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TARGETING NEUROTOXICITY WITH CAROTENOIDS: MOLECULAR MECHANISMS AND THERAPEUTIC IMPLICATIONS IN NEURODEGENERATIVE DISORDERS

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Abstract: Neurotoxicity represents a major contributor to the global burden of neurological and neurodegenerative disorders through interconnected mechanisms involving oxidative stress, neuroinflammation, mitochondrial dysfunction, protein misfolding, and neuronal apoptosis. Accumulating evidence suggests that carotenoids exert significant neuroprotective effects by modulating these pathological pathways through antioxidant, anti-inflammatory, anti-apoptotic, and neurotrophic actions. Among the various carotenoids such as lycopene, lutein, zeaxanthin, astaxanthin, fucoxanthin, and crocin have demonstrated promising therapeutic potential in experimental models of neurodegeneration. Carotenoids exert neuroprotective effects through multiple complementary mechanisms that target the major pathological processes involved in neurotoxicity and neurodegeneration. They directly scavenge reactive oxygen species and inhibit lipid peroxidation, thereby reducing oxidative stress. Carotenoids suppress neuroinflammation by downregulating NF-κB and pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Additionally, they preserve mitochondrial function, enhance ATP production, inhibit apoptotic pathways, and regulate protein homeostasis by reducing amyloid-β, tau, and α-synuclein aggregation. Furthermore, carotenoids activate Nrf2-mediated antioxidant defenses and enhance BDNF/CREB signaling, promoting neuronal survival, synaptic plasticity, and cognitive function.Although current findings support the role of carotenoids as attractive nutraceutical candidates for preventing and attenuating neurotoxicity.

Keywords: Neurotoxicity, Carotenoids, oxidative stress, inflammation, Alzheimer and Parkinson

I. INTRODUCTION

Neurodegenerative diseases (NDs) are a heterogeneous group of chronic and progressive neurological disorders characterized by gradual neuronal dysfunction, synaptic loss, and irreversible neuronal death within the central nervous system (Feigin et al., 2021; Dugger and Dickson, 2017). Neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and other forms of dementia, which collectively contribute to substantial disability, mortality, and socioeconomic burden (Chen et al., 2023; Knopman et al., 2021). The progressive nature of these disorders severely impairs cognitive, behavioral, and motor functions, significantly reducing quality of life and increasing healthcare expenditure globally (Livingston et al., 2020; Nichols et al., 2022).

According to recent epidemiological studies, neurological disorders are among the leading causes of disability-adjusted life years (DALYs) and mortality worldwide (Feigin et al., 2021). Alzheimer's disease is the most prevalent neurodegenerative disorder and accounts for approximately 60–70% of all dementia cases globally (Knopman et al., 2021). It is estimated that more than 55 million individuals are currently living with dementia worldwide, and this number is expected to rise to nearly 139 million by 2050, particularly in low- and middle-income countries (Nichols et al., 2022; Livingston et al., 2020). Alzheimer's disease is clinically characterized by progressive memory loss, cognitive impairment, and behavioral disturbances, whereas pathologically it is associated with extracellular amyloid-β plaque deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, oxidative damage, and neuroinflammation (Butterfield and Halliwell, 2019; Leng and Edison, 2021).

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease and affects more than 10 million people globally (Bloem et al., 2021). Parkinson's disease is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta and accumulation of α-synuclein-containing Lewy bodies (Schapira et al., 2022). Clinically, PD manifests as resting tremor, bradykinesia, muscular rigidity, and postural instability along with non-motor symptoms such as depression, sleep disorders, and cognitive dysfunction (Dorsey et al., 2018; Bloem et al., 2021). The prevalence of Parkinson's disease has increased rapidly over the last two decades due to aging populations and environmental risk factors (Dorsey et al., 2018).

Pathophysiology of Neurodegenerative Diseases

Neurodegenerative diseases share several common molecular mechanisms including oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity, impaired autophagy, apoptosis, and abnormal protein aggregation (Chen et al., 2023; Dugger and Dickson, 2017). Among these mechanisms, oxidative stress is considered one of the most important contributors to neuronal degeneration (Angelova and Abramov, 2018; Singh et al., 2024). Oxidative stress occurs due to an imbalance between reactive oxygen species (ROS) production and endogenous antioxidant defense systems. Neurons are highly vulnerable to oxidative injury because of their high oxygen consumption, elevated lipid content, abundant polyunsaturated fatty acids, and relatively limited antioxidant capacity (Butterfield and Halliwell, 2019; Chen et al., 2023).

Oxidative stress

Excessive generation of reactive oxygen species such as superoxide anion, hydroxyl radicals, hydrogen peroxide, and peroxynitrite can damage proteins, lipids, DNA, and mitochondria, leading to neuronal dysfunction and apoptosis (Uttara et al., 2017; Wang et al., 2023). Lipid peroxidation produces toxic metabolites including malondialdehyde and 4-hydroxynonenal, which further aggravate neuronal damage and synaptic dysfunction (Butterfield and Halliwell, 2019). Mitochondrial dysfunction is another major hallmark of neurodegeneration and contributes to impaired ATP synthesis, calcium dysregulation, and increased ROS generation (Johri and Beal, 2019; Bose and Beal, 2019). In Alzheimer's disease, oxidative stress accelerates amyloid-β toxicity and tau hyperphosphorylation, whereas in Parkinson's disease mitochondrial complex I dysfunction contributes to dopaminergic neuronal degeneration (Dias et al., 2018; Tönnies and Trushina, 2017).

Neuroinflammation

Neuroinflammation plays a critical role in the initiation and progression of neurodegenerative diseases (Heneka et al., 2018; Leng and Edison, 2021). Neuroinflammation is primarily mediated by activated microglia and astrocytes, which release pro-inflammatory cytokines, chemokines, nitric oxide, and reactive oxygen species (Heneka et al., 2018). Chronic activation of microglia results in excessive production of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), leading to neuronal dysfunction and synaptic degeneration (Leng and Edison, 2021; Orfali et al., 2024). Furthermore, oxidative stress and neuroinflammation interact closely to create a vicious cycle that amplifies neuronal injury through activation of signaling pathways including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and NLRP3 inflammasome pathways (Stockwell, 2022; Singh et al., 2024).

Mitochondrial Dysfunction

Mitochondria are essential organelles responsible for cellular energy production, calcium homeostasis, reactive oxygen species (ROS) regulation, and apoptotic signaling. Neurons are particularly dependent on mitochondrial function due to their high energy demand and limited regenerative capacity. Consequently, mitochondrial dysfunction is recognized as a central pathological mechanism underlying numerous neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Johri and Beal, 2019; Wang et al., 2023).

Impairment of the mitochondrial electron transport chain results in reduced ATP production and excessive generation of ROS, leading to oxidative stress and neuronal damage (Chen et al., 2023). In Alzheimer's disease, mitochondrial dysfunction promotes amyloid-β accumulation, tau hyperphosphorylation, and synaptic degeneration (Butterfield and Halliwell, 2019). In Parkinson's disease, defects in mitochondrial complex I activity and impaired mitophagy contribute to the degeneration of dopaminergic neurons in the substantia nigra (Bose and Beal, 2019). Similarly, mutant huntingtin protein disrupts mitochondrial dynamics, calcium buffering, and energy metabolism, thereby accelerating neuronal loss in Huntington's disease (Johri and Beal, 2019).

Furthermore, mitochondrial dysfunction activates intrinsic apoptotic pathways through cytochrome c release and caspase activation, resulting in progressive neuronal death. Therefore, strategies aimed at restoring mitochondrial function represent promising therapeutic approaches for the prevention and treatment of neurodegenerative disorders (Wang et al., 2023; Kumar et al., 2024).

Protein Misfolding, Aggregation, and Neurotoxicity

Protein misfolding and aggregation are fundamental pathological events in neurodegenerative disorders and contribute significantly to neuronal dysfunction, synaptic loss, and cognitive decline. Under physiological conditions, proteins attain specific three-dimensional conformations necessary for their biological functions. However, oxidative stress, mitochondrial dysfunction, genetic mutations, and impaired protein clearance mechanisms can induce protein misfolding and aggregation, resulting in the formation of toxic oligomers and insoluble protein deposits that disrupt neuronal homeostasis (Dugger and Dickson, 2017; Chen et al., 2023).

Amyloid-β (Aβ) is one of the principal pathogenic proteins implicated in Alzheimer's disease. It is generated through abnormal cleavage of amyloid precursor protein (APP) by β- and γ-secretases. Misfolded Aβ peptides aggregate into soluble oligomers and extracellular plaques that impair synaptic transmission, induce oxidative stress, disrupt calcium homeostasis, and activate microglial-mediated neuroinflammation (Knopman et al., 2021; Butterfield and Halliwell, 2019). Accumulating evidence suggests that soluble Aβ oligomers are more neurotoxic than mature plaques and play a crucial role in cognitive impairment.

Tau protein is a microtubule-associated protein responsible for stabilizing neuronal cytoskeletal structures. In neurodegenerative diseases, particularly Alzheimer's disease, abnormal hyperphosphorylation of tau causes its dissociation from microtubules and subsequent aggregation into neurofibrillary tangles (NFTs) (Wang and Mandelkow, 2016). Tau aggregates impair axonal transport, mitochondrial trafficking, and synaptic function, ultimately leading to neuronal death. Furthermore, pathological tau can spread between neurons in a prion-like manner, contributing to disease progression (Vogels et al., 2020).

Brain-derived neurotrophic factor (BDNF) is a critical neurotrophin involved in neuronal survival, synaptic plasticity, learning, and memory. Although BDNF itself does not form toxic aggregates, reduced BDNF expression is frequently observed in neurodegenerative diseases and is associated with increased neuronal vulnerability (Miranda et al., 2019). Amyloid-β and tau pathology suppress BDNF signaling, thereby impairing neurogenesis, synaptic maintenance, and cognitive function. Reduced BDNF levels further exacerbate oxidative stress and neuronal degeneration.

cAMP response element-binding protein (CREB) is a transcription factor that regulates the expression of genes involved in neuronal survival, memory formation, and synaptic plasticity, including BDNF. Neurotoxic proteins such as amyloid-β inhibit CREB phosphorylation and activation, leading to impaired transcription of neuroprotective genes (Sharma et al., 2019). Dysregulation of the CREB-BDNF signaling pathway contributes significantly to cognitive deficits and neuronal apoptosis observed in neurodegenerative disorders.

Available therapies for neurodegenerative disorders

Currently available pharmacological therapies for neurodegenerative diseases mainly provide symptomatic relief and fail to prevent disease progression or neuronal loss (Schapira et al., 2022). Therefore, there is increasing interest in identifying safer and more effective therapeutic agents capable of targeting multiple pathological pathways involved in neurodegeneration (Kumar et al., 2024; Houldsworth, 2024). In recent years, naturally occurring phytochemicals have attracted considerable attention because of their antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties (Cory et al., 2018; Islam et al., 2021). Phytochemicals are bioactive compounds derived from fruits, vegetables, herbs, spices, and medicinal plants and include polyphenols, flavonoids, alkaloids, terpenoids, and carotenoids (Bhandari et al., 2024; Vauzour et al., 2017).

Growing evidence suggests that phytochemicals may play an important role in preventing and managing chronic diseases such as diabetes mellitus, cardiovascular disorders, obesity, cancer, and neurodegenerative diseases (Cory et al., 2018; Rehman et al., 2019). These compounds can modulate oxidative stress, suppress inflammatory pathways, regulate apoptosis, improve mitochondrial function, and enhance endogenous antioxidant defense systems (Islam et al., 2021; Singh et al., 2022). Among various phytochemicals, lycopene has emerged as a promising neuroprotective carotenoid because of its potent free radical scavenging activity and ability to modulate multiple signaling pathways involved in neurodegeneration (Imran et al., 2020; Sachdeva et al., 2020).

Role of Different Carotenoids as Neuroprotective Agents

Carotenoids are naturally occurring lipophilic pigments synthesized by plants, algae, fungi, and certain microorganisms. More than 800 carotenoids have been identified, of which approximately 40 are regularly consumed in the human diet. Growing evidence indicates that carotenoids possess potent antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties, making them promising therapeutic candidates for neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) (Gandla et al., 2023; Angelova and Abramov, 2018). Carotenoids can cross the blood-brain barrier and protect neurons against oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregation, which are major pathological mechanisms underlying neurodegeneration (Gandla et al., 2023; Gilgun-Sherki et al., 2001).

Lycopene

Lycopene is a non-provitamin A carotenoid predominantly found in tomatoes, watermelon, guava, and papaya. Among all dietary carotenoids, lycopene exhibits one of the strongest singlet oxygen-quenching capacities due to its highly conjugated polyene structure. Numerous experimental studies have demonstrated that lycopene attenuates oxidative stress by reducing reactive oxygen species (ROS) generation and enhancing endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Imran et al., 2020; Sachdeva et al., 2020).

In Alzheimer's disease models, lycopene reduces amyloid-β accumulation, inhibits tau hyperphosphorylation, and improves cognitive performance. In Parkinson's disease models, lycopene protects dopaminergic neurons by suppressing mitochondrial dysfunction and neuroinflammation. Lycopene also modulates NF-κB, Nrf2, PI3K/Akt, and MAPK signaling pathways, contributing to its neuroprotective actions (Prakash and Kumar, 2021; Gandla et al., 2023).

β-Carotene

β-Carotene is one of the most abundant dietary carotenoids and serves as a major precursor of vitamin A. It is present in carrots, sweet potatoes, pumpkin, spinach, and other colorful vegetables. β-Carotene exhibits strong antioxidant activity by scavenging free radicals and reducing lipid peroxidation (Kaulmann and Bohn, 2014).

Experimental studies have demonstrated that β-carotene protects neuronal cells against oxidative damage induced by neurotoxins and aging-related stress. It improves mitochondrial function, suppresses inflammatory cytokine production, and reduces neuronal apoptosis. Furthermore, vitamin A derived from β-carotene plays an important role in neuronal differentiation, synaptic plasticity, and cognitive function (Fiedor and Burda, 2014; Gandla et al., 2023). However, excessive β-carotene supplementation may exhibit pro-oxidant effects under certain pathological conditions, emphasizing the importance of physiological dosing.

Lutein

Lutein is a xanthophyll carotenoid highly concentrated in the retina and brain. Green leafy vegetables such as spinach, kale, broccoli, and peas are major dietary sources of lutein. Emerging evidence suggests that lutein accumulates selectively in brain tissues and plays a critical role in cognitive development and neuroprotection (Johnson, 2014).

Lutein exerts neuroprotective effects through multiple mechanisms, including scavenging reactive oxygen species, suppressing neuroinflammation, preserving mitochondrial function, and enhancing synaptic plasticity. Recent studies have shown that lutein increases brain-derived neurotrophic factor (BDNF) levels and activates Nrf2-mediated antioxidant signaling pathways (Jayakanthan et al., 2024). Lutein supplementation has been associated with improved memory, executive function, and cognitive performance in aging populations and experimental models of Alzheimer's disease (Sanlier et al., 2024; Jayakanthan et al., 2024).

Zeaxanthin

Zeaxanthin is structurally similar to lutein and is abundant in corn, orange peppers, egg yolks, and various fruits. Like lutein, zeaxanthin accumulates in neural tissues and contributes to protection against oxidative stress and inflammation (Sanlier et al., 2024).

Zeaxanthin protects neuronal membranes from lipid peroxidation and enhances antioxidant defenses. Several studies have reported that higher plasma concentrations of lutein and zeaxanthin are associated with better cognitive performance and reduced risk of age-related cognitive decline. Zeaxanthin also modulates inflammatory signaling pathways and improves mitochondrial integrity in neuronal cells (Johnson et al., 2018; Sanlier et al., 2024).

Astaxanthin

Astaxanthin is a keto-carotenoid naturally found in microalgae, salmon, trout, shrimp, and krill. It is considered one of the most potent natural antioxidants due to its unique molecular structure. Astaxanthin effectively crosses the blood-brain barrier and exerts strong neuroprotective effects (Adıgüzel and Ülger, 2024).

Numerous studies have demonstrated that astaxanthin reduces oxidative stress, inhibits microglial activation, suppresses neuroinflammation, and prevents neuronal apoptosis. In Alzheimer's disease models, astaxanthin decreases amyloid-β toxicity and improves cognitive function. In Parkinson's disease models, it protects dopaminergic neurons by regulating mitochondrial function and autophagy pathways. Astaxanthin also activates Nrf2 signaling and inhibits NF-κB-mediated inflammatory responses (Adıgüzel and Ülger, 2024; Fakhri et al., 2018).

Fucoxanthin

Fucoxanthin is a marine carotenoid predominantly found in brown seaweeds such as *Undaria pinnatifida* and *Laminaria japonica*. Recent studies have highlighted fucoxanthin's potent neuroprotective properties against oxidative stress-induced neuronal damage (Pangestuti and Kim, 2011).

Fucoxanthin suppresses ROS production, improves mitochondrial function, and inhibits inflammatory mediators such as TNF-α and IL-1β. It also activates Nrf2 and HO-1 signaling pathways, thereby enhancing cellular antioxidant defenses. Experimental evidence suggests that fucoxanthin can attenuate amyloid-β-induced neurotoxicity and improve memory impairment in animal models of Alzheimer's disease (Gandla et al., 2023).

Crocin and Crocetin

Crocin and crocetin are carotenoid derivatives isolated from saffron (*Crocus sativus*). These compounds possess remarkable antioxidant and anti-inflammatory activities and have gained attention for their neuroprotective potential (Pitsikas, 2016).

Crocin reduces oxidative stress, inhibits neuronal apoptosis, and improves learning and memory. Studies have shown that crocin suppresses amyloid-β aggregation and reduces neuroinflammation in Alzheimer's disease models. Crocetin also improves mitochondrial function and protects neurons against ischemic and excitotoxic injury (Pitsikas, 2016; Ghasemi et al., 2022).

Canthaxanthin

Canthaxanthin is an oxygenated carotenoid found in fungi, algae, crustaceans, and fish. Although less extensively studied than other carotenoids, canthaxanthin exhibits antioxidant and anti-inflammatory properties that may contribute to neuroprotection (Tanaka et al., 2012).

Experimental studies suggest that canthaxanthin protects neuronal cells from oxidative damage and modulates inflammatory signaling pathways. It has also been reported to enhance endogenous antioxidant defenses and reduce apoptosis in oxidative stress-induced neuronal injury models.

Mechanisms Underlying Carotenoid-Mediated Neuroprotection

The neuroprotective effects of carotenoids are mediated through multiple interconnected mechanisms:

Antioxidant Activity: Direct scavenging of ROS and prevention of lipid peroxidation.

Anti-inflammatory Effects: Inhibition of NF-κB, TNF-α, IL-1β, and IL-6 production.

Mitochondrial Protection: Preservation of ATP production and reduction of mitochondrial ROS generation.

Anti-apoptotic Activity: Regulation of Bax/Bcl-2 ratio and suppression of caspase activation.

Protein Homeostasis: Reduction of amyloid-β aggregation, tau pathology, and α-synuclein accumulation.

Activation of Nrf2 Signaling: Enhancement of endogenous antioxidant defense mechanisms.

Promotion of Neurotrophic Factors: Upregulation of BDNF and CREB signaling pathways that support neuronal survival and synaptic plasticity (Gandla et al., 2023; Adıgüzel and Ülger, 2024).

Conclusion

Neurotoxicity is a multifactorial process characterized by progressive neuronal dysfunction and death resulting from interconnected pathological mechanisms. Oxidative stress plays a central role by generating excessive reactive oxygen species (ROS), which damage lipids, proteins, DNA, and cellular membranes. Persistent oxidative injury triggers neuroinflammation through activation of microglia and astrocytes, leading to the release of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 that exacerbate neuronal damage. Simultaneously, mitochondrial dysfunction impairs ATP production, disrupts calcium homeostasis, and increases ROS generation, creating a vicious cycle of cellular injury. Protein misfolding and aggregation further contribute to neurotoxicity through the accumulation of neurotoxic proteins such as amyloid-β, hyperphosphorylated tau, and α-synuclein, which impair synaptic transmission and neuronal survival. These pathological events collectively activate apoptotic pathways, promote synaptic degeneration, and accelerate neuronal loss. The interaction among oxidative stress, neuroinflammation, mitochondrial dysfunction, and protein aggregation ultimately drives the onset and progression of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Accumulating evidence indicates that carotenoids represent a promising class of neuroprotective phytochemicals capable of targeting multiple pathological pathways involved in neurodegenerative diseases. Lycopene, lutein, zeaxanthin, astaxanthin, fucoxanthin, crocin, crocetin, and β-carotene have demonstrated significant antioxidant, anti-inflammatory, anti-apoptotic, and neurotrophic effects in experimental studies. Their ability to modulate oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregation highlights their potential as preventive and therapeutic agents against Alzheimer's disease, Parkinson's disease, Huntington's disease, and related neurological disorders. Further well-designed clinical studies are required to validate their efficacy and establish optimal therapeutic strategies for neurodegenerative disease management.

Figures and Tables

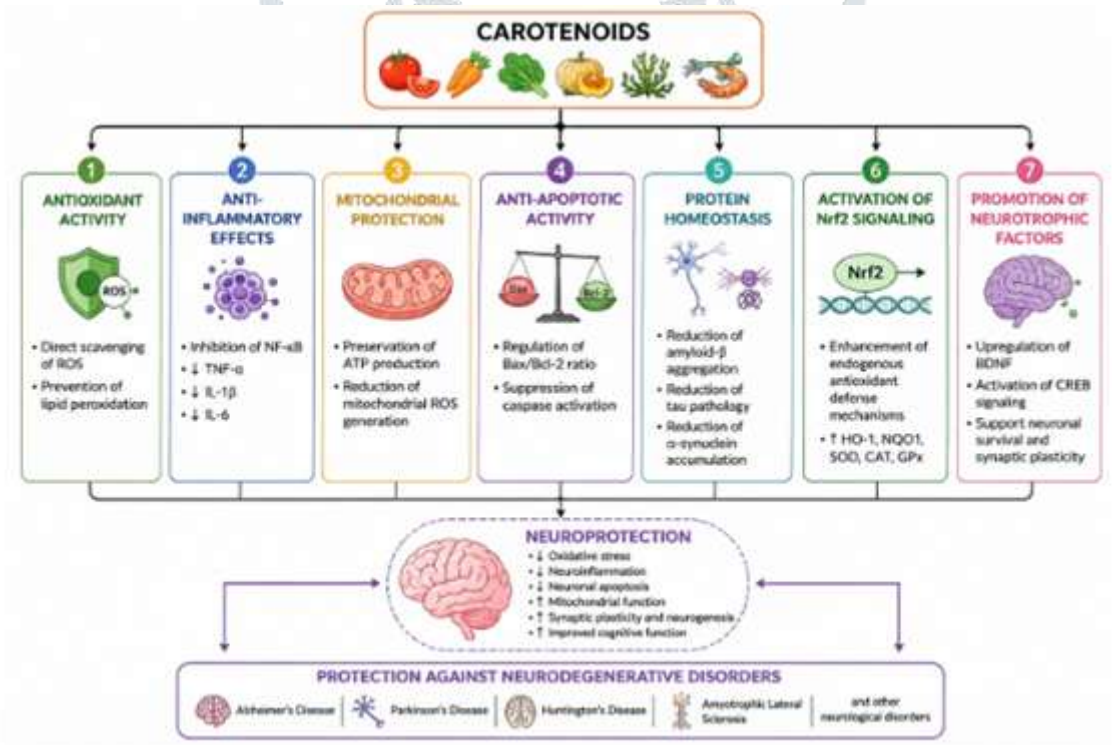

Figure 1: Neuroprotective mechanism of carotenoids

II. ACKNOWLEDGMENT

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