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Review Article

Mechanisms and Protective Strategies in Cognitive Impairment Induced by Combination of Doxorubicin and Cyclophosphamide

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ABSTRACT

The introduction of combination chemotherapy raised the survival rate of cancer patients. However, it is associated with chemotherapy-induced cognitive impairment, often referred to as "chemobrain", which is a distressing adverse effect of cancer treatment. Doxorubicin and cyclophosphamide, two widely used chemotherapeutic agents in the treatment of various malignancies, have been shown to induce cognitive dysfunction. This review explores the underlying mechanisms that contribute to the chemobrain induced by doxorubicin and cyclophosphamide combination therapy, shedding light on oxidative stress, inflammation, neurotransmitter dysregulation, and neuroinflammation. Studies have shown that chemobrain is associated with activated inflammation and oxidative damage in the hippocampus. We also delve into the molecular pathways activated by doxorubicin and cyclophosphamide, such as the extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) signaling pathways, which are implicated in cognitive dysfunction. Additionally, this article explores protective approaches, including antioxidants like L-Carnitine, polyphenolic-rich compounds from *Thunbergia erecta*, and N-acetylcysteine, offering potential solutions for alleviating doxorubicin and cyclophosphamide-induced chemobrain. Notably, these protective agents, although promising in pre-clinical models, await clinical investigation. Therefore, there is a gap in data to support the application of any neuroprotective medication in a clinical context. Thus, clinical trials are necessary to assess their therapeutic potential. In conclusion, this review integrates data from diverse studies to elucidate the mechanisms and suggests potential protective strategies, offering insights for researchers seeking to alleviate cognitive challenges in doxorubicin and cyclophosphamide-treated cancer patients.

Keywords: *Chemobrain; Doxorubicin; Cyclophosphamide; Inflammation; Oxidative stress*.

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1. Introduction

The survival rate of patients with cancer has been rising due to advancements in chemotherapy and the emerging use of combination therapies involving multiple chemotherapeutic drugs **[1]**. However, a distressing side effect has been accompanied by this therapeutic advancement, referred to as “chemobrain”. This term is a pertinent term that has emerged recently, denoting the cognitive impairment induced by chemotherapeutic drugs due to their neurotoxic effects. This could affect the overall quality of life since it encompasses a spectrum of cognitive deficits, including attention disturbances, memory loss, and learning deficiency, which could persist after treatment completion **[2]**. Doxorubicin and cyclophosphamide, widely employed chemotherapeutic drugs for different cancers, have been reported to induce cognitive dysfunction experimentally in rats **[3, 4]** and

clinically in breast cancer patients **[5-7]**. Although protective strategies have been investigated in rats experimentally, no clinical trials have reported protective strategies in this context. Therefore, this review aims to systematically elucidate the mechanisms underlying doxorubicin and cyclophosphamide-induced chemobrain, offering a comprehensive exploration of the current chemobrain understanding and paving the way for potential protective strategies for mitigating the impact of chemobrain.

Doxorubicin is an anthracycline class member that is commonly employed in protocols of adjuvant chemotherapy in breast cancer treatment **[8]**. The antitumor effects of doxorubicin are due to its inhibition effect on topoisomerase-II, thereby halting the replication process by hindering the biosynthesis of DNA **[9]**. Even though doxorubicin has a limited ability to penetrate the blood-brain barrier (BBB), it can cause deleterious impacts on the brain since doxorubicin undergoes redox cycles, triggering the release of invasive free radicals **[10]**. Moreover, doxorubicin instigates inflammation owing to its potential ability to boost the release of inflammatory cytokines. These, in turn, may cross the BBB, giving rise to oxidative damage within the brain **[11]**.

Additionally, cyclophosphamide, an alkylating agent, is an inactive prodrug that has been documented to undergo hepatic enzymatic transformation, generating two metabolites: phosphoramide mustard and acrolein **[12]**. The therapeutic active metabolite is phosphoramide mustard, thanks to its substantial DNA alkylating activity, which is achieved by intercalating between the DNA strands, leading to its damage. Acrolein, the second metabolite, is thought to be accountable for the majority of organ toxicity induced by cyclophosphamide treatment since it is highly reactive and leads to the generation of reactive oxygen species (ROS), disrupting the antioxidant mechanisms of the body **[13]**. These free radicals generated by both doxorubicin and cyclophosphamide stimulate oxidative stress, promoting damage to mitochondria and, consequently, cell death **[3, 14]**.

2. Doxorubicin and cyclophosphamide-induced cognitive impairment underlying mechanisms

Multiple intricate molecular mechanisms have been linked with cognitive dysfunction induced by chemotherapy. Doxorubicin and cyclophosphamide combination exhibit the capacity to trigger some of these mechanisms, such as oxidative stress, neuroinflammation, and neurodegeneration, which are summarized in **Fig. 1**.

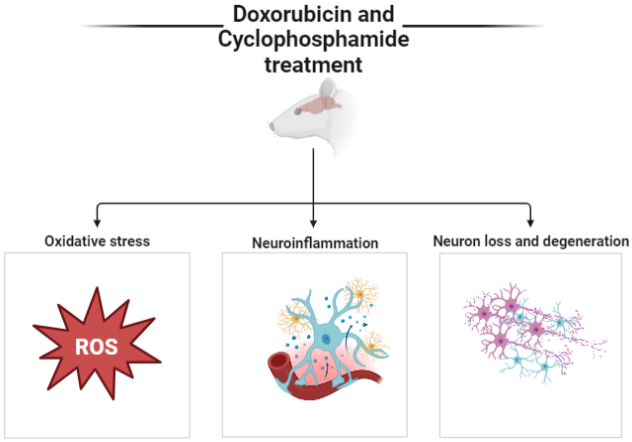

Fig. 1. Summarized mechanistic insight into Doxorubicin and cyclophosphamide-induced cognitive dysfunction.

2.1. Oxidative Stress

One of the fundamental factors underlying doxorubicin and cyclophosphamide-induced neurotoxicity pathophysiology is oxidative stress. Due to their constrained antioxidant capacity, brain tissues are extremely vulnerable to oxidative damage **[15]**. Doxorubicin and cyclophosphamide-induced oxidative stress was demonstrated to be orchestrated by an excessive generation of free radicals, reactive nitrogen

species, and ROS, reduced glutathione (GSH) depletion, and suppressing the activity of antioxidant enzymes **[14, 16]**. The substantial elevation in ROS levels plays a pivotal role in triggering oxidative damage to several cellular components, featuring lipid peroxidation, DNA damage, and mitochondrial dysfunction **[14, 17]**. The cumulative impact of these processes exacerbates cellular oxidative stress, creating a cascade that may ultimately contribute to the adverse effects observed in response to the combined doxorubicin and cyclophosphamide treatment. **Fig. 2**. illustrates the mechanisms of doxorubicin and cyclophosphamide-induced oxidative stress.

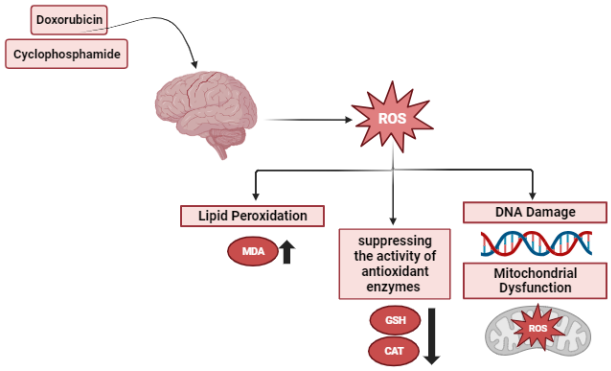

Fig. 2. Doxorubicin and cyclophosphamide-induced oxidative stress.
ROS: Reactive oxygen species, MDA: Malondialdehyde, GSH: Glutathione, CAT: Catalase

2.2. Inflammation

Extensive research has substantiated the pivotal involvement of neuroinflammation in the emergence and advancement of neurological complications linked to chemotherapeutic treatments **[18]**. Moreover, numerous experimental investigations have suggested that persistent inflammation concomitant with the considerable release of pro-inflammatory cytokines, notably tumor necrosis factor-alpha (TNF-α) and interleukins, constitute one of the principal driving forces for the neurodegenerative cascades associated with the administration of both doxorubicin and cyclophosphamide **[3, 19, 20]**. In this context, the pathogenesis of neuronal inflammation prompted by combined doxorubicin and cyclophosphamide chemotherapy involves critical inflammatory signaling pathways, which encompass oxidative stress-induced inflammation, nuclear factor kappa B (NF-κB), and high-mobility group box 1 (HMGB1)/receptor of advanced glycation end-products (RAGE) signaling transduction **[14, 16]**.

2.2.1. Nuclear factor kappa B (NF-κB) cascade activation

In regulating the expression of a wide range of pro-inflammatory genes, NF-κB is acknowledged as the principal transcription factor **[21]**. In unstimulated conditions, the NF-κB complex remains inactive within the cytosol, bound to inhibitors of κB (IκB), its inhibitory proteins **[22]**. Activation takes place when subjected to diverse pernicious stimuli, including ROS, this subsequently stimulates the activation of the IκB kinase complex (IKK), which in turn initiates phosphorylation of IκB, marking it for ubiquitination, subsequently triggering its degradation by proteases **[23]**. Consequently, the liberation of the κB transcription factor allows its translocation to the nucleus, where it activates the proinflammatory genes **[24]**. Interestingly, investigations have demonstrated that doxorubicin and cyclophosphamide concomitant administration induces the upregulation of NFκB expression, consequently the overproduction of inflammatory cytokines, such as TNF-α and interleukin-1 beta (IL-1β) **[14, 16]**.

2.2.2. HMGB1-RAGE axis activation

Necrotic cells or activated cells generate damage-associated molecular patterns (DAMPs), which have been identified as a key factor in triggering and amplifying the synthesis of pro-inflammatory mediators **[25]**. One of these DAMPs is HMGB1, a nuclear DNA-binding

protein displaying high preservation **[26]**. Due to the widespread expression of HMGB1 in mostly all nucleated animal cells, its passive release from necrotic cells positions it as a potent trigger of inflammation **[27]**. Upon its binding to RAGE, HMGB1, via activation of distinct signaling pathways, triggers pro-inflammatory cascades that result in the generation of cytokines and chemokines that promote inflammation **[28, 29]**. A recent study has demonstrated that doxorubicin and cyclophosphamide coadministration induced HMGB1 and RAGE expression, leading to stimulation of the p65 subunit of NF-κB and enhancing the release of IL-1β, as evidenced by their increased expression **[16]**. **Fig. 3** represents the HMGB1/RAGE inflammatory pathway activation in doxorubicin and cyclophosphamide neurotoxicity.

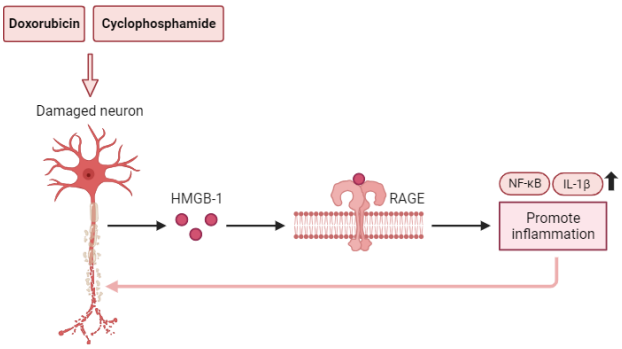

Fig. 3. Effect of doxorubicin and cyclophosphamide on HMGB1-RAGE axis.
HMGB1: high mobility group box 1, RAGE: receptor for advanced glycation end products, NFkB: Nuclear factor kappa B, IL-1β: Interleukin 1 beta

2.3. Neuronal plasticity and survival alteration

2.3.1. CREB/BDNF pathway

Functioning as a critical neurotrophic factor in the brain, the brain-derived neurotrophic factor (BDNF) is acknowledged to be a broadly distributed neurotrophic factor that promotes synaptic plasticity, neuronal growth, and survival. The role that it plays has been established, especially throughout the prefrontal cortex and hippocampus **[30]**. One of the pathogenic pathways operating in neurodegenerative disorders has been demonstrated through research, revealing that diminished levels of BDNF play a part in this phenomenon **[31]**. In the hippocampus, the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), is a protein that is accountable for both short-term and long-term memory. Once activated, CREB undergoes conversion into its phosphorylated form (p-CREB). Subsequent activation has been found to induce cortical and hippocampal BDNF transcription, enhancing the transmission of molecular signals crucial to maintaining neuronal survival. The CREB/BDNF pathway plays a critical role in cognitive functions and synaptic plasticity. Earlier investigations have indicated that this pathway is involved in cognitive impairment pathogenesis **[30]**. A recent report has highlighted the reduction in the cortical and hippocampal expression of BDNF and p-CREB in the pathogenesis of cognitive impairment following the concurrent administration of doxorubicin and cyclophosphamide **[14]**.

2.3.2. Extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) signaling pathways

The ERK pathway is a mitogen-activated protein kinase (MAPK) cascade that transmits extracellular signals to the nucleus from the cell surface. The mechanism is normally activated by the binding of growth factors or other extracellular ligands to cell surface receptors, triggering a sequence of phosphorylation processes **[32]**. This activation allows Raf kinases to become active, which in turn phosphorylates and activates MEK (Mitogen-Activated Protein Kinase). Once activated, MEK then phosphorylates and activates ERK, enabling ERK to translocate into the nucleus, where it modulates the activity of various transcription factors. Notably, synaptic plasticity and neuronal

development, a fundamental mechanism for learning and memory, rely on the functionality of the ERK pathway **[33]**. Aberrant activation of this ERK pathway has been linked to abnormalities in memory processes, including long-term depression (LTD) and long-term potentiation (LTP). Moreover, the modulation of the activity of the transcriptional repressor CREB2 could potentially be influenced by the differential activation of these isoforms of MAPK **[34]**. Furthermore, previous investigations illustrated that ERK½ signaling activities were enhanced in the hippocampus of rats treated with the doxorubicin and cyclophosphamide cocktail **[19]**.

AKT, a serine/threonine kinase, is linked to numerous cellular functions, encompassing protein synthesis, neuronal morphology, plasticity as well as, cell survival and apoptosis **[35]**. The AKT signaling pathway has been demonstrated to be important in the central nervous system due to its paramount role **[36]**. Moreover, AKT phosphorylation can activate the MAPK/ERK½ pathway **[37]**. Interestingly, a study has disclosed that doxorubicin and cyclophosphamide impact cognitive function and affect synaptic plasticity via enhanced activation of Erk1/2 and AKT **[38]**.

2.3.3. Presynaptic and postsynaptic proteins

Synaptic proteins such as synaptophysin and postsynaptic density protein PSD-95 are not only structural components of synapses but also key indicators of synaptic activity, reflecting their pivotal roles in memory and learning **[39]**. Operating within the presynaptic terminal, synaptophysin, a vesicular synaptic protein, plays an active role in both neurotransmitter release and synaptic vesicle recycling **[40]**. PSD-95, an excitatory synaptic scaffolding protein, interacts with N-methyl-D-aspartate (NMDA) receptors, facilitating their expression in the postsynaptic membrane. Furthermore, PSD-95 is considered a crucial protein for synaptic plasticity, with its levels mirroring the size and strength of synapses **[41-43]**. Besides, a correlation between memory impairment and PSD-95 levels has been suggested by reports from previous studies **[38]**. In this context, a recent study demonstrated that the combination treatment of doxorubicin and cyclophosphamide resulted in a drastic reduction in the prefrontal cortical and hippocampal expression of both synaptic proteins, synaptophysin and PSD-95, impairing synaptic plasticity and altering rats' memory **[14]**.

2.4. Down-regulation of neurotransmitters

Recently, disturbances in the equilibrium among brain neurotransmitters have been shown in multiple chemotherapy-induced cognitive deficits and behavioral abnormalities **[44-46]**. Evidence continues to emerge that the combination of doxorubicin and cyclophosphamide-induced cognitive impairment is closely linked to a reduction in acetylcholine (Ach) neuronal reserves. Ach is widely recognized as a vital neurotransmitter essential for healthy functions, memory, as well as learning since it stands as a crucial neurotransmitter within the cholinergic nervous system, allowing LTP **[3, 14, 47]**. The observed phenomenon may be ascribed to enhanced acetylcholinesterase enzyme (AchE) upregulation and activation **[48]**. AchE is responsible for the hydrolysis of Ach, and subsequently, its degradation effectively halts the transmission of cholinergic signals across synapses **[49]**. Furthermore, recent demonstrations have highlighted that doxorubicin and cyclophosphamide are linked to a drop in serotonin (5-HT) and dopamine levels in the brain. This action exacerbates the decline of cognitive functions while also potentially provoking a depression-like illness **[50, 51]**. Playing a significant role in regulating hippocampal synaptic plasticity, 5-HTergic

neurons exert inhibitory control through 5-HT1A receptors. The depletion of 5-HT has a negative impact on hippocampus-dependent declarative memory, resulting in poor performance in a novel object recognition task **[52]**.

3. Promising neuroprotective strategies to combat cognitive impairment induced by doxorubicin and cyclophosphamide

Currently, definitive treatments for doxorubicin and cyclophosphamide cocktail-induced cognitive impairment remain elusive. However, select studies have highlighted potential drug interventions that show promise in mitigating the cognitive damage caused by this combination treatment. Nevertheless, emerging research has highlighted potential neuroprotective strategies that show promise in mitigating cognitive damage caused by this combination therapy. **Table 1** and **Fig. 4** comprehensively summarize each preventive measure alongside the molecular mechanisms underlying their neuroprotective effects.

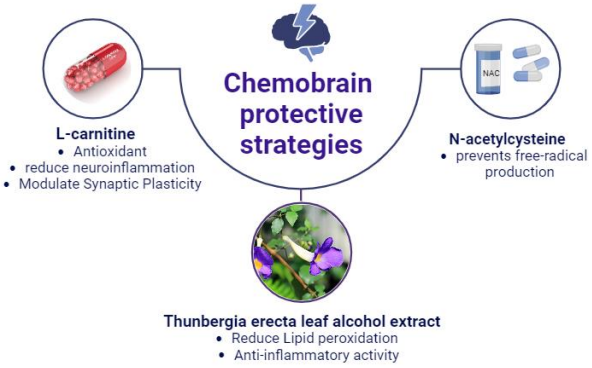

Fig. 4. Summary of the preventive strategies with the molecular mechanisms molecular mechanisms that underscore their neuroprotective benefits.

3.1. L-Carnitine

L-Carnitine is an endogenous molecule that naturally exists in almost every mammalian species and tissue **[53]**. L-Carnitine is synthesized in the human body and plays a vital function in energy metabolism by facilitating the transport of fatty acids into the mitochondria, subsequently assisting in cellular energy production. Beyond being a dietary essential, L-Carnitine isn't just gained from what we eat; our bodies also synthesize it from essential amino acids such as L-lysine and L-methionine, mostly in the kidney and liver. Going beyond its primary role in energy production, L-Carnitine has sparked interest in its potential health benefits and therapeutic applications **[54]**. Moreover, L-Carnitine, with its recognized involvement in diverse biological activities, has been reported for its, anti-inflammatory **[55]**, antioxidant **[56]**, neuroprotective **[57]**, learning, and memory enhancement **[58]**. Additionally, research highlights L-Carnitine's reported anticancer activity through its ability to reduce angiogenesis **[59]**. As evidenced by an experimental model, L-Carnitine demonstrated neuroprotective properties against doxorubicin and cyclophosphamide co-administration-induced chemobrain where Doxorubicin (4 mg/kg) and Cyclophosphamide (40 mg/kg) were administered to rats intravenously through the rat tail vein once weekly, along with L-Carnitine at doses of 150 and 300 mg/kg intraperitoneally five times per week for three weeks. Demonstrating neuroprotective effects, L-Carnitine positively influenced spatial memory and learning as well as memory acquisition and retention. Moreover, it prevented the histopathological alterations that resulted from doxorubicin and cyclophosphamide treatment. Furthermore, through its antioxidant properties, L-Carnitine exhibited further neuroprotective effects. Additionally, it contributed to the reduction of neuroinflammation, as displayed by its impact on NF-κB and the related cytokines, namely TNF-α and IL-1β, in both the prefrontal cortex and hippocampus. On top of that, using its modulation of synaptic plasticity, L-Carnitine exhibited the potential to mitigate cognitive impairment driven by Doxorubicin and

Cyclophosphamide co-treatment. These findings indicate that L-Carnitine holds promise as a potential candidate for clinical trials in evaluating chemobrain prevention. This potential is particularly noteworthy given its current market approval and the absence of serious side effects **[14]**.

Table 1. Mechanistic neuroprotective targets to alleviate doxorubicin and cyclophosphamide-induced neurotoxicity

Agent used	Methodology	Mechanisms of neuroprotection	References
L-Carnitine	Animals: Male Wistar rats Experimental design: Doxorubicin (4 mg/kg) and Cyclophosphamide (40 mg/kg) were given intravenously through the rat tail vein once a week in parallel with the administration of L-Carnitine intraperitoneally at doses of 150 and 300 mg/kg five times per week for a consecutive three weeks. Behavioral tests: Locomotor activity Novel object recognition test Morris water maze Passive avoidance	Anti-inflammatory: ↓ NF-κB, TNF-α & IL-1β Antioxidant: ↓ MDA ↑ GSH, CAT Effect on neurotransmitters: ↓ AChE Effect on neurogenesis and synaptic plasticity: ↑ BDNF, pCREB, synaptophysin & PSD-95	**[14]**
N-acetylcysteine	Animals: Male Wistar rats Experimental design: doxorubicin (5 mg/kg) and cyclophosphamide (50 mg/kg) were administered intraperitoneally once a week for 2 weeks, N-acetylcysteine was given three times: 30 minutes before, 30 minutes, and 1 hour after Behavioral tests: Light-Dark test Novel location recognition test	Antioxidant: ↑ GSH/GSSG ratio	**[66]**
Thunbergia erecta	Animals: Male Wistar rats Experimental design: Rats were administered intravenously once per week for 3 weeks with Doxorubicin (4 mg/kg) and Cyclophosphamide (40 mg/kg), in addition to, TEAF 50, 100, and 200 mg/kg were administered orally one hour later 5 times per week for 3 weeks Behavioral tests: Locomotor activity Novel object recognition test Morris water maze Step-through passive avoidance	Anti-inflammatory: ↓ HMBG1, RAGE, NF-κB, TNF-α & IL-1β Antioxidant: ↓ MDA & hydrogen peroxide ↑ GSH, CAT	**[16]**

3.2. N-acetylcysteine

N-acetylcysteine, a naturally occurring antioxidant, stands as a notable compound known for its multifaceted medical applications. Serving as a precursor to L-cysteine and subsequently GSH, it holds a key role in the management of paracetamol overdose and has acquired prominence in mucolytic therapy. Furthermore, its importance extends to its global recognition by the World Health Organization (WHO) as an essential medication and an antidote to poisoning **[60]**. Demonstrating its efficacy, N-acetylcysteine has been observed to boost GSH, the brain's principal antioxidant, while simultaneously lowering pro-inflammatory cytokine levels, contributing to improved neurogenesis **[61]**. Besides, reported findings indicate that N-acetylcysteine exhibits favorable outcomes in combating neuropsychiatric conditions, such as anxiety, obsessive-compulsive disorder, and cognitive impairment associated with chemotherapy **[62-65]**. In rats subjected to combination treatment with doxorubicin (5 mg/kg) and cyclophosphamide (50 mg/kg) intraperitoneally once a week for two weeks, N-acetylcysteine administration three times: 30 minutes before, and 30 minutes and 1 hour after was investigated for its impact on cognition impairment and anxiety-like behavior induced. The findings revealed that the anxiety-like behavior and cognitive deficits induced by doxorubicin and cyclophosphamide were effectively reversed by N-acetylcysteine via its impact on GSH-dependent oxidative stress protection **[66]**.

3.3. *Thunbergia erecta*

Native to tropical West Africa, *Thunbergia erecta* is a known species within the *Acanthaceae* family. Cultivated globally, it serves as an ornamental plant **[67]**. Interestingly, the leaves of Thunbergia erecta have a traditional history of being used medically due to their anti-inflammatory, antidepressant, sedative, and anxiolytic effects **[68]**. It has been stated that this plant is capable of producing flavonoids, alkaloids, glucosides, and phenolic acid derivatives **[67]**. Reportedly, the plant exhibited sedative and anxiolytic properties. Added to that, certain isolated phytoconstituents were noted for their anticholinesterase activities **[69]**. A recent study investigated the effect of *Thunbergia erecta* especially the ethyl acetate fraction of its alcohol extract (TEAF) against chemobrain induced by the administration of both doxorubicin and cyclophosphamide. The rats received doxorubicin at a dose of 4 mg/kg and cyclophosphamide at a dose of 40 mg/kg intravenously once a week for 3 weeks. The 50, 100, and 200 mg/kg doses of TEAF were tested for their impact on chemotherapy-induced cognitive impairment. When administered at a dose of 200 mg/kg, TEAF exhibited more favorable outcomes compared to lower doses. Its consumption successfully mitigated the chemobrain triggered by combinational chemotherapy. This was evident through its influence on spatial memory, memory acquisition, and learning. Additionally, at the dosage of 200 mg/kg, TEAF ameliorated the histological alterations caused by the doxorubicin and cyclophosphamide combination, while also impeding the induced oxidative stress and lipid peroxidation prompted by the chemotherapy combination. Furthermore, TEAF showed anti-inflammatory and neuroprotective effects through its ability to inhibit the HMGB1/RAGE/p65 NF-κB signaling pathway which was evidenced by reduced protein expression of prefrontal cortical and hippocampal HMGB1, RAGE, p65 NF-κB, and Il-1β, suggesting that *Thunbergia erecta* holds promise as a potential future therapeutic solution for chemobrain, addressing the cognitive challenges affecting cancer patients globally. This reinforces its traditional significance as a neuroprotective agent **[16]**.

Conclusion

In conclusion, this comprehensive review systematically elucidates the mechanisms underlying the cognitive impairment induced by the combination of doxorubicin and cyclophosphamide. The findings from various experimental studies have unveiled diverse mechanisms contributing to the pathogenesis of this neurotoxicity. Notably, oxidative stress emerges as a cornerstone, with this combination triggering substantial ROS generation, concurrently downregulating antioxidant enzyme activities. Moreover, neuroinflammation plays a crucial role in this pathological process, as doxorubicin and cyclophosphamide induce the release of pro-inflammatory cytokines through modulation of inflammatory signaling cascades such as the NF-κB and HMGB1-RAGE axis. Additionally, it alters neuronal plasticity and survival by acting on the CREB/BDNF pathway, ERK /AKT signaling pathways, and presynaptic and postsynaptic proteins. Furthermore, doxorubicin and cyclophosphamide-induced chemobrain are associated with the repression of cholinergic neurotransmission, activation of AchE, and disruption of the balance of neurotransmitters, including dopamine and 5-HT. While many experimental studies explore potential neuroprotective agents, both synthetic and phytochemical, the absence of a clinically approved adjunct underscores the necessity for robust clinical trials. Verifying the safety and efficacy of candidate agents. Bridging the translational gap is imperative, and future research efforts should focus on unraveling novel therapeutic avenues. The ultimate goal is to not only alleviate cognitive impairment but also enhance patient outcomes and overall quality of life in the face of doxorubicin and cyclophosphamide treatment.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Conflict of Interest

The authors assert that there are no conflicts of interest.

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Authors Contribution

NKG: data curation, writing – original draft. RNE: data curation, supervision, writing – review and editing. MY: Conceptualization, data curation, supervision, writing – review and editing.

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