Archives of Pharmaceutical Sciences Ain Shams University 2024; Vol. 8(1): 59-75

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Pharmacology and Toxicology

Review Article

Chemobrain: Insight the possible mechanisms of action induced by chemotherapeutic agents

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ABSTRACT

Cancer is a chief burden of disease all over the world and is perceived as a terrifying and uncurable illness that implies death. Chemotherapy is one of the most common therapeutic approaches in cancer treatment. The effectiveness of chemotherapy led to a great elevation in survival rates of cancer patients with different types of cancer. Chemobrain is a group of symptoms showing reversible or irreversible cognitive decline, which a subset of adult, non-CNS cancer patients complain of as a direct consequence of chemotherapy. Several studies were conducted to investigate the possible chemotherapeutic agents that may precipitate chemobrain and their possible underlying pathways and mechanisms of action. In this review, we were interested in providing an insight into chemobrain, the possible mechanistic pathways of chemobrain-inducing chemotherapeutic drugs, the possible neuroprotective agents, diagnostic methods, the possible management methods, and the possible neuroprotective agent. The data of this review were based on review articles, books, and original articles obtained from PubMed, Google Scholar, and Elsevier.

Keywords: *Chemobrain; Cognitive impairment; Chemotherapeutic drugs; Inflammation; oxidative stress*.

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Citation | Hassan MM, Wahdan SA, El-Naga RN, Abdelghany TM, El-Demerdash E, 2024. Chemobrain: Insight the possible mechanisms of action induced by chemotherapeutic agents. Arch Pharm Sci ASU 8(1): 59-75

DOI: 10.21608/aps.2024.266919.1157

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 09 February 2024. **Accepted** 23 February 2024.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

Cancer is a chief burden of disease all over the world and is perceived as a terrifying and uncurable illness that implies death. Chemotherapy is one of the most common therapeutic approaches in cancer treatment. The effectiveness of chemotherapy led to great elevation in survival rates of cancer patients with different types of cancer **[1]**. Regrettably, about 70% of cancer survivors who were previously receiving chemotherapy suffer from cognitive deficits throughout or after treatment and this affects their quality of life **[2]**.

It has been recognized since the 1990s that chemotherapeutic agents have a bad influence on brain function. The aspects that are influenced include attention, learning, memory, executive function in addition to locomotor activity **[3]**. It is known that cancer remedies are accompanied by substantial central (CNS) and peripheral (PNS) nervous system toxicity, including a variety of clinical disorders, such as posterior reversible

encephalopathy, acute, subacute, and chronic encephalopathies, myelopathy, meningitis, neurovascular syndromes, acute cerebellar dysfunction, chronic cognitive impairment, and neuropathies **[4, 5]**. The effect of chemotherapy on cognition is mentioned as chemotherapy-induced cognitive impairment (CICI), informally acknowledged as "Chemobrain".

Chemobrain was originally defined by Dr. Peter Silberfarb and colleagues in 1980. It was mentioned as language disturbing, attention, hastening, learning, and recognition **[6]**. It was proposed that short-term memory, working memory, and verbal ability are the furthermost commonly affected, subsequently executive functions, visuospatial memory, and attention span **[7]**.

1.1 Symptoms of Chemobrain

Symptoms of chemobrain include memory loss, defective attention, speech and psychomotor slowing, learning coordination problems, and executive function disturbance. The symptoms might be fleeting but they are usually long-term negatively affecting quality of life **[8]**.

1.2 Structural brain areas involved in cognition

It was found that the hippocampus and its related brain structure have a crucial role in cognition **[9]**. The hippocampus is an area important for learning and memory in the brain. Chemotherapy disrupted the structure and function of the hippocampus and impaired its neurogenesis, leading to cognitive deficits **[10]**.

Additionally, current studies proposed that the medial prefrontal cortex plays a vital regulatory role in various cognitive functions, such as attention, and spatial or long-term memory. The medial prefrontal cortex is vastly interconnected with subcortical regions (hippocampus, thalamus, and amygdala) and exhibits top-down executive control over different cognitive domains and stimuli **[11]**. The decrease in the integrity of white matter in the frontal, temporal, and parietal lobes involving long association fibers proposes that subcortical involvement may trigger both cognitive and functional changes **[12]**.

1.3 Examples of Chemotherapeutic Agents That Induce Chemobrain and the Proposed Possible Underlying Mechanism Causing Chemobrain

The mechanisms underlying CICI are still not completely understood. Various studies specify chemobrain as a multifactorial disorder, that arises from different mechanisms, such as neuroinflammation, deoxyribonucleic acid (DNA) damage, oxidative stress, programmed cell death, and abnormal hippocampal neurogenesis **[13] Fig. 1.**

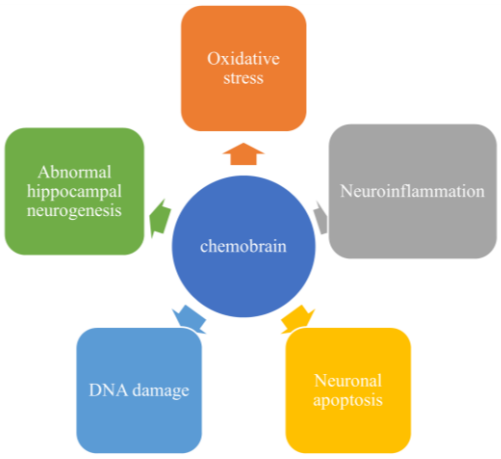

Fig. 1. A diagrammatic illustration of the possible mechanisms mediating chemotherapy-induced chemobrain

The secondary insult that chemotherapeutics may exert on the body and its several organ systems has been well-known in the literature. Despite being effective at fighting cancer, different existing agents lack the specificity to attack only cancer cells without causing damage to normal healthy tissue **[14]**. The circumstances induced by chemotherapy-induced inflammation and damage to the CNS and PNS are all probably

multifactorial and include various mechanisms **[14]**.

Neuroinflammation is one of the main mechanisms believed to trigger long-standing cognitive dysfunction in the elderly and neurological illnesses such as chemobrain **[15]**. Peripheral cytokines originate from the gut and neighboring tissue because chemotherapy is supposed to travel through the bloodstream, crossing the blood-brain barrier (BBB), and inducing inflammation in brain tissue that can disturb BBB permitting chemotherapeutic drugs to cross and directly damage brain tissue **[16]**. They trigger localized neuroinflammation via stimulating other neuronal cells, such as astrocytes, neurons, and oligodendrocytes leading to localized cytokine/chemokine release and resultant cognitive deficits **[17]**.

Microglial cells are well-thought-out as the brain's resident immune system and recruit neuroinflammation as a response to several insults [18] counting chemical insults, caused by chemotherapeutics. Persistent neuroinflammation leads to persistently stimulated microglia and the release of inflammatory intermediaries like tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) that may cause neuronal and glial cell damage **[19]**.

Here we are going to show some examples of chemotherapeutic agents that induce chemobrain and their possible mechanism of action.

1.3.1 Alkylating Agents: Cyclophosphamide-Induced Chemobrain

Cyclophosphamide is an alkylating agent, that is frequently used in acute and chronic lymphocytic leukemia regimens. It was approved by the Food and Drug Administration (FDA) as an anti-cancer agent in 1959. It is used widely in lung, breast, and hematological cancers **[20]**. Its anticancer mechanisms include breaking down to phosphoramide metabolite, which leads to cell death through cross-linking adjacent DNA strands at the guanine N-7 **[21]**. It is converted to 4-hydoxycyclophasphamide, which possesses a chemotherapeutic effect, and acrolein, which is responsible for its toxic effects by hepatic microsomal cytochrome 450 enzyme **[21]**.

Cyclophosphamide was linked to verbal memory drawbacks in breast cancer patients **[22]**. Several studies stated that cyclophosphamide might cause cognitive impairment by inducing oxidative stress, that sequentially, leads to mitochondrial damage and the release of inflammatory cytokines **[23]**. In a typical dose, it might cause neurotoxicity but when given in a high dose it may induce confusion and visual blurring **[24]**. Studies of cyclophosphamide showed that toxicity is caused by metabolites of cyclophosphamide, such as acrolein or phosphoramide mustard **[25]** According to Alfarhan, Jafari, and Narayanan **[26]**, acrolein can directly activate mitochondrial oxidative stress by elevating reactive oxygen species (ROS) level and consequently reduce cell defense mechanism through decreasing catalase or glutathione expression. Moreover, acrolein increases malonaldehyde (MDA) levels, an important indicator of lipid peroxidation, in the cerebral cortex and decreases glutathione which is considered the first-line protector antioxidant **[27]**. The general result is to diminish cellular resistance to oxidative stress that can impair the BBB and therefore permit the entry of possible neurotoxic molecules into the brain **[28]**.

Upon histopathological examination, cyclophosphamide showed focal gliosis associated with microglia infiltration and neuronophagia. In addition, vascular dilatation and perivascular edema were noticed. Neuronal degeneration showed in shrunken dark pyknotic nuclei and dense basophilic bodies surrounded by halo zone were detected signifying neuronal

degeneration **[29]**.

Regarding neuroinflammation, It was suggested that high mobility group box 1 protein (HMBG1), receptors for advanced glycation end products (RAGE), P65 nuclear factor-kappa B (p65 NF-kB), and IL-1β protein expression may relate to underlying mechanisms of chemobrain in rats subjecting to cyclophosphamide, that cyclophosphamide-treated rats showed increased HMBG1, RAGE, p65, and IL-1β protein expression **[29]**.

It appears that cyclophosphamide oxidative action is attained by elevated TNF-α and interleukin-6 (IL6) release. In corresponding, following cyclophosphamide administration, there is an amplified production of cyclooxygenase-2 (COX-2), inducible nitric oxide synthetase (iNOS), NF-$_k$B, and P38 mitogen-activated protein kinase (p38-MAPK) **[32]**. Furthermore, it was demonstrated that following cyclophosphamide administration in combination with Adriamycin showed a decreased level of the antioxidants including glutathione peroxidase-1, peroxiredoxin-1, and heme oxygenase-1 levels, additionally, they revealed increased extracellular signal-regulated kinase (ERK)/MAPK Signaling in the hippocampus that leads to oxidative damage, which triggers the microglia to produce proinflammatory cytokines like interleukin-2 (IL2), IL16, interleukin-10 (IL-10), and TNF-α causing neuronal damage and disturbs cognitive functions **[34] Table 1.**

Table 1. The Possible Mechanistic Pathways Involved in Cyclophosphamide-Induced Chemobrain.

Chemotherapeutic agent	Mechanistic pathways	Reference
Cyclophosphamide	Lipid peroxidation by reducing antioxidant activity and depletion of cerebral glutathione.	**[30]**
	Impair the blood-brain barrier and permit the entry of possible neurotoxic molecules into the brain.	**[28].**
	Induces ROS generation, lipid peroxidation, and worn-out cerebral glutathione content.	**[31]**
	Cyclophosphamide increased HMBG1, RAGE, p65, and IL-1β protein expression.	**[29]**
	Cyclophosphamide elevated TNF-α and IL6 release. Besides, amplified production of COX-2, iNOS, Nf-$_k$B, and p38-MAPK.	**[32]**
	Cyclophosphamide inhibits brain catalase activity, superoxide dismutase, and the anti-oxidant potential of the plasma.	**[33]**
	Cyclophosphamide decreased glutathione peroxidase 1, peroxiredoxin-1, and heme oxygenase-1 levels, and increased ERK/MAPK signaling in the hippocampus that leads to the release of proinflammatory cytokines like IL2, IL16, IL-10, and TNF-α causing neuronal damage that affects cognitive functions.	**[34]**

ROS, Reactive oxygen species; HMBG1, High mobility group box 1 protein; RAGE, Receptors for advanced glycation end products; IL-1β, Interleukin-1β; TNF-α, Tumor necrosis factor-alpha; IL16, Interleukin-16; COX-2, Cyclooxygenase-2; iNOS, Inducible nitric oxide synthetase; NF-kB, Nuclear factor-kappa B; P38-MAPK, P38 mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; IL2, Interleukin-2; IL10, Interleukin-10; PET, Positron emission tomography.

1.3.2 Chemotherapeutic Platinum Agents: Cisplatin-Induced Chemobrain

Cisplatin, one of the furthermost commonly used DNA-modifying chemotherapeutic drugs, is frequently used to treat bladder, cervical, esophageal, head, neck, testicular, ovarian, and

small-cell lung cancers **[35]**. Despite its high efficacy, several adverse effects, including nephrotoxicity, neurotoxicity, ototoxicity, and germ cell toxicity, are accompanied by cisplatin **[36]**. Cisplatin adverse effects might result from direct and/or indirect mechanisms; still, the overall mechanisms remain indefinable. Thus, the possible mechanistic pathways responsible for chemobrain, cisplatin, ought to be more examined to establish therapeutic regimens to enhance patients' quality of life **[37]**.

Former studies stated that injection of cisplatin 5 mg/kg for 7 weeks activates NF-κB and the release of inflammatory cytokines that cause inflammation in rats **[38]**. On the other hand, some experiments did not distinguish any inflammatory response in the brain, recognized as IL-1β, and TNF-α expression **[39, 40]**. Additionally, cisplatin did not trigger microglia and astrocyte activation as detected at 1- and 3 weeks post-injection **[39, 40]**. Though, the dose used was 2.3 mg/kg minor than that triggered NF-κB activation, it is conceivable that inflammation induced by cisplatin happens in a dose- and time-dependent manner.

Chronic treatment with a high dose of cisplatin provoked inflammation in vivo **[38]**. Cisplatin showed elevation in the proinflammatory IL-6, IL-1β, TNF-α, and caspase-3 levels in experimental models **[41]**.

Regarding neuronal apoptosis, the caspase cascade is a well-known pathway in cellular apoptosis and the killing of cancer cells. Generally, chemotherapy activates caspase in both cancer and normal cells. This procedure may be performed via either stimulation of an extracellular surface receptor signaling or intracellular mitochondrial signaling. DNA fragments and oxidative stressors activate the mitochondrial pathway that leads to caspase 9 activation **[42]**. Experimental indication shows that the protein damage produced by cisplatin, relatively more than DNA damage, plays a role in activating apoptotic pathways **[43]**.

In an earlier study, a solitary cisplatin dose (12 mg/kg) triggered the transcription of five pro-apoptotic genes in a rat hippocampus **[44]**. On the contrary, two rounds of cisplatin (2.3 mg/kg) did not elevate either brain cytosolic cytochrome c or caspase-3, while doublecortin (DCX+) precursor cells were still lost **[39]**. These results may be attributable to mitochondrial p53 tumor suppressor gene aggregation **Fig. 2.**

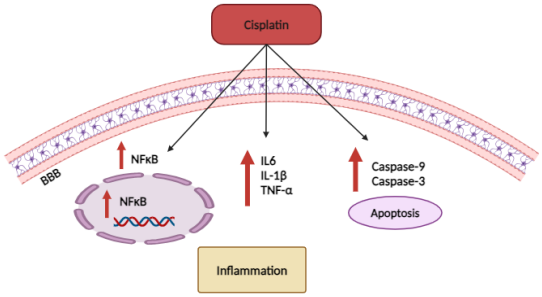

Fig. 2. A graphical illustration of the mechanistic pathways involved in Cisplatin-Induced Chemobrain

1.3.3 Antimetabolites: Methotrexate-Induced Chemobrain

Methotrexate is a dihydrofolate reductase antagonist that is used in the treatment of lymphomas and breast cancer **[45]**. Several studies demonstrated that a normal dose of methotrexate has a noteworthy consequence on spatial and non-spatial memory tests. These atypical cognitive tests could be clarified by the functional alternations induced by methotrexate in the frontal lobes and hippocampus **[3]**.

Although many chemotherapeutic agents are unable to cross the BBB, some studies have demonstrated the ability of methotrexate to cross this barrier **[19, 46]**. Studies on a murine model inoculated with a breast cancer cell line (FM3A) showed cognitive deficits and depression following methotrexate administration **[47]**. Other research revealed that methotrexate

administration reduces neurogenesis in the brain, resulting in learning and memory defects **[19]** Clinical reports demonstrated that in children with acute lymphoblastic leukemia, methotrexate initiates oxidative stress in CNS membrane phospholipids and causes CNS tissue damage that might illustrate perfusion debits, atrophy and cognitive alternations **[48]**. Methotrexate triggers plasma lipid peroxidation and it leads to a significant rise in 70 kDa heat shock protein (HSP70) and lessening of glutathione in different brain areas **[49]**.

Regarding the effect of methotrexate on the inflammatory pathways, methotrexate remarkably increased several pro-inflammatory factors such as COX-2 and iNOS **[47]**. Additionally, methotrexate caused persistent microglial activation and consequent astrocyte activation which is reliant on inflammatory microglia, which directs that exposure to methotrexate is accompanied by constant tri-glial dysregulation and classify inflammatory microglia as a therapeutic goal to revoke chemotherapy-induced neurological impairment **[50]**. Gibson, and Nagaraja **[50]** verified that tri-glial dysfunction underlies methotrexate CICI, with a direct influence on microglial activity afterward inducing neurotoxic astrocyte reactivity and oligodendroglial lineage dysregulation. Methotrexate reduced cortical brain-derived neurotrophic factor (BDNF) expression, which is re-established by microglial diminution **[51]**. Briones and Woods **[19]** showed that methotrexate combination therapy leads to chronic neuroinflammation, and is involved in cognitive deficits and alternation in myelin structure and myelination. They led to elevation of IL-1β, TNF-α, and COX-2 levels whereas the anti-inflammatory cytokine IL-10 diminished.

Chronically, it was indicated that methotrexate can cause a marked and chronic reduction in oligodendrocytes count and their progenitors in the white matter, in corpus callosum volumes, and myelin basic protein at 6 and 16 months post-chemotherapy, which is related to cognitive impairment **[52]**. Additionally, it was illustrated that both cognitive dysfunction and neuroinflammation resulting from methotrexate combination therapy continued 4 weeks after treatment **[19] Table 2.**

Table 2. The Possible Mechanistic Pathways Involved in Methotrexate-Induced Chemobrain

Chemotherapeutic agent	Mechanistic pathways	Reference
Methotrexate	In children with acute lymphoblastic leukemia, methotrexate induces oxidative stress in CNS membrane phospholipids.	**[48]**
	Methotrexate induced oxidative stress markers as oxidated phosphatidylcholine in the cerebral spinal fluid of patients with cognitive dysfunction.	**[53]**
	Methotrexate causes lipid peroxidation in the plasma as well as a significant rise in HSP70 and reduction of glutathione in different brain areas.	**[49]**
	Methotrexate significantly increased the levels of COX2 and iNOS.	**[47]**
	Methotrexate decreases cortical BDNF expression.	**[51]**
	Methotrexate combination therapy leads to chronic neuroinflammation, that is involved in cognitive impairment and alternations in myelin structure and myelination.	**[19]**
	Methotrexate can cause a significant and permanent reduction in oligodendrocytes count and their progenitors in the white matte.	**[52]**

CNS, Central nervous system; HSP70, 70 kDa heat shock protein; COX-2, Cyclooxygenase-2; iNOS, Inducible nitric oxide synthetase; BDNF,

1.3.4 Cytotoxic Antibodies: Doxorubicin-Induced Chemobrain

Doxorubicin, an anthracycline anti-tumor antibiotic used in various types of malignancies, produces intracellular oxygen species as its influence on the heart is explained by ROS production **[54, 55]**. Doxorubicin cannot harm the CNS directly as it cannot readily cross the BBB, the sustaining damage arises indirectly via different mechanisms, most markedly inflammation **[14]**.

Doxorubicin has been aligned with verbal memory problems in breast cancer patients **[22]**. In vitro studies established that neurons treated with doxorubicin revealed an indication of protein and lipid oxidation. Likewise, other studies revealed that doxorubicin allows a noteworthy level of generalized CNS oxidative stress that is verified by the elevated protein oxidation levels as well as lipid peroxidation in brain parenchyma **[56]**.

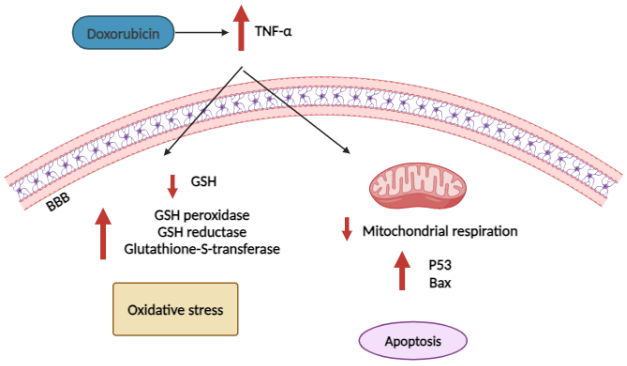

Fig. 3. A graphical illustration of the mechanistic pathways involved in Doxorubicin-Induced Chemobrain

Successive work verified that doxorubicin exhibits a secondary CNS toxic effect resulting from an upsurge in plasma TNF-α that passes across BBB and exerts a remarked oxidative stress accompanied by a drop in glutathione levels, with elevated glutathione peroxidase and reductase levels as well as elevated glutathione-S-transferase levels in the brain **[57]**. Further research illustrates that plasma doxorubicin-mediated TNF-α causes a remarked reduction in brain mitochondrial respiration that resulted from an upsurge in p53, Bax, and associated apoptosis **[58]**. All of these results recommend that TNF-α is a vital therapeutic aim in patients with chemo brain. **Fig. 3.**

1.3.5 Anti-Microtubule Agents: Paclitaxel Induced-Chemobrain

Paclitaxel is a taxane agent that binds microtubules, stabilizes microtubule dynamics, and captures the cell at the mitotic stage **[59]**. It is the drug of choice for widespread cancer types, including breast cancer, ovarian cancer **[60]**, and other solid cancers **[61, 62]**. However, it causes various adverse effects that are tubulin-independent, such as peripheral neuropathy **[63]**, arthralgia, ataxia, and myalgia, in addition to emotional distress, including depression, as well as limited mental quality of life **[64]**.

Studies have found that paclitaxel can enter the brain through the BBB, causing dose-dependent neurotoxicity and neuronal apoptosis **[65]**. The endoplasmic reticulum (ER) stress response, also known as the unfolded protein response, is considered a defense structure that deals with the accretion of unfolded proteins in the ER lumen. Gathering data proves the significance of ER stress and unfolded protein response in the pathophysiology of neurological disorders, such as cognitive impairment **[66]**. Tanimukai, and Kanayama **[67]** showed that paclitaxel-induced ER stress mediates neuronal apoptosis in SK-N-SH neuroblastoma cells by inducing C/EBP homologous protein and activating caspase 4. Chen, Chen, and Zhou **[68]** provide evidence that protein kinase C α (PKCα) was probably involved in the beginning of the chemobrain pathogenesis, that early paclitaxel exposure was shown to mediate calcium response and PKCα upregulation and was recognized to have a vital role in the chemobrain pathogenesis.

It was also demonstrated that the intervention of inositol trisphosphate receptor (InsP3R)-dependent calcium release in the early stages of chemobrain can aid in the prevention or the delay in disease progression. Indeed, Nguyen, Fischer, and Ehrlich **[69]** explained that paclitaxel binding to neuronal calcium sensor 1 (NCS1) improved NCS1 linking to the InsP3R leading to an elevation of calcium release from the ER into the cytoplasm. The upsurge in calcium levels, also, the upregulation of PKCα, results in PKC hyperactivity. PKCα, sequentially, phosphorylates myristoylated alanine-rich C-kinase substrate (MARCKS) into pMARCKS, resulting in actin instability. This instability later leads to loss of spines and dendrites, and later cognitive impairment.

It was also stated that alternations to synaptic structure and plasticity were directly linked to cognitive impairment that is characterized by broadening of the synaptic cleft, reduced length, and thickness of postsynaptic density, paclitaxel remarkedly lessened the dendrite spine density, and also, paclitaxel reduced BDNF expression in the hippocampal tissue significantly **[70]**.

Additionally, numerous studies have established that paclitaxel can induce apoptosis of hippocampal neurons, associated with the release of inflammatory mediators such as TNF-α and IL-1 β **[71] Fig. 4.**

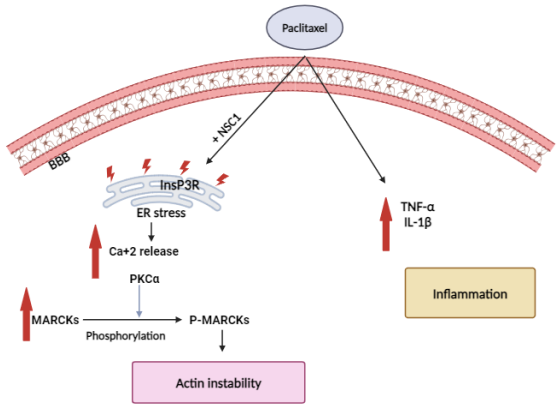

Fig. 4. A graphical illustration of the mechanistic pathways involved in Paclitaxel-Induced Chemobrain

1.4 Management of Chemobrain

1.4.1 Non-pharmacologic Interventions

Cancer-associated cognitive impairment can be controlled with various non-pharmacologic approaches that define brain changes **Fig. 5**.

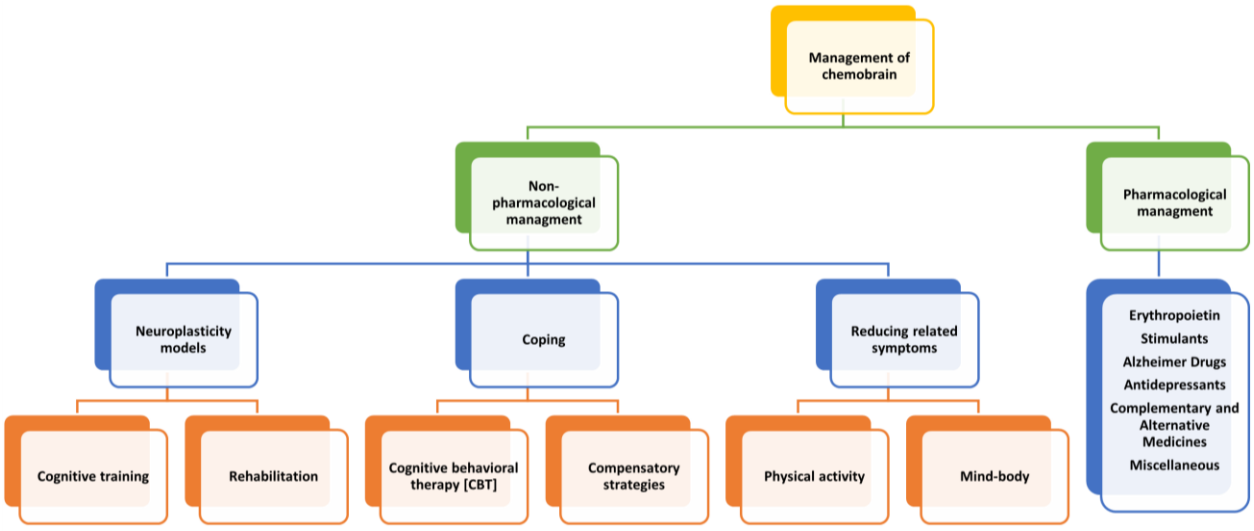

Fig. 5. A diagrammatic scheme for the pharmacological and non-pharmacological approaches for the management of chemobrain

1.4.1.1 Cognitive Training

Cognitive training also known as 'brain training' includes training specific facets of your memory and other thinking skills. This is regularly through an exercise or a game on a computer, also regular activities such as crosswords and Sudoku could count as cognitive training **[72]**. Cognitive training depends on exercises aiming at the causal neural pathways, such as speed of information processing or auditory consideration, to raise cognitive capacity via systematic exercise with gradually increasing difficulty stages. Previous studies revealed decreased cognitive symptoms in cancer survivors after cognitive training **[73]** At least, cognitive training can be brought to survivors in a convenient format and at a comparatively low cost to decrease cognitive symptoms **[74]**.

1.4.1.2 CBT and Compensatory Strategies

Cognitive behavioral therapy (CBT) is a psychotherapeutic tactic including short-range, goal-oriented problem-solving tactics to modify thinking patterns. Previous studies evaluated the effectiveness of CBT in women with breast cancer. Outcomes among all trials were vague, with a randomized clinical trial signifying an enhancement in cognitive symptoms compared to active controls **[75]**.

1.4.1.3 Cognitive Rehabilitation

Cognitive rehabilitation proposes to regain normal functioning via special skills training and meta-cognitive tactics in patients with cognitive deficits. Former trials stated cognitive rehabilitation usefulness in breast cancer survivors **[76]** and in adult cancer survivors of non-CNS tumors **[77]** All trials revealed enhanced cognitive symptoms, the same results were also found in control participants.

1.4.1.4 Mind-Body Interventions

Few studies have evaluated mind-body interventions effectiveness, such as mindfulness-based stress reduction (MBSR). Former studies examined MBSR in cancer survivors, but cancer-associated fatigue was an inclusion norm. It showed an enhancement in cognitive symptoms, but not neuropsychological performance **[78]**.

1.4.1.5 Physical Activity Interventions

A study in breast cancer survivors, that evaluated a 12-week program of goal setting, activity monitoring, and distant support, proved enhanced cognitive functions but not neuropsychological act. Despite many studies suggesting improved cognitive functioning and symptoms, examination in this field is insufficient; still, at least four randomized clinical trials (RCTs) are proceeding. Meanwhile, Yoga involvement showed positive impacts on cognitive symptoms **[79]**.

1.4.2 Pharmacologic Interventions

There is a lack of data on the usage of pharmacological agents in treating CICI. Some drugs have been examined but they were neither not effective nor have been examined in pilot studies only. **Fig. 5**.

1.4.2.1 Erythropoietin

Two trials investigated erythropoietin administration through adjunct chemotherapy in breast cancer survivors. One study showed an enhanced cognitive performance in the erythropoietin group at cycle four, but not at 6 months **[80]**. The second indicated no change in cognitive performance when measured 12 to 30 months later **[81]**.

1.4.2.2 Stimulants

1.4.2.3. Methylphenidate/Modafinil

Methylphenidate is frequently used in the treatment of attention-deficit/hyperactivity disorder. Two studies of methylphenidate presented no enhancement in CICI **[82]**. Both

were underpowered to reveal a variation, with one trial finished early because of malaccrual; furthermore, the cognitive evaluation used was not expected to figure out small variances. Further study of patients suffering from fatigue at least 2 months after completing chemotherapy, showed an enhancement in fatigue, but no cognitive function was shown **[83]**.

Modafinil is a CNS stimulant usually used in the treatment of narcolepsy. It was found to decrease severe fatigue in cancer patients **[84]**. A secondary analysis estimating cognitive performance in breast cancer survivors complaining of fatigue proposed some enhancement in speed and episodic memory on a computerized test in the modafinil group **[85]**. An additional trial of patients with progressive cancer showed some development in processing psychomotor speed and visual information 4.5 hours following modafinil related to placebo **[86]**.

1.4.2.4 Antidepressants

Most of the research on the usage of antidepressants to control chemobrain is presently in preclinical models. Yet, one clinical trial assessed paroxetine hydrochloride in breast cancer survivors, patients on paroxetine showed better enhancement in attention and memory signs related to placebo **[87]**. Yet, neuropsychological performance was not examined.

1.4.2.5 Complementary and Alternative Medicines

A trial of a standardized extract of the Chinese herb Ginkgo biloba comparing 10 weeks of Chinese herb Ginkgo biloba 60 mg twice daily vs placebo throughout adjunct chemotherapy in breast cancer patients **[88]**. Showed no enhancement in neuropsychological function or cognitive symptoms, yet the cognitive test used was a deprived assessment of performance.

Conclusion

This review aims to deliver an insight into the molecular mechanisms underlying CICI, and the possible neuroprotective agents that help alleviate this cognitive deficit. Various studies focused on the neurotoxicity resulting from several chemotherapeutic drugs including alkylating agents, microtubule inhibitors and antimetabolites, Neuroinflammation, oxidative stress, and apoptotic pathways, as well as brain structural alternations, are some of the possible pathways that underlie chemobrain. Additionally, a remarkable number of studies revealed various pharmacological and non-pharmacological approaches for the management of chemobrain that enhance anticancer treatment compliance by reducing chemotherapy secondary insults.

List of abbreviations

CICI, Chemotherapy-induced cognitive impairment; P38-MAPK, P38 mitogen-activated protein kinase; mtDNA, mitochondrial DNA; JNK, c-Jun NH2-terminal kinase pathway; ER, Endoplasmic reticulum; PKCα, Protein kinase C α.

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.

Funding Statement

The author(s) received no specific funding for this work.

Authors Contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Ebtehal El-Demerdash, Mennat-Allah M. Hassan, Tamer M. Abdelghany, Reem N. El-Naga, and Sara A. Wahdan. The first draft of the manuscript was written by Mennat-Allah M. Hassan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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