



PHARMACOLOGICAL IMPORTANCE OF LYCOPENE FROM WILD CHERRY TOMATOES AGAINST HUNTINGTON'S DISEASE

Maharabam Anandi Devi*

*Department of Biochemistry, Manipur College, Imphal, Manipur, India

***Corresponding Author:** Maharabam Anandi Devi

*anandimaharabam85@gmail.com

Abstract

Huntington's Disease (HD) is a progressive neurodegenerative disorder that severely impacts the aging population and is characterized by complex genetic and biochemical pathologies. Among various natural compounds under investigation, lycopene, an aliphatic polyunsaturated carotenoid abundantly present in tomatoes and other red fruits, has shown significant potential in mitigating the oxidative and inflammatory mechanisms underlying HD. Due to its lipophilic nature, lycopene efficiently traverses the blood–brain barrier, exerting direct neuroprotective effects within the central nervous system. Its potent antioxidant capacity enables the neutralization of reactive oxygen species, thereby reducing neuronal oxidative damage—a hallmark of neurodegeneration. Concurrently, its anti-inflammatory activity downregulates chronic neuroinflammation, which is implicated in the progression of neuropsychiatric disorders. Given that impaired antioxidant defenses and aberrant protein folding contribute to neurodegenerative diseases such as Alzheimer's and Huntington's enhancing the bioavailability of natural neuroprotective agents like lycopene is of growing interest. Recent advances in nanocarrier-based drug delivery systems have demonstrated promise in improving lycopene's stability, permeability, and clinical efficacy for brain-targeted therapies. Additionally, wild cherry tomatoes, a rich natural source of lycopene and other phytonutrients, provide synergistic neuroprotective effects through the modulation of oxy-inflammatory pathways, including PI3K/Akt signaling. This review highlights the pharmacological potential of lycopene derived from wild cherry tomatoes as a promising therapeutic candidate against Huntington's Disease, emphasizing its multifaceted role in antioxidant defense, anti-inflammatory regulation, and neuronal survival.

Key words: Lycopene, Huntington's Disease, Neuroprotection, Oxidative Stress, Anti-inflammatory Mechanisms

Introduction

Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's disease (HD), constitute one of the most pressing global health challenges due to their progressive nature and devastating effects on cognitive, behavioral, and motor functions (Nahar et al., 2021). These disorders share common pathological features such as increased oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation, all of which contribute to irreversible neuronal damage and synaptic loss (Lima et al., 2021). Among them, Huntington's Disease—a hereditary neurodegenerative disorder caused by an expanded CAG trinucleotide repeat in the *huntingtin (HTT)* gene—stands out as particularly debilitating. It is clinically characterized by motor dysfunction, psychiatric disturbances,

and cognitive decline, all stemming from progressive degeneration of striatal and cortical neurons. The rising global prevalence of such neurodegenerative conditions underscores an urgent need for effective preventive and therapeutic interventions (Lim et al., 2020).

Current pharmacological treatments for HD and related disorders largely provide symptomatic relief and are often accompanied by adverse effects. Consequently, there is growing scientific and clinical interest in the exploration of natural compounds—especially those with established antioxidant and anti-inflammatory properties—as alternative therapeutic strategies (Tarkhasi, 2016). Bioactive plant-derived molecules, including polyphenols, flavonoids, and carotenoids, have demonstrated considerable neuroprotective potential owing to their ability to modulate multiple molecular targets implicated in oxidative stress, neuroinflammation, apoptosis, and protein aggregation (Grosso et al., 2013; Shoaib et al., 2013; Sairazi & Sirajudeen, 2020).

Among these, terpenoid natural products, particularly carotenoids such as lycopene, have shown pronounced neuroprotective effects by influencing key signaling cascades involved in neuronal survival and inflammation (Xu et al., 2016). Lycopene, a naturally occurring tetraterpene responsible for the red pigmentation of tomatoes and other fruits, exhibits exceptional antioxidant potency due to its conjugated polyene structure. It effectively neutralizes reactive oxygen and nitrogen species, thereby preventing oxidative damage to cellular lipids, proteins, and DNA (Umaraw et al., 2020). Moreover, lycopene modulates signaling pathways such as PI3K/Akt and brain-derived neurotrophic factor–tropomyosin receptor kinase B–cAMP response element-binding protein (BDNF–TrkB–CREB), which are crucial for neuronal growth, differentiation, and protection against apoptosis (Xu et al., 2016; Lim et al., 2020).

Mechanistically, lycopene has been shown to attenuate neuronal apoptosis by upregulating antiapoptotic proteins, stabilizing mitochondrial membrane potential, and enhancing calcium efflux (Naik et al., 2020). It also reduces neuroinflammation by downregulating proinflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β), leading to improved cognitive and motor outcomes in neurodegenerative disease models (Naik et al., 2020; Rahman et al., 2021). These multifaceted pharmacological actions underscore lycopene's potential as a therapeutic agent in complex neurological disorders where oxidative and inflammatory pathways intersect.

Importantly, wild cherry tomatoes (*Solanum peruvianum*), a lesser-studied tomato species, are particularly rich in lycopene and other phytochemicals such as flavonoids, phenolic acids, and ascorbic acid, which synergistically enhance its neuroprotective efficacy. Compared to cultivated varieties, wild cherry tomatoes exhibit higher antioxidant capacity and greater concentrations of bioactive compounds, making them a promising natural reservoir for nutraceutical and pharmacological development (Grosso et al., 2013).

Given these attributes, lycopene represents a compelling candidate for further research in the prevention and management of Huntington's Disease. Its ability to modulate oxidative stress, inflammation, and apoptotic pathways positions it as a multifunctional neuroprotective molecule. This review, therefore, aims to synthesize contemporary preclinical and clinical evidence on the pharmacological importance of lycopene derived from wild cherry tomatoes, with particular emphasis on its mechanisms in attenuating oxidative stress, neuroinflammation, and neuronal apoptosis in Huntington's Disease.

Background on Huntington's Disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by progressive deterioration of motor, cognitive, and psychiatric functions, primarily caused by the degeneration of GABAergic medium spiny neurons in the striatum and cortex (Babazadeh et al., 2013). The disease results from an autosomal dominant mutation in the *huntingtin* (*HTT*) gene, involving an abnormal expansion of CAG trinucleotide repeats that encode a toxic, misfolded huntingtin protein (Nahar et al., 2021). The resultant mutant huntingtin (mHTT) protein triggers a cascade of pathological cellular events—mitochondrial dysfunction, excitotoxicity, transcriptional dysregulation, and oxidative stress—that collectively culminate in neuronal damage and death (Cruz et al., 2008; Rekatsina et al.,

2019). These processes give rise to the hallmark clinical symptoms of HD, including involuntary movements, cognitive decline, and psychiatric disturbances.

Currently, treatment strategies for HD are limited to symptomatic management, with no curative therapy available (Shin et al., 2020). This underscores the urgent need for novel therapeutic interventions that can modulate the multiple pathological mechanisms underlying the disease (Jayawickreme et al., 2020). A key driver of HD progression is oxidative stress—an imbalance between reactive oxygen species (ROS) production and antioxidant defenses—which accelerates neuronal injury and neurodegeneration (Kumar & Ratan, 2016; D'Egidio et al., 2013). Mitochondrial dysfunction, energy deficits, excessive ROS generation, neuroinflammation, and depletion of antioxidants all converge to create a toxic oxidative environment, leading to selective vulnerability of striatal medium spiny neurons (D'Egidio et al., 2021; Tong et al., 2020).

The expanded polyglutamine tract in mHTT protein further contributes to neuropathological changes within the striatum, including the loss of medium spiny neurons and parvalbumin-expressing interneurons, disrupting both the striosome and matrix compartments and impairing movement, cognition, and speech (Morigaki & Goto, 2017). Transcriptional dysregulation, synaptic dysfunction, impaired axonal trafficking, proteostasis failure, and mitochondrial malfunction compound this degeneration (Komatsu, 2021; Ramaswamy et al., 2007; Jurcău, 2016). Moreover, mHTT disrupts the ubiquitin-proteasome pathway and axonal vesicle transport, aggravating cellular stress and promoting neuronal death (Pinto et al., 2020; Villegas et al., 2021).

The pathogenesis of HD involves multiple overlapping mechanisms, including impaired bioenergetic metabolism, calcium signaling disruptions, and defective mitochondrial quality control (D'Egidio et al., 2013). The accumulation of toxic mHTT fragments leads to mitochondrial dysfunction, impaired ATP production, and elevated oxidative stress (Hu et al., 2021). This bioenergetic crisis follows a region-specific progression—beginning in the striatum and cortex and advancing to the cerebellum and thalamus as the disease worsens (D'Egidio et al., 2013). The degeneration predominantly affects the corpus striatum and associated structures, such as the globus pallidus, thalamus, and subthalamic nucleus (Bustamante-Barrientos et al., 2013; Bano et al., 2011; Martin-Solana et al., 2020).

The mutant huntingtin protein disrupts diverse cellular processes, including transcriptional regulation, axonal transport, cytoskeletal integrity, signal transduction, and autophagy, leading to progressive neuronal death (Askeland et al., 2018; Bano et al., 2011). Interestingly, although mHTT is ubiquitously expressed, its toxicity preferentially targets medium spiny neurons due to their high metabolic demand and susceptibility to proteostatic dysfunction (Margulis & Finkbeiner, 2014; Bano et al., 2011). This toxic gain-of-function mechanism drives abnormalities in receptor signaling, proteostasis, and synaptic transmission, particularly within basal ganglia circuits (Morigaki et al., 2020; Jiang et al., 2013). Mitochondrial dysfunction—manifested as disrupted morphology, impaired calcium handling, and compromised ATP synthesis—is strongly associated with HD pathology (Hu et al., 2021; Shafie et al., 2020; Bečanović et al., 2021; Norat et al., 2020).

Deficits in mitochondrial biogenesis, membrane potential, electron transport, and oxidative phosphorylation exacerbate neurodegeneration (Tung et al., 2021). Impairments in mitophagy and mitochondrial quality control result in the accumulation of damaged organelles and heightened oxidative burden (Braun & Puglielli, 2016). Consequently, bioenergetic compromise and cellular stress drive the neuronal vulnerability characteristic of HD (Cilleros-Holgado et al., 2013; Guedes-Dias et al., 2015). Beyond mitochondrial dysfunction, transcriptional dysregulation and impaired proteostasis further perpetuate disease progression (Jiang et al., 2013).

Pathophysiology of Huntington's Disease

At the molecular level, HD involves a complex interplay of pathogenic processes, including conformational alterations in mHTT, defective cellular processing, and proteotoxic stress (Gatto et al., 2020). The expanded CAG repeats in the *HTT* gene produce mutant huntingtin proteins with elongated polyglutamine tracts that aggregate in neuronal nuclei and axons, disrupting normal cellular homeostasis (Tong et al., 2020). These misfolded proteins form β -sheet-rich aggregates such as

dimers, trimers, and oligomers, which impair mitochondrial function, transcriptional regulation, and ultimately trigger apoptosis (Tung et al., 2021; Zhang et al., 2020).

Studies reveal that neurons expressing mHTT display decreased ATP content, diminished glycolytic capacity, and reduced mitochondrial oxygen consumption even before clinical onset (Hu et al., 2021; Bustamante-Barrientos et al., 2013). These bioenergetic deficits are pivotal in HD pathogenesis (Agrawal et al., 2018). Early research using the mitochondrial toxin 3-nitropropionic acid—an inhibitor of complex II—reproduced HD-like pathology, underscoring the central role of energy metabolism in disease progression (Tsunemi et al., 2012; Landles & Bates, 2004). Consistent with this, postmortem studies reveal mitochondrial complex II, III, and IV impairments and elevated lactate production in HD brains (Giorgi et al., 2018; Guo et al., 2013; Tabrizi et al., 2020; Tao et al., 2020; Schon & Manfredi, 2003). Reduced expression of hexokinase II and disruption of glucose metabolism further compound the energetic crisis (Tramutola et al., 2013; Tassone et al., 2013).

These metabolic and oxidative abnormalities, coupled with impaired mitophagy and fragmented mitochondrial networks, contribute to progressive neuronal degeneration (Neueder & Orth, 2020). The synergistic interaction between mHTT aggregation and mitochondrial dysfunction creates a self-perpetuating cycle of oxidative damage and energy depletion, amplifying neurodegeneration (Hu et al., 2021).

Current Therapeutic Strategies for Huntington's Disease

Current therapies for HD are largely symptomatic, aiming to alleviate motor and psychiatric symptoms. However, emerging strategies focus on modifying disease progression through **gene-editing**, **allele-specific silencing**, and **mitochondrial restoration** (Martin-Solana et al., 2020). Enhancing mitochondrial health has emerged as a critical therapeutic avenue to restore bioenergetic balance and mitigate oxidative stress (Clemente-Suárez et al., 2013; Cilleros-Holgado et al., 2013). Among these, targeting mitochondrial iron accumulation has shown promise, as excessive mitochondrial iron contributes to oxidative stress and neuronal loss (Agrawal et al., 2018).

Membrane-permeable iron chelators like **deferiprone** have demonstrated efficacy in reducing mitochondrial iron overload, restoring mitochondrial membrane potential, and improving motor performance in HD mouse models (Agrawal et al., 2018). The therapeutic relevance of iron modulation is further supported by studies showing that neonatal iron supplementation exacerbates disease progression in HD mice (Agrawal et al., 2018). Thus, regulating mitochondrial iron levels represents a promising approach to preserving neuronal viability and delaying disease progression.

Lycopene: A Pharmacological Overview

Lycopene, a potent carotenoid, exhibits strong antioxidant capacity essential for mitigating oxidative stress associated with neurodegenerative diseases (Agrawal et al., 2018). As a non-provitamin A carotenoid, its biological effects arise from its ability to quench ROS and prevent lipid peroxidation, thus preserving cellular integrity (Agrawal et al., 2018). In HD, lycopene's antioxidative and anti-inflammatory effects can counteract iron-mediated oxidative damage and mitochondrial dysfunction (Agrawal et al., 2018). Lycopene's lipophilic nature facilitates its integration into cellular and mitochondrial membranes, where it neutralizes free radicals and stabilizes lipid structures, directly preventing neurodegenerative damage (Agrawal et al., 2018). Furthermore, its capacity to cross the blood-brain barrier allows it to exert protective effects directly within neural tissues, attenuating oxidative stress and inflammation (Paul et al., 2020; Ugbaja et al., 2021; Park et al., 2021).

Sources and Bioavailability of Lycopene

Lycopene is abundant in red fruits and vegetables such as tomatoes, watermelon, papaya, and guava (Ugbaja et al., 2021). Its bioavailability is enhanced by thermal processing and the presence of dietary lipids, which promote isomerization from *trans* to more absorbable *cis* forms (Saini et al., 2020; Przybylska, 2019). Absorbed via chylomicrons and transported through lipoproteins, lycopene readily distributes to tissues including the brain (Imran et al., 2020; Ali et al., 2020). Its ability to cross the blood-brain barrier (Ugbaja et al., 2021; Gambino et al., 2013; Naiel et al., 2013) enables modulation

of key neuroprotective signaling pathways such as PI3K/Akt and BDNF-TrkB-CREB (Xu et al., 2016; Wu et al., 2021), which are essential for neuronal survival and plasticity. This mechanism underpins lycopene's therapeutic potential in mitigating the oxidative and inflammatory burden characteristic of Huntington's disease.

Mechanisms of Action of Lycopene

Lycopene exhibits multifaceted neuroprotective mechanisms against neurodegenerative disorders such as Huntington's disease by modulating key cellular pathways involved in inflammation, apoptosis, and mitochondrial function (Naik et al., 2020). It exerts its beneficial effects primarily through the suppression of pro-inflammatory cytokines—including IL-1 β and TNF- α —while simultaneously enhancing anti-inflammatory mediators such as IL-10, thereby restoring immune homeostasis and mitigating chronic neuroinflammation (Ugbaja et al., 2021). This anti-inflammatory action is of particular importance in neurodegenerative contexts, where persistent inflammation accelerates neuronal injury. Additionally, lycopene effectively counteracts oxidative stress—one of the principal contributors to neurodegeneration—by augmenting endogenous antioxidant defenses and directly scavenging reactive oxygen species (Ugbaja et al., 2021).

Beyond its antioxidant function, lycopene significantly attenuates neuroinflammation by downregulating microglial release of TNF- α , thereby enhancing neuronal survival (Darwish et al., 2013). This property is especially relevant in Huntington's disease, where neuroinflammation is a central factor driving neuronal degeneration (Naik et al., 2020; Singh et al., 2016). Lycopene also inhibits the activation of glial cells—microglia and astrocytes—by suppressing the NF- κ B signaling cascade, a pivotal regulator of inflammatory gene expression (Darwish et al., 2013). Inhibition of this pathway results in reduced synthesis of pro-inflammatory cytokines and chemokines within the central nervous system, further alleviating neuroinflammatory stress (Ugbaja et al., 2021).

Moreover, lycopene's modulation of the PI3K/Akt signaling pathway underscores its potent neuroprotective potential, as this pathway governs essential cellular processes including survival, growth, and synaptic plasticity (Xu et al., 2016; Lim et al., 2020). Activation of PI3K/Akt by lycopene enhances neuronal resistance to apoptotic stimuli, promoting cellular longevity and functional recovery (Naik et al., 2020). Improved behavioral and histopathological outcomes observed in experimental models of Huntington's disease following lycopene administration provide strong preclinical support for its therapeutic value (Mousavi et al., 2018; Darwish et al., 2013).

In addition to these mechanisms, lycopene activates key transcriptional regulators such as nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1), which play pivotal roles in cellular antioxidant defense and neurogenesis (Vassal et al., 2020). This dual regulation—suppression of NF- κ B-mediated inflammation and activation of Nrf2-driven antioxidant pathways—reflects lycopene's broad cytoprotective influence. Furthermore, lycopene modulates Toll-like receptor 4 (TLR4) signaling, promoting microglial polarization toward a neuroprotective phenotype, thereby reducing neuronal loss (Ugbaja et al., 2021; Darwish et al., 2013). Collectively, these interconnected molecular actions position lycopene as a promising therapeutic agent capable of counteracting oxidative, inflammatory, and apoptotic processes that underpin neurodegeneration in Huntington's disease.

Proposed Mechanistic Pathways of Lycopene in Neuroprotection Against Huntington's Disease

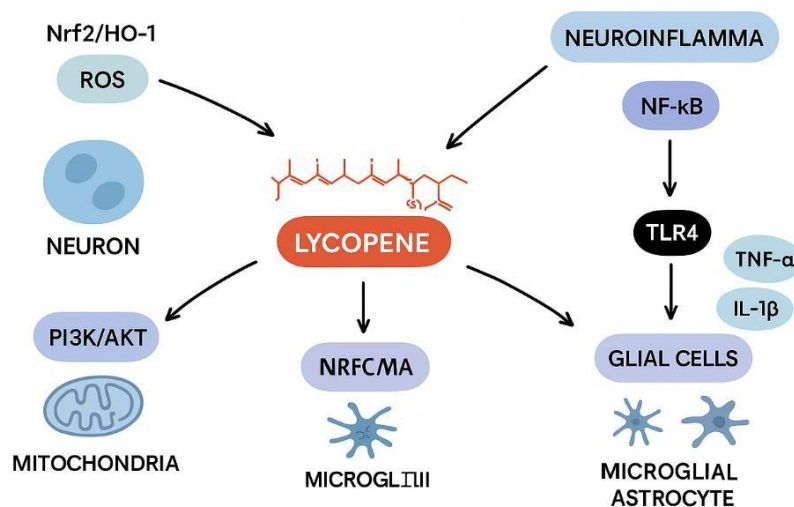


Figure 1. Pathways of lycopene in Neuroprotection Against Huntington's Diseases

PHARMACOLOGICAL IMPORTANCE OF LYCOPENE AGAINST HUNTINGTON'S DISEASE

Neuroprotective Effects of Lycopene

Lycopene, a potent carotenoid, exerts pronounced neuroprotective effects through its strong antioxidant and anti-inflammatory properties—both critical in mitigating the neuronal degeneration characteristic of Huntington's disease. Its ability to modulate vital signaling pathways, including MAPK and NF-κB, underpins its therapeutic potential by attenuating neuroinflammation and enhancing neuronal survival (Darwish et al., 2013; Gambino et al., 2013; Khayatan et al., 2020). Specifically, lycopene suppresses NF-κB-mediated neuroinflammation via the TLR4 pathway, thereby inhibiting the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as evidenced by studies linking NF-κB-p65 upregulation with elevated IL-1β and IL-6 expression (Ugbaja et al., 2021).

In addition to its anti-inflammatory actions, lycopene inhibits acetylcholinesterase activity, thereby enhancing cholinergic neurotransmission—an important neuroprotective mechanism in conditions marked by cognitive decline (Ugbaja et al., 2021). Furthermore, lycopene, along with other carotenoids, can enhance antioxidant capacity by activating the Nrf2-dependent antioxidant response pathway, which regulates the expression of detoxification and redox-balancing genes (Rodríguez-Concepción et al., 2018). This multifaceted mechanism positions lycopene as a promising therapeutic molecule for oxidative stress- and inflammation-driven disorders, including Huntington's disease (Ugbaja et al., 2021).

The suppression of microglial activation and reduced secretion of neuroinflammatory cytokines such as IL-6, IL-1β, and TNF-α further support lycopene's neuroprotective role (Darwish et al., 2013; Figueira et al., 2017). Similar anti-inflammatory effects have been reported for compounds such as oleocanthal, which inhibit inflammatory gene expression and oxidative damage (Barbalace et al., 2020). Lycopene's capacity to elevate glutathione levels and stimulate antioxidant enzyme activities enhances its ability to neutralize reactive oxygen species (Raza et al., 2016; Barbalace et al., 2020; Xia et al., 2013). Its regulatory influence on microglial activation, and consequent reduction in cytokine release, is particularly important in slowing the neuroinflammatory cascades associated with Huntington's pathology (Rekatsina et al., 2019; Wang et al., 2019). This broad antioxidant and anti-inflammatory profile underscores lycopene's role in controlling chronic inflammation that drives neurodegenerative progression (Santarsiero et al., 2020).

Moreover, the attenuation of adenosine deaminase activity—a marker of pathological inflammation—further highlights lycopene's anti-inflammatory capacity (Ugbaja et al., 2021). Evidence also suggests that exogenous Prx-6 can reduce oxidative stress and neuroinflammation in hippocampal neuroglial cultures, supporting the potential benefits of antioxidant-based interventions (Liberto & Mudò, 2016). Lycopene's ability to lower malondialdehyde levels while enhancing glutathione peroxidase and catalase activities strengthens neuronal defenses against oxidative damage (Ugbaja et al., 2021). Additionally, lycopene has been shown to counteract palmitic acid-induced oxidative stress, neuro-signaling hyperactivity, and microglial proliferation, thus alleviating neuroinflammation and cellular injury (Ugbaja et al., 2021). These combined mechanisms—normalizing myeloperoxidase activity and restoring glutathione balance—highlight lycopene's therapeutic promise in mitigating Huntington's disease pathology (Ugbaja et al., 2021).

Antioxidant Properties in Neurodegeneration

The brain's high oxygen consumption and lipid-rich structure make it especially prone to oxidative stress, a major contributor to neurodegenerative diseases such as Huntington's (Simonian, 1996). Lycopene acts as a potent free radical scavenger, preserving neuronal redox homeostasis and preventing oxidative neuronal injury (Ugbaja et al., 2021). This function is vital in Huntington's pathology, where elevated lipid peroxidation and diminished antioxidant enzyme activities accelerate neurodegeneration (Simonian & Coyle, 1996; Rekatsina et al., 2019).

Lycopene supplementation has been found to significantly reduce malondialdehyde levels—an indicator of lipid peroxidation—while enhancing the activity of antioxidant enzymes including superoxide dismutase and glutathione peroxidase (Ugbaja et al., 2021; Alotaibi et al., 2020). These effects preserve membrane integrity and prevent protein oxidation, maintaining overall neuronal homeostasis (Alotaibi et al., 2020). Palmitic acid-induced oxidative stress, which typically suppresses catalase and glutathione peroxidase activity, can be effectively countered by lycopene (Ugbaja et al., 2021).

Furthermore, lycopene reduces aberrant enzymatic activities linked to neurodegeneration, such as acetylcholinesterase, adenosine deaminase, and monoamine oxidase-A (Ugbaja et al., 2021). The inhibition of monoamine oxidase-A suggests that lycopene may alleviate cognitive deficits by curbing neuroinflammation and oxidative stress, possibly through the upregulation of brain-derived neurotrophic factor (Ugbaja et al., 2021). Additionally, lycopene modulates the hyperactivity of NTPDase and 5'-nucleotidase—enzymes involved in maintaining nucleotide and energy pools—thus preventing neurodegenerative energy depletion and cell death (Ugbaja et al., 2021).

Anti-inflammatory Effects in Neurological Disorders

Beyond its antioxidant capabilities, lycopene exhibits robust anti-inflammatory properties that are particularly relevant to neurodegenerative diseases characterized by chronic inflammation. Lycopene modulates purinergic signaling, helping restore ATP balance essential for neuronal activity (Ugbaja et al., 2021). It also reduces inflammatory responses by lowering phospholipid accumulation and regulating transcription factors involved in lipid biosynthesis, thereby preventing lipid-driven neuroinflammation (Ugbaja et al., 2021).

Importantly, lycopene reduces the elevated activities of adenosine deaminase and myeloperoxidase—key markers of neuroinflammation—demonstrating its ability to suppress inflammatory processes in the central nervous system (Ugbaja et al., 2021). By mitigating lipid dysregulation and inflammation, lycopene offers dual protection against neurodegenerative cascades (Ugbaja et al., 2021). Its inhibition of monoamine oxidase-A further alleviates ammonia-induced neurotoxicity and inflammatory stress (Ugbaja et al., 2021).

Moreover, lycopene supplementation enhances memory function and reduces seizure susceptibility, reflecting its neuroprotective influence on cognitive and excitatory circuits (Taşkıran & Taştür, 2021). This combination of antioxidant, anti-inflammatory, and neurochemical modulatory properties underscores lycopene's potential as a therapeutic candidate for Huntington's disease, where current

treatments largely address symptoms rather than underlying mechanisms (Elbandy, 2016; Wang et al., 2020).

Modulation of Apoptotic Pathways

Lycopene's neuroprotective activity also encompasses the regulation of apoptotic pathways, which play a pivotal role in neuronal survival under neurodegenerative stress (Elkader et al., 2013). It inhibits programmed cell death by suppressing caspase activation and balancing the expression of pro- and anti-apoptotic proteins, thereby maintaining neuronal integrity (Naik et al., 2020). In models of cerebral ischemia-reperfusion and neurotoxicity, lycopene significantly reduces neuronal apoptosis and functional impairment by modulating key apoptotic markers (Elkader et al., 2013; Bhardwaj & Kumar, 2015; Pekdemir et al., 2020).

Notably, lycopene downregulates Bax and upregulates Bcl-2 expression—key regulators of mitochondrial membrane permeability and cytochrome c release—thereby preventing intrinsic apoptosis. Its interaction with the PI3K/Akt pathway further supports neuronal survival and regeneration under stress (Avola et al., 2020). Collectively, these mechanisms demonstrate lycopene's capacity to inhibit neuronal death through a coordinated balance of antioxidant, anti-inflammatory, and anti-apoptotic effects (Sharifi-Rad et al., 2020; Gambino et al., 2013).

Given the limitations of current pharmacological treatments that largely fail to halt disease progression, the multifunctional profile of lycopene and other natural neuroprotective compounds offers a promising alternative approach (Sairazi & Sirajudeen, 2020; Shoaib et al., 2013; Grosso et al., 2013). By enhancing neuroplasticity, reducing apoptosis, and promoting neurogenesis, lycopene represents a compelling therapeutic candidate for managing complex neurological conditions such as Huntington's disease (Pekdemir et al., 2020).

Comprehensive Mechanistic Approaches of Lycopene Against Huntington's Disease Progression

The following table comprehensively summarizes the multifaceted mechanisms through which lycopene exerts its neuroprotective effects against the progression of Huntington's Disease (HD). It highlights molecular targets, signaling pathways, evidence types, and specific outcomes observed in experimental models, demonstrating lycopene's potential as a therapeutic nutraceutical for mitigating oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal apoptosis associated with HD pathology.

Mechanism of Action	Molecular Targets/Pathways	Effect of Lycopene	Evidence Type	Outcome in HD	References
Reduction of oxidative stress	Nrf2/HO-1 pathway, ROS scavenging	Enhances endogenous antioxidants (SOD, CAT, GSH); neutralizes free radicals	In vitro & In vivo	Protects neurons from oxidative injury and mitochondrial dysfunction	Ugbaja et al., 2021; Vassal et al., 2020
Anti-inflammatory regulation	NF- κ B, TLR4, IL-1 β , TNF- α , IL-10	Suppresses NF- κ B activation and pro-inflammatory cytokines; upregulates IL-10	In vitro & In vivo	Reduces microglial activation and neuroinflammation	Naik et al., 2020; Darwish et al., 2013
Mitochondrial protection	Mitochondrial respiratory enzymes, membrane	Preserves mitochondrial integrity and ATP generation;	In vivo	Improves neuronal survival and motor coordination	Rafe, 2013; Rahman et al., 2021

	potential stabilization	reduces lipid peroxidation			
Regulation of apoptosis	PI3K/Akt, Bax/Bcl-2, Caspase-3	Activates PI3K/Akt signaling; increases Bcl-2; inhibits Bax and Caspase-3 expression	In vitro	Prevents neuronal apoptosis and promotes cell survival	Xu et al., 2016; Lim et al., 2020
Modulation of lipid metabolism	Palmitic acid, TLR4/NF- κ B axis	Attenuates palmitic acid-induced inflammation and lipid peroxidation	In vitro & In vivo	Mitigates lipid-induced neurotoxicity and inflammation	Ugbaja et al., 2021; McGarry et al., 2020
Microglial and astrocyte regulation	Microglial polarization, TLR4 pathway	Promotes M2 (anti-inflammatory) phenotype; inhibits M1 activation	In vitro	Enhances neuronal protection through controlled immune response	Darwish et al., 2013; Singh et al., 2016
Gene expression modulation	Nrf2/ARE, HO-1, SOD1, GPx	Upregulates antioxidant and detoxifying genes	In vitro & In vivo	Restores redox balance and supports neuronal health	Vassal et al., 2020; Naik et al., 2020
Neurotransmitter balance	Dopaminergic and glutamatergic signaling	Stabilizes neurotransmitter levels by reducing oxidative degradation	In vivo	Improves behavioral performance and cognitive functions	Mousavi et al., 2018; Rafe, 2013
Molecular crosstalk in neuroprotection	NF- κ B–Nrf2 interplay	Inhibits NF- κ B-mediated inflammation while activating Nrf2 antioxidative pathways	In vitro	Dual regulation enhances neuroprotection and reduces HD progression	Ugbaja et al., 2021; Darwish et al., 2013
Enhancement of neuronal plasticity	BDNF, PI3K/Akt, CREB signaling	Upregulates neurotrophic factors promoting synaptic growth and repair	In vivo	Improves learning and memory functions	Lim et al., 2020; Xu et al., 2016

Experimental Evidence and Clinical Relevance

An expanding body of experimental evidence supports the neuroprotective potential of natural bioactive compounds such as lycopene in combating various neurodegenerative diseases (Lim et al., 2020). Preclinical studies have consistently demonstrated that these natural agents can ameliorate fundamental pathological features—including aberrant protein aggregation, oxidative stress, and neuroinflammation—that are common hallmarks of disorders like Alzheimer's, Parkinson's, and Huntington's diseases (Shoaib et al., 2013; Xu et al., 2016). The robust preclinical data advocate strongly for translating these findings into clinical studies, particularly for compounds like lycopene that exhibit wide-ranging neuroprotective effects (Nahar et al., 2021).

The growing interest in natural products stems from the recognition that conventional pharmacological therapies often fail to provide long-term disease-modifying effects in neurodegenerative conditions (Wang et al., 2020; Nahar et al., 2021). Moreover, the complex interplay of diverse secondary metabolites derived from plants, marine organisms, and fungi offers an abundant reservoir for novel drug discovery, with unique mechanisms that may address the multifactorial pathology of neurodegenerative disorders (Nahar et al., 2021). Despite significant progress in elucidating disease mechanisms, current pharmacological interventions remain largely symptomatic, emphasizing the urgent need for alternative strategies such as phytochemical-based therapeutics (Andrade et al., 2013).

In Vitro Studies on Lycopene and Huntington's Disease Models

In vitro studies have provided foundational insight into lycopene's neuroprotective mechanisms in Huntington's disease (HD) models, primarily through the use of neuronal cell lines exposed to excitotoxic insults or mutant huntingtin fragments. These experimental systems replicate critical aspects of HD pathology, enabling evaluation of lycopene's capacity to mitigate oxidative stress, suppress apoptosis, and modulate inflammatory responses (Vassal et al., 2020; Goyal et al., 2020).

Evidence demonstrates that lycopene treatment significantly reduces reactive oxygen species (ROS) generation and lipid peroxidation in cultured neurons under oxidative challenge, thereby preserving mitochondrial function and reducing cellular damage (Rahman et al., 2021). Lycopene also enhances antioxidant enzyme activities and directly scavenges free radicals, bolstering neuronal resilience against chronic oxidative stress—a central driver of HD pathogenesis (Rasool et al., 2014; Babazadeh et al., 2013; Limanaqi et al., 2020).

Moreover, in vitro research highlights lycopene's ability to attenuate neuroinflammation through microglial deactivation and downregulation of pro-inflammatory cytokines such as TNF- α and IL-6, both of which are critical mediators of neurotoxicity in HD (Paul et al., 2020). Collectively, these studies emphasize lycopene's capacity to target multiple molecular pathways simultaneously—oxidative, inflammatory, and apoptotic—offering a multitarget therapeutic advantage in addressing the complex pathology of Huntington's disease (Andrade et al., 2013; Goyal et al., 2020).

In Vivo Studies on Lycopene and Huntington's Disease Models

In vivo studies using animal models have further substantiated the neuroprotective properties of lycopene. Notably, administration of lycopene in 3-nitropropionic acid (3-NP)-induced HD models has been shown to improve motor coordination, reduce striatal oxidative stress, and attenuate behavioral impairments (Rafe, 2013). These outcomes are consistent with findings from other neuroprotective phytochemicals, such as naringin, curcumin, and sulforaphane, which act via activation of NRF2-dependent antioxidant pathways to alleviate oxidative stress and enhance motor function (Chen & Dodson, 2013).

As an aliphatic polyunsaturated carotene, lycopene exerts its effects through potent antioxidant and anti-inflammatory actions, neutralizing free radicals via electron donation and chain-breaking mechanisms (Ugbaja et al., 2021; Paul et al., 2020). Importantly, lycopene's lipophilicity enables it to cross the blood-brain barrier effectively, allowing direct interaction with neural tissues to scavenge reactive oxygen species and mitigate neuroinflammation at the site of pathology (Ugbaja et al., 2021; Ali et al., 2020).

Further mechanistic studies reveal that lycopene activates the Nrf2 signaling cascade, thereby enhancing the transcription of antioxidant and cytoprotective genes involved in redox regulation (Tucci et al., 2016). This activity parallels that of other neuro-nutraceuticals, such as polyphenols and curcumin, which similarly cross the blood-brain barrier and confer central nervous system protection (Gambino et al., 2013). Additionally, lycopene modulates key cellular signaling pathways, including PI3K/Akt and COX-2/NF- κ B, offering a multifaceted mechanism to combat oxidative and inflammatory neurodegeneration (Gambino et al., 2013; Xu et al., 2016; Naik et al., 2020). These findings collectively reinforce lycopene's potential as a broad-spectrum neuroprotective agent capable of intervening in multiple pathological pathways.

Potential Therapeutic Applications and Challenges

Despite substantial preclinical evidence supporting lycopene's neuroprotective efficacy, translating these findings into clinical practice presents several challenges. A primary obstacle is determining the optimal therapeutic dose and delivery method required to achieve effective concentrations within the central nervous system, given the constraints imposed by the blood-brain barrier (Naiel et al., 2013). While antioxidant strategies show encouraging outcomes in preclinical models, their limited clinical translation underscores the need for optimizing dosing regimens, treatment duration, and delivery technologies (Carvalho et al., 2016; Liu et al., 2016).

Lycopene's pharmacokinetics—particularly its bioavailability and metabolism—vary considerably among individuals, complicating standardization of therapeutic protocols. Moreover, the heterogeneous progression of Huntington's disease necessitates personalized treatment strategies to accommodate patient-specific metabolic and pathological variations. Although lycopene mitigates palmitic acid-induced neuroinflammation through modulation of the TLR4/NF- κ B-p65 signaling axis and lipid metabolism, further studies are needed to elucidate its precise molecular interactions within HD pathophysiology (Ugbaja et al., 2021).

Additionally, emerging evidence suggests that sex-specific differences may influence neuroinflammatory responses in HD, emphasizing the importance of investigating lycopene's effects across demographic and biological variables (Risby-Jones et al., 2020). Comprehensive clinical trials are therefore essential to validate the safety, efficacy, and optimal therapeutic window of lycopene in human HD patients (Singh et al., 2016; Satyam & Bairy, 2016). Such studies must also evaluate long-term outcomes, drug interactions, and potential impacts on lipid metabolism, given the intricate link between dietary lipids and brain health (Catani et al., 2017).

To overcome bioavailability limitations, nanocarrier-based delivery systems such as liposomes, nano emulsions, and polymeric nanoparticles have emerged as promising strategies for improving lycopene's solubility, stability, and targeted brain delivery (Vishwas et al., 2020; Marino et al., 2021; Baburaj et al., 2013). These advanced delivery approaches could enhance lycopene's pharmacological efficacy, allowing consistent therapeutic concentrations within neural tissues and paving the way for its successful clinical application in Huntington's disease therapy.

Discussion

The dysregulation of fatty acid metabolism, inflammation, and energy homeostasis observed in Huntington's disease (HD) underscores the complex molecular network underlying this progressive neurodegenerative disorder (Neueder et al., 2016; McGarry et al., 2020). Elevated concentrations of long-chain saturated fatty acids such as palmitic acid have been strongly associated with the clinical progression of HD and the exacerbation of neuroinflammation, highlighting the role of dietary lipids as modulators of disease pathology (McGarry et al., 2020; Ugbaja et al., 2021). These metabolic perturbations trigger mitochondrial dysfunction and oxidative stress—two principal drivers of neuronal loss and cognitive decline in HD (Ugbaja et al., 2021). Concomitant reductions in lipid species such as cholesterol esters and phosphatidylcholines have been observed throughout disease stages, suggesting systemic disruption of lipid metabolism (McGarry et al., 2020).

Within this biochemical framework, **lycopene**, a potent antioxidant and anti-inflammatory carotenoid, emerges as a promising neuroprotective candidate capable of counteracting these lipid-related imbalances. Lycopene's well-established ability to attenuate oxidative stress, inhibit lipid peroxidation, and modulate inflammatory signaling pathways directly addresses key pathogenic mechanisms implicated in HD (Naik et al., 2020; Ugbaja et al., 2021). Through scavenging reactive oxygen species (ROS) and upregulating endogenous antioxidant enzymes, lycopene restores redox balance and preserves mitochondrial function, thereby mitigating oxidative lipid damage—a crucial step in protecting neuronal membranes from peroxidative injury. Moreover, its lipophilic nature enables it to integrate into cellular membranes and the blood–brain barrier, where it can directly influence membrane stability and lipid signaling (Ugbaja et al., 2021).

Interestingly, certain lipid species such as sphingolipids, particularly sphingosine-1-phosphate, exhibit neuroprotective effects by promoting glial survival and neurite extension (McGarry et al.,

2020). Lycopene may enhance such compensatory mechanisms by modulating sphingolipid metabolism and reducing the pro-apoptotic effects of ceramide accumulation. Additionally, metabolic abnormalities in the urea cycle, including elevated arginine and citrulline levels, have been reported in HD (McGarry et al., 2020). Lycopene's influence on nitric oxide synthase activity and its anti-nitrosative potential may thus indirectly help regulate arginine metabolism, preventing excessive generation of reactive nitrogen species that contribute to neuronal injury.

Moreover, polyunsaturated fatty acids such as omega-3s have been shown to alleviate HD-related symptoms, including cachexia, mood disturbances, and cognitive deficits (Vega & Cepeda, 2021). Lycopene may synergize with such neuroprotective lipids by preserving membrane fluidity, reducing inflammatory lipid mediators, and enhancing neuronal signaling efficiency. Altered circulating phospholipids, including phosphatidylcholine and diacylglycerol, have been correlated with HD progression, indicating impaired membrane integrity and disrupted lipid signaling cascades (McGarry et al., 2020). Lycopene's modulation of key lipid-regulatory enzymes—such as phospholipase A2 and cyclooxygenase-2 (COX-2)—offers a mechanism to normalize these lipid dynamics and prevent further neuronal deterioration (Naik et al., 2020).

The dynamic alterations in ceramide and sphingomyelin species further emphasize the widespread lipid dyshomeostasis characteristic of HD. Interestingly, certain sphingomyelin species (e.g., SM 20:0 and SM 20:1) have shown positive correlations with cognitive function scores (McGarry et al., 2020; Mohandas, 1 C.E.), suggesting that maintaining sphingolipid balance could support cognitive integrity. Lycopene's anti-inflammatory actions—mediated through suppression of NF- κ B and activation of the Nrf2/HO-1 antioxidant axis—could stabilize these lipid species by limiting inflammatory lipid turnover and oxidative degradation (Darwish et al., 2013; Vassal et al., 2020).

Furthermore, alterations in diacylglyceride and triacylglyceride levels in plasma and cerebrospinal fluid (CSF) serve as indicators of HD progression, with declining plasma triglycerides and rising CSF triglycerides correlating with worsening clinical features (McGarry et al., 2020). This compartment-specific dyslipidemia reflects localized energy deficits within the brain. Lycopene's capacity to improve mitochondrial bioenergetics and reduce oxidative stress may help restore lipid equilibrium between plasma and CSF compartments, enhancing neuronal energy metabolism.

These lipid alterations in HD parallel those observed in systemic metabolic disorders such as diabetes, where dyslipidemia contributes to multi-organ complications (Lv et al., 2015; Nemezc et al., 2013). Lycopene has been shown to normalize lipid metabolism and reduce hyperlipidemia through modulation of PPAR γ and AMPK pathways, indicating its broader metabolic relevance (Ugbaja et al., 2021). By influencing lipid oxidation and transport, lycopene may mitigate both peripheral and central lipid abnormalities in HD, providing a dual protective benefit.

Emerging evidence further implicates microRNAs (miRNAs) in the regulation of lipid metabolism and neuroinflammation in HD. Dysregulated miRNAs such as miR-122 and miR-155, known biomarkers of diabetic dyslipidemia, may similarly influence lipid pathways in HD (Nemezc et al., 2013). Lycopene's interaction with epigenetic regulators, including miRNAs and transcription factors such as Nrf2 and NF- κ B, suggests a potential to restore transcriptional balance and normalize lipid-associated gene expression. Investigating miRNAs like miR-143-3p, miR-132-3p, miR-218-5p, miR-21, miR-122, and miR-155 could further clarify how lycopene modulates lipid biosynthesis and inflammatory signaling in neurodegenerative contexts (Nemezc et al., 2013).

Additionally, miR-223, miR-21-5p, and miR-126-3p—key regulators of inflammation and vascular homeostasis—may mediate some of lycopene's systemic effects, linking lipid metabolism to vascular and neuronal protection (Olivieri et al., 2015; Amr et al., 2018). Lycopene's ability to suppress miR-155 and enhance miR-126 expression could thus offer a molecular route to reduce neurovascular inflammation and support endothelial function in HD.

Overall, these findings converge to indicate that lycopene can modulate multiple metabolic and inflammatory pathways implicated in HD, offering protection at both neuronal and systemic levels. By stabilizing lipid metabolism, attenuating oxidative stress, modulating inflammatory mediators, and interacting with regulatory miRNAs, lycopene addresses the multifactorial nature of HD pathology. The selective vulnerability of the striatum and cortex—regions showing early metabolic and

histopathological changes—further highlights the therapeutic potential of lycopene in maintaining mitochondrial and lipid homeostasis within these critical brain areas (McGarry et al., 2020). Moreover, the extensive transcriptional alterations in energy metabolism genes observed in HD patients and models (Krzysztoń-Russjan et al., 2012) may be mitigated by lycopene through its regulation of redox-sensitive transcriptional networks, contributing to overall neuroprotection. In summary, lycopene represents a promising neurotherapeutic compound capable of correcting metabolic, inflammatory, and oxidative imbalances in Huntington's disease, potentially slowing disease progression and improving neuronal resilience. Further clinical research integrating lipidomics, transcriptomics, and metabolomics will be critical to fully elucidate lycopene's mechanistic role and therapeutic efficacy in HD.

Conclusion

The findings from this review underscore the multifaceted role of lipid metabolism dysregulation in the progression of Huntington's disease (HD), while highlighting the therapeutic promise of bioactive compounds such as lycopene present in wild cherry tomatoes. The extensive metabolic disruptions involving fatty acids, phospholipids, sphingolipids, and triacylglycerides contribute to oxidative stress, mitochondrial dysfunction, and neuronal degeneration. These disturbances are further intertwined with microRNA-mediated regulatory pathways, amplifying neuroinflammation and impairing energy homeostasis. Importantly, the compartment-specific differences between plasma and cerebrospinal fluid lipid profiles indicate that systemic and central metabolic alterations jointly contribute to the pathogenesis of HD. Such complexity necessitates a multidimensional therapeutic approach that integrates metabolic modulation, antioxidant protection, and gene regulatory strategies. Within this framework, lycopene emerges as a potent neuroprotective compound capable of mitigating many of the pathophysiological hallmarks of HD. Its exceptional antioxidant capacity enables it to scavenge reactive oxygen species, stabilize mitochondrial function, and suppress lipid peroxidation—processes intimately linked with HD progression. Additionally, lycopene's ability to modulate lipid metabolism, reduce neuroinflammation, and influence signaling pathways associated with neuronal survival underscores its pharmacological relevance. By targeting the oxidative and metabolic imbalances central to HD, lycopene from wild cherry tomatoes holds potential not only as a dietary neuroprotectant but also as an adjunct therapeutic agent in managing neurodegenerative diseases. Future investigations focusing on molecular interactions, dosage optimization, and clinical translation are vital for harnessing the full pharmacological potential of lycopene against Huntington's disease.

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