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Review Article

Citicoline and L-Carnosine in Neuroprotection

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Abstract

Neurodegenerative disorders are a leading cause of disability worldwide, with increasing prevalence driven by population aging and limited disease-modifying treatment options. Oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal membrane damage are key contributors to disease progression, highlighting the need for effective neuroprotective strategies. Citicoline (CDP-choline) and L-carnosine are two promising nutraceuticals that exhibit complementary mechanisms of action. Citicoline primarily promotes phospholipid synthesis, neuronal membrane repair, cholinergic neurotransmission, and mitochondrial function, whereas L-carnosine exerts potent antioxidant, anti-inflammatory, anti-glycation, and metal-chelating effects. This narrative review summarizes the current evidence regarding the chemistry, metabolism, mechanisms of action, pharmacological effects, clinical applications, and safety of both compounds. Available experimental and clinical studies suggest that citicoline shows therapeutic potential in ischemic stroke, traumatic brain injury, glaucoma, and cognitive impairment, while L-carnosine may help reduce oxidative stress and preserve neuronal function. Although both compounds demonstrate significant neuroprotective properties, further large-scale clinical studies are required to establish their long-term efficacy and explore the potential benefits of combination therapy. Overall, citicoline and L-carnosine represent promising nutraceutical approaches for supporting neurological health and managing neurodegenerative disorders.

Keywords: Citicoline; CDP-Choline; L-Carnosine; Neuroprotection; Neurodegenerative Disorders; Oxidative Stress; Cognitive Impairment; Ischemic Stroke; Nutraceuticals; Pharmacological Effects

Abbreviations

AD: Alzheimer's Disease; AGEs: Advanced Glycation End Products; ATP: Adenosine Triphosphate; BBB: Blood–Brain Barrier; CARNS1: Carnosine Synthase 1; CDP-Choline: Cytidine Diphosphate Choline (Citicoline); CNDP1: Carnosinase 1; CNS: Central Nervous System; CTP: Cytidine Triphosphate; DNA: Deoxyribonucleic Acid; IL: Interleukin; IL-1β: Interleukin-1 Beta; IL-6: Interleukin-6; NF-κB: Nuclear Factor-kappa B; PC: Phosphatidylcholine; PEPT1: Peptide Transporter 1; PEPT2: Peptide Transporter 2; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; TBI: Traumatic Brain Injury; TNF-α: Tumor Necrosis Factor-alpha.

Introduction

Neurological disorders, including stroke, traumatic brain injury (TBI), Alzheimer's disease, Parkinson's disease, glaucoma, and

age-related cognitive decline, are among the leading causes of disability and mortality worldwide. Despite significant advances in medical treatment, many neurological conditions continue to lack effective therapies capable of preventing neuronal degeneration and restoring cognitive function. Consequently, increasing attention has been directed toward nutraceuticals and endogenous neuroprotective compounds that can complement conventional treatment by targeting multiple pathological pathways simultaneously [1,2].

Among these compounds, citicoline (cytidine-5'-diphosphocholine, CDP-choline) has emerged as one of the most extensively investigated neuroprotective agents. Citicoline is a naturally occurring intermediate in the biosynthesis of phosphatidylcholine, a major phospholipid component of neuronal cell membranes. Following oral or parenteral administration, citicoline is metabolized into cytidine and choline, which readily cross the blood-brain barrier and are utilized for phospholipid synthesis, membrane repair, and acetylcholine production [1,3]. Beyond serving as a precursor for membrane phospholipids, citicoline has been shown to enhance neuronal membrane stability, increase cerebral metabolism, promote neuroplasticity, reduce excitotoxicity, and improve neurotransmitter synthesis. Experimental studies have also demonstrated its ability to preserve phospholipid integrity, restore glutathione levels, and reduce oxidative damage following cerebral ischemia [4].

Over the past several decades, citicoline has been evaluated in numerous clinical studies involving acute ischemic stroke, traumatic brain injury, vascular cognitive impairment, dementia, glaucoma, and other neurodegenerative disorders. While some randomized clinical trials have reported improvements in neurological recovery and cognitive performance, others have shown limited clinical benefit, resulting in ongoing debate regarding its therapeutic efficacy in specific patient populations [5,6]. Nevertheless, systematic reviews continue to support its excellent safety profile and suggest potential benefits when used as an adjunctive therapy, particularly in chronic neurological conditions and ophthalmic neurodegenerative diseases [2].

Another endogenous dipeptide receiving increasing scientific attention is L-carnosine (β-alanyl-L-histidine). Naturally abundant in skeletal muscle and nervous tissue, L-carnosine possesses diverse biological activities, including antioxidant, anti-inflammatory, anti-glycation, metal-chelating, and pH-buffering properties [8,9]. These multifunctional characteristics make carnosine an attractive candidate for protecting neurons against oxidative stress, mitochondrial dysfunction, and protein aggregation, which are recognized contributors to the progression of neurodegenerative diseases. Recent evidence also suggests that carnosine may regulate cellular metabolism, improve mitochondrial function, and support synaptic activity, thereby contributing to cognitive preservation [10].

Clinical and experimental studies have increasingly explored the effects of carnosine supplementation on cognitive performance and mental health. Recent systematic reviews and meta-analyses indicate that carnosine supplementation may improve certain aspects of memory, attention, executive function, and psychological well-being, although further large-scale randomized controlled trials are required to establish optimal dosage, duration, and target populations [11]. In addition, carnosine's ability to neutralize reactive oxygen species and inhibit advanced glycation end-product formation has generated interest in its application for age-related neurological disorders characterized by chronic oxidative damage [8,10].

Choline metabolism also plays a critical role in maintaining neurological health. Choline serves as a precursor for acetylcholine synthesis and phospholipid metabolism while participating in one-carbon metabolism through its conversion to betaine. Adequate choline availability contributes to the remethylation of homocysteine to methionine, thereby reducing plasma homocysteine concentrations, an established risk factor for vascular disease and cognitive impairment [11]. Conversely, choline deficiency has been associated with elevated homocysteine levels and impaired neurological function, highlighting the importance of maintaining sufficient choline status for normal brain physiology [12].

Given the complementary biological activities of citicoline and L-carnosine, there is growing interest in evaluating their combined potential for neuroprotection. While citicoline primarily supports membrane phospholipid synthesis, neurotransmitter production, and neuronal repair, carnosine provides antioxidant defence, anti-inflammatory effects, and protection against protein glycation and mitochondrial dysfunction. Together, these mechanisms may address multiple aspects of neuronal injury and

neurodegeneration, making them promising candidates for the prevention and management of various neurological disorders [2,3,8,10].

This review aims to critically evaluate the current evidence regarding the pharmacology, mechanisms of action, therapeutic applications, clinical efficacy, and safety of citicoline and L-carnosine. Furthermore, it discusses recent advances, existing controversies, and future research directions to better define the role of these compounds in neuroprotection and cognitive health.

Methodology

Literature search strategy

This review was conducted as a narrative literature review to summarize and critically evaluate the available evidence regarding the chemistry, metabolism, mechanisms of action, pharmacological effects, clinical applications, and safety of citicoline (CDP-choline) and L-carnosine in neuroprotection. A comprehensive literature search was performed using the electronic databases PubMed, Scopus, Web of Science, and Google Scholar. The literature search included studies published from January 2000 to June 2026, and the final database search was completed in June 2026. The search strategy was designed to identify high-quality experimental and clinical studies, systematic reviews, and meta-analyses relevant to the neuroprotective effects of citicoline and L-carnosine [2,3,10].

The search strategy employed combinations of the following keywords using Boolean operators (AND/OR): "citicoline" OR "CDP-choline", "L-carnosine", "neuroprotection", "oxidative stress", "Alzheimer's disease", "Parkinson's disease", "ischemic stroke", "traumatic brain injury", "glaucoma", "cognitive impairment", "clinical trials", "systematic review", and "meta-analysis".

Study selection

Titles and abstracts identified through the database search were initially screened for relevance. Eligible full-text articles were subsequently evaluated according to predefined inclusion and exclusion criteria. Duplicate publications were removed before final selection. Preference was given to systematic reviews, meta-analyses, randomized controlled trials, observational studies, and well-designed experimental investigations to ensure that the review was based on the highest available level of scientific evidence [2,3,10].

Inclusion criteria

The following studies were included:

- Peer-reviewed articles published in English.
- Original research articles, randomized controlled trials, observational studies, systematic reviews, and meta-analyses.
- Experimental and clinical studies evaluating the chemistry, metabolism, mechanisms of action, pharmacological effects, safety, or therapeutic applications of citicoline and/or L-carnosine.
- Studies related to neuroprotection, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, ischemic stroke, traumatic brain injury, glaucoma, and cognitive impairment.

Exclusion criteria

The following publications were excluded:

- Conference abstracts without full-text availability.
- Editorials, letters to the editor, commentaries, opinion articles, and unpublished reports.
- Duplicate publications.
- Studies unrelated to neurological disorders or lacking sufficient scientific evidence.
- Articles not published in English.

Data extraction and evidence synthesis

Relevant information regarding study characteristics, mechanisms of action, pharmacological effects, clinical efficacy, safety, and therapeutic outcomes was extracted from the selected studies. The available evidence was synthesized according to the hierarchy of evidence, with priority given to systematic reviews and meta-analyses, followed by randomized controlled trials, observational and open-label studies, and preclinical investigations. Areas of agreement, conflicting findings, and research gaps were critically evaluated to provide a balanced overview of the current evidence supporting the neuroprotective potential of citicoline and L-carnosine [2,3,10].

Chemistry and metabolism of citicoline (CDP-Choline)

Citicoline (cytidine-5′-diphosphocholine; CDP-choline) is an endogenous nucleotide composed of cytidine and choline linked

by a diphosphate bridge. It is a key intermediate in the Kennedy pathway responsible for the biosynthesis of phosphatidylcholine, one of the principal phospholipids of neuronal cell membranes. Phosphatidylcholine plays a crucial role in maintaining membrane integrity, neuronal signaling, synaptic transmission, and membrane repair following ischemic or traumatic injury [1-3].

Following oral administration, citicoline is rapidly hydrolyzed in the gastrointestinal tract into cytidine and choline, which are readily absorbed into the circulation. In humans, much of the circulating cytidine is converted to uridine in the systemic circulation, and uridine readily crosses the blood–brain barrier. Within the brain, uridine is phosphorylated to uridine monophosphate (UMP), uridine diphosphate (UDP), and uridine triphosphate (UTP), thereby contributing to the intracellular pyrimidine nucleotide pool required for the synthesis of cytidine triphosphate (CTP). Together with choline, CTP participates in the resynthesis of CDP-choline via the Kennedy pathway, thereby supporting phosphatidylcholine synthesis, neuronal membrane repair, and synaptic function [2,3].

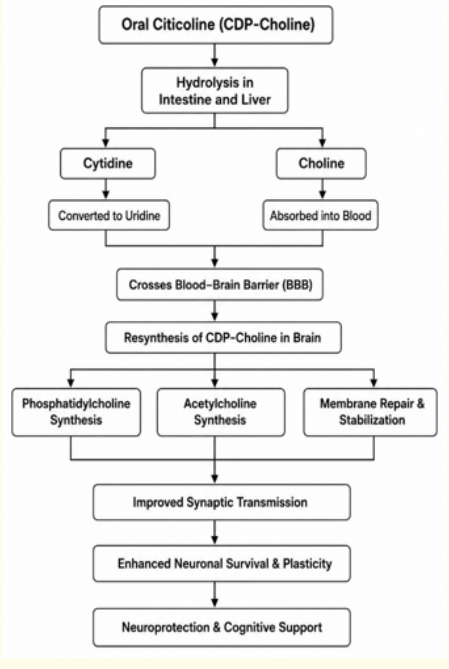

Figure 1: Metabolism and neuroprotective actions of citicoline (CDP-choline). Following oral administration, citicoline is hydrolysed into cytidine and choline, which are absorbed and cross the blood–brain barrier. Within the brain, these metabolites are utilized for the resynthesis of CDP-choline, phosphatidylcholine biosynthesis, acetylcholine production, and neuronal membrane repair, ultimately supporting synaptic transmission, neuroplasticity, and neuroprotection [1-3].

Citicoline exhibits an oral bioavailability exceeding 90%, with efficient systemic absorption and widespread tissue distribution. Plasma choline concentrations increase shortly after administration, while uridine-derived nucleotides contribute to sustained phospholipid synthesis and membrane turnover. Most administered citicoline is metabolically utilized, with only a small fraction eliminated through urinary excretion or expired carbon dioxide [3].

Beyond serving as a precursor for phospholipid biosynthesis, citicoline modulates several biochemical pathways involved in neuronal survival. Experimental studies have demonstrated that citicoline restores phosphatidylcholine levels following cerebral ischemia, inhibits phospholipase activation, preserves membrane ATPase activity, reduces free fatty acid accumulation, and enhances glutathione synthesis, thereby limiting oxidative stress and promoting neuronal recovery [1,4].

Collectively, these biochemical and pharmacokinetic properties provide the mechanistic basis for the neuroprotective effects of citicoline observed in experimental models and clinical studies of stroke, traumatic brain injury, glaucoma, and cognitive disorders [1-4].

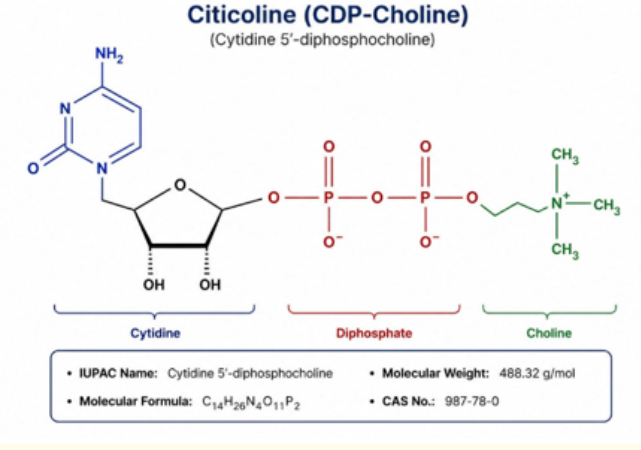

Figure 2: Citicoline (CDP-Choline).

Chemistry and metabolism of L-Carnosine

L-Carnosine (β-alanyl-L-histidine) is a naturally occurring histidine-containing dipeptide synthesized from β-alanine and L-histidine by the enzyme carnosine synthase. It is highly concentrated in excitable tissues such as skeletal muscle, the brain, olfactory bulb, and cardiac muscle, where it contributes to cellular homeostasis and protection against metabolic stress. Owing to its

unique molecular structure, carnosine exhibits antioxidant, anti-inflammatory, anti-glycation, metal-chelating, and intracellular buffering properties that are relevant to neurological health [8,9].

Dietary carnosine is primarily obtained from meat and fish products, although endogenous synthesis also contributes significantly to tissue concentrations. After absorption in the small intestine through peptide transporters, circulating carnosine is hydrolysed by serum carnosinase (CNDP1) into β-alanine and histidine. Despite this enzymatic degradation, significant intracellular concentrations of carnosine are maintained in tissues capable of endogenous synthesis. Within the central nervous system, locally synthesized carnosine participates in antioxidant defence, neurotransmitter modulation, and maintenance of mitochondrial function [8,10].

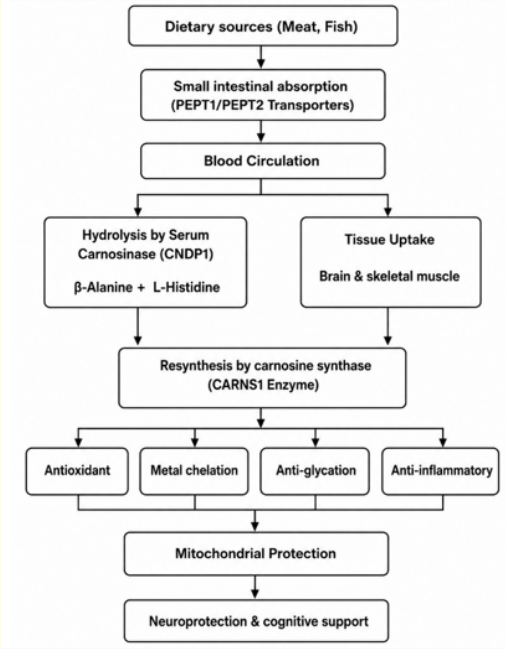

Figure 3: Metabolism and biological functions of L-carnosine. Dietary L-carnosine is absorbed in the small intestine via peptide transporters (PEPT1/PEPT2) and enters the circulation. Although circulating carnosine is hydrolyzed by serum carnosinase (CNDP1) into β-alanine and L-histidine, these components are taken up by tissues and resynthesized by carnosine synthase (CARNS1). Intracellular L-carnosine exerts antioxidant, anti-inflammatory, anti-glycation, and metal-chelating effects, contributing to mitochondrial protection, neuronal survival, and cognitive support [8-11].

The antioxidant activity of carnosine results from its ability to directly scavenge reactive oxygen and nitrogen species while chelating transition metals such as copper and iron, thereby reducing metal-catalysed free radical formation. Additionally, carnosine inhibits lipid peroxidation and prevents the formation of advanced glycation end products (AGEs), which accumulate during aging and neurodegenerative diseases. These biochemical properties contribute to the preservation of neuronal proteins, nucleic acids, and membrane lipids under conditions of oxidative stress [8,10].

Recent investigations have also demonstrated that carnosine regulates mitochondrial bioenergetics, modulates intracellular calcium homeostasis, and suppresses inflammatory signalling pathways associated with neurodegeneration. These multiple mechanisms support its growing role as a promising functional ingredient in neuroprotective nutraceutical formulations and cognitive health interventions [10,11].

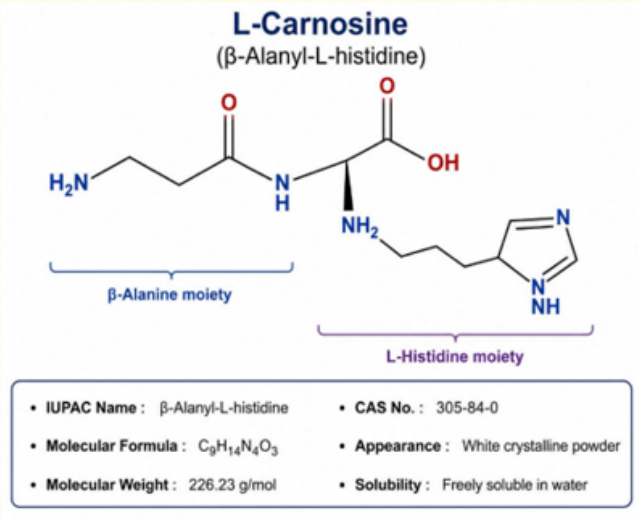

Figure 4: Chemical Structure of L-Carnosine.

Choline metabolism and homocysteine regulation

Choline is an essential nutrient involved in phospholipid synthesis, neurotransmitter production, and one-carbon metabolism. Following absorption, choline is either incorporated into phosphatidylcholine for membrane synthesis or oxidized to betaine, which functions as a methyl donor during the

remethylation of homocysteine to methionine. This metabolic pathway contributes to DNA methylation, protein synthesis, and maintenance of normal neuronal function [12].

Elevated plasma homocysteine is an established risk factor for vascular disease, stroke, and cognitive decline. Clinical studies have shown that phosphatidylcholine supplementation significantly reduces fasting and post-methionine plasma homocysteine concentrations, suggesting that adequate choline intake supports vascular and neurological health through improved methyl-group metabolism [11]. Conversely, experimental models of choline deficiency demonstrate elevated homocysteine concentrations and impaired methylation capacity, emphasizing the importance of sufficient choline availability for maintaining normal neurological function [12].

Because citicoline serves as an efficient source of bioavailable choline, supplementation may indirectly contribute to homocysteine regulation while simultaneously enhancing phosphatidylcholine synthesis and acetylcholine production. These complementary metabolic effects provide an additional rationale for investigating citicoline as a therapeutic agent in neurological disorders characterized by vascular dysfunction and neurodegeneration [3,11,12].

Mechanism of action

The therapeutic potential of citicoline (CDP-choline) and L-carnosine is attributed to their ability to modulate multiple molecular pathways involved in neuronal survival, membrane repair, neurotransmission, oxidative stress, inflammation, mitochondrial function, and apoptosis. Unlike conventional drugs that typically target a single mechanism, these compounds exhibit pleiotropic actions that collectively promote neuroprotection and functional recovery. The following sections describe the major mechanisms responsible for their beneficial effects in neurological disorders.

Membrane repair and phospholipid synthesis

Neuronal cell membranes consist primarily of phospholipids, with phosphatidylcholine representing one of the most abundant structural components. During ischemia, traumatic brain injury, and neurodegenerative diseases, activation of phospholipases results in phospholipid degradation, disruption of membrane integrity, and release of free fatty acids that promote oxidative damage and inflammation. Restoration of membrane phospholipids is therefore essential for neuronal survival [1,4].

Citicoline acts as a direct precursor in the Kennedy pathway, providing cytidine and choline required for phosphatidylcholine synthesis. Increased phosphatidylcholine production stabilizes neuronal membranes, restores membrane fluidity, and facilitates repair of damaged axons and synaptic membranes. Experimental studies have demonstrated that citicoline accelerates membrane phospholipid regeneration, inhibits phospholipase A_2 activation, and decreases the accumulation of toxic free fatty acids following cerebral ischemia [1,4].

Maintenance of membrane integrity also preserves the function of membrane-bound enzymes, ion channels, and receptors essential for neuronal signalling. By restoring ATP-dependent membrane pumps such as Na^+/K^+-ATPase, citicoline reduces intracellular sodium and calcium overload, thereby preventing neuronal swelling and excitotoxic injury. These effects contribute significantly to improved neuronal survival following ischemic and traumatic insults [3,4].

Enhancement of neurotransmitter synthesis

Citicoline enhances neurotransmission by supplying bioavailable choline for acetylcholine synthesis. Acetylcholine is a critical neurotransmitter involved in learning, memory, attention, and executive function. Degeneration of cholinergic neurons is a hallmark of Alzheimer's disease and other cognitive disorders; therefore, increasing acetylcholine availability may improve cognitive performance [1,2].

In addition to acetylcholine, citicoline has been shown to modulate several neurotransmitter systems, including dopamine, norepinephrine, and serotonin. Experimental studies suggest that citicoline increases dopamine synthesis by stimulating tyrosine hydroxylase activity while enhancing dopamine release within the striatum. These effects may contribute to improved motor function and cognitive performance in Parkinson's disease and vascular cognitive impairment [2,3].

Antioxidant activity and reduction of oxidative stress

Oxidative stress is one of the primary mechanisms responsible for neuronal injury in stroke, traumatic brain injury, Alzheimer's

disease, Parkinson's disease, and aging. Excessive production of reactive oxygen species (ROS) damages membrane lipids, proteins, mitochondrial DNA, and nuclear DNA, ultimately leading to neuronal dysfunction and apoptosis [8,10].

Citicoline indirectly reduces oxidative stress by preserving membrane phospholipids, decreasing lipid peroxidation, and restoring intracellular glutathione levels. Adibhatla., *et al*. demonstrated that citicoline treatment significantly increased glutathione concentrations and reduced oxidative injury following transient cerebral ischemia, thereby protecting neuronal tissue from free radical-mediated damage [4].

L-Carnosine functions as a potent endogenous antioxidant capable of directly scavenging hydroxyl radicals, superoxide anions, singlet oxygen, and peroxynitrite. In addition, it chelates transition metals such as iron and copper, preventing metal-catalysed free radical generation through the Fenton reaction. These antioxidant properties reduce lipid peroxidation and preserve neuronal membrane integrity under pathological conditions [8,10].

Furthermore, carnosine inhibits the formation of advanced glycation end products (AGEs), which accumulate during aging and contribute to oxidative stress and chronic inflammation. By limiting glycation-mediated protein damage, carnosine helps preserve neuronal protein function and cellular homeostasis [10].

Anti-inflammatory effects

Neuroinflammation plays a central role in the progression of neurodegenerative diseases. Following neuronal injury, activated microglia and astrocytes release pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which exacerbate neuronal damage and impair tissue repair [2].

Citicoline suppresses inflammatory responses by reducing phospholipase activation and decreasing the production of inflammatory mediators generated from arachidonic acid metabolism. Experimental evidence suggests that citicoline also inhibits activation of nuclear factor-kappa B (NF-κB), thereby reducing cytokine expression and secondary neuronal injury [1,2].

L-Carnosine further contributes to anti-inflammatory activity by suppressing oxidative stress-induced activation of inflammatory signalling pathways. Experimental studies have shown reductions in cytokine production, microglial activation, and inflammatory mediator release following carnosine supplementation, thereby limiting chronic neuroinflammation associated with aging and neurodegenerative disorders [8,10].

Mitochondrial protection and energy metabolism

Mitochondria are essential for neuronal energy production through oxidative phosphorylation. Mitochondrial dysfunction leads to ATP depletion, increased reactive oxygen species production, calcium dysregulation, and activation of apoptotic pathways. Such dysfunction is frequently observed in ischemic stroke and neurodegenerative diseases [8].

Citicoline preserves mitochondrial membrane phospholipids, particularly cardiolipin, thereby maintaining mitochondrial membrane integrity and improving ATP synthesis. Preservation of mitochondrial function reduces energy failure and supports neuronal recovery following ischemic injury [4].

L-Carnosine further supports mitochondrial function by reducing oxidative damage to mitochondrial proteins and DNA, improving respiratory chain efficiency, and maintaining intracellular pH during metabolic stress. These actions contribute to improved cellular bioenergetics and enhanced neuronal survival [8,10].

Inhibition of apoptosis

Apoptosis is a regulated form of programmed cell death that contributes to neuronal loss after ischemia and neurodegeneration. Excessive intracellular calcium, oxidative stress, mitochondrial dysfunction, and inflammatory cytokines activate caspase-dependent apoptotic pathways, resulting in irreversible neuronal injury [4].

Citicoline attenuates apoptosis by stabilizing mitochondrial membranes, reducing cytochrome c release, and inhibiting activation of caspase-3. Restoration of membrane phospholipids also decreases calcium-mediated neuronal toxicity, thereby limiting apoptotic signalling [4].

L-Carnosine protects neurons by reducing oxidative DNA damage and maintaining mitochondrial integrity, thereby preventing activation of intrinsic apoptotic pathways. Experimental

studies have demonstrated increased neuronal viability and reduced apoptotic cell death following carnosine administration under oxidative stress conditions [8,10].

Anti-glycation and protein protection

Accumulation of advanced glycation end products (AGEs) contributes significantly to aging, Alzheimer's disease, diabetic neuropathy, and other neurodegenerative disorders. Glycation alters protein structure, promotes protein aggregation, and induces oxidative stress and inflammation [10].

L-Carnosine reacts with reactive carbonyl species generated during glycation, thereby preventing AGE formation and preserving protein function. This carbonyl-scavenging activity protects structural proteins, enzymes, and membrane components from irreversible glycation damage. Consequently, carnosine may slow age-related neuronal degeneration and maintain normal cellular function [8,10].

Regulation of Homocysteine and One-Carbon Metabolism

Elevated plasma homocysteine is associated with endothelial dysfunction, vascular injury, oxidative stress, and increased risk of stroke and cognitive decline. Choline-derived betaine serves as a methyl donor for the remethylation of homocysteine to methionine, thereby maintaining one-carbon metabolism and DNA methylation [12].

Since citicoline supplies bioavailable choline, supplementation may indirectly lower homocysteine concentrations while supporting phosphatidylcholine synthesis and acetylcholine production. Clinical studies have demonstrated that phosphatidylcholine supplementation significantly reduces fasting and post-methionine plasma homocysteine concentrations, suggesting an additional vascular protective mechanism for citicoline [12,13].

Potential complementary neuroprotective actions of citicoline and L-Carnosine

Citicoline and L-carnosine exert distinct but complementary biological activities that target several key mechanisms involved in neuronal injury and neurodegeneration. Citicoline primarily promotes phosphatidylcholine synthesis, neuronal membrane repair, cholinergic neurotransmission, mitochondrial integrity, and neuroplasticity, whereas L-carnosine exhibits potent antioxidant, anti-inflammatory, anti-glycation, metal-chelating, and intracellular buffering properties that help protect neurons against oxidative and metabolic stress [2,3,8,10].

From a mechanistic perspective, these complementary actions suggest that the two compounds could theoretically target multiple pathological processes associated with neurological disorders, including oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity, and apoptosis. Such multimodal mechanisms provide a scientific rationale for considering combination therapy as a potential neuroprotective strategy [2,3,8,10].

However, to date, no preclinical or clinical studies included in this review have directly evaluated the combined administration of citicoline and L-carnosine or demonstrate a synergetic therapeutic effect. Consequently, any proposed synergistic interaction remains hypothetical and should not be interpreted as established clinical evidence. Future experimental studies should first investigate the pharmacodynamic and mechanistic clinical trials to determine whether combination therapy offers additional therapeutic benefits beyond those observed with either agent alone [2,5,7,10,11,13].

At present, the available evidence supports the individual neuroprotective potential and favourable safety profiles of citicoline and L-carnosine; however, the efficacy of their combined use remains an important area for future investigation rather than a clinically validated therapeutic approach [2,10,11,13].

Pharmacological effects

Pharmacological effects of citicoline

Citicoline exhibits a broad spectrum of pharmacological activities that contribute to its neuroprotective efficacy in both acute and chronic neurological disorders [1,8,12].

One of its primary pharmacological actions is the restoration of neuronal membrane phospholipids through enhanced phosphatidylcholine synthesis, thereby maintaining membrane integrity and cellular homeostasis following neuronal injury [1,8].

Citicoline also enhances cholinergic neurotransmission by increasing the availability of choline for acetylcholine biosynthesis, which is essential for memory formation, attention, and cognitive processing [4,10,12].

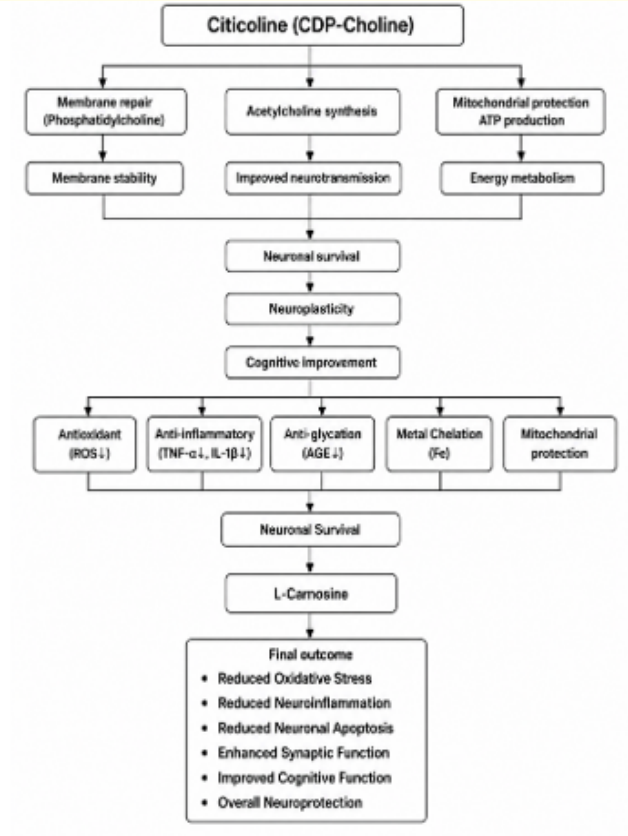

Figure 5: Proposed mechanisms of neuroprotection. Citicoline promotes phosphatidylcholine synthesis, neuronal membrane repair, cholinergic neurotransmission, mitochondrial function, and neuroplasticity, whereas L-carnosine exhibits antioxidant, anti-inflammatory, anti-glycation, and metal-chelating activities. These mechanisms are biologically complementary and provide a theoretical rationale for combination therapy; however, direct experimental and clinical evidence demonstrating synergistic efficacy of combined administration is currently unavailable [2,3,10,11].

Experimental studies have demonstrated that citicoline improves cerebral energy metabolism by preserving mitochondrial function and enhancing adenosine triphosphate (ATP) production under ischemic conditions [1].

In addition, citicoline reduces oxidative damage by limiting phospholipid degradation, decreasing free fatty acid accumulation, and preserving endogenous antioxidant defence systems [1,6,8].

The compound has also been shown to inhibit neuronal apoptosis and promote neuronal survival by modulating multiple intracellular signalling pathways involved in cell death and tissue repair [1,5,8].

Clinical investigations have reported improvements in neurological recovery, cognitive function, and functional outcomes in patients with ischemic stroke, traumatic brain injury, glaucoma, and vascular cognitive impairment following citicoline administration, although the magnitude of benefit varies among studies [5,11,13].

Overall, the diverse pharmacological properties of citicoline support its therapeutic role as a neuroprotective and neurorestorative agent in several neurological disorders [8,12].

Pharmacological effects of L-Carnosine

L-Carnosine possesses multiple pharmacological activities that primarily arise from its antioxidant, anti-inflammatory, anti-glycation, and cytoprotective properties [2,3,7,9].

Its antioxidant activity is mediated through direct scavenging of reactive oxygen species and reactive nitrogen species, thereby protecting neuronal lipids, proteins, and DNA from oxidative damage [2,3,9].

L-Carnosine also inhibits lipid peroxidation and stabilizes cellular membranes, reducing oxidative injury associated with neurodegenerative diseases and aging [2,3].

The anti-glycation activity of L-carnosine prevents the formation of advanced glycation end products, which are implicated in neuronal dysfunction, protein aggregation, and cognitive decline [2,3,9].

Another important pharmacological property is its ability to chelate transition metals, thereby reducing metal-catalysed oxidative reactions that contribute to neuronal toxicity [3,9].

Experimental studies have further demonstrated that L-carnosine suppresses inflammatory signalling pathways, decreases pro-inflammatory cytokine production, and protects mitochondrial function under pathological conditions [3,7,9].

Recent clinical evidence suggests that L-carnosine supplementation may improve cognitive performance and mental health outcomes, although additional large-scale randomized controlled trials are required to confirm its long-term therapeutic efficacy [7].

Collectively, these pharmacological properties make L-carnosine a promising nutraceutical candidate for preventing oxidative stress-related neuronal injury and cognitive impairment [3,7,9].

Clinical application

Alzheimer's disease and cognitive impairment

Systematic reviews and meta-analyses

Systematic reviews suggest that citicoline may improve memory, attention, and executive function, particularly when used as an adjunct to standard therapy in patients with mild cognitive impairment and Alzheimer's disease [2]. A recent systematic review and meta-analysis also reported that L-carnosine supplementation may improve selected aspects of cognitive function and mental health [11].

Randomized controlled trials

Several randomized controlled trials have evaluated citicoline in patients with cognitive impairment and demonstrated improvements in cognitive performance. However, differences in study design, treatment duration, and outcome measures have produced variable results .

Open-label studies

Open-label studies have suggested that long-term citicoline administration may stabilize cognitive decline and improve quality of life when used alongside conventional anti- dementia therapy, although larger controlled studies are required [2].

Preclinical evidence

Experimental studies demonstrate that citicoline enhances phospholipid synthesis, neuronal membrane repair, and cholinergic neurotransmission, whereas L-carnosine reduces oxidative stress, neuroinflammation, protein glycation, and mitochondrial dysfunction, supporting their potential neuroprotective roles [1,8,10].

Ischemic stroke

Systematic reviews and meta-analyses

Systematic reviews indicate that citicoline has an excellent safety profile and may provide modest neurological benefits in selected patients with acute ischemic stroke. However, the overall evidence remains inconsistent because of heterogeneity among clinical studies [2].

Randomized controlled trials

The ICTUS trial, one of the largest randomized controlled trials evaluating citicoline in acute ischemic stroke, demonstrated that citicoline was safe and well tolerated but did not significantly improve functional recovery compared with placebo [5]. Variability in treatment timing, dosage, and patient characteristics may explain differences among studies.

Open-label studies

Several smaller clinical studies have reported improved neurological recovery and functional outcomes following citicoline administration, although these findings require confirmation in larger randomized trials [2].

Preclinical evidence

Animal studies consistently demonstrate that citicoline reduces infarct size, preserves membrane phospholipids, improves mitochondrial function, and inhibits neuronal apoptosis after cerebral ischemia. L-carnosine has also shown antioxidant and anti-inflammatory effects that reduce ischemic neuronal injury in experimental models [1,8,10].

Traumatic brain injury

Systematic reviews and meta-analyses

Current reviews suggest that although citicoline possesses strong biological plausibility as a neuroprotective agent, clinical evidence supporting routine use in traumatic brain injury remains inconclusive [2].

Randomized controlled trials

The COBRIT trial demonstrated that citicoline was safe but did not significantly improve cognitive or functional outcomes in patients with traumatic brain injury [6]. These findings indicate the need for additional well-designed randomized clinical trials.

Open-label studies

Some smaller clinical investigations have reported improvements in neurological recovery following citicoline therapy, although methodological limitations prevent definitive conclusions [2].

Preclinical evidence

Experimental studies indicate that citicoline enhances membrane repair and neuronal survival following traumatic injury, while L-carnosine reduces oxidative stress, preserves mitochondrial function, and limits secondary neuronal damage [8,10].

Glaucoma

Systematic reviews and meta-analyses

A recent systematic review reported that citicoline supplementation may improve visual function and electrophysiological parameters in glaucoma patients, supporting its use as an adjunctive therapy alongside intraocular pressure-lowering treatment [13].

Randomized controlled trials

Several controlled clinical studies have demonstrated improvements in retinal ganglion cell function and visual pathway responses following citicoline supplementation, although further multicenter trials are required to establish long-term efficacy [13].

Open-label studies

Open-label investigations have reported beneficial effects on visual field progression and retinal function in patients receiving prolonged citicoline therapy, but these findings require confirmation in larger controlled studies [13].

Preclinical evidence

Experimental evidence suggests that citicoline supports retinal neuronal metabolism and promotes retinal ganglion cell survival. Although direct clinical evidence for L-carnosine in glaucoma is limited, its antioxidant properties may provide protection against retinal oxidative stress [8,10].

Safety and limitations

Citicoline has consistently demonstrated an excellent safety profile in both experimental and clinical studies. It is generally well tolerated even during prolonged administration, with only mild adverse effects such as headache, insomnia, nausea, gastrointestinal discomfort, or dizziness reported in a small proportion of patients. Serious treatment-related adverse events are uncommon, making citicoline one of the safest neuroprotective agents currently available [1,2,5].

Similarly, L-carnosine is considered a safe endogenous dipeptide with very low toxicity. Clinical studies have reported good tolerability across different age groups, with only occasional mild gastrointestinal discomfort observed following supplementation. Its natural occurrence in human tissues contributes to its favourable safety profile [8,10,11].

Despite these advantages, several limitations remain. Clinical evidence for citicoline has produced inconsistent efficacy results across different neurological disorders. While smaller studies have reported beneficial outcomes, some large randomized clinical trials have failed to demonstrate statistically significant improvements in primary clinical endpoints, particularly in acute stroke and traumatic brain injury [5,7].

Another limitation is the variability in dosage, treatment duration, patient selection, and outcome measures among published studies, making direct comparisons difficult. Further multicentre randomized controlled trials using standardized protocols are necessary to identify patient populations that may derive the greatest benefit from therapy [2].

Although L-carnosine demonstrates strong biological activity in experimental models, high-quality human clinical evidence remains relatively limited. Long-term efficacy, optimal dosing strategies, pharmacokinetic variability, and interactions with other neuroprotective agents require additional investigation before widespread clinical recommendations can be established [10,11].

Therefore, while both compounds possess excellent safety profiles and considerable therapeutic potential, further large-scale clinical research is needed to strengthen evidence supporting their routine use in neurological practice [2,10,11].

Conclusion

Citicoline and L-carnosine are multifunctional neuroprotective agents with complementary mechanisms of action that individually target oxidative stress, neuroinflammation, mitochondrial

dysfunction, membrane instability, and neurotransmitter imbalance. While both compounds have demonstrated favourable safety profiles and promising neuroprotective effects in experimental studies, clinical evidence remains variable, particularly in large randomized controlled trials evaluating citicoline. Although their complementary mechanisms provide a biological rationale for investigating combination therapy, there is currently no direct experimental or clinical evidence confirming synergistic efficacy. Therefore, the combined use of citicoline and L-carnosine should be regarded as a promising research hypothesis that requires rigorous preclinical investigation and adequately powered randomized clinical trials before clinical recommendations can be made [2,5,7,10,11,13].

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