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The Effectiveness of Oral Citicoline Administration as a Therapy for Memory Enhancement in Post-COVID-19 Patients: An Evidence-Based Case Report

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ABSTRACT

Background: Coronavirus Disease 2019 can cause both acute and chronic neurological problems, including cognitive impairment, which can develop at various times post-exposure and persist indefinitely. Citicoline is an alternative treatment option that can function as a neuroprotector. ***Objective:*** To determine the effectiveness of oral Citicoline administration as a therapy for memory enhancement in post-COVID-19 patients. ***Methods:*** A search was conducted on PubMed, Cochrane, EBSCOhost, Scopus, and Google Scholar for review articles and original studies. Researchers found only three studies linking Citicoline, COVID-19, and memory. ***Results:*** Turana et al. (2021) stated that Citicoline combats COVID-19-related cognitive decline through anti-inflammatory, antiviral, neuroprotective, neurorestorative, and acetylcholine neurotransmitter synthesis mechanisms. Al-Kuraishy (2022) concluded that Citicoline improves memory through mechanisms involving neural energy, neurogenesis, anti-inflammatory, antioxidant, and silent information regulator 1 (SIRT1). Zueva et al. (2021) reported that 18 (75%) COVID-19 patients with cognitive impairment who received Citicoline 1000 mg/day in an oral solution (100 mg / 1 ml) for 14 days showed significant memory improvement with $p < 0.05$. This study reported that administering Citicoline 500 mg tablets every 12 hours for two months improved MoCA-INA scores by 16 points and MMSE scores by 13 points. ***Conclusion:*** Citicoline can be a significant consideration in memory therapy for post-COVID-19 patients.

Keywords: COVID-19; Citicoline; memory; neuroprotector.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease first emerged in December 2019 in Wuhan, China. According to the World Health Organization (WHO), by early August 2022, there were 578 million confirmed cases globally, with 6.4 million deaths [1]. In Indonesia, there were 6.21 million confirmed COVID-19 cases with 157,000 deaths [2]. COVID-19 has varied clinical symptoms, ranging from asymptomatic to mild, moderate, severe, and critical conditions. Patients generally recover within the second to sixth week. The incidence of COVID-19 in the elderly ranges from 10-40%, with comorbidities worsening the condition [3].

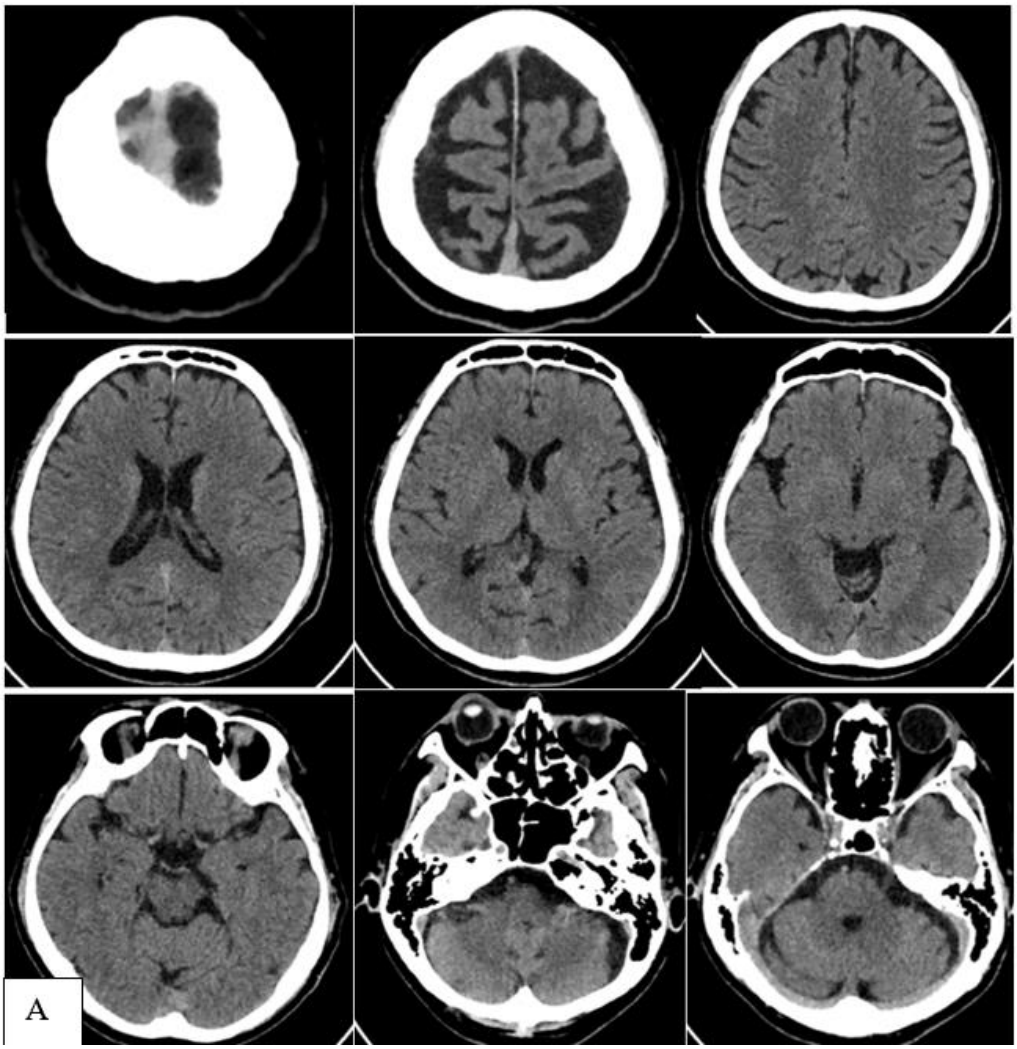
COVID-19 infection can impair memory function, with an incidence rate of over 30% within 3-9 months post-infection, ranging from mild to severe cases [4]. A study by Søraas et al. (2021) found that 267 out of 649 participants (41%) in the COVID-19 positive group reported memory decline from the previous year, and 81 out of 651 participants (12%) reported decreased concentration [5]. Hampshire et al. found that among 81,337 patients who tested positive for COVID-19, there was a statistically significant memory decline compared to before COVID-19 infection ($p=0.046$) [6].

Memory decline in COVID-19 patients is caused by multisystem organ inflammation, which is interrelated as follows: (1) Hypoxemia due to lung damage indirectly causes nerve damage, which can lead to memory decline [7]. COVID-19 patients typically experience silent hypoxemia, where oxygen levels drop below normal without causing shortness of breath, delaying hypoxemia treatment [8–10]. (2) Thrombosis and coagulopathy due to systemic vasculitis, hyperinflammatory conditions causing cytokine storms, can lead to multi-organ damage and susceptibility to silent infarctions due to microemboli. This condition is found in severe COVID-19 patients, showing increased risk of delirium, which can progress to memory decline [11]. (3) Damage and dysfunction of the blood-brain barrier due to pro-inflammatory cytokines disrupt permeability, causing microglial activation and oxidative stress. Neural inflammation and nerve injury can develop into short-term delirium and long-term memory decline [12]. All these mechanisms contribute to memory decline development, particularly disrupting phospholipase A2 (PLA2) and autophagy activities, both linked to memory impairment in neurodegenerative diseases like Alzheimer's disease [13].

Citicoline, a crucial substance for cell membrane phospholipid structure, has been found to have neuroprotective effects in patients with neurological diseases [14]. Additionally, Citicoline is proposed to limit inflammation and viral replication, causing cytokine storms, as seen in COVID-19 patients [15]. There is some evidence of Citicoline use in neurological studies involving traumatic brain injury patients [16]. Citicoline has also been found to be the only neuroprotective agent through confirmatory clinical trials demonstrating its safety and sustained beneficial effects on acute ischemic stroke, improving memory decline and functional recovery post-stroke [17,18]. A prospective study also showed Citicoline's efficacy in ischemic, hemorrhagic, and subarachnoid stroke, improving MMSE (Mini-Mental State Examination) and Disability Rating Score [19].

CASE REPORT

A 61-year-old female patient presented to the clinic with complaints from her husband about her inability to recall information within a short time (<24 hours) and recent events (within the last week). She could remember her childhood clearly and also her siblings and parents, but had difficulty remembering new people. Her daily activities were disrupted; she would forget she was washing, drying clothes, or cooking. A head CT scan was normal, as shown in Figure 1. The results of the Indonesian Version of the Montreal Cognitive Assessment (MoCA-INA) were 7, and the Mini-Mental State Examination (MMSE) was 10. The patient was diagnosed with moderate COVID-19 three months prior, confirmed in the Emergency Department with symptoms of shortness of breath. The breathlessness persisted throughout the day, requiring the patient to sleep in a semi-sitting position and use 2-4 liters of oxygen per minute via a nasal cannula. She also experienced a cough with thick yellow phlegm and a cold with similar symptoms. These respiratory issues severely disrupted her rest. She had a fluctuating fever that did not subside with 500 mg paracetamol every 8 hours. The patient could eat and drink well but needed assistance with mobility due to her breathlessness. She lived only with her husband and was a housewife. A Polymerase Chain Reaction (PCR) test confirmed COVID-19, and laboratory tests indicated infection. Her husband noticed her memory decline and brought her to the hospital, where she received Citicoline treatment for two months. The MoCA-INA score improved to 16 and MMSE to 13.



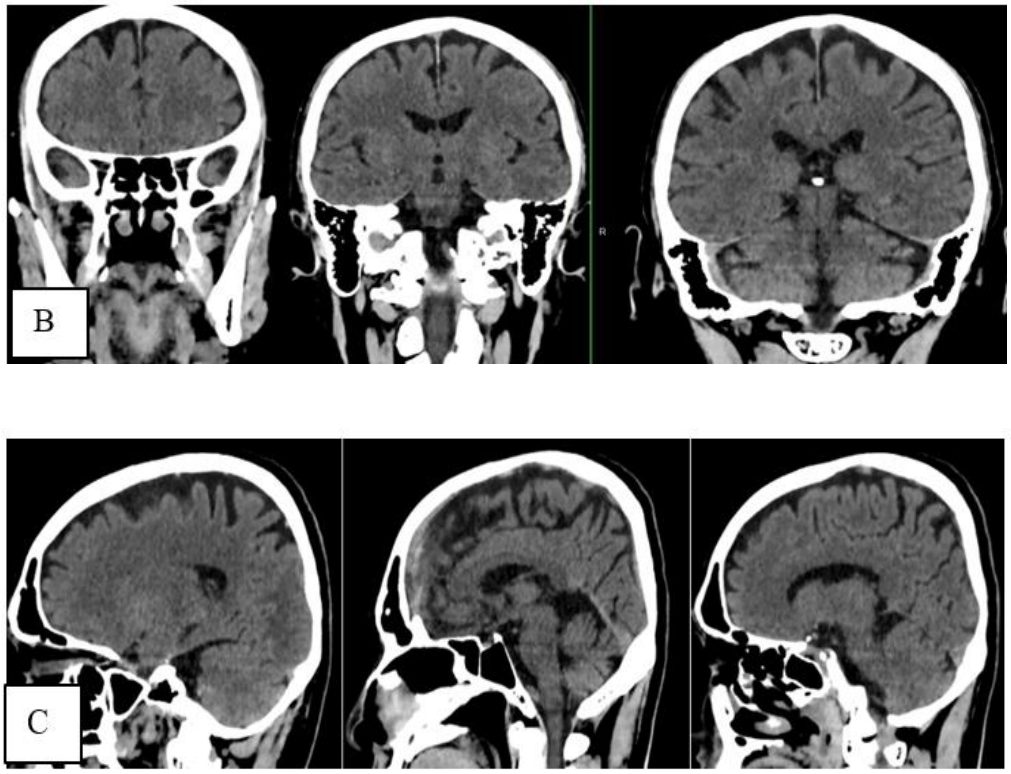


FIGURE 1: Head CT scan without contrast, showing normal slices in A. Axial; B. Coronal; and C. Sagittal views.

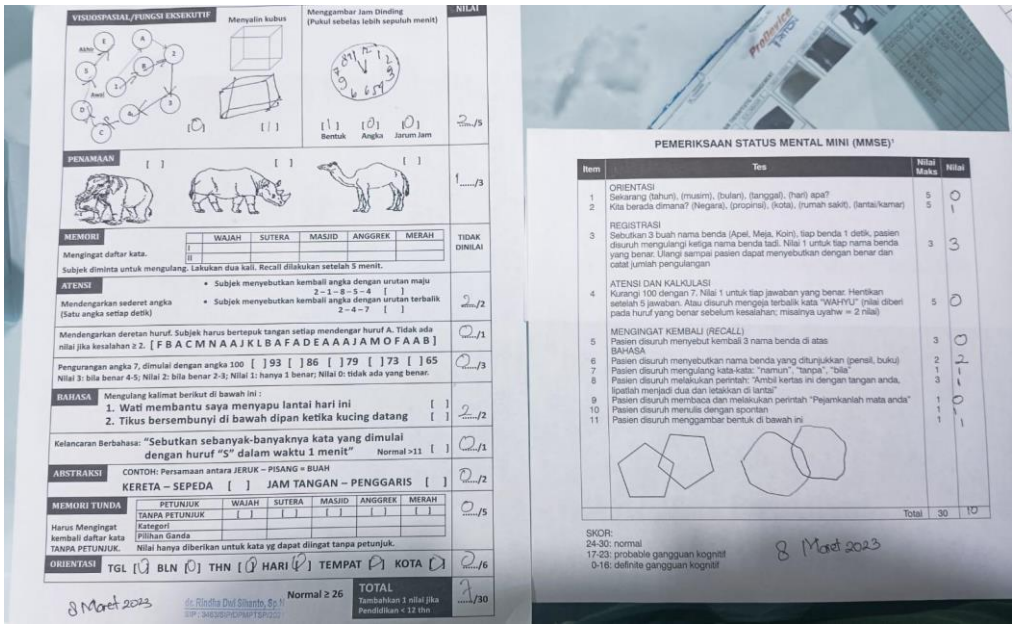


FIGURE 2: Results of MoCA-INA and MMSE assessments three months post-COVID-19 before Citicoline treatment, showing MoCA-INA score of 7 and MMSE score of 10.

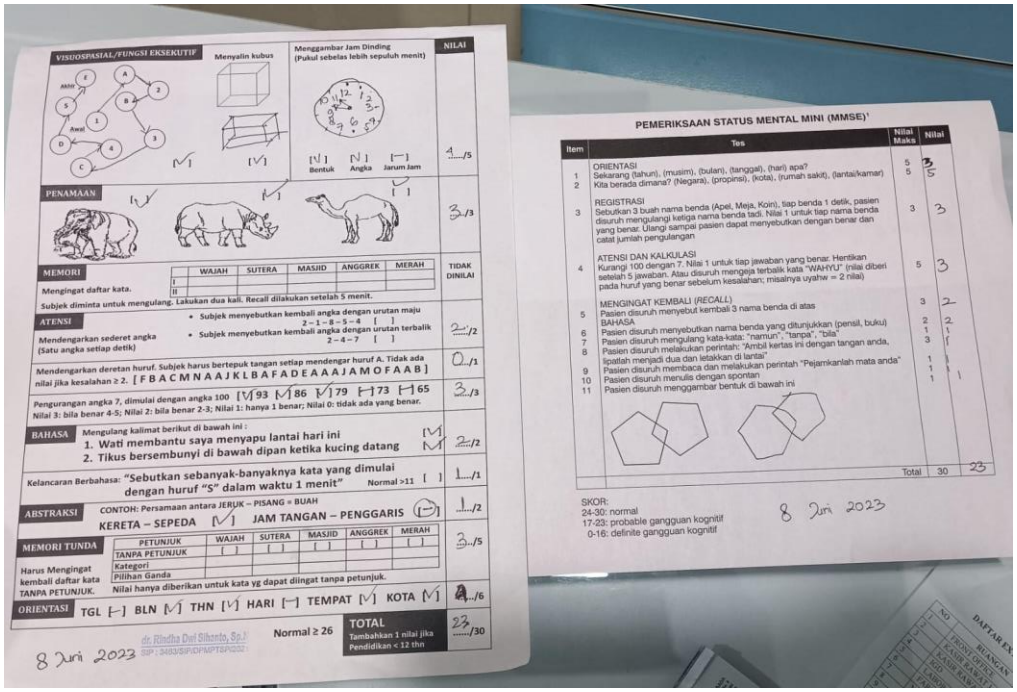


FIGURE 3: Results of MoCA-INA and MMSE assessments two months post-Citicoline treatment, showing improved MoCA-INA score of 23 and MMSE score of 23.

PROBLEM STATEMENT

The clinical question arising from the case illustration and background described is to determine the effectiveness of oral Citicoline administration as a therapy for memory enhancement in post-COVID-19 patients. The PICO formulation of this review is presented in Table 1.

TABLE 1: PICO formulation.

Patient/ Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Treated COVID-19 patients	*Citicoline*500 mg every 12 hours orally	-	Increased MoCA-INA and MMSE scores
Question type	Correlation		
Study design	*Review articles* and Original research		

METHODS

The literature search strategy was conducted using four electronic databases: PubMed, Cochrane, EBSCOhost, Scopus, and Google Scholar, employing keywords related to the clinical question, as shown in Table 2. Screening was performed to find studies investigating COVID-19, Citicoline, and cognitive or memory issues.

TABLE 2: Literature Search Strategy.

PubMed	*COVID-19 AND (Citicoline) AND (Cognitive) OR (memory))*
Cochrane	*COVID-19 AND (Citicoline) AND (Cognitive) OR (memory)– All in Title Abstract Keyword, Words variations have been searched*
EBSCOhost	*COVID-19 AND (Citicoline) AND (Cognitive) OR (memory)*
Scopus	*COVID-19 AND (Citicoline) AND (Cognitive) OR (memory)*
Google Scholar	*COVID-19 AND (Citicoline) AND (Cognitive) OR (memory)*

ELIGIBILITY

Inclusion Criteria:

(1) Studies providing information on the benefits of Citicoline in COVID-19 cases with memory impairment.
(2) Study designs including original research and review articles.
(3) Adult population.

Exclusion Criteria:

(1) Full-text articles not available.

The search results found only 2 review articles and 1 original research study linking Citicoline, memory, and COVID-19.

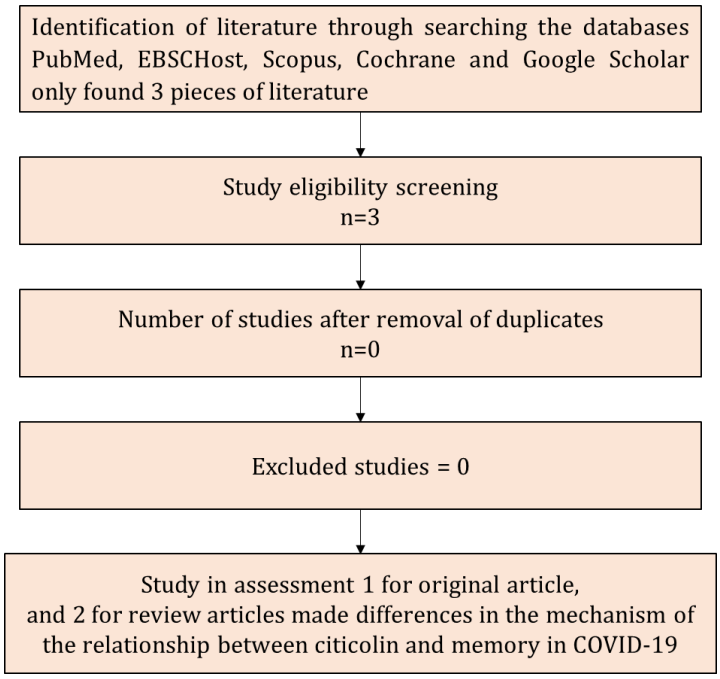


FIGURE 4: Literature search mechanism.

RESULTS

The data search revealed only three pieces of literature discussing memory decline in COVID-19 patients with Citicoline administration. This includes one clinical research study and two review articles, with evaluations presented in Tables 3-6. The mechanisms of Citicoline action are illustrated in Figures 5 and 6.

TABLE 3: Study Characteristics.

Author (Year)	Study Design	Population (Mean±SD)	Intervention	Results
Turana et al., (2021)[20]	*review articles*	-	-	*Citicoline*combats COVID-19 related memory decline through anti-inflammatory, anti-viral, neuroprotective, neurorestorative, and synthesis of the neurotransmitter acetylcholine
Al Kuraishy, et al., (2022)[21]	*review articles*		-	*Citicoline*in improving memory with the mechanisms of neural energy, neurogenesis, anti-inflammatory, antioxidant and silent information regulator 1 (SIRT1)
Zueva et al., (2021)[22]	*original research (case-control)*	A total of 48 after COVID-19 with age 43.72 ± 5.21 years	Intervention Group: Administration of Citicoline 1000 mg/day at 24 in oral solution 100 mg/ml to COVID-19 respondents Control group: healthy patient volunteers totaling 24 respondents	As many as 75% of COVID-19 respondents experienced memory loss. After administering the intervention, there were improvements in MMSE scores, short-term memory function, Coding speed test results, improved sleep and a decrease in anxiety levels compared to the control group ($p<0.05$)

TABLE 4: Validity Study.

Question		
Original Research	Zueva (2021)	
Are patients selected randomly?	No, the respondent has already been determined	
Do the two groups have the same characteristics?	Yes	
Has anyone dropped out of the study?	There isn't any	
Are confounding factors controlled?	Yes	
Is the dose of the intervention carried out in accordance with national/international guidelines?	Yes	
Review Articles	Turana et al (2021)	Al Kuraishy, et al (2022)
Does it explain the incidence of memory decline in post-COVID-19 patients?	Yes	Yes
Does it explain the mechanism for using Citicoline in patients with post-COVID-19 memory loss?	Yes	Yes
Does it explain cases of Citicoline use in patients with memory loss after COVID-19?	No	No
Is this review article relevant to the case in research?	Yes	Yes

TABLE 5: Interest Analysis.

Question	Zueva (2021)
How big is the effect of Citicoline treatment?	- The MMSE results for the intervention group (Citicoline) were 27.51 ± 2.13 to 28.89 ± 2.41, while the control group was from 27.62 ± 2.29 to 27.95 ± 2.36. - Short term memory results in the intervention group (Citicoline) from 6.48 ± 1.15 points to 8.32 ± 1.49 points and in the control group from 6.53 ± 1.18 points to 7.34 ± 1.25 points - The results of the 'Coding' speed test in the intervention group (Citicoline) were from 40.37 ± 9.64 seconds to 48.91 ± 9.86 seconds while the control group was from 41.56 ± 9.62 to 42.28 ± 9.75 seconds - Sleep quality results were obtained in the intervention group (Citicoline) from 19.38 ± 0.16 points to 21.64 ± 0.74 points while the control group was obtained from 19.82 ± 0.63 - Anxiety examination results were obtained in the intervention group (Citicoline) from 9.27 ± 0.47 to 7.14 ± 0.31, while the control group was obtained from 9.35 ± 0.46 to 8.81 ± 0.44
How precise is the estimate of therapy effect?	Not explained

TABLE 6: Implementation Study.

Question	Zueva (2021)
Are my patients different from the study patients so that the study results cannot be applied?	No
In my condition, is the therapy given effective?	Yes
Do the benefits of treatment outweigh the potential harm to my patient	Yes

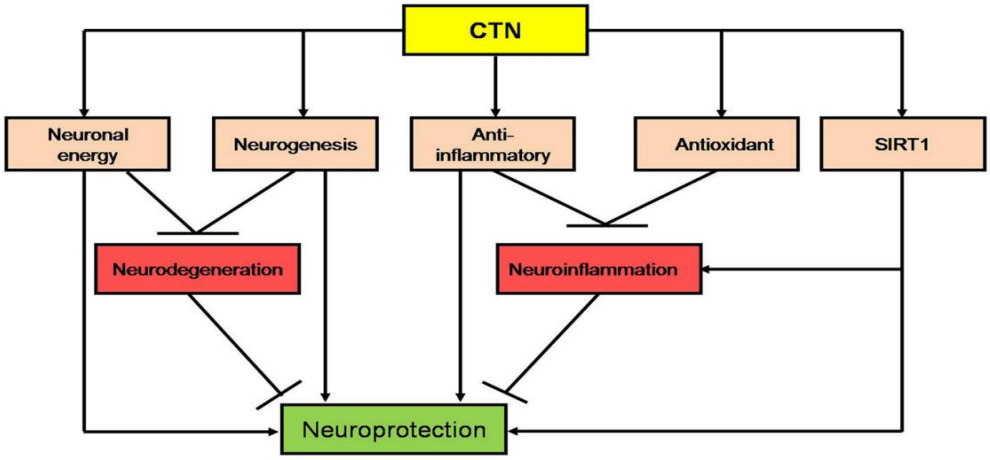


FIGURE 5: Neuroprotective effects of [21].

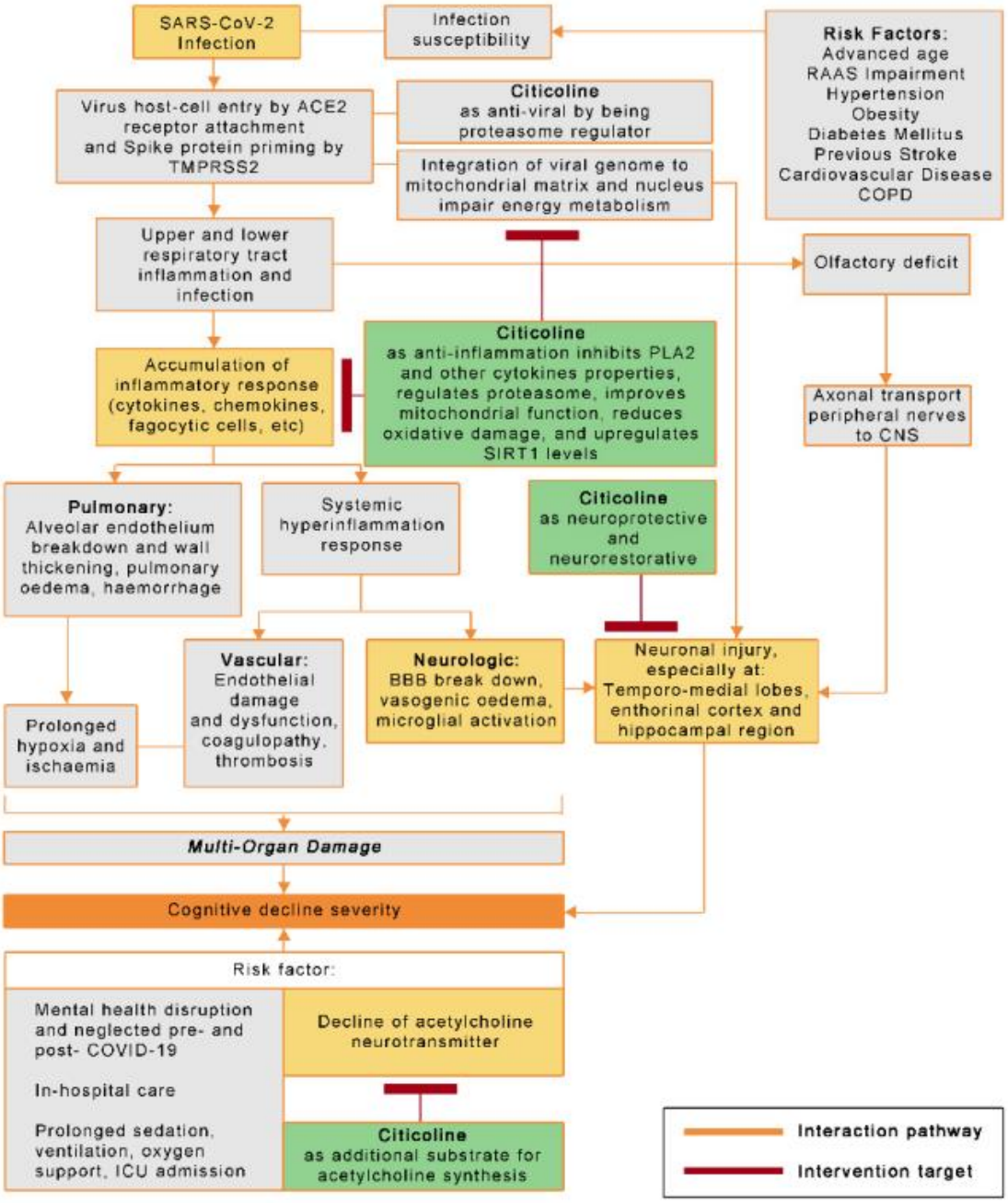


FIGURE 6: Mechanism of Citicoline administration in improving memory impairment in COVID-19 patients [20].

DISCUSSION

The World Health Organization has recommended that all recovered COVID-19 patients undergo memory assessment and rehabilitation [23]. Based on study reviews and case reports, it is known that post-COVID-19 patients can experience memory decline. The COVID-19 virus infection in the central nervous system (CNS) primarily targets the temporal area, especially the hippocampus, which is responsible for memory functions [9]. Between 59–65% of COVID-19 patients, in follow-ups 3–4 months after hospital discharge, experience severe memory impairment, particularly in verbal learning and executive function, as well as working memory, verbal fluency, and processing speed [24]. Further investigation found that memory impairment was associated with the degree of lung dysfunction and d-dimer levels during the acute phase of the disease, indicating restricted oxygen delivery to the brain [25].

Case reports have shown that administering Citicoline at a dose of 1000 milligrams for 2 months successfully improved memory. Zueva et al. also demonstrated significant memory improvement with just 1000 mg of Citicoline in a liquid solution of 100 mg in 1 ml for 14 days [22]. The Food and Drug Administration (FDA) recommends a Citicoline dose of 1000 mg – 2000 mg for improving memory function [26]. A systematic literature review by Jasielski et al. in 2020, involving 47 journals, found no significant difference between the use of 1000 mg and 2000 mg doses in patients with memory decline over 12 weeks, with both doses showing statistically significant benefits for memory enhancement [19]

Citicoline has a potentially influential role as an adjunct therapy and in preventing memory decline related to COVID-19 and other neurological complications. Citicoline's ability to improve memory in COVID-19 patients is explained by Turana et al. (2021) [20] through its anti-inflammatory, antiviral, neuroprotective, neurorestorative, and acetylcholine neurotransmitter synthesis mechanisms, while Al Kuraishy et al. (2022) describe it through neural energy, neurogenesis, anti-inflammatory, antioxidant, and silent information regulator 1 (SIRT1) activation mechanisms [21].

Cytidine-5'-diphosphocholine (CDP)-choline, commonly known as Citicoline, is a chemical identical to the phospholipid precursor phosphatidylcholine, a natural metabolite involved in the synthesis of intracellular phospholipids and also an exogenous source of choline and cytidine. Citicoline has rare side effects and low toxicity in the human body [16]. Since the 1900s, Citicoline has been proven to increase cerebral blood flow velocity and reduce pulsatility and resistance indexes by improving cerebrovascular perfusion. As an intermediary in phosphatidylcholine synthesis, Citicoline can minimize phospholipid hydrolysis, decrease increased PLA2 activity in membrane and mitochondrial fractions, thus improving changes related to cognitive impairment in the brain [27].

Citicoline has the potential to improve mitochondrial dysfunction, a contributor to neurological issues in COVID-19, by maintaining sphingomyelin and cardiolipin, components of the inner mitochondrial membrane [28]. Side effects of Citicoline can include diarrhea, epigastric discomfort, abdominal pain, fatigue, dizziness, headache, rash, and rare allergies [25].

Citicoline has been found to trigger upregulation of SIRT1 expression through the modulation of dendritic and axonal growth, benefiting neural plasticity and memory function. Upregulation of SIRT1 expression also reduces neural inflammation responses in hyperinflammatory conditions such as SARS-CoV-2 infection, aiding neural protection and recovery. Citicoline has advantages in addressing mitochondrial dysfunction known to occur in COVID-19, which underlies neuronal dysfunction and memory impairment due to energy metabolism and tissue oxygen supply issues [20]. In vitro and in vivo studies found that Citicoline reduces tissue damage caused by ischemia and reperfusion by enhancing mitochondrial function and reducing oxidative damage [29].

Given the increased incidence of cytokine storms due to COVID-19, Citicoline's anti-inflammatory properties can be beneficial by reducing macrophage inflammatory protein 1-alpha (MIP-1α), Tumor necrosis factor-alpha (TNFα), Interleukin-1 Beta (IL-1β), Monocyte chemoattractant protein-1 (MCP-1), Interleukin-6 (IL-6), Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), and IL-10 secretion [21]. Citicoline possesses neuroprotective properties by affecting cellular energy balance, glutamate excitotoxicity, oxidative cascades, apoptosis, and endothelial barrier disruption. Citicoline has also been found to have many positive effects on neuroregeneration by maintaining neurogenesis, synaptogenesis, gliogenesis, angiogenesis, and improving neuronal morphological structure [18].

This study has limitations as only one piece of literature directly addressed Citicoline use in COVID-19 patients, making comparisons difficult. Future research should involve prospective cohort studies on Citicoline use with longer durations and larger sample sizes.

CONCLUSION

Administration of Citicoline, either in oral tablet form or as an oral solution at a dose of 1000 mg/day, can improve memory function in post-COVID-19 patients due to its neuroprotective effects.

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Declarations

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Conflict of interest: None declared

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