**ASTAXANTHIN'S ROLE IN MODULATING NEUROINFLAMMATION AND OXIDATIVE STRESS IN CHEMOBRAIN**

Abstract

Chemobrain, or chemotherapy-induced cognitive impairment (CICI), is a significant side effect affecting cancer survivors, characterized by neuroinflammation and oxidative stress. This review examines the potential role of astaxanthin, a potent antioxidant and anti-inflammatory carotenoid, in mitigating these key pathological features. A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Web of Science, focusing on studies that investigated the effects of astaxanthin on neuroinflammation, oxidative stress, and cognitive function in models relevant to chemobrain. Studies included both in vitro and in vivo models, as well as clinical trials where available. Preclinical studies demonstrate that astaxanthin can effectively reduce neuroinflammation by inhibiting the activation of microglia and astrocytes, and decreasing the production of pro-inflammatory cytokines. Furthermore, astaxanthin exhibits strong antioxidant properties, scavenging free radicals and boosting endogenous antioxidant defense mechanisms. These effects are reflected in improved cognitive performance in animal models of chemobrain exposed to chemotherapeutic agents. The potential mechanisms of action of astaxanthin in modulating neuroinflammation and oxidative stress are discussed, highlighting its ability to cross the blood-brain barrier and directly influence neuronal health. Astaxanthin shows promise as a potential therapeutic agent for alleviating chemobrain by targeting neuroinflammation and oxidative stress. Further research, particularly well-designed clinical trials, is warranted to validate these findings and determine the optimal dosage and administration strategies for astaxanthin in cancer survivors at risk of or suffering from CICI.

**Keywords:** Astaxanthin, Chemobrain, Neuroinflammation, Oxidative stress, Antioxidant.

1.0. INTRODUCTION

1.1 Background on Chemobrain:

Chemobrain, more formally and accurately termed chemotherapy-induced cognitive impairment (CICI), is a distressing and often debilitating side effect that affects a significant proportion of cancer survivors (Fleming et al., 2023; George et al., 2021). This complex condition is characterized by a cluster of cognitive deficits that emerge during or following chemotherapy treatment, negatively impacting fundamental mental functions (Di Iulio et al., 2019). These commonly include, but are not limited to, difficulties with memory (both short-term and long-term), impaired attention and focus, slowed processing speed, and compromised executive function, which encompasses planning, organization, and problem-solving abilities (Udi, 2025). The impact of chemobrain extends far beyond simple forgetfulness or occasional mental fogginess; it profoundly diminishes the overall quality of life for those affected. The cognitive impairments can significantly impair an individual's ability to perform effectively at work, maintain meaningful relationships with family and friends, and successfully engage in routine everyday activities like driving, managing finances, or even following conversations. The symptoms can be subtle or severe, persistent or fluctuating, making diagnosis and management challenging. Due to its prevalence, disruptive nature, and the long-term consequences it can have on cancer survivors, understanding and addressing chemobrain is a critical and growing focus in cancer survivorship research and clinical care (Greene, 2019). Current research efforts are directed at identifying the underlying biological mechanisms responsible for CICI, developing effective diagnostic tools to accurately assess the severity of cognitive impairment, and exploring a range of interventions, including pharmacological treatments, cognitive rehabilitation strategies, and lifestyle modifications, to mitigate its effects and improve the lives of cancer survivors. Ultimately, the goal is to minimize the impact of chemobrain and empower individuals to regain their cognitive function and lead fulfilling lives after cancer treatment.

1.2 Pathophysiology of Chemobrain

The emergence of Chemobrain is not a simple consequence, but rather a complex interplay of factors stemming from the neurotoxic effects of chemotherapy agents. These agents, designed to target rapidly dividing cancer cells, can unfortunately cross the blood-brain barrier and directly damage sensitive neural cells. This initial assault triggers a cascade of downstream events that ultimately manifest as cognitive dysfunction. Several key mechanisms have been implicated in the pathophysiology of chemobrain, each contributing to the overall picture of neuronal damage and cognitive decline. One prominent factor is **oxidative stress**. Chemotherapy can disrupt the delicate balance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) – highly reactive molecules that can damage cellular components – and the body's inherent antioxidant defenses. This imbalance leads to an overabundance of ROS and RNS, causing significant cellular damage to neurons and supporting glial cells (Dias-Carvalho et al., 2022; Rao et al., 2022). **Neuroinflammation** also plays a significant and detrimental role. Chemotherapy acts as an inflammatory trigger, activating microglia and astrocytes, the brain's resident immune cells (Gupta et al., 2022). While these cells are normally responsible for protecting the brain, their activation in response to chemotherapy leads to the release of pro-inflammatory cytokines. These cytokines, while intended to fight off perceived threats, further exacerbate neuronal dysfunction by disrupting normal signaling pathways and contributing to neuronal death (Rummel et al., 2021). Beyond oxidative stress and neuroinflammation, **mitochondrial dysfunction** is another critical contributing factor. Mitochondria, the powerhouses of cells, are particularly vulnerable to the effects of chemotherapy. Damage to these organelles impairs their ability to produce energy efficiently, leading to neuronal energy deficits and further increasing susceptibility to damage. **Excitotoxicity**, a process where excessive stimulation by excitatory neurotransmitters like glutamate leads to neuronal injury and death, is also implicated. This overstimulation overwhelms the neurons' ability to regulate calcium influx, leading to cellular damage (Udi et al., 2025; Oyovwi et al., 2024; Picca et al., 2020).

Studies have also revealed that Chemotherapy can disrupt **neurogenesis**, the formation of new neurons in specific brain regions, and **synaptic plasticity**, the brain's ability to reorganize itself by forming new neural connections. These disruptions impair the brain's capacity to repair damage and adapt to changes, further compounding the cognitive deficits. These interconnected and overlapping mechanisms, working in concert, ultimately contribute to the impairment of crucial cognitive functions observed in cancer survivors experiencing chemobrain. These impairments can manifest as difficulties with **memory** (encoding, storing, and retrieving information), **attention** (focusing and maintaining concentration), and **executive function** (planning, problem-solving, and decision-making). The impact of chemobrain on a survivor's quality of life can be significant, affecting their ability to work, maintain relationships, and participate fully in daily activities (Udi, 2025; Semendric et al., 2023; Sekeres et al., 2021) Understanding these complex mechanisms is crucial for developing effective strategies to prevent and treat chemobrain and improve the long-term well-being of cancer survivors.

1.3 Introduction to Astaxanthin:

Astaxanthin, a naturally occurring carotenoid pigment, is instantly recognizable by its vibrant red hue and celebrated for its impressive array of health-promoting properties (Shaaban et al., 2024). This powerful compound is primarily synthesized by microalgae species like *Haematococcus pluvialis*, forming the bedrock of the food chain for numerous marine organisms. When crustaceans such as shrimp, lobster, and salmon consume these astaxanthin-rich algae, they, in turn, accumulate the pigment, contributing to their characteristic reddish-pink coloration. Salmon, in particular, rely on astaxanthin for muscle function and endurance during their arduous upstream spawning migrations. On a chemical level, astaxanthin possesses a unique molecular structure featuring hydroxyl and ketone groups on each ionone ring, a configuration that grants it truly remarkable characteristics. Foremost among these is its exceptional antioxidant activity. Studies have repeatedly demonstrated that astaxanthin significantly surpasses the antioxidant capabilities of other well-known compounds like vitamin E, beta-carotene, and even lutein. This heightened antioxidant capacity allows astaxanthin to effectively neutralize free radicals and protect cells from oxidative stress, a key factor in aging and numerous chronic diseases (Sivadurga et al., 2025; Adamantidi et al., 2025; Zia-Ul-Haq, 2021) . Furthermore, astaxanthin exhibits a unique advantage over some other antioxidant compounds: it possesses the ability to cross the blood-brain barrier. This crucial feature opens up possibilities for direct neuroprotective effects, suggesting potential benefits for cognitive function, memory, and overall brain health. Research exploring astaxanthin's impact on neurodegenerative diseases like Alzheimer's and Parkinson's is ongoing and promising (Mohd Shafie et al., 2025).

The diverse range of potential health benefits stemming from astaxanthin's powerful antioxidant and anti-inflammatory effects has been well-documented in numerous studies. These benefits encompass a broad spectrum, including (Alugoju et al., 2023; Aneesh et al., 2022):

* Cardiovascular Health: Astaxanthin may contribute to improved blood lipid profiles, reduced oxidative stress within the cardiovascular system, and enhanced blood flow, potentially lowering the risk of heart disease.
* Eye Function: Its antioxidant properties offer protection against age-related macular degeneration (AMD) and cataracts by combating oxidative damage to the retina and lens.
* Athletic Performance: By reducing muscle damage and inflammation after exercise, astaxanthin can contribute to improved endurance, reduced recovery time, and enhanced overall athletic performance.
* Skin Protection: Astaxanthin acts as an internal sunscreen, protecting the skin from the damaging effects of UV radiation, reducing wrinkles, and improving skin elasticity.
* Immune System Modulation: Some studies suggest that astaxanthin may help modulate the immune system, potentially enhancing its ability to fight off infections.

1.4 Rationale and Scope of the Review:

Chemobrain, a distressing and often long-lasting cognitive impairment affecting cancer survivors post-chemotherapy, presents a substantial and largely unaddressed challenge. Characterized by difficulties with memory, attention, executive function, and processing speed, chemobrain profoundly impacts quality of life and daily functioning. Existing interventions, including cognitive training and pharmacological approaches, offer only limited and often inconsistent relief, underscoring the critical and urgent need for effective and targeted therapeutic strategies to alleviate its debilitating effects. This review seeks to provide a comprehensive and critical evaluation of the existing scientific evidence supporting the potential of astaxanthin, a naturally occurring carotenoid with potent antioxidant and anti-inflammatory properties, as a therapeutic agent in combating chemobrain. Specifically, the study will delve into astaxanthin's potential role in mitigating neuroinflammation and oxidative stress, two pivotal and interconnected pathological mechanisms strongly implicated in the development and progression of chemobrain. By modulating these key pathways, astaxanthin may offer a novel approach to protecting the brain from chemotherapy-induced damage.

2.0. OXIDATIVE STRESS AND NEUROINFLAMMATION IN CHEMOBRAIN

2.1 Chemotherapy-Induced Oxidative Stress:

Chemotherapy, while targeting cancerous cells, can unfortunately trigger a cascade of events leading to oxidative stress within the brain. This occurs through various mechanisms, with many chemotherapy agents directly or indirectly inducing the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These highly reactive molecules can overwhelm the brain's antioxidant defense systems, leading to an imbalance and subsequent oxidative damage (Rummel et al., 2021). The impact of this oxidative stress is far-reaching, affecting various cellular components of the brain. Neurons, the fundamental units of the nervous system, are particularly vulnerable due to their high metabolic demands and limited regenerative capacity. Oxidative stress can impair neuronal function, leading to synaptic dysfunction and ultimately neuronal death. Glial cells, which support and protect neurons, are also susceptible. Oxidative damage to astrocytes and oligodendrocytes can disrupt their neuroprotective roles, further exacerbating neuronal vulnerability. Furthermore, the brain vasculature, essential for nutrient and oxygen delivery, can be compromised by oxidative stress, leading to impaired blood-brain barrier integrity and reduced cerebral blood flow (Eduviere et al., 2024; Kim et al., 2024; Chen et al., 2020; Abdullahi et al., 2018).

Preclinical and clinical studies provide mounting evidence for the role of oxidative stress in the development of "chemobrain," or chemotherapy-related cognitive impairment. These studies often reveal elevated levels of oxidative stress markers, such as lipid peroxidation products, protein carbonyls, and DNA oxidation products, in the brains of chemotherapy-treated subjects compared to controls. These elevated markers are often correlated with cognitive deficits, suggesting a direct link between chemotherapy-induced oxidative stress and the cognitive impairments associated with chemobrain. This growing body of evidence reinforces the importance of understanding and mitigating oxidative stress as a therapeutic target to protect the brain during chemotherapy (Kim et al., 2024; Chen et al., 2020).

2.2 Chemotherapy-Induced Neuroinflammation:

While chemotherapeutic agents are designed to target and eradicate rapidly dividing cancer cells, they unfortunately lack specificity and can also trigger a detrimental inflammatory response within the central nervous system (CNS). This response, driven by the systemic effects of chemotherapy, is characterized by the activation of microglia and astrocytes, the resident immune cells of the brain and spinal cord. Once activated, these glial cells undergo morphological changes and release a cascade of pro-inflammatory mediators, including cytokines such as TNF-α (Tumor Necrosis Factor-alpha), IL-1β (Interleukin-1 beta), and IL-6 (Interleukin-6), as well as various chemokines that further amplify the inflammatory milieu. This sustained and dysregulated neuroinflammation plays a crucial role in mediating neuronal damage, disrupting synaptic plasticity, and ultimately leading to the cognitive deficits associated with chemobrain. These deficits frequently impact critical cognitive domains, including memory (both working and long-term), attention, executive function (such as planning, decision-making, and cognitive flexibility), and processing speed, significantly impacting the quality of life for cancer survivors. Preclinical studies, often utilizing animal models exposed to chemotherapeutic agents, have consistently demonstrated elevated levels of neuroinflammatory markers in the brain. Furthermore, clinical studies involving cancer patients undergoing chemotherapy have also provided increasing evidence supporting the link between treatment and increased neuroinflammatory markers detectable in cerebrospinal fluid and through neuroimaging techniques (Anand et al., 2023; Behranvand et al., 2022; Brown et al., 2021). These findings further solidify the importance of understanding the specific mechanisms by which chemotherapy induces neuroinflammation and targeting this mechanism as a key therapeutic strategy to mitigate or prevent the onset and progression of chemobrain, ultimately improving the long-term well-being of individuals undergoing cancer treatment. Further research is needed to identify specific chemotherapeutic agents that are particularly prone to inducing neuroinflammation, explore individual susceptibility factors, and develop targeted interventions to protect the brain during chemotherapy.

2.3 Interplay between Oxidative Stress and Neuroinflammation:

**The interplay between oxidative stress and neuroinflammation is a complex, bidirectional relationship, where each process can trigger and amplify the other, creating a vicious cycle that contributes significantly to neurodegeneration (**Sălcudean et al., 2025; Liu et al., 2025)**. This reciprocal interaction is not merely a parallel occurrence but a deeply intertwined cascade of events, where the consequences of one directly exacerbate the other, ultimately accelerating neuronal damage and loss of function.** **Oxidative stress, characterized by an imbalance between the production of reactive oxygen and nitrogen species (ROS/RNS) and the antioxidant defense systems, can directly activate inflammatory pathways in the brain. This imbalance isn't just a static condition; it represents a dynamic shift where the cellular environment is overwhelmed by damaging free radicals. For example, ROS can damage cellular structures, including lipids, proteins, and DNA, releasing damage-associated molecular patterns (DAMPs) that act as alarm signals, activating microglia and astrocytes, the primary immune cells of the central nervous system. These DAMPs, such as fragmented DNA, heat shock proteins, and modified lipids, bind to pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) on glial cells, initiating an inflammatory response. These activated glial cells then release a cascade of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and chemokines (e.g., CCL2, CXCL10), recruiting more immune cells to the site of damage and sustaining neuroinflammation. This chronic inflammatory state further compromises neuronal health and function (**Mishra et al., 2024; Kaur et al., 2023)**.**

**Conversely, neuroinflammation itself fuels oxidative stress. Activated microglia and astrocytes, in their attempt to clear debris and combat perceived threats, generate a respiratory burst, a rapid release of ROS/RNS as part of their immune response. While this burst is initially intended to be protective, the excessive and prolonged production of ROS/RNS overwhelms the endogenous antioxidant systems. This further exacerbates oxidative damage to surrounding neurons and glial cells, promoting neuronal dysfunction, synaptic loss, and ultimately, cell death. Moreover, inflammatory mediators released during neuroinflammation can directly impair the function of mitochondria, the primary energy-producing organelles in cells, leading to increased ROS production from this source as well.** **Redox signaling pathways play a crucial role in mediating this intricate interaction. Key signaling molecules, such as NF-κB (nuclear factor kappa B) and Nrf2 (nuclear factor erythroid 2-related factor 2), are sensitive to changes in cellular redox state and act as critical sensors and transducers of oxidative and inflammatory signals. Oxidative stress can activate NF-κB, a master regulator of inflammation, by promoting its translocation to the nucleus, leading to the transcription and expression of a wide array of pro-inflammatory genes. This positive feedback loop further amplifies the inflammatory response. Conversely, Nrf2, a transcription factor that promotes the expression of antioxidant genes (e.g., superoxide dismutase, catalase, glutathione peroxidase), is often suppressed under inflammatory conditions, either through direct oxidation or via inflammatory cytokines that interfere with its activation or stability. This reduces the cell's ability to combat oxidative stress, leaving it more vulnerable to damage. Furthermore, inflammatory mediators can modulate the activity of enzymes involved in ROS production (e.g., NADPH oxidase) and scavenging (e.g., superoxide dismutase), further impacting the redox balance and tipping the scales towards oxidative stress (**Salvagno et al., 2024; Olufunmilayo et al., 2023; Nieves-Cordones et al., 2019)**.**

**Understanding these redox signaling pathways and the specific molecular mechanisms driving the interplay between oxidative stress and neuroinflammation is critical for developing targeted therapeutic strategies aimed at breaking the cycle of oxidative stress and neuroinflammation in neurodegenerative diseases. Potential therapeutic interventions could include: (1) antioxidant therapies to reduce ROS/RNS levels, (2) anti-inflammatory agents to dampen glial activation and cytokine production, (3) Nrf2 activators to boost antioxidant defenses, (4) inhibitors of NADPH oxidase to reduce ROS production from immune cells, and (5) strategies targeting specific inflammatory cytokines or signaling pathways. A multi-pronged approach that addresses both oxidative stress and neuroinflammation may be necessary to effectively slow or prevent the progression of neurodegenerative diseases.**

3.0. ASTAXANTHIN: ANTIOXIDANT AND ANTI-INFLAMMATORY MECHANISMS

3.1 Antioxidant Properties of Astaxanthin:

Astaxanthin has garnered significant attention in the realm of nutritional science for its remarkable antioxidant capabilities, particularly its role as a direct Reactive Oxygen Species (ROS) scavenger (Alugoju et al., 2023). ROS, including free radicals and peroxides, are unstable molecules that can damage cellular structures and contribute to aging and various diseases (Udi et al., 2025). Astaxanthin's distinctive molecular structure, featuring conjugated double bonds and hydroxyl groups, endows it with the ability to effectively neutralize a wide spectrum of free radicals, safeguarding cells from the detrimental effects of oxidative damage. This direct scavenging action is a key mechanism by which astaxanthin exerts its protective effects. However, astaxanthin's benefits extend beyond simple direct scavenging. It also profoundly enhances the body's inherent defense mechanisms by stimulating the activity of endogenous antioxidant enzymes. These enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), act as crucial components of the body's antioxidant network. SOD converts superoxide radicals into hydrogen peroxide, which is then broken down into water and oxygen by catalase. GPx, on the other hand, reduces hydrogen peroxide and lipid hydroperoxides using glutathione as a reducing agent. By boosting the activity of these critical enzymes, astaxanthin promotes a synergistic effect in eliminating ROS and maintaining a healthy cellular redox balance, preventing the accumulation of oxidative stress (Anthony and Onoriode, 2025; Alugoju et al., 2023; Davinelli et al., 2022).

Research comparing astaxanthin with other well-established antioxidants, such as vitamin E and vitamin C, consistently reveals its superior efficacy in neutralizing free radicals and mitigating lipid peroxidation, a process where free radicals damage cell membranes (Shanaida et al., 2025). These studies often demonstrate that astaxanthin possesses a significantly greater capacity to combat oxidative stress compared to these other antioxidants, suggesting its potential as a more potent and comprehensive approach to protecting against age-related diseases, inflammation, and other conditions linked to oxidative damage. Its dual action of direct ROS scavenging and enhancement of endogenous antioxidant enzymes positions astaxanthin as a particularly valuable nutrient for promoting overall health and well-being (Bakac et al., 2023; Sztretye et al., 2019)

3.2 Anti-inflammatory Properties of Astaxanthin:

Astaxanthin demonstrates potent anti-inflammatory capabilities by targeting multiple pathways involved in the inflammatory process. At the forefront, it actively reduces the synthesis and release of pro-inflammatory cytokines, specifically TNF-α (Tumor Necrosis Factor alpha), IL-1β (Interleukin-1 beta), and IL-6 (Interleukin-6). These cytokines are pivotal signaling molecules that amplify and perpetuate inflammation throughout the body. Beyond simply reducing cytokine production, astaxanthin also modulates critical inflammatory signaling pathways, including NF-κB (Nuclear Factor kappa B) and MAPK (Mitogen-Activated Protein Kinases). By interfering with these pathways, astaxanthin effectively dampens the cellular inflammatory response, preventing the cascade of events that lead to chronic inflammation and tissue damage (Kohandel et al., 2023; Li et al., 2019). Moreover, research indicates that astaxanthin plays a significant role in regulating the activation of microglia and astrocytes, which are key immune cells residing in the brain. These cells, when over-activated, can contribute to neuroinflammation, a factor implicated in various neurological disorders. By modulating the activity of microglia and astrocytes, astaxanthin suggests a promising avenue for managing neuroinflammation and potentially protecting against neurodegenerative diseases. The collective impact of astaxanthin's ability to suppress pro-inflammatory cytokine production, regulate inflammatory signaling pathways, and modulate neuroinflammation positions it as a compelling candidate for therapeutic intervention in a diverse range of inflammatory conditions, ranging from arthritis to cardiovascular disease and neurodegenerative disorders. Its multi-faceted mechanism of action offers a potentially safer and more comprehensive approach to managing inflammation compared to traditional anti-inflammatory drugs (Medoro et al., 2023; Zhou et al., 2021; Chang et al., 2020).

3.3 Blood-Brain Barrier Permeability and Brain Accumulation of Astaxanthin:

A key element of Astaxanthin efficacy lies in its ability to penetrate the blood-brain barrier (BBB), a highly selective and dynamic interface that meticulously regulates the passage of substances between the bloodstream and the brain's delicate microenvironment (Cunha et al., 2024). This barrier, composed of tightly joined endothelial cells, actively protects the brain from harmful toxins, pathogens, and large molecules while ensuring a stable environment for optimal neuronal function. The feasibility of astaxanthin's neuroprotective effects is thus intrinsically linked to its BBB permeability. Research indicates that astaxanthin can, in fact, traverse the BBB (Cunha et al., 2024). However, the degree to which it accumulates in the brain is not a simple one-to-one relationship with ingested dosage. The concentration of astaxanthin reaching brain tissue is modulated by several interwoven factors. These include the administered dose, the duration of supplementation, and the individual's physiological state, encompassing age, underlying health conditions, and the presence of any existing neurological disorders (Cunha et al., 2024). Furthermore, the formulation of astaxanthin itself – whether it's a pure form, an oil-based suspension, or part of a complex supplement – significantly affects its absorption, metabolism, and ultimately, its ability to cross the BBB (Jafari et al., 2021). Recognizing the limitations and complexities of BBB penetration, researchers are actively investigating strategies to optimize astaxanthin's brain delivery. A promising avenue involves encapsulating astaxanthin within nanoformulations, such as liposomes or nanoparticles. These nanocarriers offer several advantages, including improved stability, enhanced bioavailability, and the potential to target specific brain regions. By shielding astaxanthin from degradation and facilitating its transport across the BBB via specialized mechanisms like receptor-mediated endocytosis, nanoformulations hold the potential to significantly enhance its neuroprotective benefits (Cunha et al., 2024). Ultimately, maximizing astaxanthin's delivery to the brain could open new therapeutic avenues for preventing and treating age-related cognitive decline, neurodegenerative diseases, and other neurological disorders.

4.0. PRECLINICAL EVIDENCE: ASTAXANTHIN IN CHEMOBRAIN MODELS

4.1 In Vitro Studies:

In vitro studies investigating astaxanthin's neuroprotective effects against chemotherapy-induced neurotoxicity rely heavily on neuronal and glial cell cultures as simplified, yet informative, model systems. These cell cultures, mimicking the key cellular components of the central nervous system (CNS), are directly exposed to various chemotherapy agents known for their neurotoxic potential. This direct exposure allows for a focused and controlled analysis of the effects of these drugs and the potential protective role of astaxanthin. Specifically, researchers meticulously examine the influence of astaxanthin on a spectrum of markers indicating cellular stress and damage within these cultured cells. A central focus is the assessment of oxidative stress, a major contributor to chemotherapy-induced neurotoxicity (Abdelaziz et al., 2021). This involves quantifying levels of reactive oxygen species (ROS), highly reactive molecules that can damage cellular structures, and measuring the extent of lipid peroxidation, a process where lipids in cell membranes are damaged by ROS. Elevated levels of ROS and lipid peroxidation are considered hallmarks of oxidative damage and are strongly linked to neuronal injury, dysfunction, and ultimately, neurodegeneration (Teleanu et al., 2022). Beyond oxidative stress, the research extends to investigating astaxanthin's impact on inflammatory pathways within the neuronal environment. This involves carefully evaluating the modulation of inflammatory mediators, such as cytokines like interleukins (e.g., IL-1β, IL-6) and Tumor Necrosis Factor-alpha (TNF-α). By analyzing changes in the levels of these inflammatory signals, researchers aim to understand astaxanthin's potential anti-inflammatory properties and its ability to reduce the amplified inflammatory response commonly triggered by chemotherapy. This is crucial because chronic inflammation contributes significantly to neuronal damage and accelerates the neurodegenerative process (Olufunmilayo et al., 2023; Grimmig et al., 2017).

A critical component of these in vitro studies is the evaluation of neuronal survival rates and the quantification of astaxanthin's protective effects against apoptosis, or programmed cell death, a major mechanism of neuronal loss in chemotherapy-induced neurotoxicity. By assessing changes in apoptotic markers like caspase activation, DNA fragmentation, and alterations in the expression of pro- and anti-apoptotic proteins, and by measuring cellular viability through various methods like MTT assays or trypan blue exclusion, researchers can gain valuable insights into the specific mechanisms by which astaxanthin may mitigate chemotherapy-induced neurodegeneration and promote neuronal resilience. This detailed investigation often involves probing astaxanthin's influence on fundamental cellular processes, including mitochondrial function (assessing mitochondrial membrane potential and ATP production), DNA integrity (examining DNA damage and repair mechanisms), and the activation or suppression of key signaling pathways involved in cell survival (e.g., PI3K/Akt) and death (e.g., MAPK). By understanding these molecular mechanisms, researchers can gain a more complete picture of how astaxanthin exerts its neuroprotective effects. Ultimately, the findings derived from these carefully controlled in vitro investigations provide a crucial foundation for subsequent in vivo studies, typically involving animal models of chemotherapy-induced neurotoxicity. The in vitro results help to refine hypotheses, identify promising targets for intervention, and justify further investigation in more complex biological systems. The cumulative knowledge gained from both in vitro and in vivo studies is essential for the development of potential therapeutic strategies aimed at preventing or treating chemotherapy-induced neurotoxicity, ultimately improving the quality of life for cancer patients undergoing chemotherapy treatment. These strategies could involve developing astaxanthin-based supplements or incorporating astaxanthin as a component of novel therapeutic interventions specifically designed to protect the nervous system during chemotherapy (Salah et al., 2025; Rao et al., 2022).

4.2 In Vivo Studies (Animal Models of Chemobrain):

**In vivo research, leveraging the strengths of animal models—especially rats and mice—has been indispensable in preclinical investigations seeking to understand and potentially mitigate chemobrain, also formally recognized as chemotherapy-induced cognitive impairment (CICI).** These animal studies provide a controlled environment to examine the complex interactions of chemotherapy drugs and potential therapeutic interventions. **A fundamental step in these investigations involves inducing chemobrain in the animal models through exposure to commonly employed chemotherapy agents known to elicit cognitive dysfunction. Cisplatin, methotrexate, and 5-fluorouracil are frequently used for this purpose, as their neurotoxic effects are well-documented and reliably produce cognitive deficits analogous to those observed in human cancer patients undergoing chemotherapy (**El-Agamy et al., 2018)**.** This controlled induction allows researchers to establish a baseline of impaired cognitive function against which the effects of astaxanthin can be measured. **Following the chemobrain induction phase, astaxanthin, a potent antioxidant carotenoid, is administered to the animal models across a carefully selected range of dosages. This is done to determine the optimal therapeutic window for its protective effects. Moreover, various delivery methods, such as oral gavage (direct administration into the stomach) or intraperitoneal injection (injection into the abdominal cavity), are employed to explore the influence of different administration routes on astaxanthin bioavailability and efficacy.** This systematic approach enables a thorough assessment of astaxanthin's potential to counteract chemobrain (Abdelaziz et al., 2021). **The impact of astaxanthin on cognitive function is then rigorously evaluated using a comprehensive battery of behavioral tests designed to probe different aspects of learning and memory.** Spatial learning and memory, crucial for navigation and orientation, are frequently assessed using the Morris water maze, a classic test requiring animals to learn and remember the location of a hidden platform in a pool of water. Recognition memory, the ability to identify previously encountered stimuli, is often assessed using novel object recognition tasks, where animals are presented with familiar and novel objects, and their exploratory behavior is observed. These behavioral tests provide quantifiable measures of cognitive performance, allowing researchers to determine whether astaxanthin treatment improves or restores cognitive function in the chemobrain models. **To gain a deeper understanding of the biological mechanisms underlying astaxanthin's observed effects on cognitive function, researchers often quantify oxidative stress markers in brain tissue. Oxidative stress, an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, is implicated in the pathogenesis of chemobrain. Malondialdehyde (MDA) levels, a marker of lipid peroxidation (a process where free radicals damage cell membranes), and glutathione (GSH) levels, a key antioxidant in the brain, are commonly measured. These markers provide crucial insights into the extent of oxidative damage and the antioxidant capacity within the brain tissue following chemotherapy and astaxanthin treatment.** Changes in these markers can suggest whether astaxanthin exerts its protective effects by reducing oxidative stress (Ji et al., 2017).

**Furthermore, neuroinflammatory markers are also closely monitored, as inflammation in the brain is another key contributing factor to chemobrain.** This involves measuring the levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which are involved in the inflammatory response. The degree of microglia activation, the brain's resident immune cells, is also assessed, as activated microglia can release inflammatory mediators that contribute to neuronal damage. By quantifying these neuroinflammatory markers, researchers can determine whether astaxanthin helps to reduce inflammation in the brain, providing another potential mechanism for its protective effects (Bahbah et al., 2021). **Finally, comprehensive histopathological analysis is conducted on brain tissue samples to meticulously examine any structural alterations or damage at the cellular level. This involves microscopic examination of brain sections to assess neuronal integrity, including cell morphology and viability. Synaptic density, the number of synapses (connections between neurons), is also evaluated, as synaptic loss is a hallmark of cognitive impairment. Researchers also look for the presence of any pathological hallmarks associated with chemobrain, such as abnormal protein aggregates or signs of neurodegeneration.** This cellular-level analysis provides valuable information about the extent of brain damage caused by chemotherapy and whether astaxanthin administration can mitigate this damage (Qin et al., 2021).

**By integrating these diverse measures—behavioral performance, oxidative stress markers, neuroinflammatory markers, and histopathological analysis—researchers aim to gain a comprehensive and multi-faceted understanding of astaxanthin's impact on chemobrain, from its effects on cognitive function to the underlying molecular and cellular mechanisms. This holistic approach allows for a more complete picture of astaxanthin's therapeutic potential and informs future translational studies aimed at developing effective interventions for chemotherapy-induced cognitive impairment in human cancer patients.**

4.3 Key Findings and Limitations of Preclinical Studies:

Preclinical research provides a compelling foundation for exploring astaxanthin's potential to alleviate chemobrain, largely due to its demonstrated neuroprotective and anti-inflammatory effects. Studies consistently reveal that astaxanthin can combat the key hallmarks of chemobrain in animal models. Specifically, administration of astaxanthin has been shown to mitigate oxidative stress, a major contributor to neuronal dysfunction, and reduce direct neuronal damage. The anti-inflammatory properties of astaxanthin also appear to play a crucial role, as it effectively dampens inflammation in the brain, a process strongly linked to cognitive deficits following chemotherapy. These beneficial effects translate into observable improvements in cognitive function. Animal models treated with astaxanthin after exposure to chemotherapy agents frequently exhibit enhanced performance in cognitive assessments, including tasks that assess memory retention, spatial learning, and overall cognitive processing speed (Raghu et al., 2021; El-Agamy et al., 2018). This suggests that astaxanthin may directly protect and support neural circuits essential for cognitive function during and after chemotherapy exposure. However, it's vital to approach these promising preclinical results with a degree of caution. The inherent limitations of animal models must be carefully considered before extrapolating findings to human patients. Significant differences exist between the brains of different species, affecting drug metabolism, neurological pathways, and overall response to chemotherapy. These disparities make direct translation of dosages and effects challenging. Moreover, the experimental designs often utilized in preclinical studies, such as the administration of high doses of chemotherapy over a condensed timeframe, may not accurately mimic the chronic, evolving nature of chemobrain experienced by cancer patients in clinical settings. Real-world scenarios are far more complex than controlled laboratory environments. The influence of co-morbidities, such as pre-existing cognitive decline, depression, or cardiovascular disease, as well as lifestyle factors, including chronic stress, poor diet, and inadequate sleep, can significantly impact the severity and trajectory of chemotherapy-induced cognitive impairment (Fleming et al., 2023). These factors are difficult to replicate comprehensively in controlled animal studies. Consequently, while preclinical data offers valuable insights and justifies further research, definitive conclusions regarding the efficacy of astaxanthin in treating chemobrain in humans must await the results of well-designed, rigorously controlled clinical trials that account for the complexities of the human condition. These clinical trials must carefully consider appropriate dosage, patient selection, and relevant outcome measures to accurately assess the true potential of astaxanthin in mitigating chemobrain.

5.0. CLINICAL EVIDENCE: ASTAXANTHIN IN CHEMOBRAIN

5.1 Review of Clinical Trials and Observational Studies:

A thorough review of the existing scientific literature highlights a critical void in our understanding of astaxanthin's potential benefits for cognitive health in cancer patients undergoing chemotherapy. Despite astaxanthin's well-established antioxidant and anti-inflammatory capabilities, which hold promise for counteracting chemotherapy-induced cognitive impairment (often referred to as "chemobrain"), there is a stark absence of clinical trials and observational studies specifically designed to investigate this link within this vulnerable population. Comprehensive searches conducted across major biomedical databases, including PubMed, the Cochrane Library, and others, reveal a landscape dominated by preclinical studies (primarily conducted in vitro or in animal models) or clinical trials focused on alternative health outcomes, such as cardiovascular health or age-related macular degeneration. This leaves a significant dearth of robust evidence directly addressing the impact of astaxanthin supplementation on cognitive function in patients actively receiving chemotherapy (Safahi & Lotfabadi, 2024; Cunha et al., 2024).

The scarcity of clinical data makes it exceedingly difficult to draw firm conclusions regarding astaxanthin's efficacy in mitigating chemobrain. Consequently, informed decisions regarding its use as a supportive therapy for cancer patients are hampered. Future research efforts must prioritize well-designed clinical trials to address this gap. A rigorous, randomized, placebo-controlled study design is essential. Such a trial should enroll a carefully selected cohort of cancer patients undergoing standard chemotherapy regimens known to frequently induce cognitive side effects. To ensure the validity and generalizability of the findings, key parameters must be standardized. This includes meticulous control over the specific chemotherapy protocol administered, a clearly defined and consistent astaxanthin dosage, and a precisely determined schedule for astaxanthin administration relative to the chemotherapy cycles (e.g., starting before, during, or after chemotherapy). Furthermore, comprehensive outcome measures are crucial for accurately assessing cognitive function. These should incorporate a battery of standardized neuropsychological tests that are specifically sensitive to the range of cognitive domains typically affected by chemotherapy, such as memory, attention, executive function, and processing speed. Critically, the study should also include patient-reported outcome measures, such as questionnaires or surveys that capture patients' subjective experiences of cognitive function and overall quality of life. These patient-reported outcomes provide valuable insights into the real-world impact of astaxanthin on the individual's perceived cognitive abilities and daily functioning. Addressing this significant research gap through well-designed and rigorously executed clinical trials would provide invaluable insights into the potential role of astaxanthin as a supportive therapy for cancer patients undergoing chemotherapy, ultimately contributing to improved cognitive health and overall well-being.

5.2 Safety and Tolerability of Astaxanthin:

**A substantial body of research, encompassing both preclinical studies and human clinical trials, has examined the safety and tolerability of astaxanthin across a diverse spectrum of dosages and treatment durations (**Mohd Shafie et al., 2025; Nishida et al., 2023; Donoso et al., 2021)**. In these studies, astaxanthin has been administered at various levels, ranging from relatively low daily doses to significantly higher amounts for extended periods. The consistent finding is that the vast majority of individuals tolerate astaxanthin well, with any reported side effects being typically mild, transient, and infrequent.** **The most commonly observed side effect, though not experienced by everyone, is a slight reddening or orange tinge to the skin. This is a direct consequence of astaxanthin's pigment properties, similar to how consuming large quantities of carrots can cause a temporary change in skin tone. In rarer instances, some individuals have reported minor gastrointestinal disturbances, which may include mild stomach upset, changes in bowel movement frequency or consistency, or a feeling of bloating. These gastrointestinal effects are usually self-limiting and resolve without intervention.**

**Regarding potential drug interactions, the existing literature provides limited robust evidence of significant or clinically relevant interactions between astaxanthin and commonly prescribed medications (**Alugoju et al., 2023)**. However, due to astaxanthin's antioxidant and anti-inflammatory properties, and its potential influence on lipid metabolism and immune function, caution is warranted when it is taken concurrently with certain classes of drugs (**Kohandel et al., 2022)**. This includes medications that affect lipid metabolism (e.g., statins), anticoagulants or antiplatelet drugs that influence blood clotting (e.g., warfarin, aspirin), and immunosuppressants or immunomodulatory agents that impact the immune system (e.g., corticosteroids). The theoretical risk is that astaxanthin's biological activities could have an additive or synergistic effect with these medications, potentially altering their efficacy or increasing the risk of side effects. For instance, the combination of astaxanthin and an anticoagulant could, in theory, further reduce blood clotting ability.** **Therefore, while astaxanthin appears to be generally safe, it is crucial for individuals, especially those taking prescription medications or with pre-existing medical conditions, to consult with a qualified healthcare professional before incorporating astaxanthin into their supplement regimen. Further research, including well-designed clinical trials specifically investigating potential drug interactions, is necessary to fully elucidate the interaction profile of astaxanthin and to provide more definitive guidance on its safe and effective usage, especially in vulnerable populations.**

6.0. FUTURE DIRECTIONS AND CONCLUSION

6.1 Future Research Directions:

Future research on astaxanthin's potential role in mitigating chemobrain necessitates a comprehensive and meticulously planned multi-faceted approach. At its core lie well-designed, rigorous, and adequately powered clinical trials. These trials are crucial to objectively evaluate astaxanthin's efficacy in alleviating the cognitive impairments associated with chemotherapy, moving beyond preclinical findings and anecdotal evidence. Crucially, these trials should incorporate robust methodologies, including randomization, blinding, and appropriate control groups, to minimize bias and ensure the reliability of the results. Within these clinical trials, specific attention should be given to determining the optimal dosage of astaxanthin. This involves a thorough dose-response assessment to identify the amount needed to achieve therapeutic benefits without inducing adverse effects. Similarly, the formulation of astaxanthin (e.g., standard capsules, liposomes, nano-formulations) needs careful consideration, as different delivery systems can significantly impact bioavailability and ultimately, efficacy. The treatment duration, or length of time patients receive astaxanthin, is another vital parameter that requires optimization to maximize therapeutic effects while ensuring patient safety and adherence. Furthermore, exploring combination therapies presents a promising avenue for enhanced outcomes in chemobrain. Investigating the synergistic potential of astaxanthin when combined with existing or novel neuroprotective agents, such as other antioxidants, anti-inflammatory compounds, or cognitive enhancers, could lead to more potent and effective treatments. These combination therapies should be rationally designed based on a strong understanding of the underlying mechanisms of action and potential drug interactions. A fundamental aspect of future research involves a deeper, more granular understanding of the mechanisms by which astaxanthin exerts its neuroprotective effects. This requires elucidating its intricate roles in mitigating oxidative stress, reducing neuroinflammation, promoting neurotrophic support (e.g., increasing Brain-Derived Neurotrophic Factor (BDNF) levels), and potentially influencing neurogenesis. Studies should investigate astaxanthin's impact on specific molecular pathways and cellular processes involved in chemobrain pathology. Finally, the integration of advanced neuroimaging techniques is essential for gaining comprehensive insights into the effects of astaxanthin on brain structure, function, and connectivity in chemobrain patients. Techniques like MRI, fMRI, DTI, MRS, and PET scans can provide valuable information about changes in brain volume, white matter integrity, and functional activity during cognitive tasks, neurochemical profiles, and glucose metabolism. These neuroimaging findings, in conjunction with cognitive assessments, can provide a more complete picture of astaxanthin's impact on the brain and allow for the identification of biomarkers predictive of treatment response. This comprehensive approach will ultimately pave the way for personalized and targeted interventions tailored to the specific needs of individual chemobrain patients, maximizing the potential benefits of astaxanthin and improving their quality of life.

6.2 Conclusion:

In conclusion, the existing body of scientific literature strongly suggests that further exploration of astaxanthin as a therapeutic agent for chemobrain, or chemotherapy-induced cognitive impairment, is warranted. The compelling evidence lies in astaxanthin's potent antioxidant and anti-inflammatory properties, characteristics that make it a particularly attractive candidate for precisely targeting the neuroinflammation and oxidative stress now understood to be pivotal factors in the development and progression of chemobrain. By directly modulating these fundamental pathological mechanisms, astaxanthin holds the potential to translate into concrete improvements for cancer survivors struggling with cognitive challenges. This could manifest as enhanced cognitive function across a range of domains, including memory consolidation and recall, sustained attention and concentration, and efficient executive functions such as planning, problem-solving, and cognitive flexibility. These improvements, in turn, could significantly enhance their overall quality of life, restoring independence and facilitating a return to normalcy. However, while preclinical investigations and initial data offer considerable encouragement, definitive conclusions regarding astaxanthin's efficacy in managing chemobrain require rigorously designed and adequately powered clinical trials. These trials should meticulously investigate optimal dosages of astaxanthin, determine the most effective treatment durations, and identify specific patient populations most likely to experience significant benefit from astaxanthin supplementation. Moreover, future research endeavors should delve into the long-term effects of astaxanthin on cognitive health, including its potential for preventative use, and explore potential synergistic benefits when combined with other therapeutic interventions, such as cognitive rehabilitation programs or other neuroprotective agents. Understanding the interplay between astaxanthin and other therapies will be crucial in developing comprehensive, multi-faceted strategies aimed at effectively mitigating chemobrain and comprehensively supporting the cognitive well-being of cancer survivors, ultimately empowering them to thrive in their post-treatment lives.

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