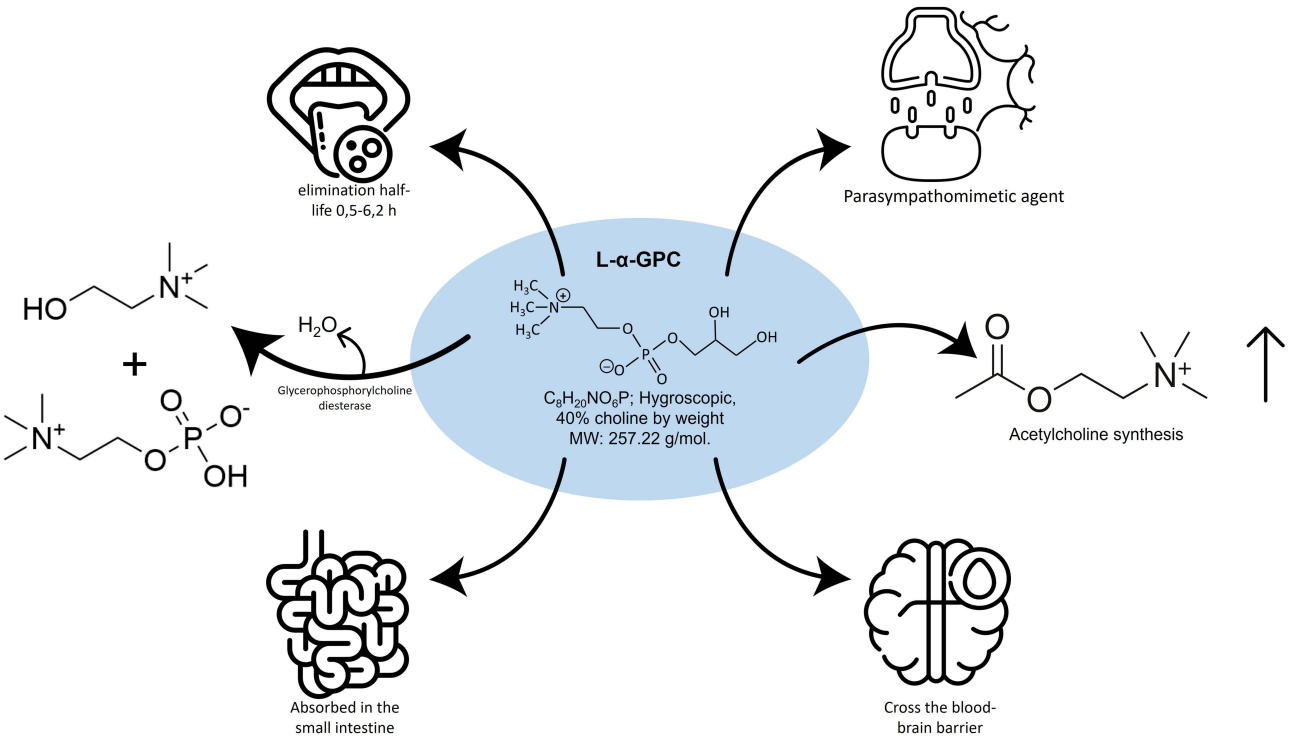

Figure 3 Pharmacological overview of choline of L-α-GPC. α-GPC is a choline-containing phospholipid metabolized by glycerophosphorylcholine diesterase, capable of crossing the blood–brain barrier and enhancing acetylcholine synthesis.

damage.[34–36] This dual action on ACh and GABA suggests that L-α-GPC maintains neural circuit stability while enhancing cognitive performance.

At the molecular level, L-α-GPC activates protein kinase C (PKC), a key signaling molecule involved in synaptic plasticity and long-term potentiation, both of which are critical for learning and memory consolidation.[37,38] It also promotes hippocampal neurogenesis, potentially via phospholipid metabolites that modulate receptor phosphorylation and counteract inflammatory stress, ultimately supporting neuronal proliferation and survival.[39–42] In addition, L-α-GPC upregulates neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Through activation of their respective receptors (TrkB and TrkA), these pathways stimulate downstream cascades, including AKT and ERK, that promote neuronal survival, synaptic integrity, and resilience against neurotoxic insults.[42–44] Collectively, these findings suggest mechanisms by which L-α-GPC may influence cognitive processes by integrating neurotransmitter regulation, kinase activation, neurogenesis, and neurotrophic support, thereby contributing to neuroprotection and memory-related effects. Figure 4 summarizes the proposed molecular mechanism by which L-α-GPC enhances cognitive function.

Overview of Neurodegenerative Diseases

Neurodegenerative diseases (NDs) are irreversible and progressive disorders characterized by the dysfunction and eventual loss of neurons, leading to significant impairment in memory, movement, cognition, and other essential bodily functions.[45] These conditions are commonly associated with disrupted synaptic communication, altered dendritic structures, synapse loss,

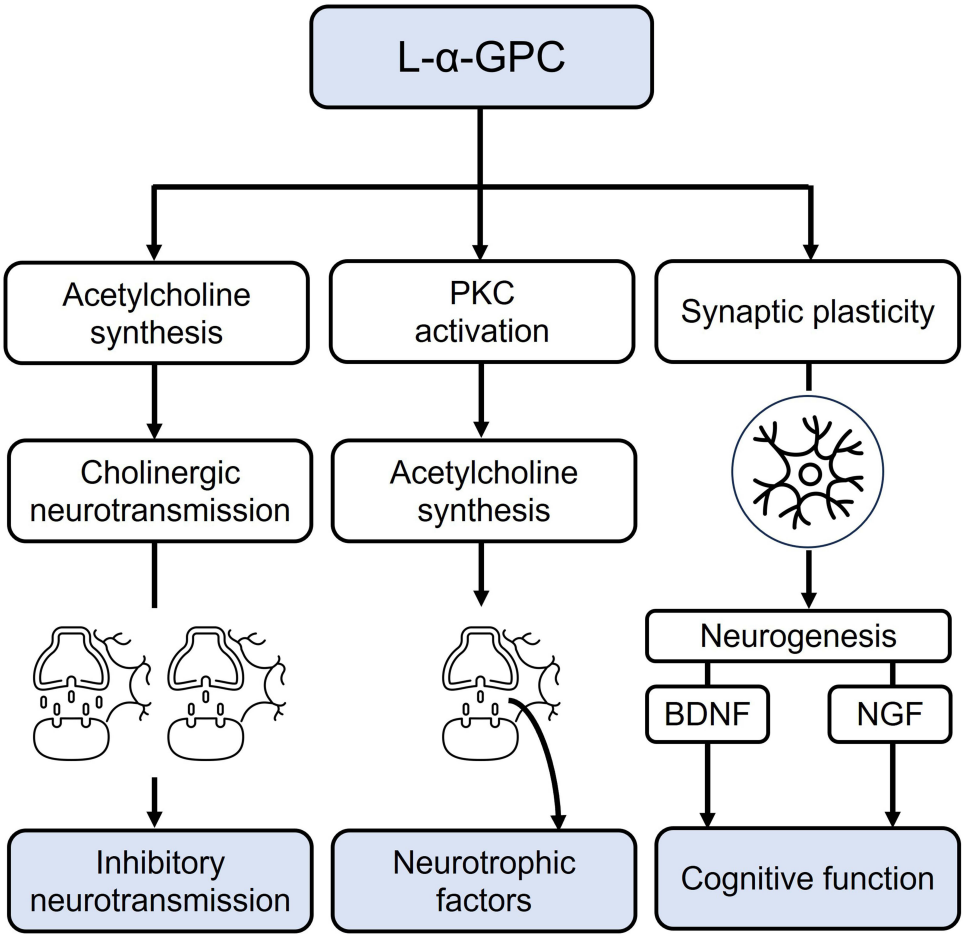

Figure 4 Proposed molecular mechanism of L-α-GPC in enhancing cognitive function. L-α-GPC enhances acetylcholine synthesis and cholinergic neurotransmission in cortical and hippocampal regions, facilitates GABA release to balance excitatory and inhibitory signaling, activates protein kinase C (PKC) to promote synaptic plasticity, and upregulates neurotrophic factors (BDNF, NGF) through TrkB/TrkA-AKT/ERK signaling. These integrated pathways support neurogenesis, synaptic integrity, and overall cognitive performance.

and the accumulation of misfolded proteins such as amyloid-beta (Aβ), tau, and α-synuclein.[2,33] The loss of synaptic integrity and neural network disruption plays a central role in the progression of cognitive decline, as observed in Alzheimer's disease (AD) and Parkinson's disease (PD), where toxic oligomeric forms of Aβ and α-synuclein interfere with synaptic plasticity and promote neuronal cell death. Under normal conditions, these pathological proteins are cleared by microglia, the resident immune cells of the central nervous system. However, chronic neuroinflammation impairs microglial function, leading to inefficient clearance and the further accumulation of toxic aggregates.[46]

Age is the most prominent risk factor for neurodegenerative diseases, although genetic predispositions and environmental exposures also significantly influence disease onset and progression.[47] As global life expectancy continues to rise, the prevalence of NDs is increasing, contributing to a growing socioeconomic and healthcare burden. From a pathophysiological perspective, these diseases involve biochemical changes that affect protein homeostasis. Aβ monomers, for instance, can aggregate into toxic oligomers and fibrils, forming plaques that promote tau aggregation and inflammatory responses. This cascade of inflammation and neurotoxicity ultimately results in neuronal loss, cerebral atrophy, and morphological changes such as widened gyri and reduced brain volume.[48]

Clinically and pathologically, NDs exhibit considerable heterogeneity depending on the brain regions affected, resulting in diverse symptom profiles across different conditions. Patients may present with impairments ranging from basic functions, such as speech, mobility, and balance, to more complex processes, including cognition and autonomic control. While disease-modifying therapies remain limited, current treatments can alleviate symptoms, reduce pain, or temporarily restore function. Significantly, biochemical abnormalities often precede overt clinical manifestations by decades, complicating efforts to determine the initial triggers of disease and distinguish them from secondary pathological events.[49] Additionally, the failure of autophagy and other cellular protein degradation mechanisms exacerbates the accumulation of misfolded proteins, reinforcing the need for early diagnostic strategies and targeted molecular interventions.[46]

Therapeutic Efficacy of L-α-GPC in Alzheimer's Disease

Multiple preclinical studies have reported that L-α-GPC exerts significant neuroprotective effects in Alzheimer's disease (AD). In vitro, L-α-GPC (1 mM) was shown to inhibit Aβ-induced inflammation by modulating microglial activation via α7 nicotinic acetylcholine receptors (α7nAChR).[50] Additional in vitro research revealed that pre-treatment with 100 nM L-α-GPC for 1 hour, followed by exposure to Aβ25–35 (10 μM) for 72 hours, significantly reduced tau phosphorylation and neurotoxicity through NGF/TrkA signaling engagement.[50] At higher concentrations (0.1–50 mM), L-α-GPC was also reported to limit Aβ1–induced cell death by promoting pro-survival signaling pathways.[51]

Ex vivo analysis using radiolabeled L-α-GPC (1.3 mM) confirmed its incorporation into the brain, where it affected key lipid metabolic pathways, including phosphatidylcholine (PtdCho) and phosphatidylethanolamine (PtdEtn) metabolism, suggesting a role in membrane repair and neurotransmitter support.[52] Moreover, post-mortem AD brain tissues exhibited preserved L-α-GPC levels, supporting the concept of L-α-GPC as an acetylcholine reservoir.[30] These molecular and cellular findings provide a biological rationale for further clinical investigation of L-α-GPC.

In vivo animal studies have also reported benefits. Co-administration of 100 mg/kg/day L-α-GPC with 3 mg/kg/day galantamine improved cholinergic function and exhibited anti-apoptotic activity via α4β2 and α7nAChR pathways.[53] Long-term treatment with 150 mg/kg/day L-α-GPC for 4 weeks increased expression of the choline transporter (CHT) and the vesicular acetylcholine transporter (VAChT), facilitating acetylcholine synthesis and storage.[54] In a nutrient blend including L-α-GPC, ALA, DHA, ALCAR, and PS, L-α-GPC contributed to maintaining cognitive performance in healthy mice.[55] Clinical studies reinforced these outcomes: daily supplementation with 1200 mg L-α-GPC and donepezil (10 mg/day) improved cognitive and behavioral outcomes, slowed brain atrophy, and reduced caregiver stress in AD patients.[15,56,57]

Efficacy of L-α-GPC in Dementia and Mild Cognitive Impairment

L-α-GPC has also been widely studied in the context of dementia and mild cognitive impairment (MCI). In vivo experiments showed that 100 mg/kg L-α-GPC protected hippocampal neurons and glia, particularly in the CA1 and

dentate gyrus regions, enhancing structural integrity and neuronal viability.[54] In a related study, one week of treatment with 150 mg/kg/day L-α-GPC modulated neurotransmitter levels by altering CHT and VAChT expression in the cortex.[58] Notably, healthy human subjects receiving 50–200 mg/kg L-α-GPC exhibited enhanced CNS choline transport, indicating improved brain choline availability.[59]

Multiple clinical trials have evaluated L-α-GPC in MCI, and several have reported improvements in cognitive outcomes, with effects varying by study design and endpoints. A randomized controlled trial using 1200 mg/day for 12 months reported improved cognitive performance and detectable structural changes in the hippocampus.[60] Another placebo-controlled study showed that L-α-GPC (600 mg/day) increased brain choline and acetylcholine levels and significantly improved ADAS-Cog scores.[61] Similar effects were observed in trials using 400 mg three times daily, in which L-α-GPC improved non-cognitive symptoms and supported vascular health in patients with vascular cognitive impairment (VCI).[16,62] These findings suggest potential clinical relevance of L-α-GPC in early cognitive impairment, although the strength and consistency of evidence remain heterogeneous across studies.

Additionally, L-α-GPC was combined with donepezil (10 mg/day) in trials involving mild-to-moderate AD and MCI patients, yielding better cognitive and behavioral outcomes than monotherapy. Improvements were observed across MMSE, ADAS-Cog, NPI, and IADL scores, confirming the additive benefits of L-α-GPC in enhancing cholinergic neurotransmission and cognitive reserve.[15,63,64] Moreover, in non-randomized and open-label studies, L-α-GPC treatment influenced electrophysiological markers such as P300 latency, further suggesting its impact on cognitive processing speed and attention.[65]

Potential Role of L-α-GPC in Parkinson's Disease

Parkinson's disease (PD) is mainly caused by dopamine loss, but also involves cholinergic deficits in the basal forebrain and pedunculopontine nucleus, which contribute to problems with cognition and gait.[66] Given this cholinergic involvement, therapeutic strategies that enhance acetylcholine availability have been explored as adjunctive treatments for cognitive symptoms in PD.[67] Although less extensively investigated, L-α-GPC has shown promise in managing cognitive symptoms associated with Parkinson's disease (PD). A prospective, open-label clinical trial by Levin et al (2011) evaluated the efficacy of L-α-GPC in PD patients with mild-to-moderate cognitive impairment.[68] Sixty participants received L-α-GPC at 1200 mg/day for twelve weeks. Approximately 40% of patients in the L-α-GPC group showed moderate to marked cognitive improvement, as measured by Clinical Global Impressions (CGI) and Mini-Mental State Examination (MMSE) scores, compared to 25% in the piracetam group. Patients receiving L-α-GPC exhibited improvements in attention and psychological status.[69]

In another controlled clinical trial, intravenous administration of L-α-GPC (1000 mg and 2000 mg doses) resulted in greater cognitive improvement compared to placebo.[56] The proposed mechanism involves L-α-GPC's conversion to acetylcholine in the brain, supporting cholinergic transmission, which is often impaired in Parkinsonian dementia. These findings are further supported by previous AD research that noted L-α-GPC's impact on dopaminergic signaling, mood regulation, and behavioral symptoms.[27] While data are currently limited, this evidence highlights L-α-GPC's potential for broader application across neurodegenerative diseases.

Preclinical and Clinical Evidence of L-α-GPC in Neurodegenerative Disorders

L-α-glycerylphosphorylcholine (α-GPC) has been reported across multiple preclinical and clinical studies to exhibit neuroprotective properties, particularly in modulating cholinergic neurotransmission, preserving synaptic integrity, and enhancing cognitive performance in neurodegenerative conditions. As summarized in Table 1, preclinical studies have shown that L-α-GPC exerts multifaceted effects via multiple mechanisms. In vitro studies have revealed its ability to reduce Aβ-induced inflammation by activating the α7 nicotinic acetylcholine receptor (α7nAChR) (44) and to limit tau phosphorylation by engaging the NGF/TrkA pathway.[44,47] Other studies demonstrated its role in enhancing pro-survival signaling and reducing oxidative stress-induced cell death in Alzheimer's disease (AD) models.[51] In vivo studies further confirmed that L-α-GPC improves memory, cholinergic tone, and hippocampal plasticity by regulating the expression of choline acetyltransferase (ChAT), the vesicular ACh transporter (VAChT), and BDNF.[45,48] Additionally, L-α-GPC supports the integrity of cholinergic synapses and contributes to the protection of both glial

Table 1 Mechanisms and Clinical Evidence of L-α-Glycerylphosphorylcholine (α-GPC) in Cognitive and Neurodegenerative Disorders

No.	Disease	Method	Mechanism	Result	Dose	Reference
1.	Alzheimer's disease (AD)	In vitro (BV2 murine microglial cell line)	Modulates microglia via α7nAChR	Inhibits Aβ-induced inflammation	1 mM α-GPC	Cantone et al, 2024[50]
2.	Cognitive dysfunction after stress	In vivo (animal study; rats)	Regulates ChAT, BDNF, and neuroblasts in the hippocampus	Improves memory and immune markers	Alpha-GPC (400 mg/kg) was administered orally after stress exposure for 7 days.	Yu et al, 2022[70]
3.	Dementia	In vivo (animal study, rats)	Affects CA1 and the dentate gyrus	Protects neurons and glia	100 mg/kg	Tomassoni et al, 2006[54]
4.	Alzheimer's disease (AD)	In vivo (animal study, rats)	Acts via α4β2, α7nAChR and anti-apoptosis	Strengthens the effect of galantamine	Oral dose of 3 mg/kg/day of galantamine and 100 mg/kg/day of L-α-GPC	Tayebati et al, 2009[53]
5.	Alzheimer's disease (AD)	In vitro (SH-SY5Y neuronal cell line)	Engages NGF/TrkA, reduces Tau phosphorylation	Counters Aβ25-35 neurotoxicity	Pre-treated for 1h with L-α-GPC 100nM and treated for 72 h with Aβ25-35 10μM.	Burgaletto et al, 2021[71]
6.	Dementia	In vivo (animal study, rats)	Alters AChT and VAChT in the cortex	Changes in neurotransmitter levels	One week treatment of CDP-L-α-GPC: 325 mg/kg/day; L-α-GPC 150 mg/kg/day	Tayebati et al, 2011[58]
7.	Alzheimer's disease (AD)	In vivo (animal study, rats)	Influences CHT and VAChT expression	Supports ACh synthesis and storage	Treated for 4 weeks with 150 mg/kg/day L-α-GPC	Tomassoni et al, 2012[54]
8.	Dementia	Clinical (human study)	Enhances CNS choline transport	Maintains brain choline levels over time	50 mg/kg L-α-GPC in four normal control subjects. One subject also received a dose of 200 mg/kg L-α-GPC	Stoll et al, 1995[59]
9.	Alzheimer's disease (AD)	Ex vivo (human brain tissue)	Affects PtdCho, PtdEtn metabolism	Raises GPC in the AD cortex	L-α-GPC (1.3 mM, 70,500 dpm/mmol)	Nitsch et al, 1992[52]
10.	Alzheimer's disease (AD)	In vitro (cell line human neuroblastoma SH-SY5Y)	Promotes pro-survival signaling	Limits Aβ-induced cell death	Different concentrations of L-α-GPC (0.1 mM, 1 mM, 10 mM, 50 mM) and oligomeric β-amyloid (1–42) (10 μM)	Catanesi et al, 2020[43]
11.	Alzheimer's disease (AD)	Ex vivo (human brain tissue)	Serves as an ACh reservoir	GPC levels found in AD brains	–	Blusztajn et al, 1990[30]
12.	Alzheimer's disease (AD)	In vivo (animal study, mouse)	–	Maintains cognition in normal mice	200 mg ALA, 500 mg ALCAR, 6 g DHA, 100 mg GPC, and 50 mg PS per kg of total diet dry weight	Suchy et al, 2009[55]
13.	Alzheimer's disease (AD)	In vivo (animal study, mouse)	Acts on inflammatory markers	Modifies amyloid levels and synaptic markers	Daily dose of 100 mg/kg	Munafò et al, 2024[72]
14.	Aging-related decline	In vivo (animal study, mice)	Interacts with long-term potentiation genes	Changes the expression profile in the aging brain	0.0136% L-α-GPC -containing solid diet	Narukawa et al, 2024[73]
15.	Cognitive impairment	In vivo (animal study, rats)	Converts to PC, supports α7nAChR	Preserves structure after irradiation	50 mg/kg bw, dissolved in 0.5 mL sterile saline	Plangár et al, 2014[74]
16.	Mild cognitive impairment (MCI)	Clinical (human study)	Crosses BBB, acts as a choline donor	Shows a change in the hippocampus and cognitive scores	1200 mg/day for 12 months	Carotenuto et al, 2024[60]
17.	Mild cognitive impairment (MCI)	Clinical (human study)	Raises brain choline and ACh	Improves ADAS-Cog vs placebo	600 mg L-α-GPC soft capsule	Jeon et al, 2024[61]

(*Continued*)

Table 1 (Continued).

No.	Disease	Method	Mechanism	Result	Dose	Reference
18.	Dementia	Clinical (human study)	Enhances circulation and membrane	Affects the ADAS-Noncog measure	400 mg tablet, 3 times a day.	Lee et al, 2024[16]
19.	Vascular cognitive impairment (VCI)	Clinical (human study)	Combined with nimodipine for brain flow	Protocol described; no results	Nimodipine 90 mg t.i.d plus L-α-GPC 1200 mg/day b.i.d. for a total of 12 months	Salvadori et al, 2020[62]
20.	Mild-to-moderate Alzheimer's disease (AD)	Clinical (human study)	Enhances ACh with donepezil	More cognitive and behavioural effects than monotherapy	ChE-I (donepezil 10 mg/day) + precursor cholinergic (L-α-GPC 1200 mg/day)	Amenta et al, 2014[15]
21.	Alzheimer's disease (AD)	Clinical (human study)	Choline source	Benefits in MMSE, ADAS-Cog, IADL, NPI	Combination of L-α-GPC 1200 mg/day + donepezil 10 mg/day	Amenta et al, 2012[63]
22.	Mild cognitive impairment (MCI)	Clinical (human study)	Affects P300 latency	Suggests cognitive change	After the baseline P300, patients took L-α-GPC 400 mg twice daily for 3 months. A follow-up P300 was then performed within 7 days.	Han et al, 2018[65]
23.	Alzheimer's Disease (AD)	Clinical (human study)	Slows brain volume loss	Improves function and cognition	1200 mg of L-α-GPC with 10 mg of donepezil a day	Traini et al, 2020[56]
24.	Alzheimer's Disease (AD)	Clinical (human study)	Affects dopaminergic activity	Influences apathy and caregiver stress	Donepezil 10 mg/day + L-α-GPC 1200 mg/day	Rea et al, 2015[57]
25.	Mild to moderate dementia of the Alzheimer's type	Clinical (human study)	Supports ACh release	Scores higher in ADAS-Cog, MMSE, etc.	400-mg capsules 3 times daily	De and Moreno, 2003[51]
26.	Mild to moderate vascular dementia	Clinical (human study)	Promotes membrane and ACh synthesis	Performs better than CDP-choline	1 g/day intramuscularly for 90 days.	Perri et al, 1991[64]
27.	Cognitive deficit of an acute ischemic cerebral event	Clinical (human study)	Supports ACh and the membrane	Benefits in neurology and mood	1000 mg/day IM (baseline and first month) and 3×400 mg/day orally (third month and sixth month)	Sangiorgi et al, 1994[18]
28.	Probable senile dementia of Alzheimer's type	Clinical (human study)	Choline and membrane support	Changes verbal memory and emotion tests	Oral 800mg at 8 am and 400mg at 4 pm	Parnetti et al, 1993[75]
29.	Alzheimer's Disease	Clinical (human study)	Acts in the hippocampus and frontal areas	Improves depression symptoms	Donepezil 10 mg + L-α-GPC 1200 mg/day	Levin et al, 2009[68]
30.	Alzheimer's Disease (AD)	Clinical (human study)	Affects mood-related cholinergic areas	Influences BPSD and mood	Group A (donepezil 10 mg/day + L-α-GPC 1200 mg/day), group B (donepezil 10 mg/day + placebo)	Carotenuto et al, 2024[60]
31.	Alzheimer's Disease (AD)	Clinical (human study)	Supports membrane and ACh metabolism	Results in less gray matter loss	Donepezil 10 mg/day + L-α-GPC 1200 mg/day	Carotenuto et al, 2017[76]
32.	Parkinson's disease	Clinical (human study)	Converts to brain ACh	More cognitive improvement than placebo	Group 1 (1000 mg) and Group 2 (2000 mg) IV	Traini et al, 2020[56]

and neuronal cells in models of dementia, irradiation-induced damage, and aging.[46,56] Doses used in these studies ranged from 50 to 400 mg/kg, with outcomes generally indicating improved neurotransmission and reduced neuropathology.

Table 2 outlines key clinical trials supporting the therapeutic role of L-α-GPC in patients with mild cognitive impairment (MCI), Alzheimer's disease, vascular dementia, and post-stroke cognitive decline. Clinical trials have

Table 2 Clinical Studies on L-α-GPC in Cognitive and Neurodegenerative Disorders

No.	Disease	Method	Result	Dose	Reference
1.	Mild to moderate dementia of the Alzheimer's type	Multicentre, double-blind, randomized, placebo-controlled trial	Scores higher in ADAS-Cog, MMSE, etc.	400-mg capsules 3 times daily	De and Moreno, 2003[51]
2.	Alzheimer's Disease (AD)	Randomized, placebo-controlled, double-blind trial	Results in less gray matter loss	Donepezil 10 mg/day + L-α-GPC 1200 mg/day	Carotenuto et al, 2017[76]
3.	Alzheimer's Disease (AD)	Randomized, placebo-controlled, double-blind trial	Improves function and cognition	1200 mg of L-α-GPC with 10 mg of donepezil a day	Traini et al, 2020[56]
4.	Mild cognitive impairment (MCI)	Randomized double-blind placebo-controlled trial	Improves ADAS-Cog vs placebo	600 mg L-α-GPC soft capsule	Jeon et al, 2024[61]
5.	Alzheimer's disease (AD)	Double-blind multicentre trial	Benefits in MMSE, ADAS-Cog, IADL, NPI	Combination of L-α-GPC 1200 mg/day + donepezil 10 mg/day	Amenta et al, 2012[63]
6.	Alzheimer's Disease (AD)	Double-blind randomized trial	Influences BPSD and mood	Group A (donepezil 10 mg/day + L-α-GPC 1200 mg/day), group B (donepezil 10 mg/day + placebo)	Carotenuto et al, 2024[60]
7.	Vascular cognitive impairment (VCI)	Randomized placebo-controlled trial	Protocol described; no results	Nimodipine 90 mg t.i.d plus L-α-GPC 1200 mg/day b.i.d. for a total of 12 months	Salvadori et al, 2020[62]
8.	Alzheimer's Disease (AD)	Randomized double-blind trial	Influences apathy and caregiver stress	Donepezil 10 mg/day + L-α-GPC 1200 mg/day	Rea et al, 2015[57]
9.	Mild cognitive impairment (MCI)	Randomized controlled trials	Shows a change in the hippocampus and cognitive scores	1200 mg/day for 12 months	Carotenuto et al, 2024[60]
10.	Alzheimer's Disease	Randomized trial	Improves depression symptoms	Donepezil 10 mg + L-α-GPC 1200 mg/day	Levin et al, 2009[68]
11.	Parkinson's disease	Controlled clinical trial	More cognitive improvement than placebo	Group 1 (1000 mg) and Group 2 (2000 mg) IV	Traini et al, 2020[56]
12.	Mild-to-moderate Alzheimer's disease (AD)	Double blind trial	More cognitive and behavioural effects than monotherapy	ChE-I (donepezil 10 mg/day) + precursor cholinergic (L-α-GPC 1200 mg/day)	Amenta et al, 2014[15]
13.	Dementia	Mixed double-blind randomized controlled and open-label observation trial	Affects the ADAS-Noncog measure	400 mg tablet, 3 times a day.	Lee et al, 2024[16]
14.	Mild to moderate vascular dementia	Multicentre trial	Performs better than CDP-choline	1 g/day intramuscularly for 90 days.	Perri et al, 1991[64]
15.	Cognitive deficit of an acute ischemic cerebral event	Multicentre clinical trial	Benefits in neurology and mood	1000 mg/day IM (baseline and first month) and 3×400 mg/day orally (third month and sixth month)	Sangiorgi et al, 1994[18]
16.	Probable senile dementia of Alzheimer's type	Multicentre clinical trial	Changes verbal memory and emotion tests	Oral 800mg at 8 am and 400mg at 4 pm	Parnetti et al, 1993[75]
17.	Mild cognitive impairment (MCI)	Preliminary, open-label, and non-randomized trial	Suggests cognitive change	After the baseline P300, patients took L-α-GPC 400 mg twice daily for 3 months. A follow-up P300 was then performed within 7 days.	Han et al, 2018[65]

reported improvements in cognitive scores with L-α-GPC, either as monotherapy or in combination with donepezil, including the MMSE, ADAS-Cog, and IADL, and slowing gray matter loss.[43,57,58] Notably, several studies have reported improved outcomes when L-α-GPC is combined with cholinesterase inhibitors, suggesting synergistic effects on both cognitive and behavioral symptoms.[36,39] Across trials, L-α-GPC doses ranged from 600 mg/day to 1200 mg/day orally, or 1 g/day intramuscularly, with durations extending up to 12 months.

In patients with vascular cognitive impairment and post-stroke cognitive deficits, L-α-GPC improved not only cognition but also mood and neurological function.[18,42] Additionally, in Parkinson's disease, L-α-GPC administration was associated with improved cognition compared with placebo, reinforcing its broader application beyond Alzheimer-type dementia.[43] Together, the evidence from both preclinical and clinical studies underscores the potential of L-α-GPC as a disease-modifying adjunct that supports cholinergic function, protects neural structures, and enhances cognitive resilience in neurodegenerative and cerebrovascular disorders.

Adverse Effects and Safety Profile of L-α-GPC

Choline, as a metabolic product of L-α-GPC, has been associated with several adverse effects, including fish-like body odor, gastrointestinal discomfort, hypotension, excessive sweating and potential liver dysfunction.[28,77,78] Gastrointestinal disturbances such as abdominal pain, constipation, dyspepsia, and nausea were reported as the most frequent adverse events in L-α-GPC.[61] Increasing evidence also indicates that elevated choline levels may contribute to cardiovascular risk through its conversion by gut microbiota into trimethylamine-N-oxide (TMAO), a metabolite linked to stroke and cardiovascular disease.[79] Epidemiological data demonstrate that individuals prescribed α-GPC exhibit a significantly higher risk of total, ischemic, and hemorrhagic stroke compared to nonusers, with the risk of ischemic stroke increasing in a duration-dependent manner.[28]

Preclinical toxicological studies suggest that L-α-GPC has low acute toxicity, as no adverse effects were observed in male or female rats administered single oral doses up to 10.0 g/kg body weight. However, in a 90-day oral toxicity study, female rats receiving 2000 mg/kg showed reduced body weight and alterations in liver function parameters, including increased ALT, AST, and ALP levels, whereas no genotoxic effects were detected in micronucleus, chromosomal aberration, or Ames tests. The no-observed-adverse-effect level (NOAEL) was determined to be 1000 mg/kg body weight for female rats and 2000 mg/kg for male rats, with similar thresholds observed in teratogenicity assessments.[80] At the cellular level, experimental findings indicate that pretreatment with 10 μM L-α-GPC under oxidative stress conditions downregulated the expression of Survivin, HO-1, and HIF-1α, thereby increasing astrocyte susceptibility to isoflurane-induced cytotoxicity.[81] Together, these data suggest that although L-α-GPC is generally considered safe, prolonged exposure, high doses, or oxidative stress conditions may reveal adverse effects.

Discussion

This review highlights accumulating evidence from both preclinical and clinical studies supporting the therapeutic potential of L-α-GPC as a neuroprotective and cholinergic agent in neurodegenerative disorders. Clinical trials and meta-analyses have reported cognitive benefits in conditions such as Alzheimer's disease (AD), mild cognitive impairment (MCI), and Parkinson's disease (PD). For instance, a meta-analysis by Sagaro et al (2023) found that L-α-GPC monotherapy significantly improved MMSE scores and, in combination with donepezil, led to greater improvements in ADAS-Cog.[82] An extensive cohort study also showed that long-term L-α-GPC use was associated with a reduced risk of progression from MCI to AD and vascular dementia.[26] In PD, L-α-GPC was reported to be associated with better cognitive outcomes compared to piracetam in limited clinical settings.[68]

Emerging evidence indicates that mild cognitive impairment and dementia are not solely characterized by neurotransmitter deficits or protein aggregation but are also accompanied by broader metabolic alterations, including disturbances in amino acid, lipid, and energy metabolism. Metabolomic and biomarker-based studies have demonstrated that such metabolic signatures are associated with the severity of cognitive impairment and disease progression, highlighting their potential value for patient stratification and outcome assessment in future intervention trials.[83,84] In this context, biomarker-informed phenotyping may help to better contextualize heterogeneous treatment responses observed across

clinical studies and improve the interpretability of therapeutic signals, without implying direct mechanistic specificity for any single intervention.

Reported cognitive outcomes of L-α-GPC vary across studies, likely reflecting substantial heterogeneity in both biological and methodological factors. Genetic background has been proposed as an effect modifier in neurodegenerative disorders and may contribute to inter-individual differences in cognitive trajectories and treatment responsiveness.[85,86] In addition, variability in diagnostic criteria, baseline disease severity, cognitive endpoints, follow-up duration, and co-interventions further complicates cross-study comparisons. These considerations support cautious interpretation of efficacy signals and highlight the need for biomarker- and genotype-informed approaches in future trials.

Across clinical studies, reported benefits of L-α-GPC primarily relate to improvements in cognitive test scores, particularly in short- to medium-term trials using standardized neuropsychological endpoints. In some study settings, these improvements were accompanied by signals suggestive of slower cognitive decline over the study period; however, available evidence remains heterogeneous and insufficient to establish a definitive disease-modifying effect. Variability in study design, populations, outcome measures, follow-up duration, and co-interventions likely contributes to the mixed findings observed across AD, MCI, and PD, underscoring the need for cautious interpretation of clinical benefits.

Mechanistically, L-α-GPC acts as a bioavailable precursor of acetylcholine, aligning with the cholinergic hypothesis of cognitive decline.[19,26] It crosses the blood–brain barrier, increases brain choline levels, and promotes the synthesis and release of acetylcholine (ACh). Additionally, it enhances neurotrophic signaling (eg, BDNF), modulates α7nAChR, reduces Aβ-induced inflammation, inhibits tau phosphorylation, and prevents neuronal apoptosis.[20,43] L-α-GPC also upregulates choline transporters (CHT, VAChT), contributing to sustained cholinergic neurotransmission.[53]

Compared to acetylcholinesterase inhibitors (AChEIs), which prevent ACh degradation, L-α-GPC supports synthesis and release, offering complementary and potentially longer-lasting effects.[10,11] Combining AChEIs has shown synergistic benefits; the ASCOMALVA trial reported reduced hippocampal atrophy and improved cognition with L-α-GPC plus donepezil compared with donepezil alone.[15] Safety profiles are favorable, with most adverse effects being mild and transient.[16]

Preclinical findings further reinforce these outcomes. In animal models, L-α-GPC enhances memory, increases hippocampal acetylcholine (ACh) levels, and mitigates neuronal injury resulting from insults such as irradiation or seizures[15,75] Clinically, several studies have reported improvements in neuropsychological scores among patients with dementia receiving L-α-GPC, with some suggesting an association with slower cognitive decline over the study period.[68] Its dual role in enhancing both cholinergic neurotransmission and membrane phospholipid metabolism supports its broad neuroprotective actions.[15,75]

Despite promising evidence, limitations remain. Many clinical studies are limited by small sample sizes, short durations, and heterogeneous designs, which complicate comparisons. Some trials, particularly in vascular cognitive impairment and post-stroke dementia, have yielded inconclusive or negative results.[62] Optimal dosing regimens and treatment durations are not standardized, and mechanisms beyond cholinergic pathways (eg, anti-inflammatory, neurotrophic) require further clarification. Additionally, evidence in non-Alzheimer dementias such as Parkinson's disease dementia or Lewy body dementia is still sparse, and many studies lack methodological rigor (eg, blinding, placebo controls).

To establish L-α-GPC's role more definitively, future research should prioritize large-scale, multicenter randomized controlled trials with standardized cognitive endpoints. Investigating L-α-GPC in early disease stages, such as prodromal AD or MCI, may reveal disease-modifying potential.[61] Biomarker-guided studies, including neuroimaging and fluid-based markers, are essential to elucidate its effects on brain structure and pathology.[56] Combination strategies, such as pairing L-α-GPC with other neuroprotective agents or lifestyle interventions, may enhance outcomes. Given its observed neurotrophic and cerebrovascular actions, expanding indications to include post-ischemic, vascular, or Parkinsonian dementias is warranted.

In conclusion, L-α-GPC emerges as a promising adjunct or standalone therapy with multifaceted actions in the management of neurodegenerative diseases. However, robust, well-designed trials are essential to validate its efficacy, define its optimal use, and extend its application across broader clinical contexts.

Conclusion

L-α-GPC represents a promising therapeutic candidate for the management of cognitive impairment associated with neurodegenerative diseases, particularly Alzheimer's disease, vascular dementia, and Parkinson's disease. Evidence from both preclinical and clinical studies highlights the multifaceted mechanisms of action of this compound, including enhancement of cholinergic neurotransmission, neurotrophic support, anti-inflammatory effects, and neuroprotection.

Clinical trials have consistently shown that L-α-GPC, whether used alone or in combination with standard therapies such as donepezil, improves cognitive performance and slows disease progression more effectively than monotherapy. In addition, observational data suggest that long-term L-α-GPC use may reduce the risk of conversion from MCI to dementia and confer protection against cerebrovascular events. However, the interpretation of these findings should be considered in light of several limitations. This review was based solely on studies indexed in PubMed, which may have resulted in the exclusion of relevant data from other databases or unpublished sources.

Despite its favorable safety profile and encouraging clinical outcomes, current evidence is limited by heterogeneous trial designs, non-standardized endpoints, and underrepresentation of specific neurodegenerative populations. To fully establish the clinical utility and potential disease-modifying effects of L-α-GPC, future studies should focus on well-powered, randomized controlled trials that incorporate biomarker-based endpoints and target early stages of the disease.

In summary, L-α-GPC offers a well-tolerated, mechanistically robust therapeutic option with both symptomatic and neuroprotective benefits, reinforcing its potential as a valuable component in the treatment landscape for cognitive decline and neurodegenerative disorders.

Acknowledgments

The authors gratefully acknowledge financial support from the Internal Research Grant of Universitas Padjadjaran. We also thank Universitas Padjadjaran for covering the article processing charge (APC) and for institutional support throughout the research process.

Disclosure

The authors declare no conflicts of interest related to this work.

References

1. Cox D, Raeburn C, Sui X, Hatters DM. Protein aggregation in cell biology: an aggregomics perspective of health and disease. *Semin Cell Dev Biol*. 2020;99:40–54. doi:10.1016/j.semcdb.2018.05.003
2. Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. *Cell*. 2023;186(4):693–714. doi:10.1016/j.cell.2022.12.032
3. Wang B, Lan C, Liu K, et al. Global, regional, and national burden and attributable risk factors of depressive disorders among older adults, 1990-2021. *Int Psychogeriatr*. 2025;37:100069. doi:10.1016/j.inpsyc.2025.100069
4. Huang Y, Li Y, Pan H, Han L. Global, regional, and national burden of neurological disorders in 204 countries and territories worldwide. *J Glob Health*. 2023;13. doi:10.7189/JOGH.13.04160
5. Pan Y, Nicolazzo JA. Impact of aging, Alzheimer's disease and Parkinson's disease on the blood-brain barrier transport of therapeutics. *Adv Drug Deliv Rev*. 2018;135:62–74. doi:10.1016/j.addr.2018.04.009
6. Wallin MT, Culpepper WJ, Nichols E, et al. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(3):269–285. doi:10.1016/S1474-4422(18)30443-5
7. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204–1222. doi:10.1016/S0140-6736(20)30925-9
8. Adkins-Jackson PB, George KM, Besser LM, et al. The structural and social determinants of Alzheimer's disease related dementias. *Alzheimers Dementia*. 2023;19(7):3171–3185. doi:10.1002/alz.13027
9. Kuiper JS, Zuidersma M, Oude voshaar RC, et al. Social relationships and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res Rev*. 2015;22:39–57. doi:10.1016/j.arr.2015.04.006
10. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: an update. *J Cent Nerv Syst Dis*. 2020;12:117957352090739. doi:10.1177/1179573520907397
11. Dekker MJHJ, Bouvy JC, O'Rourke D, et al. Alignment of European Regulatory and Health Technology Assessments: a review of licensed products for Alzheimer's disease. *Front Med*. 2019;6. doi:10.3389/fmed.2019.00073
12. Gajendra K, Pratap GK, Poornima DV, Shantaram M, Ranjita G. Natural acetylcholinesterase inhibitors: a multi-targeted therapeutic potential in Alzheimer's disease. *Eur J Med Chem Rep*. 2024;11:100154. doi:10.1016/j.ejmcr.2024.100154
13. Liu PP, Xie Y, Meng XY, Kang JS. History and progress of hypotheses and clinical trials for Alzheimer's disease. *Signal Transduct Target Ther*. 2019;4(1). doi:10.1038/s41392-019-0063-8

14. Hampel H, Mesulam MM, Cuello AC, et al. WITHDRAWN: revisiting the cholinergic hypothesis in Alzheimer's disease: emerging evidence from translational and clinical research. *Alzheimers Dementia*. 2017. doi:10.1016/j.jalz.2017.08.016
15. Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E. The ASCOMALVA (Association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in Alzheimer's disease) Trial: interim results after two years of treatment. *J Alzheimers Dis*. 2014;42: S281–S288. doi:10.3233/JAD-140150
16. Lee W, Kim M. Comparative study of choline alfoscerate as a combination therapy with donepezil: a mixed double-blind randomized controlled and open-label observation trial. *Medicine*. 2024;103(24):e38067. doi:10.1097/MD.0000000000038067
17. Cao J, Su E. Unlocking the potential of l-α-glycerylphosphorylcholine in the food industry: from safety approvals to market prospects. *Compr Rev Food Sci Food Saf*. 2025;24(2). doi:10.1111/1541-4337.70117
18. Sangiorgi GB, Barbagallo M, Giordano M, Meli M, Panzarasa R. A-Glycerophosphocholine in the mental recovery of cerebral ischemic attacks an Italian multicenter clinical trial. *Ann N Y Acad Sci*. 1994;717:253–269. doi:10.1111/j.1749-6632.1994.tb12095.x
19. Schettini G, Ventra C, Florio T, et al. Molecular mechanisms mediating the effects of L-c-glycerylphosphorylcholine, a new cognition-enhancing drug, on behavioral and biochemical parameters in young and aged rats. *Pharmacol Biochem Behav*. 1992;43(1):139–151. doi:10.1016/0091-3057(92)90650-5
20. Jamal M, Ito A, Tanaka N, et al. The role of apolipoprotein e and ethanol exposure in age-related changes in choline acetyltransferase and brain-derived neurotrophic factor expression in the mouse hippocampus. *J Mol Neurosci*. 2018;65(1):84–92. doi:10.1007/s12031-018-1074-6
21. Kansakar U, Trimarco V, Mone P, Varzideh F, Lombardi A, Santulli G. Choline supplements: an update. *Front Endocrinol*. 2023;14. doi:10.3389/fendo.2023.1148166
22. Kim J, Song Y, Lee SJ, et al. Enzymatic preparation of food-grade l-α-glycerylphosphorylcholine from soy phosphatidylcholine or fractionated soy lecithin. *Biotechnol Prog*. 2020;36(1). doi:10.1002/btpr.2910
23. Kang M, Lee DB, Kwon S, Lee E, Kim WJ. Effectiveness of nootropics in combination with cholinesterase inhibitors on cognitive function in mild-to-moderate dementia: a study using real-world data. *J Clin Med*. 2022;11(16):4661. doi:10.3390/jcm11164661
24. PubChem. Choline Alfoscerate. PubChem; 2025. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Choline-Alfoscerate. Accessed November 4, 2025.
25. Min MH, Park JH, Hur JH, Shin HC, Cho Y, Kim DD. Formulation and bioequivalence studies of choline alfoscerate tablet comparing with soft gelatin capsule in healthy male volunteers. *Drug Des Devel Ther*. 2019;13:1049–1058. doi:10.2147/DDDT.S193424
26. Kim HK, Park S, Kim SW, et al. Association between L-α glycerylphosphorylcholine use and delayed dementia conversion: a nationwide longitudinal study in South Korea. *J Prev Alzheimers Dis*. 2025;12(4):100059. doi:10.1016/j.tjpad.2025.100059
27. Granata N, Vercesi M, Bonfanti A, et al. Choline alphoscerate: a therapeutic option for the management of subthreshold depression in the older population. *Geriatrics*. 2025;10(2):32. doi:10.3390/geriatrics10020032
28. Lee G, Choi S, Chang J, et al. Association of L-α glycerylphosphorylcholine with subsequent stroke risk after 10 years. *JAMA Network Open*. 2021;4(11):e2136008. doi:10.1001/jamanetworkopen.2021.36008
29. Duong KL, Jung H, Lee HK, et al. Effect of choline alfoscerate in older adult patients with dementia: an observational study from the claims data of national health insurance. *BMC Geriatr*. 2024;24(1). doi:10.1186/s12877-024-05531-y
30. Krzysztof Blusztajn J, Lopez Gonzalez-Coviella I, Logue M, Growdon JH, Wurtman RJ. Levels of phospholipid catabolic intermediates, glycerophosphocholine and glycerophosphoethanolamine, are elevated in brains of Alzheimer's disease but not of Down's syndrome patients. *Brain Res*. 1990;536(1–2):240–244. doi:10.1016/0006-8993(90)90030-F
31. Lopez CM, Govoni S, Battaini F, et al. Effect of a new cognition enhancer, alpha-glycerylphosphorylcholine, on scopolamine-induced amnesia and brain acetylcholine. *Pharmacol Biochem Behav*. 1991;39(4):835–840. doi:10.1016/0091-3057(91)90040-9
32. Amenta F, Franch F, Ricci A, Vega JA. Cholinergic neurotransmission in the hippocampus of aged rats: influence of L-a-glycerylphosphorylcholine treatment. *Ann N Y Acad Sci*. 1993;695(1):311–313. doi:10.1111/j.1749-6632.1993.tb23073.x
33. Amenta F, Bronzetti E, Mancini M, Vega A, Zaccheo D. Choline acetyltransferase and acetylcholinesterase in the hippocampus of aged rats: sensitivity to choline alphoscerate treatment. *Mech Ageing Dev*. 1994;74(1–2):47–58. doi:10.1016/0047-6374(94)90097-3
34. Nabeshima T, Noda Y, Tohyama K, Itoh J, Kameyama T. Effects of DM-9384 in a model of amnesia based on animals with GABAergic neuronal dysfunctions. *Eur J Pharmacol*. 1990;178:143–149. doi:10.1016/0014-2999(90)90469-M
35. Noremberg K, Strosznajder J. Modification of GABA and calcium uptake by lipids in synaptosomes from normoxic and ischemic brain. *Neurochem Int*. 1986;8(1):59–66. doi:10.1016/0197-0186(86)90101-4
36. Luo H, Fernandez de Velasco EM, Wickman K. Neuronal G protein-gated K 1 channels. *Am J Physiol Cell Physiol*. 2022;323(2):C439–C460. doi:10.1152/ajpcell.00102.2022
37. Govoni S, Battaini F, Lucchi L, Pascale A, Trabucchi M. Cognition-enhancing drug.
38. Lucchi L, Pascale A, Battaini F, Govoni S, Trabucchi M. Cognition stimulating drugs modulate protein kinase C activity in cerebral cortex and hippocampus of adult rats. *Life Sci*. 1993;53(24):1821–1832. doi:10.1016/0024-3205(93)90490-T
39. Tokés T, Eros G, Bebes A, et al. Protective effects of a phosphatidylcholine-enriched diet in lipopolysaccharide-induced experimental neuroinflammation in the rat. *Shock*. 2011;36(5):458–465. doi:10.1097/SHK.0b013e31822f36b0
40. Lee SH, Choi BY, Kim JH, et al. Late treatment with choline alfoscerate (L-alpha glycerylphosphorylcholine, α-GPC) increases hippocampal neurogenesis and provides protection against seizure-induced neuronal death and cognitive impairment. *Brain Res*. 2017;1654:66–76. doi:10.1016/j.brainres.2016.10.011
41. Edwards MJ, Wilson GC, Keitsch S, et al. Molecular targets of endothelial phosphatidic acid regulating major depressive disorder. *J Neurochem*. 2022;163(4):357–369. doi:10.1111/jnc.15708
42. Yu HJ, Kim YL, Kim MJ, et al. The effect of choline alphoscerate on non spatial memory and neuronal differentiation in a rat model of dual stress. *Brain Res*. 2022;1786:147900. doi:10.1016/j.brainres.2022.147900
43. Catanesi M, d'Angelo M, Antonosante A, et al. Neuroprotective potential of choline alfoscerate against β-amyloid injury: involvement of neurotrophic signals. *Cell Biol Int*. 2020;44(8):1734–1744. doi:10.1002/cbin.11369
44. Vega JA, Cavallotti C, Del Valle ME, Mancini M, Amenta F. Nerve growth factor receptor immunoreactivity in the cerebellar cortex of aged rats: effect of choline alfoscerate treatment. *Mech Ageing Dev*. 1993;69(1–2):119–127. doi:10.1016/0047-6374(93)90076-4

45. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A review of the common neurodegenerative disorders: current therapeutic approaches and the potential role of nanotherapeutics. *Int J Mol Sci*. 2022;23(3):1851. doi:10.3390/ijms23031851
46. Huang B. The fundamental cause of neurodegenerative diseases. 2025. Available from: https://ssrn.com/abstract=5250307. Accessed May 12, 2026.
47. Ricci C. Neurodegenerative disease: from molecular basis to therapy, 2nd Edition. *Int J Mol Sci*. 2025;26(5):1929. doi:10.3390/ijms26051929
48. Karlina I, Andriyani EFS, Pratiwi AD, et al. Gambaran Penyakit Neurodegeneratif: huntington, Alzheimer, dan Parkinson: sebuah Tinjauan. *Jurnal Biomedika Dan Kesehatan*. 2024;7(1):113–123. doi:10.18051/jbiomedkes.2024.v7.113-123
49. Davenport F, Gallacher J, Kourtzi Z, et al. Neurodegenerative disease of the brain: a survey of interdisciplinary approaches. *J R Soc Interface*. 2023;20(198). doi:10.1098/rsif.2022.0406
50. Cantone AF, Burgaletto C, Di Benedetto G, et al. Taming microglia in Alzheimer's Disease: exploring potential implications of choline alphoscerate via α7 nAChR modulation. *Cells*. 2024;13(4):309. doi:10.3390/cells13040309
51. Moreno MDJM. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: a multicenter, double-blind, randomized, placebo-controlled trial. *Clin Ther*. 2003;25(1):178–193. doi:10.1016/S0149-2918(03)90023-3
52. Nitsch RM, Blusztajn JK, Pittast AG, Slackt BE, Growdon JH, Wurtmant RJ. Evidence for a membrane defect in Alzheimer disease brain. *Proc Natl Acad Sci*. 1992;89(5):1671–1675. doi:10.1073/pnas.89.5.1671
53. Tayebati SK, Di Tullio MA, Tomassoni D, Amenta F. Neuroprotective effect of treatment with galantamine and choline alphoscerate on brain microanatomy in spontaneously hypertensive rats. *J Neurol Sci*. 2009;283(1–2):187–194. doi:10.1016/j.jns.2009.02.349
54. Tomassoni D, Avola R, Mignini F, Parnetti L, Amenta F. Effect of treatment with choline alphoscerate on hippocampus microanatomy and glial reaction in spontaneously hypertensive rats. *Brain Res*. 2006;1120(1):183–190. doi:10.1016/j.brainres.2006.08.068
55. Suchy J, Chan A, Shea TB. Dietary supplementation with a combination of α-lipoic acid, acetyl-l-carnitine, glycerophosphocoline, docosahexaenoic acid, and phosphatidylserine reduces oxidative damage to murine brain and improves cognitive performance. *Nutr Res*. 2009;29(1):70–74. doi:10.1016/j.nutres.2008.11.004
56. Traini E, Carotenuto A, Fasanaro AM, Amenta F. Volume analysis of brain cognitive areas in Alzheimer's disease: interim 3-year results from the ASCOMALVA Trial. *J Alzheimers Dis*. 2020;76(1):317–329. doi:10.3233/JAD-190623
57. Rea R, Carotenuto A, Traini E, Fasanaro AM, Manzo V, Amenta F. Apathy treatment in Alzheimer's disease: interim results of the ASCOMALVA Trial. *J Alzheimers Dis*. 2015;48(2):377–383. doi:10.3233/JAD-141983
58. Tayebati SK, Tomassoni D, Di Stefano A, Sozio P, Cerasa LS, Amenta F. Effect of choline-containing phospholipids on brain cholinergic transporters in the rat. *J Neurol Sci*. 2011;302(1–2):49–57. doi:10.1016/j.jns.2010.11.028
59. Stoll AL, Renshaw PF, De Micheli E, Wurtman R, Pillay SS, Cohen BM. Choline ingestion increases the resonance of choline-containing compounds in human brain: an in vivo proton magnetic resonance study. *Biol Psychiatry*. 1995;37(3):170–174. doi:10.1016/0006-3223(94)00120-R
60. Carotenuto A, Andreone V, Amenta F, Traini E. Effect of treatment of the cholinergic precursor choline alphoscerate in mild cognitive dysfunction: a randomized controlled trial. *Medicina*. 2024;60(6):925. doi:10.3390/medicina60060925
61. Jeon J, Lee SY, Lee S, et al. Efficacy and safety of choline alphoscerate for amnestic mild cognitive impairment: a randomized double-blind placebo-controlled trial. *BMC Geriatr*. 2024;24(1). doi:10.1186/s12877-024-05366-7
62. Salvadori E, Poggesi A, Donnini I, et al. Association of nimodipine and choline alphoscerate in the treatment of cognitive impairment in patients with cerebral small vessel disease: study protocol for a randomized placebo-controlled trial—the CONIVaD trial. *Aging Clin Exp Res*. 2020;32(3):449–457. doi:10.1007/s40520-019-01229-z
63. Amenta F, Carotenuto A, Fasanaro AM, Rea R, Traini E. The ASCOMALVA trial: association between the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate in Alzheimer's disease with cerebrovascular injury: interim results. *J Neurol Sci*. 2012;322(1–2):96–101. doi:10.1016/j.jns.2012.07.003
64. Perri RD, Coppola G, Ambrosio LA, et al. A multicentre trial to evaluate the efficacy and tolerability of a-glycerylphosphorylcholine versus cytosine diphosphocholine in patients with vascular dementia. *J Int Med Res*. 1991;19(4):330–341. doi:10.1177/030006059101900406
65. Han SH, Jeong HB, Park KY, Shin HW, Youn YC, Kim SY. P300 latency changes in patients with mild cognitive impairment after taking choline alphoscerate; A preliminary study. *eNeurologicalSci*. 2018;11:5–8. doi:10.1016/j.ensci.2018.04.004
66. Jellinger KA. Pathobiology of cognitive impairment in Parkinson disease: challenges and outlooks. *Int J Mol Sci*. 2024;25(1). doi:10.3390/ijms25010498
67. Synoradzki K, Grieb P. Citicoline: a superior form of choline? *Nutrients*. 2019;11(7):1569. doi:10.3390/nu11071569
68. Levin O, Batukaeva LA, Anikina MA, Iunishchenko NA. Efficacy and safety of choline alphoscerate (cereton) in patients with Parkinson's disease with cognitive impairments. *Neurosci Behav Physi*. 2011;41:47–51. doi:10.1007/s11055-010-9377-2
69. Levin OS, Batukaeva LA, Anikina MA, Iunishchenko NA. [Efficacy and tolerability of choline alphoscerate (cereton) in patients with Parkinson's disease with cognitive disorders]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2009;109(11):42–46. Russian.
70. Yu HJ, Kim MJ, Park JM, Park SY, Park SN, Yang DW. The effect of choline alphoscerate on non spatial memory and neurogenesis in a rat model of dual stress. 2020. doi:10.1101/2020.06.16.154310.
71. Burgalleto C, Di Benedetto G, Munafò A, Bernardini R, Cantarella G. Beneficial effects of choline alphoscerate on Amyloid-β neurotoxicity in an in vitro model of Alzheimer's disease. *Curr Alzheimer Res*. 2021;18(4):298–309. doi:10.2174/1567205018666210608093658
72. Munafò A, Cantone AF, Di Benedetto G, et al. Pharmacological enhancement of cholinergic neurotransmission alleviates neuroinflammation and improves functional outcomes in a triple transgenic mouse model of Alzheimer's disease. *Front Pharmacol*. 2024;15. doi:10.3389/fphar.2024.1386224
73. Narukawa M, Kamiyoshihara A, Izu H, Fujii T, Matsubara K, Misaka T. Efficacy of long-term feeding of α-glycerophosphocholine for aging-related phenomena in old mice. *Gerontology*. 2020;66(3):275–285. doi:10.1159/000504962
74. Plangár I, Szabó ER, Tőkés T, et al. Radio-neuroprotective effect of L-alpha-glycerylphosphorylcholine (GPC) in an experimental rat model. *J Neurooncol*. 2014;119(2):253–261. doi:10.1007/s11060-014-1489-z
75. Parnetti L, Abate G, Bartorelli L, et al. Multicentre study of L-a-Glyceryl-Phosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's Type. *Drugs Aging*. 1993;3(2):159–164. doi:10.2165/00002512-199303020-00006
76. Carotenuto A, Rea R, Traini E, et al. The effect of the association between donepezil and choline alphoscerate on behavioral disturbances in Alzheimer's Disease: interim results of the ASCOMALVA Trial. *J Alzheimers Dis*. 2017;56(2):805–815. doi:10.3233/JAD-160675
77. Erdman JW, Macdonald IA, Zeisel SH, eds.. *Present Knowledge in Nutrition*. 10th ed. Wiley-Blackwell; 2012. doi:10.1002/9781119946045

78. National Institutes of Health Office of Dietary Supplements. Choline: fact sheet for health professionals. 2020. Available from: https://ods.od.nih.gov/factsheets/Choline-HealthProfessional/. Accessed March 9, 2020.
79. Nam HS. Gut microbiota and ischemic stroke: the role of trimethylamine N-oxide. *J Stroke*. 2019;21(2):151–159. doi:10.5853/jos.2019.00472
80. Tian J, Ke X, Zhang Y, et al. Safety evaluation of alpha-glycerylphosphorylcholine as a novel food. *Food Chem Toxicol*. 2025;195:115123. doi:10.1016/j.fct.2024.115123
81. Lee HJ, Cho HR, Bang M, Lee YS, Kim YJ, Chong K. Potential risk of choline alfoscerate on isoflurane-induced toxicity in primary human astrocytes. *J Korean Neurosurg Soc*. 2024;67(4):418–430. doi:10.3340/jkns.2023.0208
82. Sagaro GG, Traini E, Amenta F. Activity of choline alphoscerate on adult-onset cognitive dysfunctions: a systematic review and meta-analysis. *J Alzheimers Dis*. 2023;92(1):59–70. doi:10.3233/JAD-221189
83. Socha E, Kośliński P, Koba M, et al. Amino acid levels as potential biomarker of elderly patients with dementia. *Brain Sci*. 2020;10(12):914. doi:10.3390/brainsci10120914
84. Socha E, Kośliński P, Koba M, et al. Serum amino acid profiles in patients with mild cognitive impairment and in patients with mild dementia or moderate dementia. *Amino Acids*. 2021;53(1):97–109. doi:10.1007/s00726-020-02928-y
85. Climacosa FMM, Ornos EDB, Gapaz NCLL, et al. The role of genetic polymorphisms on drug response in Alzheimer's disease: a systematic review. *BMC Med Genomics*. 2025;18(1):154. doi:10.1186/s12920-025-02225-1
86. Chang CW, Tan CH, Hong WP, Yu RL. GBA moderates cognitive reserve's effect on cognitive function in patients with Parkinson's disease. *J Neurol*. 2024;271(7):4392–4405. doi:10.1007/s00415-024-12374-5