Plant-Based Neuroprotection: *Euphorbia tithymaloides* as a Candidate for Managing LPS-Induced Parkinsonian Neuroinflammation

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ABSTRACT

Parkinson's disease (PD), a progressive neurodegenerative disorder, is characterized by motor dysfunction and a significant loss of dopaminergic neurons. Chronic neuroinflammation, driven by lipopolysaccharide (LPS)-induced microglial activation, plays a pivotal role in the disease's pathogenesis. The search for effective neuroprotective agents has increasingly turned to plant-based compounds due to their multifaceted therapeutic properties and minimal side effects. Among these, Euphorbia tithymaloides, a traditional medicinal plant, has garnered attention for its anti-inflammatory, antioxidant, and neuroprotective potential. This review explores the pharmacological properties of Euphorbia tithymaloides, emphasizing its potential to mitigate LPS-induced neuroinflammation and subsequent neurodegeneration in experimental models of PD. Key bioactive constituents, mechanisms of action, and preclinical evidence supporting its efficacy are analysed. The plant's ability to attenuate oxidative stress, suppress pro-inflammatory cytokine production, and modulate microglial activation suggests a promising therapeutic avenue. Additionally, the challenges and future directions in translating these findings into clinical applications are discussed. This review underscores the need for integrative approaches combining traditional knowledge with modern research to harness the full therapeutic potential of Euphorbia tithymaloides in combating PD and related neurodegenerative disorders.

Keywords: - *Parkinson's disease, Euphorbia tithymaloides, Neurodegenerative disorder, Cytokine and Inflammation.*

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by dopaminergic neuronal loss in the substantia nigra, often exacerbated by neuroinflammation. Lipopolysaccharide (LPS)-induced neuroinflammation serves as a widely recognized experimental model to study PD pathogenesis. *Euphorbia tithymaloides*, a medicinal plant known for its anti-inflammatory and antioxidant properties,

has emerged as a potential therapeutic agent against neuroinflammatory disorders. The bioactive constituents of *Euphorbia tithymaloides*, including flavonoids, terpenoids, and phenolic compounds, are known to modulate inflammatory pathways by inhibiting pro-inflammatory cytokines like TNF-α and IL-6, and reducing oxidative stress via enhanced antioxidant enzyme activity. Studies indicate that these phytochemicals can mitigate microglial activation, a key driver of neuroinflammation in PD, thereby protecting dopaminergic neurons from LPS-induced damage 1-2.

Preclinical evidence highlights the plant's neuroprotective effects through the modulation of NF-κB and Nrf2 signalling pathways, essential regulators of inflammation and oxidative stress 3. *Euphorbia tithymaloides* thus holds promise as a plant-based intervention to manage PD progression. However, further research is required to validate its efficacy in clinical settings and elucidate its precise molecular mechanisms. This review underscores the potential of *Euphorbia tithymaloides* as a natural candidate for neuroprotective therapies, advocating for its inclusion in future PD research.

2. PARKINSON'S DISEASE PATHOPHYSIOLOGY AND NEUROINFLAMMATION

2.1 Overview of PD Pathology 4-5

Parkinson's Disease (PD) is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to a reduction in striatal dopamine levels and the hallmark motor symptoms of the disease. Pathophysiological hallmarks of PD include:

- Dopaminergic Neuronal Death: The loss of dopaminergic neurons is a central feature of PD, which directly correlates with motor deficits. The underlying mechanisms involve protein aggregation, primarily α-synuclein, forming Lewy bodies.
- Mitochondrial Dysfunction: Impaired mitochondrial function contributes to reduced ATP production and increased oxidative stress, exacerbating neuronal damage. Mutations in genes like PINK1 and Parkin highlight the role of mitophagy failure in PD pathology.
- Oxidative Stress: Elevated levels of reactive oxygen species (ROS) further damage neurons through lipid peroxidation, DNA damage, and protein oxidation.
- Neuroinflammation: Chronic neuroinflammatory processes are increasingly recognized as a key contributor to PD progression, linking microglial activation, pro-inflammatory mediators, and neurodegeneration.

2.2 Role of Neuroinflammation 6

Neuroinflammation in PD is driven by the activation of microglia, the brain's resident immune cells, which shift to a pro-inflammatory phenotype upon exposure to stimuli like lipopolysaccharides (LPS). Microglial activation results in the secretion of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). These cytokines disrupt neuronal homeostasis, induce oxidative stress, and promote apoptosis in dopaminergic neurons. Moreover, inflammatory mediators can exacerbate α-synuclein aggregation, creating a feedback loop that accelerates neurodegeneration.

2.3 Limitations of Current Pharmacological Treatments 7

Although current pharmacological treatments, such as dopamine replacement therapy (e.g., levodopa) and dopamine agonists, are effective in alleviating motor symptoms, they fail to address the underlying neuroinflammatory processes. Limitations include:

- Symptomatic Relief Only: Current therapies do not modify disease progression or target neuroinflammation.
- Lack of Anti-Inflammatory Action: Most treatments focus on dopaminergic systems, neglecting the role of microglial activation and cytokine production.
- Side Effects: Chronic use of existing drugs can lead to complications like motor fluctuations and dyskinesia.
- Limited Neuroprotection: Few drugs have demonstrated consistent neuroprotective effects in clinical trials, highlighting the need for therapies targeting both inflammation and oxidative stress.

The critical role of neuroinflammation in PD pathogenesis underscores the necessity of developing therapeutic strategies that modulate microglial activity and reduce the pro-inflammatory milieu in the central nervous system**.**

3. LPS-INDUCED NEUROINFLAMMATION IN PD MODELS

3.1 Mechanism of LPS Action

Lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls, induces neuroinflammation primarily through the activation of the Toll-like receptor 4 (TLR4) pathway. Upon LPS binding to TLR4, a cascade of intracellular signalling is initiated, leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This transcription factor promotes the

expression of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These cytokines further exacerbate inflammation, oxidative stress, and neuronal damage, which are hallmark features of Parkinson's disease (PD) pathology 8-9.

3.2 Utility of LPS Models in Mimicking PD Neuroinflammation

LPS-induced models are extensively used in both in vitro and in vivo studies to replicate neuroinflammatory processes observed in PD. In in vitro models, LPS is used to stimulate microglial cells, mimicking their activation state in PD. In in vivo studies, LPS injection into the substantia nigra or striatum of rodents induces dopaminergic neuronal loss, microglial activation, and the release of pro-inflammatory mediators, closely resembling PD-like pathology. These models are valuable for studying the role of neuroinflammation in PD progression and for screening potential neuroprotective agents 10-11.

3.3 Insights from LPS Models Regarding Therapeutic Targets

LPS-induced neuroinflammation models have provided significant insights into potential therapeutic strategies for PD. They highlight key targets, including:

- TLR4 Inhibition: Suppressing TLR4 activation to reduce the inflammatory cascade.
- NF-κB Pathway Modulation: Targeting NF-κB signalling to diminish pro-inflammatory cytokine production.
- Microglial Modulation: Using compounds to transition microglial cells from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype.
- Antioxidant Therapies: Reducing oxidative stress that accompanies neuroinflammation.

These findings have paved the way for testing neuroprotective agents, such as natural compounds and pharmacological inhibitors, that can attenuate LPS-induced inflammatory responses and protect dopaminergic neurons 12-13.

4. *EUPHORBIA TITHYMALOIDES*: PHYTOCHEMISTRY AND PHARMACOLOGICAL PROFILE

4.1 Key Phytochemical Constituents

Euphorbia tithymaloides, a medicinal plant widely studied for its therapeutic potential, contains several bioactive compounds that contribute to its pharmacological properties. The primary classes of phytochemicals found in this plant include:

- Flavonoids: These compounds are known for their potent antioxidant properties, which help in neutralizing free radicals and protecting cells from oxidative damage.
- Tannins: Tannins exhibit strong anti-inflammatory and antioxidant activities, which contribute to the plant's ability to reduce tissue damage in various inflammatory diseases.
- Terpenoids: These compounds play a significant role in modulating immune responses and inflammation, showing potential for various therapeutic uses.
- Phenolic Acids: These compounds are known for their antioxidant and anti-inflammatory effects, which may protect against neurodegenerative diseases and inflammation-driven conditions.

These phytochemicals work synergistically to enhance the therapeutic efficacy of *Euphorbia tithymaloides*, making it a promising candidate for treating neuroinflammatory conditions such as Parkinson's disease.

4.2 Anti-Inflammatory and Antioxidant Mechanisms

Euphorbia tithymaloides has shown significant anti-inflammatory and antioxidant activities, which are pivotal in mitigating the effects of neuroinflammation:

- Suppression of Pro-inflammatory Cytokines: The plant has been demonstrated to reduce levels of pro-inflammatory cytokines such as TNF-α and IL-6, which are key players in the pathogenesis of neuroinflammation and various neurodegenerative diseases 14.
- Inhibition of Oxidative Stress Markers: By modulating oxidative stress markers, *Euphorbia tithymaloides* helps in mitigating cellular damage caused by oxidative species, a hallmark of neurodegenerative diseases 15.
- Modulation of Microglial Activation: The plant regulates microglial activation, which is crucial for controlling the inflammatory response in the central nervous system (CNS). Overactive microglia are implicated in the progression of neurodegenerative diseases such as Parkinson's and Alzheimer's 16.
- TLR4-NF-κB Signalling Pathway: *Euphorbia tithymaloides* has been shown to modulate the TLR4-NF-κB signalling pathway, which plays a central role in inflammation and immune responses in the brain. This pathway’s modulation could help in reducing neuroinflammation and enhancing neuroprotection 17.

4.3 Neuroprotective Properties

The neuroprotective effects of *Euphorbia tithymaloides* are well-documented and involve several mechanisms that promote neuronal survival and reduce neurodegeneration:

- Mitochondrial Stabilization: The plant has shown the ability to stabilize mitochondrial function,

which is critical in preventing mitochondrial dysfunction, a key feature of neurodegenerative diseases 18.

- Reduced Apoptosis: *Euphorbia tithymaloides* reduces neuronal apoptosis (programmed cell death), which is often triggered by neuroinflammatory conditions. This effect contributes to the preservation of neuronal integrity and function 19.
- Enhancement of Neuronal Survival: Studies have demonstrated that *Euphorbia tithymaloides* enhances neuronal survival by modulating cellular signalling pathways involved in cell survival and repair mechanisms, offering protection against the damage caused by neuroinflammation 20.

5. MECHANISMS OF *EUPHORBIA TITHYMALOIDES* IN LPS-INDUCED NEUROINFLAMMATION

5.1 Targeting Microglial Activation

Euphorbia-derived compounds have been shown to mitigate microglial overactivation by downregulating Toll-like receptor 4 (TLR4) expression. This reduction in TLR4 activation subsequently inhibits downstream NF-κB signalling, which plays a crucial role in inflammatory cytokine production. As a result, pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are lessened, thus reducing the inflammatory response in the brain 21-22.

5.2 Oxidative Stress Mitigation

Euphorbia tithymaloides has demonstrated the ability to reduce oxidative stress by enhancing the activity of key antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, which in turn lowers the concentrations for reactive oxygen species (ROS) throughout the brain. This antioxidant defence system helps to counteract cellular damage caused by oxidative stress, a hallmark of neuroinflammation 23-24.

5.3 Apoptosis Prevention

Euphorbia tithymaloides exhibits the ability to modulate the expression of apoptotic and anti-apoptotic proteins, which are crucial in regulating neuronal survival. The compound downregulates pro-apoptotic proteins like Bax and upregulates anti-apoptotic proteins such as Bcl-2, leading to a reduction in cell death in LPS-induced neuroinflammatory conditions. This balance helps protect neurons from apoptosis and supports neuroprotection 25-26.

6. PRECLINICAL EVIDENCE FOR *EUPHORBIA TITHYMALOIDES* IN PD MODELS

6.1 In Vitro Studies

Several in vitro studies have demonstrated the neuroprotective potential of *Euphorbia tithymaloides* by showing a reduction in neuroinflammatory markers, particularly in microglial cell cultures. In a study microglial cells were treated with Euphorbia extracts, leading to a significant reduction in the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are associated with neuroinflammation in Parkinson's disease (PD). Additionally, *Euphorbia tithymaloides* was shown to inhibit the activation of nuclear factor kappa B (NF-κB), a key regulator of inflammation, thereby mitigating the inflammatory cascade in microglial cells. These results suggest that *Euphorbia tithymaloides* may help alleviate neuroinflammation by modulating the immune response at the cellular level 27.

6.2. In Vivo Studies

In vivo studies involving animal models of LPS-induced PD have provided strong evidence for the therapeutic potential of *Euphorbia tithymaloides*. In a study mice were treated with Euphorbia extracts following an LPS-induced neuroinflammatory insult. The results showed significant improvements in motor function, as measured by the rotarod test and open field locomotor activity. Moreover, Euphorbia treatment led to a reduction in dopaminergic neuronal loss in the substantia nigra, as well as decreased levels of inflammatory cytokines in the brain, particularly TNF-α and IL-1β. Histological analysis also revealed diminished neuroinflammation and reduced microglial activation in treated animals, suggesting that *Euphorbia tithymaloides* has a protective effect against neurodegeneration 28.

Additionally, reported that Euphorbia treatment in rats exposed to LPS resulted in a reduction in oxidative stress, as evidenced by decreased levels of malondialdehyde (MDA) and increased activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase. This antioxidant effect, coupled with reduced neuroinflammation, may contribute to the observed neuroprotective outcomes 29.

7. THERAPEUTIC IMPLICATIONS AND CHALLENGES

7.1 Clinical Translation

- Neuroprotective Potential: Research suggests that *Euphorbia tithymaloides* possesses anti-inflammatory and neuroprotective properties, which could complement conventional PD treatments like levodopa by reducing neuroinflammation and oxidative stress 30-31.

- Adjunct Therapy: It could be explored as an adjunct to current PD therapies, potentially improving motor function and reducing the progression of neurodegeneration in PD models.
- Herbal Formulations: Some studies suggest combining Euphorbia extracts with other herbs for synergistic effects, enhancing therapeutic efficacy 32.

7.2 Safety Profile

- Toxicity Concerns: While *Euphorbia tithymaloides* has shown promise in preclinical studies, its use in humans is limited due to concerns about potential toxicity, particularly its irritant latex and compounds such as diterpenes 33.
- Recommended Doses: There is no standardized dosing for human use, and much of the information is derived from animal studies. Careful dose determination through clinical trials is essential to avoid toxicity and ensure safety 34.
- Toxicity Management: More studies are needed to determine the safe threshold for human consumption, focusing on the safety profile of standardized extracts 35.

7.3 Limitations

- Variability in Phytochemical Content: The phytochemical composition of *Euphorbia tithymaloides* can vary significantly depending on factors like plant origin, preparation methods, and extraction procedures, leading to inconsistencies in therapeutic outcomes 35.
- Need for Standardized Extracts: To ensure consistent results in clinical applications, the development of standardized extracts that provide a reproducible dosage of active compounds is critical 36.
- Insufficient Human Trials: There is a notable lack of well-conducted human clinical trials assessing the efficacy and safety of *Euphorbia tithymaloides* in treating PD. Current evidence is largely preclinical, requiring more robust clinical research to confirm its therapeutic potential 30-31.

8. FUTURE DIRECTIONS

The neuroprotective potential of *Euphorbia tithymaloides* in Parkinson's disease models has opened up new avenues for future research. Several directions are essential to fully explore and enhance its therapeutic potential:

8.1 Combination with Other Anti-Inflammatory Agents

The synergistic effects of combining *Euphorbia tithymaloides* with other well-established anti-inflammatory agents could improve its therapeutic outcomes. Studies investigating the interaction

between *Euphorbia tithymaloides* and drugs such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), or natural compounds like curcumin might provide valuable insights into enhancing efficacy and reducing side effects. Combining therapies could also offer a multi-target approach to neuroinflammation, a hallmark of Parkinson's disease 37-39.

8.2 Advances in Delivery Systems for Enhancing Bioavailability

One major challenge in translating *Euphorbia tithymaloides* into clinical practice is its bioavailability. The development of novel delivery systems, such as nanoparticles, liposomes, and solid lipid nanoparticles, can significantly enhance the pharmacokinetics and tissue penetration of the active compounds. Nanotechnology could help in overcoming the challenges of poor absorption and rapid metabolism, thus ensuring that the therapeutic compounds reach the brain in effective concentrations 40-42.

8.3 Necessity of Large-Scale Clinical Trials

Although promising preclinical data exists, large-scale clinical trials are necessary to validate the safety and efficacy of *Euphorbia tithymaloides* in humans. Clinical trials will provide critical data on optimal dosages, long-term effects, and potential adverse reactions. These studies are essential to confirm its potential as a treatment option for neuroinflammatory disorders, including Parkinson's disease 43-46.

9. RESULT AND DISCUSSION

9.1 The study demonstrated that Cassia tora exhibits significant antiparkinsonian effects in an oxotremorine-induced Parkinson's disease model. Behavioral assessments showed improvements in motor deficits, while biochemical analyses indicated a reduction in oxidative stress and restoration of neurotransmitter levels. These findings suggest that the neuroprotective properties of Cassia tora may be attributed to its antioxidant and neuromodulatory effects. This highlights its potential as a natural therapeutic agent for managing Parkinson's disease. Further studies are warranted to explore its molecular mechanisms and clinical applicability 47.

9.2 Rutin, a natural flavonoid, demonstrates significant neuroprotective potential in mitigating 6-hydroxydopamine (6-OHDA)-induced memory impairment in Parkinson's disease models. Its antioxidant, anti-inflammatory, and anti-apoptotic properties appear to play a crucial role in preserving neuronal function. Behavioral improvements observed in treated animals further support its therapeutic efficacy. These findings suggest that rutin could serve as a promising candidate for managing cognitive deficits associated with Parkinson's disease. However, further studies are needed to confirm its clinical relevance and underlying mechanisms 48.

9.3 Parkinson's disease remains a complex neurodegenerative disorder requiring multifaceted therapeutic approaches. Current treatments primarily address symptoms, with limited impact on disease progression. Emerging therapies, including neuroprotective agents, gene therapy, and stem cell interventions, hold promise for addressing underlying pathophysiology. Complementary approaches, such as dietary modifications and herbal medicines, offer potential synergistic benefits. Continued research is essential to optimize these strategies, ensuring improved quality of life for patients 49.

9.4 Mitochondrial dysfunction and oxidative stress, driven primarily by impairments in Complex-I activity, play pivotal roles in the pathogenesis of Parkinson's disease. The disruption of energy metabolism leads to increased reactive oxygen species, exacerbating neuronal damage and contributing to dopaminergic neurodegeneration. Understanding these mechanisms highlights the therapeutic potential of targeting mitochondrial function and oxidative pathways. Advances in pharmacological and genetic interventions offer hope for mitigating disease progression. Future research should focus on refining these approaches to improve clinical outcomes for Parkinson's patients 50.

9.5 Mucuna pruriens has emerged as a promising therapeutic agent for Parkinson’s disease due to its pharmacognostical, phytochemical, and neuroprotective properties. Rich in levodopa, it provides a natural alternative for dopamine replenishment, addressing the hallmark symptoms of the disorder. Beyond levodopa, its bioactive compounds exhibit antioxidant, anti-inflammatory, and neuroprotective effects, further supporting its anti-Parkinson’s profile. Pharmacognostical studies have established its quality and standardization parameters, ensuring consistency in its therapeutic use. Overall, Mucuna pruriens holds significant potential as a complementary treatment for Parkinson’s disease, warranting further clinical validation 51.

9.6 The formulated PLGA polymeric nanosuspension of pramipexole dihydrochloride demonstrated enhanced drug encapsulation, sustained release, and improved neuroprotective efficacy. This advanced delivery system holds potential for more effective Parkinson’s disease management by optimizing drug bioavailability and targeting. Further in vivo studies are recommended to validate its therapeutic benefits 52.

9.7 The study concludes that quercetin shows favorable binding interactions with α-synuclein, suggesting its potential as a therapeutic agent for Parkinson's disease. In silico analysis indicates that quercetin may stabilize α-synuclein's structure, potentially preventing aggregation. These findings highlight quercetin as a promising candidate for further in vitro and in vivo validation in Parkinson's disease treatment 53.

9.8 The molecular docking studies of selected flavonoids on inducible nitric oxide synthase (iNOS) in Parkinson’s disease reveal promising inhibitory potential, suggesting their role in mitigating

neuroinflammation. These findings highlight flavonoids as potential therapeutic agents in managing iNOS-related neurodegeneration. Further in vitro and in vivo studies are needed to validate their efficacy and clinical applicability 54.

9.9 The study demonstrated that Melissa officinalis exhibits significant neuroprotective effects in the MPTP-induced Parkinson's disease model in mice. The results suggest that its antioxidant and anti-inflammatory properties contribute to reducing neurodegeneration. Overall, Melissa officinalis shows potential as a therapeutic agent for Parkinson's disease, warranting further investigation 55.

9.10 The study demonstrated that camalexin exhibits significant in-vitro antioxidant activity, suggesting its potential as an effective anti-Parkinson's agent. The findings highlight camalexin's ability to reduce oxidative stress, a key factor in Parkinson's disease pathogenesis. These results support further investigation into camalexin as a promising therapeutic candidate for neurodegenerative disorders 56**.**

10. CONCLUSION

Euphorbia tithymaloides, a plant with significant anti-inflammatory and neuroprotective properties, presents a promising candidate for managing LPS-induced neuroinflammation in Parkinson's disease. The plant's bioactive compounds, particularly those with anti-inflammatory, antioxidant, and neuroprotective effects, have shown potential in mitigating neurodegenerative processes associated with Parkinson's disease. LPS-induced neuroinflammation models offer a valuable platform to investigate the underlying mechanisms through which *Euphorbia tithymaloides* exerts its protective effects, particularly in reducing neuroinflammation, oxidative stress, and neuronal damage.

Despite its promising preclinical data, several challenges remain, including the need for enhanced bioavailability and the optimization of therapeutic formulations. Nanoparticle-based delivery systems offer a potential solution for improving the solubility and bioavailability of the active compounds in *Euphorbia tithymaloides*. However, large-scale clinical trials are essential to validate the safety and efficacy of this plant-based therapy in human populations.

In conclusion, while further research is needed, *Euphorbia tithymaloides* holds substantial promise as a natural therapeutic agent for combating Parkinson's disease, specifically in reducing LPS-induced neuroinflammation. Its integration with modern delivery technologies and combination with other therapies could pave the way for innovative, plant-based treatments for neurodegenerative diseases.

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