

Investigating Boswellia Serrata and Boswellic Acid for Huntington's Disease: Therapeutic Prospects

Comment [H1]: The title presents the effects of a plant on Huntington's disease, known previously with its benefits on mental diseases; and this reflects the originality of the idea.

Abstract: Neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), pose significant challenges to global healthcare systems due to their progressive nature and limited therapeutic options. In recent years, natural compounds have garnered attention for their potential neuroprotective effects. Boswellic acid, derived from the resin of *Boswellia serrata*, has emerged as a promising candidate for the treatment of neurodegenerative diseases. This comprehensive review explores the therapeutic potential of boswellic acid in AD, PD, and HD. The review begins by elucidating the neuroprotective mechanisms of boswellic acid, including its anti-inflammatory, antioxidant, and neurotrophic properties. Preclinical studies demonstrating the efficacy of boswellic acid in mitigating neurodegenerative processes are summarized, highlighting its ability to modulate key signaling pathways involved in neuronal survival and apoptosis. Furthermore, the review discusses the therapeutic implications and future perspectives of boswellic acid in neurodegenerative disorders, emphasizing the need for further research to validate its clinical efficacy. Overall, this review provides valuable insights into the neuroprotective effects of boswellic acid and its potential as a therapeutic agent for neurodegenerative diseases. Understanding the mechanisms underlying its beneficial effects may pave the way for the development of novel treatment strategies targeting these devastating conditions.

Keywords: Alzheimer's disease, Parkinson's disease, and Huntington's disease, Boswellic acid

Comment [H2]: The author started with a reminder to readers with a crucial matter as they are the most with the shortage in tools and means; then he disclosed the new solution.

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Introduction:

Boswellia serrata, commonly known as Indian frankincense, is a tree native to the dry, mountainous regions of India, North Africa, and the Middle East. For centuries, it has been prized in traditional medicine for its therapeutic properties, particularly in the treatment of inflammatory conditions and pain relief. The key bioactive compounds found in *Boswellia serrata* resin are collectively known as boswellic acids, which have garnered significant attention due to their potential health benefits (1).

Boswellic acids, including β -boswellic acid, acetyl- β -boswellic acid, and 11-keto- β -boswellic acid, exhibit anti-inflammatory, anti-arthritic, analgesic, and anti-cancer properties, among others. These compounds exert their effects through various mechanisms, including inhibition of pro-inflammatory enzymes, suppression of inflammatory cytokines, and modulation of immune responses (2).

In recent years, research into the therapeutic potential of Boswelliaserrata and boswellic acid has expanded beyond traditional uses, particularly in the context of neurodegenerative diseases. Conditions such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis pose significant challenges to both patients and healthcare providers, highlighting the urgent need for effective treatment strategies (3).

The proposed review aims to provide an overview of the current scientific evidence regarding the therapeutic potential of Boswelliaserrata and boswellic acid in neurodegenerative diseases. By synthesizing findings from preclinical and clinical studies, this review seeks to elucidate the mechanisms of action underlying the neuroprotective effects of Boswelliaserrata and boswellic acid and evaluate their efficacy and safety profiles.

Comment [H4]: Introduction is well organized as it started with presentation of the plant, then, its use in traditional medicine, and finally, proposition of this work.

2. Neuroprotective Mechanisms of Boswellic Acid: An overview

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), pose significant challenges to public health globally. These conditions entail the progressive loss of neurons and cognitive functions, leading to debilitating symptoms and a compromised quality of life. Despite extensive research efforts over decades, the quest for effective treatments for neurodegenerative diseases remains unfulfilled, emphasizing the urgent need for innovative therapeutic approaches (3).

Boswelliaserrata, an indigenous tree found in India, North Africa, and the Middle East, has been a staple in traditional medicine for centuries, offering remedies for various ailments, including inflammation and pain. Among its bioactive constituents, boswellic acid has garnered considerable attention due to its potential neuroprotective properties. This review endeavors to delve into the mechanisms underlying boswellic acid's neuroprotective effects

and its prospective therapeutic applications in the realm of neurodegenerative diseases (1,19,20).

Comment [H5]: The author presents the common point between different mental diseases, treated with the main plant, including the studied disease.

Management of Neurodegenerative Diseases: Mechanistic Approach of Boswellic Acid

The possible mechanisms of Neuroprotection include anti-inflammatory effects, antioxidant activity, anti-apoptotic, neurotrophic and anti-amyloidogenic activity.

Boswellic acid exhibits potent anti-inflammatory activity by inhibiting pro-inflammatory enzymes like 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2). Through the suppression of inflammatory mediators such as leukotrienes and prostaglandins, boswellic acid mitigates neuroinflammation, a pivotal factor in numerous neurodegenerative pathologies (4).

Oxidative stress plays a central role in neurodegenerative disease progression, contributing to neuronal damage. Boswellic acid acts as an antioxidant by scavenging free radicals and reducing oxidative damage to cellular components. This property reinforces endogenous antioxidant defenses, safeguarding neurons from oxidative harm (5).

Excessive neuronal apoptosis, a common feature in neurodegenerative diseases, compromises neural integrity. Boswellic acid inhibits apoptotic signaling pathways, promoting neuronal survival by modulating key regulators like Bcl-2 and caspases. These actions support neuronal viability in pathological conditions (6).

Boswellic acid enhances the production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). These factors facilitate neuronal growth, survival, and plasticity, fostering the maintenance of neuronal networks and synaptic connections. Boswellic acid-induced neurotrophic signaling promotes neurogenesis and neuronal regeneration, critical for combating neurodegeneration (7).

Alzheimer's disease is characterized by abnormal protein aggregation, particularly amyloid-beta ($A\beta$) peptide accumulation. Boswellic acid inhibits $A\beta$ peptide formation and aggregation, along with amyloid plaque deposition in the brain. By addressing protein misfolding and aggregation, boswellic acid holds promise for mitigating Alzheimer's-related neurodegeneration (7).

The multifaceted neuroprotective mechanisms of boswellic acid from *Boswelliaserrata* offer compelling prospects for novel therapeutic interventions in neurodegenerative diseases. By targeting diverse pathogenic pathways including inflammation, oxidative stress, apoptosis, and protein aggregation, boswellic acid emerges as a versatile neuroprotective agent. Further exploration of its molecular targets and safety profile in preclinical and clinical settings is imperative. Leveraging the therapeutic potential of boswellic acid may herald a transformative approach to alleviate the burden of neurodegenerative diseases, thereby enhancing the well-being of affected individuals.

Comment [H6]: In a very organized manner the author presents effects of main components of the studied plant.

Alzheimer's Disease and Boswellic Acid: Investigating Therapeutic Pathways

Alzheimer's disease (AD) represents a significant global health challenge with limited treatment options. Recent research has explored the potential therapeutic benefits of boswellic acid, a bioactive compound derived from *Boswelliaserrata*, in managing AD. This review aims to delve into the mechanisms underlying the therapeutic effects of boswellic acid in AD and explore potential therapeutic pathways.

Neuroinflammation and oxidative stress are key pathological features of AD. Boswellic acid has been shown to possess anti-inflammatory and antioxidant properties, which could attenuate neuroinflammation and oxidative damage in AD pathogenesis. Studies have demonstrated that boswellic acid inhibits pro-inflammatory cytokines and mediators, such as tumor necrosis factor-alpha (TNF- α) and interleukin-1 beta (IL-1 β), thereby reducing neuroinflammatory responses. Additionally, boswellic acid exhibits antioxidant activity by scavenging reactive oxygen species (ROS) and enhancing endogenous antioxidant defenses, thus mitigating oxidative stress-induced neuronal injury (8).

Accumulation of amyloid beta (A β) plaques and hyperphosphorylated tau protein aggregates are hallmark pathological features of AD. Boswellic acid has been reported to modulate amyloidogenic pathways and inhibit A β aggregation, thereby potentially reducing A β plaque formation and deposition in the brain. Moreover, boswellic acid may attenuate tau hyperphosphorylation through regulation of glycogen synthase kinase-3 β (GSK-3 β) activity, a key kinase implicated in tau phosphorylation and neurofibrillary tangle formation (9).

Boswellic acid exerts neuroprotective effects by preserving neuronal integrity and enhancing synaptic function. Preclinical studies have suggested that boswellic acid protects against

neuronal apoptosis and degeneration induced by neurotoxic insults, such as A β toxicity and glutamate excitotoxicity. Furthermore, boswellic acid has been shown to promote synaptic plasticity and neurotransmission, which are essential for cognitive function and memory consolidation in AD (10).

Boswellic acid may modulate neurotransmitter systems implicated in AD pathophysiology, such as cholinergic and glutamatergic neurotransmission. Experimental evidence suggests that boswellic acid enhances cholinergic neurotransmission by inhibiting acetylcholinesterase (AChE) activity, thus increasing acetylcholine levels in the brain. Moreover, boswellic acid modulates glutamatergic signaling pathways, potentially attenuating excitotoxicity and neuronal damage associated with excessive glutamate release (11).

Emerging evidence supports the therapeutic potential of boswellic acid in AD by targeting multiple pathological pathways, including neuroinflammation, oxidative stress, amyloidogenesis, tau hyperphosphorylation, neuroprotection, synaptic dysfunction, and neurotransmitter dysregulation. Further preclinical and clinical studies are warranted to elucidate the efficacy, safety, and optimal dosage regimens of boswellic acid as a promising adjunctive therapy for AD management.

Evaluating Boswellic Acid: As a Therapeutic Approach in Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as tremors, bradykinesia, rigidity, and postural instability, along with non-motor symptoms like cognitive impairment and psychiatric disturbances. Current treatments focus on symptom management but fail to halt disease progression. Boswellic acid, derived from the resin of *Boswelliaserrata*, has garnered interest for its potential neuroprotective and anti-inflammatory properties.

Boswellic acid, derived from the resin of *Boswelliaserrata*, exhibits a range of therapeutic properties that make it a potential candidate for the management of Parkinson's disease (PD). One of its key mechanisms of action is its anti-inflammatory effects. Boswellic acid has been found to possess potent anti-inflammatory properties by inhibiting pro-inflammatory cytokines and enzymes such as cyclooxygenase and lipoxygenase. These enzymes play crucial roles in the production of inflammatory mediators, and by inhibiting them, Boswellic acid can attenuate neuroinflammation, which is a significant contributor to neuronal damage

in PD. By reducing inflammation, Boswellic acid may help protect dopaminergic neurons from damage and slow down the progression of the disease (12).

Moreover, oxidative stress is known to play a significant role in the pathogenesis of PD. Oxidative stress leads to the production of free radicals, which can cause damage to cellular components and ultimately result in neuronal death. Boswellic acid exhibits antioxidant activity by scavenging free radicals and enhancing the activity of endogenous antioxidant defenses. This antioxidant activity may help protect dopaminergic neurons from oxidative damage, thereby mitigating disease progression in PD (13).

Furthermore, Boswellic acid has demonstrated neuroprotective effects in various preclinical models of neurodegenerative diseases, including PD. It exerts its neuroprotective effects by modulating multiple signaling pathways involved in neuronal survival and apoptosis, such as the Akt/PI3K and MAPK pathways. By promoting neuronal survival and inhibiting apoptotic pathways, Boswellic acid may help preserve dopaminergic function and neuronal integrity in PD (14).

Another aspect of Boswellic acid's therapeutic potential in PD is its ability to modulate mitochondrial function. Dysfunction of mitochondrial dynamics and bioenergetics is implicated in the pathogenesis of PD. Boswellic acid has been reported to enhance mitochondrial biogenesis and improve mitochondrial respiration, thereby restoring mitochondrial homeostasis and alleviating mitochondrial dysfunction observed in PD. By enhancing mitochondrial function, Boswellic acid may help improve cellular energy production and reduce neuronal damage in PD (12).

Finally, boswellic acid holds promise as a therapeutic agent for PD due to its anti-inflammatory, antioxidant, neuroprotective, and mitochondrial modulating properties. Further research, including preclinical and clinical studies, is warranted to explore its efficacy, safety, and optimal dosage regimens in the management of PD. Harnessing the therapeutic potential of Boswellic acid may offer new avenues for disease-modifying treatments in PD.

Comment [H7]: Both sections discussed in detail the effects of the plant on Alzheimer's disease and Parkinson disease. Prowess of the author to give such details bestowed the hearticle an educative paper.

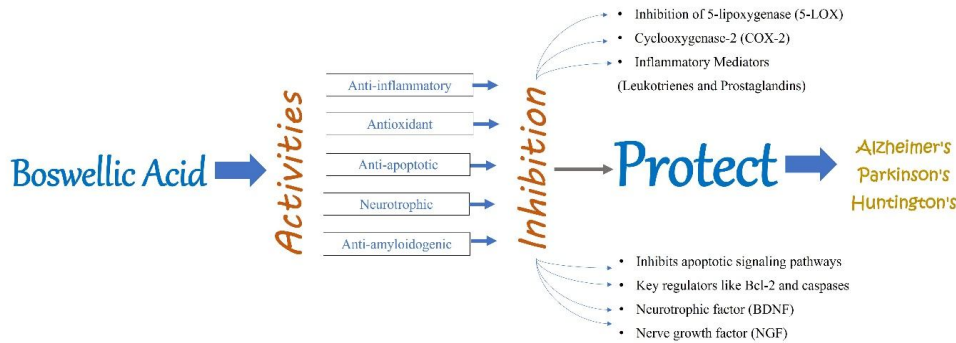


Figure 01: Diagram depicting the neuroprotective mechanism of Boswellic Acid

Comment [H8]: This figure summarizes all that mentioned in the previous section; and helps in understanding objectives of the article.

Boswellic Acid: Exploring Therapeutic Avenues for Huntington's Disease

Huntington's disease (HD) is a devastating neurodegenerative disorder characterized by progressive motor dysfunction, cognitive decline, and psychiatric symptoms. Despite extensive research efforts, effective treatments for HD remain elusive. Boswellic acid, a bioactive compound derived from the resin of *Boswellia serrata*, has emerged as a potential therapeutic agent for HD due to its diverse pharmacological properties. This review provides a comprehensive overview of the preclinical evidence and mechanisms of action underlying the neuroprotective effects of boswellic acid in HD (15).

Huntington's disease is an autosomal dominant neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the huntingtin gene (HTT). The pathological hallmark of HD is the progressive degeneration of striatal and cortical neurons, leading to motor dysfunction, cognitive impairment, and psychiatric disturbances. Currently, there are no disease-modifying treatments for HD, highlighting the urgent need for novel therapeutic strategies (16). Boswellic acid, a pentacyclic triterpenoid derived from the resin of *Boswellia serrata*, has gained attention for its potential neuroprotective effects in HD. This review aims to elucidate the preclinical evidence and underlying mechanisms of action of boswellic acid in mitigating neuronal damage and disease progression in HD (17).

Comment [H9]: Interesting in molecular studies give more trust to the article and help for future clinical studies.

Mechanisms of Action: A Possible Approach for Huntington's Disease

The neuroprotective effects of boswellic acid in HD are attributed to its multifaceted pharmacological properties. One of the key mechanisms underlying its therapeutic action is its potent anti-inflammatory activity. Boswellic acid inhibits the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), and suppresses the activation of microglia and astrocytes in the brain. By attenuating neuroinflammation, boswellic acid reduces neuronal damage and promotes neuronal survival in HD (18).

Additionally, boswellic acid exhibits robust antioxidant activity, scavenging free radicals and preventing oxidative stress-induced damage to neurons. It enhances the expression of endogenous antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, thereby bolstering the cellular defense mechanisms against oxidative injury. Furthermore, boswellic acid modulates glutamatergic neurotransmission and excitotoxicity, a process implicated in HD pathogenesis. By inhibiting glutamate release and blocking N-methyl-D-aspartate (NMDA) receptor activation, boswellic acid attenuates excitotoxic neuronal death and preserves synaptic integrity in HD models (15).

Moreover, boswellic acid enhances mitochondrial function and bioenergetics in neurons, thereby mitigating mitochondrial dysfunction, a prominent feature of HD pathology. It promotes mitochondrial biogenesis, improves mitochondrial respiration, and maintains mitochondrial membrane potential, leading to enhanced ATP production and preservation of cellular energy metabolism. These mitochondrial effects contribute to the overall neuroprotective action of boswellic acid in HD (15).

Preclinical Evidence: Numerous preclinical studies have investigated the therapeutic potential of boswellic acid in animal models of HD. In a rodent model of HD, treatment with boswellic acid resulted in significant improvements in motor function, as assessed by performance on rotarod and beam-walking tests (15). Histological analysis revealed reduced neuronal degeneration and striatal atrophy in boswellic acid-treated animals compared to untreated controls. Moreover, behavioral assays demonstrated amelioration of cognitive deficits and reduction in depressive-like behaviors following boswellic acid administration (7). These findings suggest that boswellic acid exerts neuroprotective effects and improves functional outcomes in HD models (7).

Together, the mechanistic approach and preclinical evidence supports the therapeutic potential of boswellic acid as a novel treatment approach for Huntington's disease. Its diverse

Comment [H10]: This part is considered a key section for the article that improves efforts and seriousness of the author.

pharmacological properties, including anti-inflammatory, antioxidant, anti-excitotoxic, and mitochondrial-enhancing effects, collectively contribute to its neuroprotective effects in HD models. Further investigation is warranted to elucidate the precise molecular mechanisms underlying the therapeutic action of boswellic acid and to evaluate its efficacy in clinical trials for HD patients. Boswellic acid holds promise as a disease-modifying therapy that may slow disease progression and improve quality of life for individuals affected by Huntington's disease.

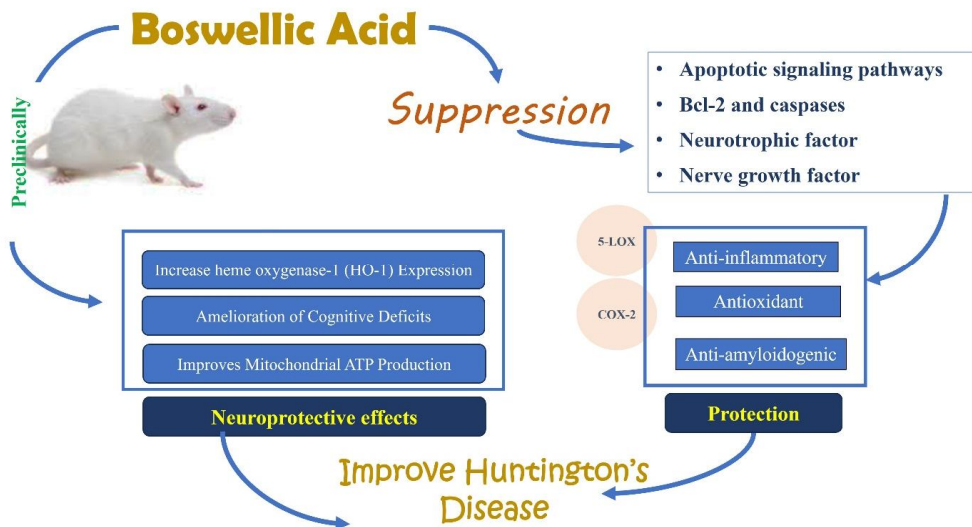


Figure no 2: Neuroprotective effects of boswellic acid in Huntington's Disease

Comment [H11]: The author tried more and more to convince that the plant has beneficial effects for treating Huntington's disease; molecular studies and preclinical study improved his right.

Therapeutic Implications and Future Perspectives:

In recent years, the exploration of natural compounds for their therapeutic potential in neurodegenerative diseases has gained traction. Among these compounds, boswellic acid, derived from *Boswellia serrata*, has emerged as a promising candidate due to its neuroprotective properties. The therapeutic implications of boswellic acid extend to a variety of neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Its ability to modulate inflammation, oxidative stress, and mitochondrial function makes it an attractive target for neuroprotection. However, despite the promising preclinical evidence, there remain challenges in translating these findings into clinical applications. Future research efforts should focus on elucidating

the underlying mechanisms of action, optimizing dosing regimens, and conducting well-designed clinical trials to fully harness the therapeutic potential of boswellic acid in the management of neurodegenerative diseases.

Comment [H12]: This study will open new horizons for further studies in neuroscience.

Conclusion:

In conclusion, the therapeutic potential of *Boswellia serrata* and its constituent boswellic acid in neurodegenerative disorders, including Huntington's disease, holds promise. With its demonstrated neuroprotective effects, anti-inflammatory properties, and antioxidant activity, boswellic acid presents a natural remedy worthy of further investigation and clinical exploration for the management of HD and other neurodegenerative conditions.

Comment [H13]: Conclusion reflects richness of the manuscript and resumes all positive points of the plant for this disease and encourage for first trials.

Table No. 1: Mechanistic Approach of Boswellic Acid in Neurodegenerative Disorders

Comment [H14]: This table resumes many parts of the manuscript and will facilitate reading of this paper, in other hands such effort give it as scholar aspect. The most important it facilitates comparison of plant effects on different studies; and help in investigation to conquer who being former in trying this plant for earliest clinical studies.

S N	Mechanism of Action	Alzheimer's Disease	Parkinson's Disease	Huntington's Disease
1	Anti-inflammatory	In Alzheimer's disease, chronic neuroinflammation contributes to neuronal damage and disease progression. Boswellic Acid's anti-inflammatory properties involve inhibition of pro-inflammatory cytokines and enzymes, reducing neuroinflammation and protecting neurons.	Parkinson's disease is characterized by neuroinflammation, exacerbating dopaminergic neuronal loss. Boswellic Acid's anti-inflammatory effects may mitigate neuroinflammation, preserving dopaminergic neurons and slowing disease progression.	Neuroinflammation plays a role in Huntington's disease pathology, contributing to neuronal dysfunction and degeneration. Boswellic Acid's anti-inflammatory actions may attenuate neuroinflammation, providing neuroprotection and potentially delaying disease onset or progression.
2	Antioxidant	Oxidative stress is implicated in Alzheimer's disease pathogenesis, leading to neuronal oxidative damage and cell death. Boswellic Acid's antioxidant activity involves scavenging free radicals and enhancing endogenous antioxidant defenses, protecting neurons from oxidative stress and supporting their survival.	Oxidative stress is a key contributor to dopaminergic neuronal degeneration in Parkinson's disease. Boswellic Acid acts as an antioxidant, scavenging free radicals and enhancing cellular antioxidant mechanisms, thereby reducing oxidative damage and promoting neuronal health.	Oxidative stress is a prominent feature of Huntington's disease pathology, contributing to mitochondrial dysfunction and neuronal death. Boswellic Acid's antioxidant properties may mitigate oxidative stress, preserving mitochondrial function and neuronal viability in Huntington's disease.
3	Neuroprotection	Boswellic Acid exhibits neuroprotective effects in Alzheimer's disease by modulating signaling pathways involved in neuronal survival and apoptosis. These mechanisms promote neuronal resilience and may mitigate neurodegeneration in Alzheimer's disease.	In Parkinson's disease, Boswellic Acid exerts neuroprotective effects by promoting neuronal survival pathways and inhibiting apoptotic pathways. These actions help preserve dopaminergic neurons and mitigate neurodegeneration, potentially slowing disease progression.	Boswellic Acid's neuroprotective properties in Huntington's disease involve promoting neuronal survival mechanisms and inhibiting apoptotic pathways. These effects may protect against neuronal degeneration and delay disease progression in Huntington's disease.

4	Mitochondrial Function	Mitochondrial dysfunction contributes to neuronal energy deficits and oxidative stress in Alzheimer's disease. Boswellic Acid enhances mitochondrial biogenesis and function, restoring energy production and reducing oxidative stress, thereby supporting neuronal health in Alzheimer's disease.	Parkinson's disease is associated with mitochondrial dysfunction, impairing cellular energy metabolism and promoting oxidative stress. Boswellic Acid improves mitochondrial function, enhancing energy production and reducing oxidative stress, which may protect dopaminergic neurons in Parkinson's disease.	Huntington's disease is characterized by mitochondrial dysfunction, leading to energy deficits and oxidative stress in neurons. Boswellic Acid enhances mitochondrial biogenesis and function, restoring cellular energy metabolism and reducing oxidative stress, thereby supporting neuronal viability in Huntington's disease.
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