

ASTAXANTHIN AS A NEUROPROTECTIVE AGENT AGAINST ACUTE STRESS-
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ABSTRACT

The sympathetic-adrenomedullary system and the hypothalamic-pituitary-adrenal (HPA) axis are both activated by acute stress. Although adaptive initially, excessive acute stress causes glucocorticoid overload, oxidative stress, mitochondrial dysfunction, and neuroinflammation. These changes particularly affect the hippocampus and prefrontal cortex, impairing synaptic plasticity, neurogenesis, and cognition, including working memory, spatial learning, attention, and executive function. Oxidative stress and inflammation are now recognised as key mediators linking HPA-axis hyperactivation to cognitive decline. Astaxanthin, a xanthophyll carotenoid derived from microalgae such as *Haematococcus pluvialis*, yeast, and marine organisms, has drawn attention for its anti-inflammatory, anti-apoptotic, and antioxidant qualities. It is a prospective neuroprotective drug because of its lipophilic nature and capacity to pass the blood–brain barrier. According to preclinical research, astaxanthin improves learning and memory in stress and neurodegenerative models, lowers lipid peroxidation, increases endogenous antioxidants, inhibits inflammatory mediators, and stimulates the Nrf2/HO-1 pathway. **Methods:** Relevant experimental, preclinical, and clinical studies were identified through systematic searches of major scientific databases focusing on acute stress, cognitive dysfunction, oxidative stress, and astaxanthin-mediated neuroprotection. **Results:** All of these results point to astaxanthin as a viable multi-target treatment option, but more carefully planned human trials are needed to determine its effectiveness, dosage recommendations, and long-term safety in stress-related cognitive impairment.

KEYWORDS: Acute stress; Cognitive impairment; Astaxanthin; Oxidative stress; Neuroinflammation; HPA axis; Hippocampus; Neuroprotection; Mitochondrial dysfunction; Memory deficit.**1. INTRODUCTION**

An adaptive response that has persisted through evolution, stress helps creatures keep their internal environments stable. In its acute and moderate forms, stress enhances survival by increasing arousal, sharpening attention, mobilising metabolic resources, and facilitating rapid decision-making. These beneficial effects are mediated by tightly regulated neuroendocrine and autonomic systems that transiently optimise cognitive and behavioural performance.^[1,2]

However, when stress is severe, unpredictable, or recurrent—even over short durations—the same adaptive mechanisms may become maladaptive. Acute severe stress can rapidly alter synaptic function, neuronal

excitability, and large-scale brain network connectivity. Cognitive domains particularly vulnerable to stress include working memory, episodic memory, spatial learning, attentional control, and executive function.^[3,4]

The amygdala, hippocampus, and prefrontal cortex (PFC) are brain areas that are very sensitive to stress, and they are essential for these higher-order activities. Particularly vulnerable to neurochemical and anatomical changes brought on by stress are the prefrontal cortex (PFC) and the hippocampus, which both have an abundance of glucocorticoid receptors.^[5] A central mechanism underlying stress-induced cognitive impairment is activation of the hypothalamic–pituitary–adrenal (HPA) axis. Upon stress perception, the

hypothalamus releases corticotropin-releasing hormone (CRH), stimulating adrenocorticotrophic hormone (ACTH) secretion from the pituitary gland, which in turn elevates circulating glucocorticoids (cortisol in humans, corticosterone in rodents). While moderate glucocorticoid signalling facilitates memory consolidation and adaptive learning, excessive or prolonged exposure disrupts synaptic plasticity. Specifically, it impairs long-term potentiation (LTP), enhances long-term depression (LTD), and induces dendritic retraction in hippocampal CA3 neurons and medial PFC pyramidal cells.^[6,7]

Beyond neuroendocrine activation, stress induces a pronounced redox imbalance in the brain. Elevated glucocorticoids increase mitochondrial metabolic demand, leading to enhanced production of reactive oxygen species (ROS). Areas of the brain that are susceptible to stress, including the amygdala, hippocampus, and prefrontal cortex (PFC), are crucial to these higher-order processes. Because of their high concentration of glucocorticoid receptors, the prefrontal cortex (PFC) and the hippocampus are particularly vulnerable to structural and neurochemical changes brought on by stress.^[5] Stress also robustly activates neuroinflammatory pathways. Microglial cells rapidly shift to a pro-inflammatory phenotype, releasing cytokines such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumour necrosis factor- α (TNF- α). Activation of transcription factors like nuclear factor kappa B (NF- κ B), along with signalling cascades such as mitogen-activated protein kinases (MAPKs), amplifies inflammatory responses.^[9] Importantly, oxidative stress and neuroinflammation are tightly interconnected, forming a self-perpetuating cycle that exacerbates synaptic dysfunction and accelerates cognitive decline.

Recognition of the central roles of oxidative stress and neuroinflammation in stress-induced neuronal damage has shifted therapeutic strategies toward antioxidant and anti-inflammatory interventions. Among emerging candidates, astaxanthin has gained considerable attention. Microalgae like *Haematococcus pluvialis* and other marine creatures naturally contain astaxanthin, a red carotenoid that belongs to the xanthophyll family. A conjugated polyene chain with hydroxyl and keto groups at the ends gives it a remarkable ability to scavenge free radicals.^[10] Unlike many conventional antioxidants, astaxanthin can integrate into lipid bilayers, enabling it to protect both cellular and mitochondrial membranes while neutralising ROS in both hydrophilic and lipophilic environments.

In addition to its antioxidant properties, astaxanthin affects other chemical pathways that contribute to neuronal damage caused by stress. The Nrf2/ARE pathway is activated, which improves the body's antioxidant defences while at the same time reduces inflammatory signalling mediated by NF- κ B.^[11]

Additionally, astaxanthin preserves mitochondrial membrane potential, improves ATP production, and inhibits apoptosis by regulating the Bcl-2/Bax ratio and caspase activity. It also upregulates brain-derived neurotrophic factor (BDNF), thereby supporting synaptic plasticity and cognitive resilience.^[12] Its high lipophilicity facilitates efficient penetration across the blood-brain barrier, making it particularly suitable for central nervous system applications.

Emerging preclinical and clinical evidence suggests that astaxanthin may mitigate stress-induced impairments in learning, memory, and executive function. As a multi-target neuroprotective agent, it acts on several interconnected pathological processes, including glucocorticoid dysregulation, oxidative stress, neuroinflammation, and mitochondrial dysfunction. These properties position astaxanthin as a promising therapeutic candidate for preventing or attenuating stress-related cognitive decline.

2. Neurobiology of Acute Stress

2.1 HPA Axis Activation

The main neuroendocrine mechanism that orchestrates the stress response is the activation of the hypothalamic-pituitary-adrenal (HPA) axis. The release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) is triggered when limbic regions, such as the amygdala, hippocampus, and prefrontal cortex, send signals to the paraventricular nucleus (PVN) of the hypothalamus in response to a.^[13,14] The release of glucocorticoids, such as cortisol in humans and corticosterone in rats, is initiated by these neuropeptides, which in turn activate the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH).^[15] The hippocampus and prefrontal cortex are highly expressed with mineralocorticoid and glucocorticoid receptors, which allow glucocorticoids to easily cross the blood-brain barrier and bind to these hormones.^[16]

Memory consolidation and adaptive learning are both aided by a short-lived spike in glucocorticoid levels.^[17] In contrast, synaptic plasticity is impaired by dysregulated or excessive glucocorticoid signalling in stress-sensitive neural circuits, which leads to dendritic retraction and suppresses long-term potentiation (LTP) while amplifying long-term depression (LTD).^[18] Neuroinflammatory signalling is intensified, mitochondrial dysfunction is worsened, and the endocrine stress response is linked to molecular pathways of neuronal damage by prolonged glucocorticoid exposure.^[19]

This regulatory control can be impaired by stress-induced hippocampal dysfunction, leading to persistent HPA axis hyperactivity and an increased susceptibility to cognitive deficits, even though glucocorticoids normally exert negative feedback inhibition at the level of the hypothalamus and pituitary.^[16,19]

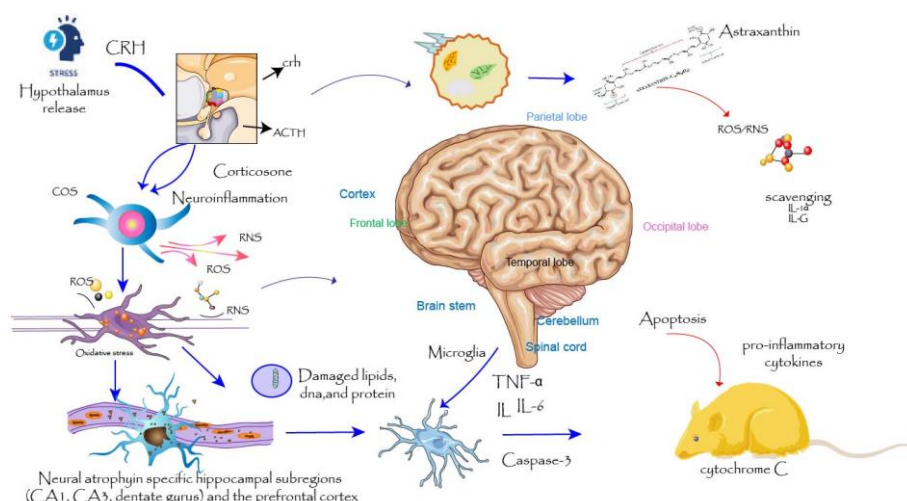


Fig1: Schematic representation of the stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis and its downstream neurobiological effects.

2.2 Oxidative Stress as a Downstream Consequence

One important side effect of long-term activation of the hypothalamic-pituitary-adrenal (HPA) axis and chronic excess of glucocorticoids is oxidative stress. When glucocorticoid levels are high, mitochondrial respiration and neuronal metabolic demand are both boosted, which in turn increases the formation of ROS. ROS include hydroxyl radicals, superoxide anions, and hydrogen peroxide.^[20,21] Endogenous antioxidant mechanisms like catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx), and the Nrf2-ARE pathway tightly regulate reactive oxygen species (ROS) under physiological settings. But this equilibrium is upset when humans experience acute or chronic stress, which increases ROS production while decreasing antioxidant defences.^[23]

Impairment of membrane integrity, enzymatic activity, and genomic stability are caused by the oxidative stress that results, which damages lipids, proteins, and nucleic acids. Because of their fat content and rapid oxygen demand, neurons are especially vulnerable.^[24] In addition, oxidative stress triggers apoptotic pathways, causes calcium dysregulation, mitochondrial malfunction, and reduced ATP generation.^[25]

2.3 Neuroinflammatory Signalling

Chronic glucocorticoid excess and sustained hypothalamic-pituitary-adrenal (HPA) axis activation lead to oxidative stress. Increased formation of reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide, and hydroxyl radicals, is a result of increased neuronal metabolic demand and mitochondrial respiration caused by elevated glucocorticoid levels.^[20,21] Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and the Nrf2-ARE pathway are some of the endogenous antioxidant systems that tighten control over ROS under normal settings. Acute or chronic stress, on the other hand, throws this equilibrium off by boosting ROS production and decreasing antioxidant defences at the same time.^[23]

Damage to lipids, proteins, and nucleic acids is caused by the oxidative stress that follows, which in turn impairs genomic stability, enzyme performance, and membrane integrity. The lipid rich makeup and high oxygen consumption of neurons make them especially.^[24] Further, mitochondrial failure, decreased ATP synthesis, calcium dysregulation, and apoptotic pathway activation are all caused by oxidative stress.^[25]

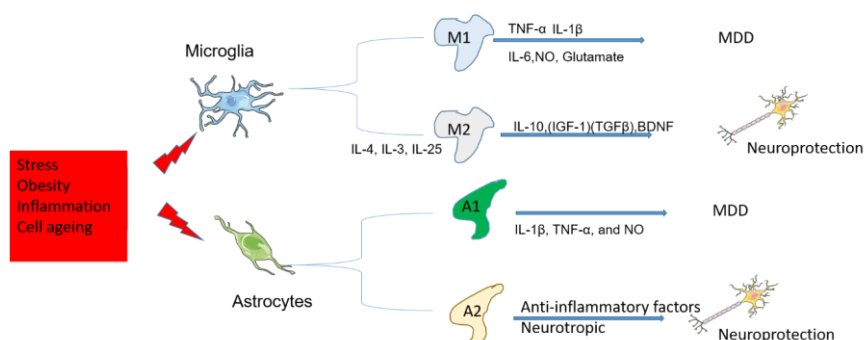


Fig 2: Stress, obesity, inflammation, and cellular ageing induce activation of microglia and astrocytes. Microglia polarize into pro-inflammatory M1 or neuroprotective M2 phenotypes, while astrocytes shift into neurotoxic A1 or reparative A2 states. The balance among these phenotypes regulates neuroinflammation, neuronal injury, and tissue repair.

2.4 Structural and Functional Brain Changes

The hippocampus, the prefrontal cortex (PFC), and the amygdala are three areas of the brain that are particularly vulnerable to the structural and functional changes brought on by chronic or acute stress. Network dysregulation, dendritic remodelling, and oxidative/inflammatory processes are all driven by elevated glucocorticoid levels.^[33] Memory problems with space and time are associated with stress-induced dendritic retraction in CA3 pyramidal neurons, decreased spine density, and a suppression of adult neurogenesis in the dentate gyrus in the hippocampus.^[34] Stress also impairs medial prefrontal cortex (MPFC) dendritic complexity and synaptic connection, which in turn leads to executive function, attention, and working memory problems.^[35]

The amygdala, on the other hand, may increase emotional reactivity and fear-related learning through dendritic hypertrophy and improved synaptic efficacy when stressed.^[36] Increased emotional response takes precedence over cognitive regulation as a result of this area-specific remodelling. By influencing glutamatergic and GABAergic transmission, reducing long-term depression (LTD), and decreasing long-term potentiation (LTP), stress functionally affects synaptic plasticity.^[37] These alterations worsen stress reactivity and cognitive dysfunction risk over time by reducing top-down regulatory control from the prefrontal cortex (PFC) and hippocampus (HPA) over the amygdala and HPA axis.^[38,39]

3. Cognitive Consequences of Acute Stress

Acute stress exerts rapid and context-dependent effects on cognition, which may be either adaptive or detrimental depending on its intensity and duration. Mild to moderate stress enhances alertness, attention, and memory consolidation through optimal glucocorticoid and catecholaminergic signalling, and can facilitate the encoding of emotionally salient memories via amygdala–hippocampal interactions.^[40,41] However, when stress becomes excessive or unpredictable, cognitive performance declines.

Higher-order cognitive functions, including working memory and executive control mediated by the prefrontal cortex (PFC), are particularly vulnerable. Elevated glucocorticoids and catecholamines disrupt PFC neuronal activity, impair synaptic plasticity, and reduce cognitive flexibility, thereby compromising decision-making and attentional regulation.^[42] Acute stress also impairs memory retrieval and spatial processing by disrupting hippocampal long-term potentiation (LTP) and altering excitatory–inhibitory balance.^[43] These neurobiological effects manifest behaviorally as reduced problem-solving ability, increased distractibility, and reliance on habitual responses.^[44,45]

4. Astaxanthin: Chemical and Pharmacological Characteristics

4.1 Chemical Structure and Sources

Astaxanthin is a naturally occurring red–orange keto-carotenoid belonging to the xanthophyll subclass. Structurally, it comprises a conjugated polyene chain with terminal β -ionone rings containing hydroxyl and keto groups, imparting both lipophilic and polar properties. This amphipathic nature enables its integration into phospholipid bilayers, stabilising cellular and mitochondrial membranes. Its extensive conjugation confers potent antioxidant activity, allowing efficient scavenging of reactive oxygen species (ROS) and quenching of singlet oxygen.^[46] Compared with non-oxygenated carotenoids such as β -carotene, astaxanthin exhibits enhanced antioxidant efficacy due to its oxygenated functional groups and favourable membrane orientation.^[47]

Astaxanthin exists in multiple stereoisomeric forms, with the 3S,3'S configuration predominating in natural sources. It is primarily derived from the microalga *Haematococcus pluvialis* and is also found in marine organisms such as shrimp, lobster, and salmon. Commercial production involves microalgal cultivation, chemical synthesis, or yeast fermentation using *Xanthophyllomyces dendrorhous*, with natural astaxanthin generally demonstrating superior bioactivity and safety.^[48]

A key attribute of astaxanthin is its ability to cross the blood–brain barrier (BBB), a selective interface regulating central nervous system homeostasis. Its lipophilic backbone facilitates passive diffusion across endothelial membranes, while polar functional groups enable interaction with membrane surfaces. Additionally, its association with circulating lipoproteins may enhance transport.^[49] Following systemic absorption, astaxanthin accumulates in neuronal and mitochondrial membranes, where it exerts antioxidant, anti-inflammatory, and membrane-stabilising effects. Its localisation in stress-sensitive regions such as the hippocampus and prefrontal cortex supports its potential as a neuroprotective agent in stress-induced cognitive dysfunction.^[50]

4.3 Mechanisms of Antioxidant Action

Astaxanthin exerts neuroprotective effects through multiple synergistic antioxidant mechanisms at both chemical and molecular levels. Its extended conjugated polyene chain enables efficient scavenging of reactive oxygen species (ROS), including superoxide, hydroxyl, and peroxy radicals. It demonstrates superior singlet oxygen–quenching capacity compared with many conventional antioxidants.^[51] By neutralising free radicals, astaxanthin inhibits lipid peroxidation and preserves the integrity of polyunsaturated fatty acid-rich neuronal membranes.^[52]

Its amphipathic structure facilitates integration into phospholipid bilayers, where polar groups align at the

membrane interface, and the hydrophobic chain embeds within the lipid core. This configuration allows astaxanthin to stabilise cellular and mitochondrial membranes, prevent membrane depolarisation, reduce mitochondrial ROS generation, and sustain ATP production.^[53]

In addition to direct antioxidant activity, astaxanthin enhances endogenous defence systems by activating the Nrf2/ARE signalling pathway, leading to upregulation of antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1).^[54] It also suppresses redox-sensitive inflammatory pathways, including NF- κ B, thereby limiting oxidative stress–inflammation crosstalk (52,55). Collectively, these actions position astaxanthin as a potent multi-target modulator of oxidative stress in stress-induced neuronal injury.^[54]

4.4 Anti-Inflammatory and Anti-Apoptotic Actions.

Astaxanthin exhibits potent anti-inflammatory and anti-apoptotic effects that complement its antioxidant activity and enhance neuroprotection. Under stress conditions, glucocorticoid dysregulation, oxidative imbalance, and excitotoxicity activate microglia and astrocytes, leading to increased production of pro-inflammatory cytokines, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6),

and tumour necrosis factor- α (TNF- α).^[55] Astaxanthin attenuates these responses primarily through inhibition of the nuclear factor kappa B (NF- κ B) pathway, thereby suppressing inflammatory gene transcription and cytokine release.^[56] Additionally, it modulates upstream signalling pathways such as mitogen-activated protein kinases (MAPKs), further reducing stress-induced inflammatory responses.^[57] Astaxanthin also inhibits activation of the NLRP3 inflammasome, a key regulator of IL-1 β and IL-18 maturation, through redox regulation and mitochondrial stabilisation, thereby limiting neuroinflammation (4).

Its anti-apoptotic effects are closely linked to mitochondrial protection. By preserving mitochondrial membrane potential, astaxanthin prevents cytochrome c release and modulates the balance between pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) proteins, ultimately inhibiting caspase-dependent apoptosis.^[58] Furthermore, astaxanthin activates the Nrf2/ARE signalling pathway, enhancing the expression of endogenous antioxidant enzymes and strengthening cellular defence mechanisms against oxidative stress.^[59] Through the coordinated regulation of oxidative stress, inflammation, and apoptosis, astaxanthin preserves neuronal integrity and function, particularly in stress-sensitive regions such as the hippocampus and prefrontal cortex.^[55]

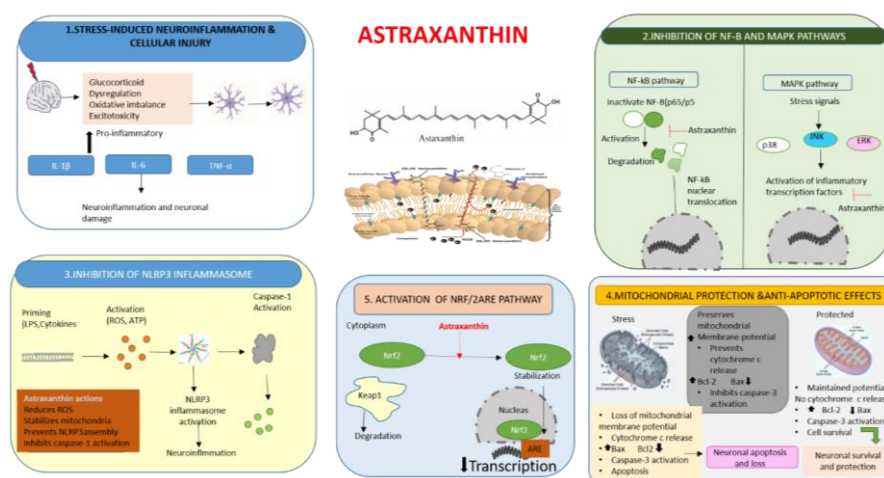


Fig 3: Proposed mechanisms of astaxanthin-mediated neuroprotection against stress-induced neuronal injury. Astaxanthin suppresses NF- κ B/MAPK signalling and NLRP3 inflammasome activation, enhances Nrf2/ARE antioxidant responses, preserves mitochondrial function, and inhibits apoptosis.

5. Preclinical Evidence of Neuroprotection

5.1 In Vitro Studies

In vitro studies provide critical mechanistic insights into the neuroprotective effects of astaxanthin under oxidative and inflammatory stress conditions. Experiments using neuronal cell lines (e.g., PC12, SH-SY5Y) and primary neurons demonstrate that astaxanthin significantly reduces reactive oxygen species (ROS) generation induced by hydrogen peroxide, glutamate excitotoxicity, or glucocorticoid exposure.^[60] It preserves membrane integrity and mitochondrial function by inhibiting lipid peroxidation and restoring

intracellular glutathione levels. Astaxanthin also stabilises mitochondrial membrane potential, reduces cytochrome c release, and suppresses caspase-3 activation through modulation of the Bax/Bcl-2 ratio, thereby preventing apoptosis.^[61]

Additionally, astaxanthin activates the Nrf2/ARE pathway, upregulating antioxidant enzymes such as superoxide dismutase (SOD), catalase, and heme oxygenase-1 (HO-1).^[58] In neuroinflammatory models, it suppresses lipopolysaccharide (LPS)-induced microglial activation and reduces pro-inflammatory cytokines (IL-

1 β , IL-6, TNF- α) by inhibiting NF- κ B nuclear translocation and MAPK signalling pathways (p38, JNK, ERK) (61). Furthermore, astaxanthin preserves synaptic proteins and neuronal morphology under stress conditions, highlighting its broader neuroprotective capacity.^[62]

Animal studies further substantiate these findings, demonstrating that astaxanthin improves cognitive function across various models, including acute restraint stress, chronic unpredictable stress, glucocorticoid exposure, and neurodegenerative conditions.^[63] Astaxanthin supplementation attenuates HPA axis hyperactivity, reduces corticosterone levels, and restores hippocampal synaptic plasticity. Behavioural assessments such as the Morris water maze, Y-maze, and novel object recognition consistently show improvements in spatial learning, working memory, and recognition memory. These cognitive benefits are associated with reduced oxidative stress markers (e.g., malondialdehyde) and enhanced antioxidant enzyme activity (SOD, catalase, GPx) in the hippocampus.^[64]

In glucocorticoid-induced models, astaxanthin mitigates dendritic atrophy in the hippocampus and prefrontal cortex, preserves long-term potentiation (LTP), and upregulates brain-derived neurotrophic factor (BDNF). In LPS-induced neuroinflammation, it reduces microglial activation and cytokine production, correlating with improved cognitive outcomes. Additionally, in neurodegenerative models such as amyloid- β toxicity and ageing, astaxanthin decreases amyloid accumulation, improves mitochondrial function, and preserves neuronal density and synaptic proteins.^[65]

5.3 Models of Diabetes and Traumatic Brain Injury

Astraxanthin has demonstrated neuroprotective efficacy in metabolic and injury-related models characterised by shared mechanisms of oxidative stress, inflammation, mitochondrial dysfunction, and cognitive decline, extending beyond traditional stress-based paradigms.^[66] In experimental diabetes models, such as streptozocin (STZ)-induced type-I diabetes and high-fat diet, or

models of type 2 diabetes-chronic hyperglycemia, promote elevated reactive oxygen species(ROS) generation, accumulation of advanced glycation end products(AGEs), impairments of insulin signalling, and neuroinflammation. These pathophysiological changes result in hippocampal dysfunction and deficits in spatial learning and memory. Astraxanthin supplementation in diabetic mice has been shown to improve cognitive performance in behavioural assays, including the Morris water maze and Y maze. Mechanistically, astraxanthin reduces lipid peroxidation, restores antioxidant enzyme activation (SOD, catalase, glutathione), enhances insulin signalling through PI3K/Akt pathway activation, and suppresses pro-inflammatory cytokine expression. Additionally, astraxanthin preserves mitochondrial membrane potential and prevents neuronal loss in hippocampal regions vulnerable to metabolic stress.^[67]

In models of traumatic brain injury (TBI), where mechanical injury induces excitotoxicity, oxidative surges, blood-brain barrier disruption, and subsequent neuroinflammatory response, astraxanthin has exhibited protective effects against both acute and chronic neuronal injury. Preclinical TBI studies reveal that astraxanthin reduces cerebral oedema, limits lipid peroxidation, suppresses microglial activation, and attenuates the activation of NF- κ B and MAPK signalling cascades. Furthermore, astraxanthin modulates apoptotic pathways by reducing Bax expression, increasing Bcl-2 levels, and lowering caspase-3 activation. Behavioural assessments in TBI models consistently demonstrate improvements in motor coordination and cognitive performance following astraxanthin treatment.^[68]

Collectively, findings for diabetes and TBI models support the concept that astraxanthin confers multi-target neuroprotection across diverse clinical contexts characterised by oxidative and inflammatory stress. These preclinical data further validate the therapeutic potential of astraxanthin in conditions where metabolic derangement or acute brain injury precipitates cognitive impairment.^[69,72]

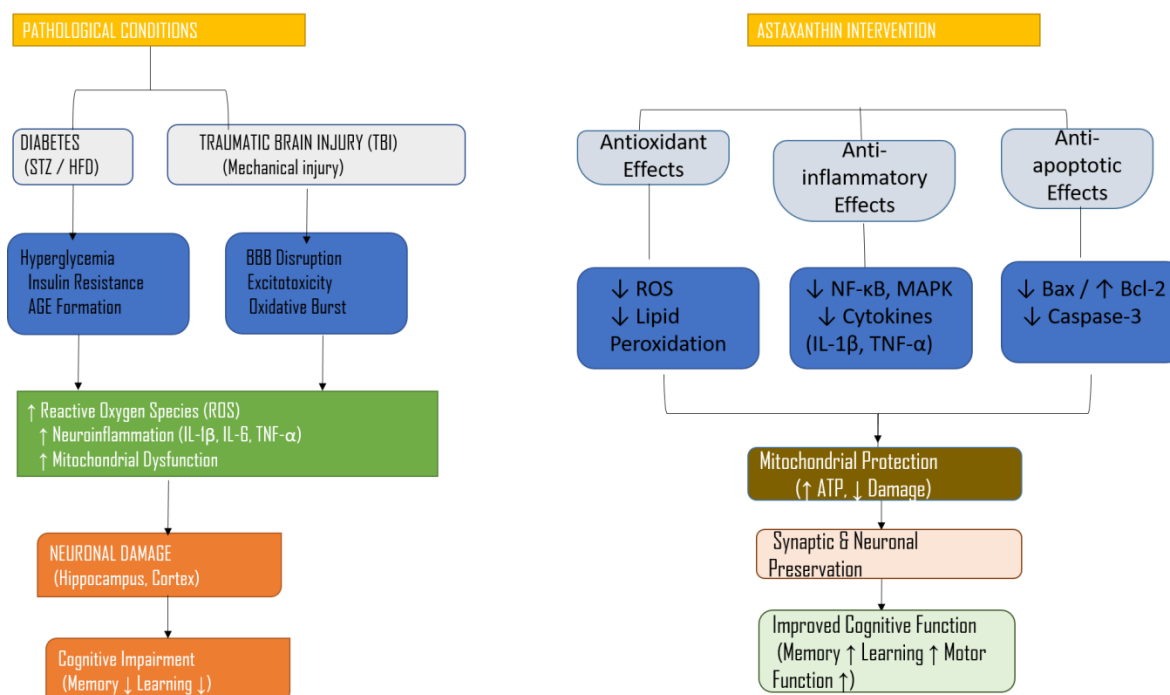


Fig4: Schematic illustrating oxidative stress, inflammation, and mitochondrial dysfunction leading to neuronal damage and cognitive impairment in diabetes and TBI. Astaxanthin counteracts these processes via antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, improving neuronal survival and cognitive function.

6. Translational Perspectives

6.1 Clinical Potential

Astraxanthin has generated considerable interest as a neuroprotective and neuromedullary agent due to its ability to target multiple pathological pathways simultaneously. Its clinical relevance extends across a spectrum of neurobiological conditions characterised by oxidative stress, inflammation, and impaired neuronal signalling.

6.1.1. Acute stress-induced cognitive dysfunction

Acute stress leads to rapid activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated glucocorticoids that impair hippocampal function and memory processing. Astraxanthin may mitigate these effects through several mechanisms.^[73]

Acute stress-induced cognitive dysfunction is primarily mediated through rapid activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated glucocorticoid levels that adversely affect brain regions critical for learning and memory, particularly the hippocampus and prefrontal cortex.^[74] Excess glucocorticoids promote the generation of reactive oxygen species (ROS), leading to oxidative stress, lipid peroxidation, and neuronal damage.^[75] Concurrently, acute stress triggers a neuroinflammatory response characterised by activation of microglial cells and increased release of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6, which disrupts synaptic signalling and plasticity.^[74] Mitochondrial dysfunction further exacerbates this condition by impairing ATP production and increasing oxidative burden, thereby

compromising neuronal energy homeostasis.^[75] In addition, stress-induced alterations in neurotrophic factors, particularly reduced brain-derived neurotrophic factor (BDNF) levels, lead to impaired synaptic plasticity and memory consolidation.^[73] Collectively, these interconnected mechanisms result in transient but significant deficits in cognitive performance, including impaired attention, learning, and memory, highlighting the need for therapeutic strategies that target multiple pathological pathways simultaneously.^[73]

6.1.2 Anxiety and depression associated cognitive deficits

Cognitive deficits associated with anxiety and depression represent a significant clinical burden, often persisting even after partial remission of mood symptoms. Overlapping neurobiological mechanisms largely drive these impairments.^[75] Chronic psychological stress underlying these disorders leads to sustained activation of the hypothalamic-pituitary-adrenal axis. (HPA) axis, resulting in exposures to glucocorticoids that negatively affect the hippocampus and prefrontal cortex.^[76] This is accompanied by increased oxidative stress and a persistent neuroinflammatory state, characterised by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, which interfere with synaptic transmission and neuronal connectivity.^[77] Additionally, dysregulation of key neurotransmitter systems, particularly serotonin, dopamine, and glutamate, contributes to both mood disturbances and cognitive dysfunction.^[78] Reduced levels of brain-derived neurotrophic factor further impair neurogenesis and synaptic plasticity, exacerbating cognitive decline.^[75]

Mitochondrial dysfunction and impaired energy metabolism also play a crucial role by limiting neuronal resilience and function. Together, these interconnected pathways lead to structural and functional alterations in brain circuits involved in cognition and emotional regulation, underscoring the importance of therapeutic approaches that simultaneously target oxidative stress, inflammation, and neuroplasticity.

6.1.3. Neurodegenerative Disease Involving Oxidative Stress

Oxidative stress plays a central role in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Excessive reactive oxygen species (ROS) damage lipids, proteins, and DNA, leading to neuronal dysfunction and death.^[79] Mitochondrial impairment further increases ROS production and reduces ATP synthesis, while chronic inflammation and accumulation of misfolded proteins accelerate disease progression. Together, these processes contribute to progressive neuronal degeneration and cognitive and motor decline.^[80]

6.2. Combination therapies

Astraxanthin may exhibit enhanced therapeutic efficacy when used in combination with other bioactive compounds and lifestyle interventions that target complementary neuroprotective pathways. Co-administration with omega-3 fatty acids (PUFAs) can improve neuronal membrane integrity, modulate inflammation, and support synaptic function, thereby amplifying cognitive benefits.^[81] Similarly, polyphenols such as curcumin and resveratrol provide additional antioxidant and anti-inflammatory effects through modulation of signalling pathways like NF- κ B and SIRT1, potentially creating synergistic protection against oxidative stress and neurodegeneration.^[82] Incorporating lifestyle interventions such as regular physical exercise further enhances these effects by promoting neurogenesis, improving mitochondrial function, and increasing brain-derived neurotrophic factor (BDNF) levels. Together, these combination strategies offer a multi-targeted approach to mitigating cognitive impairment and improving overall brain health.^[83]

FUTURE DIRECTIONS

Future research on astaxanthin as a neuroprotective agent should focus on bridging the gap between promising preclinical findings and clinical application. Well-designed, large-scale randomised controlled trials are needed to establish its efficacy in acute stress-induced cognitive impairment and related neurological conditions. Optimisation of dosing strategies, treatment duration, and patient selection will be critical for achieving consistent therapeutic outcomes. In parallel, advanced drug delivery systems such as nanoformulations, lipid-based carriers, and targeted brain delivery approaches should be developed to enhance bioavailability and blood-brain barrier penetration.

Mechanistic studies exploring molecular pathways, including oxidative stress signalling, mitochondrial biogenesis, and hypoxia-related pathways such as HIF-1 α , could provide deeper insights into its mode of action and align with emerging therapeutic targets. Integration of multi-omics approaches (genomics, proteomics, metabolomics) may further elucidate system-level effects and identify biomarkers for treatment response. Additionally, investigating combination strategies with nutraceuticals, pharmaceuticals, and lifestyle interventions may reveal synergistic benefits. Collectively, these efforts will be essential to fully realise the therapeutic potential of astraxanthin in cognitive and neurodegenerative disorders.

CONCLUSION

Astaxanthin has emerged as a highly promising neuroprotective agent with substantial potential in mitigating acute stress-induced cognitive impairment. Its unique molecular structure and lipophilic nature enable it to efficiently cross the blood-brain barrier and exert direct effects within the central nervous system. By simultaneously targeting multiple interconnected pathological pathways, including oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis, astraxanthin offers a comprehensive and multi-targeted approach to preserving neuronal integrity and cognitive function. Its ability to enhance endogenous antioxidant defences, suppress pro-inflammatory signalling, stabilise mitochondrial bioenergetics, and promote synaptic plasticity underscores its therapeutic versatility in stress-related neurological conditions.

Importantly, astaxanthin not only attenuates neuronal damage but also supports adaptive neurobiological processes such as neurogenesis and synaptic remodelling through the upregulation of neurotrophic factors like brain-derived neurotrophic factor (BDNF). These effects are particularly relevant in brain regions such as the hippocampus and prefrontal cortex, which are highly susceptible to stress-induced dysfunction. Furthermore, its modulatory influence on key signalling pathways, including NF- κ B and SIRT1/PGC-1 α , highlights its role in regulating cellular homeostasis and resilience under stress conditions.

Beyond acute stress, astaxanthin demonstrates broader applicability in conditions characterised by chronic oxidative stress and inflammation, including anxiety- and depression-associated cognitive deficits and major neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis. Its capacity to modulate shared pathogenic mechanisms such as protein aggregation, mitochondrial dysfunction, and impaired neuronal signalling positions it as a potential disease-modifying agent rather than merely a symptomatic treatment. Additionally, its favourable safety profile and natural origin enhance its appeal as a nutraceutical or adjunct therapeutic strategy.

Despite compelling preclinical evidence, several challenges remain before astraxanthin can be fully translated into clinical practice. These include limited availability of well-controlled human clinical trials, lack of standardised dosing regimens, and variability in bioavailability due to its hydrophobic nature. Advances in formulation strategies, such as nanoencapsulation, lipid-based delivery systems, and targeted brain delivery platforms, are expected to overcome these limitations and improve therapeutic efficacy. Furthermore, integrating astraxanthin into combination therapies with other bioactive compounds or lifestyle interventions may enhance its overall neuroprotective effects through synergistic mechanisms.

Future investigations should prioritise large-scale clinical studies, identification of predictive biomarkers, and exploration of molecular targets relevant to emerging research areas, including hypoxia-inducible pathways such as HIF-1 α . The application of multi-omics approaches may further elucidate its systemic effects and optimise personalised therapeutic strategies.

In conclusion, astraxanthin represents a compelling candidate for the prevention and management of stress-related cognitive dysfunction and neurodegenerative diseases. Its multi-dimensional mechanisms, combined with a strong safety profile and broad therapeutic potential, position it as a valuable agent in the evolving landscape of neuroprotective interventions. Continued interdisciplinary research will be essential to unlock its full clinical potential and translate experimental findings into effective, evidence-based therapies.

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