ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

# Role of *Withania somnifera* and Greater Cardamom in Modulating Oxidative Stress and Neurodegeneration in Parkinson's Disease

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Publication Date: 2026/04/29

**Abstract: Parkinson's disease (PD) is a progressive neurological disorder that mainly affects movement due to the gradual loss of dopamine-producing neurons in the brain. People with PD commonly experience tremors, muscle stiffness, slow movement and balance problems, along with non-motor symptoms such as sleep disturbances and mood changes. Although current medications like levodopa can relieve symptoms, they do not prevent the disease from progressing and may cause side effects over time. Therefore, researchers are increasingly interested in natural plant-based therapies that may protect nerve cells and slow disease development. *Withania somnifera* (Ashwagandha) and Greater Cardamom (*Amomum subulatum*) are traditional medicinal plants known for strong antioxidant and anti-inflammatory properties. Experimental studies suggest that Withania somnifera supports the survival of dopaminergic neurons by reducing oxidative stress, improving mitochondrial function and preventing cell damage. Similarly, Greater Cardamom has been shown to enhance dopamine levels, reduce brain inflammation and improve motor performance in animal models of PD. These findings indicate that both plants may offer potential neuroprotective benefits and could be used as supportive therapy for Parkinson's disease.**

***Keywords:*** *Parkinson's Disease; Neurodegeneration; Withania Somnifera; Ashwagandha; Greater Cardamom; Amomum Subulatum; Neuroprotection; Dopaminergic Neurons; Oxidative Stress; Antioxidant Activity; Neuroinflammation; Herbal Therapy; Phytomedicine.*

**How to Cite:** Badal Tanwar; Dr. Ashutosh Upadhayay; Neha Sorout; Nitu (2026) Role of Withania somnifera and Greater Cardamom in Modulating Oxidative Stress and Neurodegeneration in Parkinson's Disease. *International Journal of Innovative Science and Research Technology*, 11(4), 2419-2431. https://doi.org/10.38124/ijisrt/26apr1638

## I. INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that primarily affects the elderly population and represents the second most common neurodegenerative disease worldwide. It is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta of the midbrain, leading to a marked reduction in striatal dopamine levels. This neurochemical imbalance results in the hallmark motor manifestations of PD, including resting tremor, muscular rigidity, bradykinesia, and postural instability, along with several non-motor symptoms such as cognitive impairment, mood disorders, and autonomic dysfunction (Tanner & Ostrem et al., 2024).

The prevalence of Parkinson's disease increases markedly with advancing age, highlighting its strong association with aging. A recent meta-analysis reported that PD prevalence per 100,000 population rises from approximately 7 cases in individuals aged 40–49 years**,** to 158 in the 50–59 age group**,** 603 in those aged 60–69 years**,** 1,251 in the 70–79 group**,** and 2,181 cases in individuals aged 80 years and above (Pereira et al., 2024). These findings are consistent with earlier epidemiological studies that similarly demonstrated an age-dependent increase in PD prevalence, confirming the growing global disease burden among older adults (Prinsha et al., 2014).Clinically, Parkinson's disease presents with a spectrum of motor and non-motor indications. Motor symptoms arise due to dopamine depletion within the nigrostriatal pathway, while non-motor symptoms such as depression, anxiety, sleep disturbances, and cognitive decline significantly affect quality of life. The progression of PD is slow but irreversible, and current pharmacological treatments mainly provide symptomatic relief without halting disease progression.

The pathophysiology of PD is complex and multifactorial, involving oxidative stress, mitochondrial

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

dysfunction, neuroinflammation, and abnormal protein aggregation, particularly of α-synuclein. Excessive production of reactive oxygen species (ROS) contributes to neuronal damage and accelerates dopaminergic cell loss. Activation of inflammatory pathways and impairment of endogenous antioxidant defenses further exacerbate neurodegeneration, making oxidative stress a central contributor to PD pathogenesis.In this context, medicinal plants with antioxidant and neuroprotective properties have gained increasing scientific attention. *Withania somnifera* (Ashwagandha), a well-known medicinal plant in traditional Indian medicine, has been extensively studied for its adaptogenic, anti-inflammatory, antioxidant, and neuroprotective effects, particularly in stress-related and central nervous system disorders (Lerose et al., 2024a). Similarly, *Amomum subulatum* (Greater Cardamom), a perennial herb of the Zingiberaceae family predominantly cultivated in the Himalayan regions of India, especially Sikkim, is rich in bioactive phytochemicals such as flavonoids, phenolics, glycosides, steroids, and essential oils (Agnihotri & Wakode et al., 2020). These compounds possess strong antioxidant properties capable of neutralizing ROS, thereby potentially mitigating oxidative stress-induced neuronal damage. Given the central role of oxidative stress in Parkinson's disease, *Withania somnifera* and *Amomum subulatum* represent promising natural candidates for neuroprotective research in PD.

➢ *Key Symptoms (Motor And Non-Motor).*

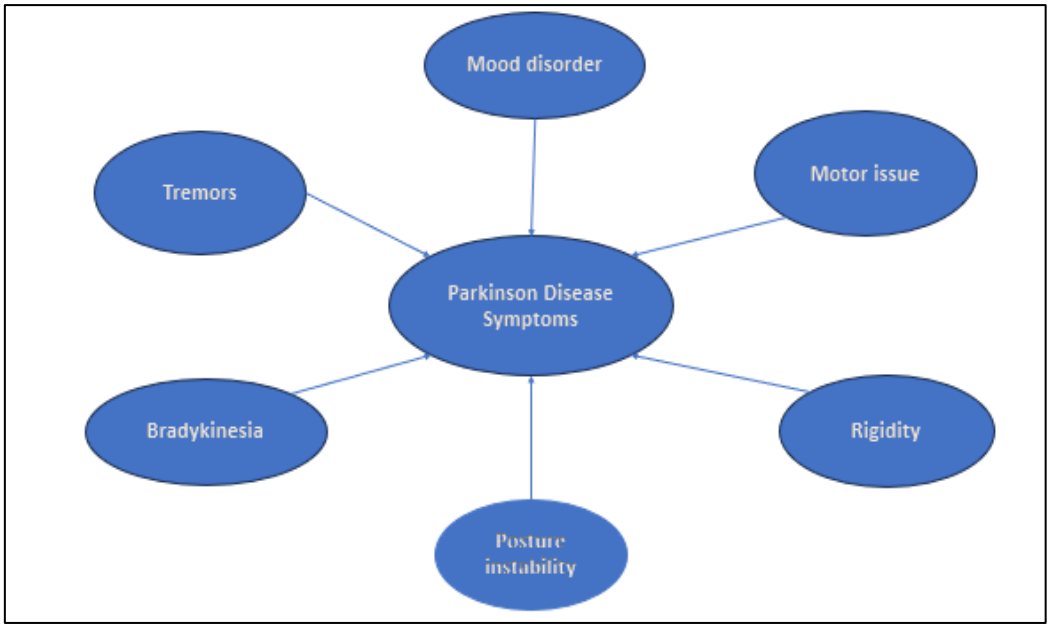


Fig 1 Parkinson's Disease Symptoms

- *Motor Symptoms*

The motor symptoms of Parkinson's disease are the ones most commonly recognized and are due to the gradual loss of dopamine-producing neurons in the mid-brain (R. Chen et al., 2022) They include:

✓ *Tremor at rest:*

A "pill-rolling" tremor of the hands is typical when the person is at rest.

✓ *Bradykinesia:*

Slowness in starting and carrying out movements, reduced spontaneous movements, small or slow steps, smaller handwriting (micrographic).(Radad et al., 2023).

✓ *Rigidity:*

Stiffness of muscles; when passively moving a patient's limb the resistance is increased ("cog-wheel rigidity").

✓ *Postural instability:*

Poor balance, tendency to fall, especially in later stages.

- *Non-Motor Symptoms*

Non-motor symptoms (NMS) are equally important and often under-recognized, but they significantly affect quality of life. They may appear even before motor symptoms. (Radad et al., 2023) Key non-motor features include:

✓ *Olfactory dysfunction (hyposmia/anosmia):*

Reduced sense of smell is common early in PD.

✓ *Sleep disorders:*

These include rapid-eye-movement (REM) sleep behavior disorder (where people act out dreams), insomnia, excessive daytime sleepiness.(Radad et al., 2023)

✓ *Mood and cognitive problems:*

Depression, anxiety, apathy, cognitive decline, hallucinations.

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✓ *Autonomic dysfunction:*
Problems with blood pressure regulation (orthostatic hypotension), bladder dysfunction, constipation, sexual dysfunction.

✓ *Sensory/pain symptoms:*
Pain, numbness, tingling, sometimes early in disease.

## II. PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

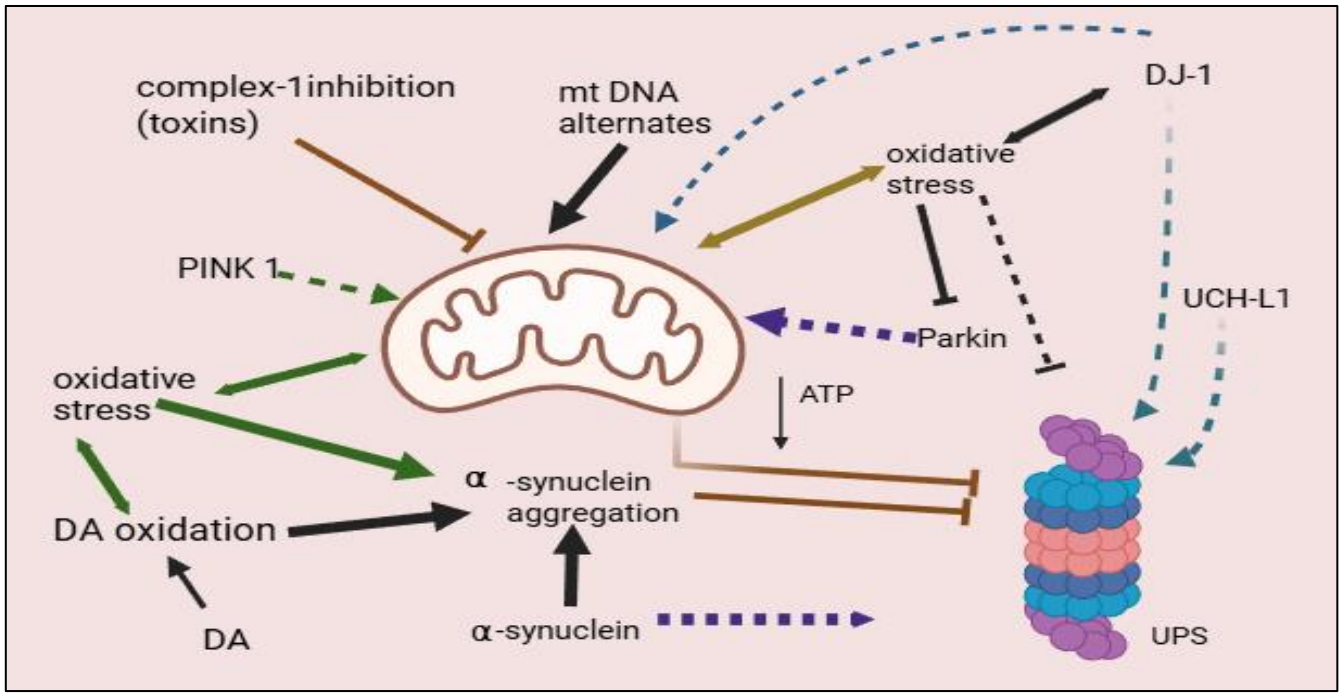


Fig 2 Pathophysiology of Parkinson's Disease

➢ *Dopamine Metabolism and Oxidative Stress*
In Parkinson's disease, the death of dopaminergic neurons in the substantia nigra pars compacta (Snaps) is a core feature. Excess dopamine in the cytosol can auto-oxidize to harmful products, creating reactive oxygen species (ROS) that damage neurons(Gao et al., 2022).

These oxidative products (like quinones) can interfere with cellular proteins, damage DNA, and overwhelm the antioxidant systems (for example, reduced glutathione), contributing to cell death.

Mitochondria also play a central role: loss of mitochondrial function leads to increased ROS production, which further damages mitochondria in a vicious cycle (Pizarro-Galleguillos et al., 2023a).

➢ *Mitochondrial Dysfunction*
Many studies link PD with impaired mitochondrial activity: mutations in genes like PINK1, Parkin, LRRK2, and others affect mitochondrial quality control, leading to fragmented or dysfunctional mitochondria. (Mc Caig et al., 1994).

Mitochondrial dysfunction reduces ATP production and increases oxidative stress, which can trigger neuronal death via apoptosis.

Moreover, damaged mitochondria may release damage-associated molecular patterns (DAMPs), which activate inflammatory processes in the brain.

➢ *α-Synuclein Aggregation (Retinopathy)*
A hallmark of PD is the accumulation of misfolded α-synuclein in neurons, forming Lewy bodies. These misfolded proteins can impair many cellular systems (Shen & Dettmer et al., 2024).

α-Synuclein oligomers and aggregates can disrupt mitochondrial membrane integrity, impair mitochondrial function, and increase ROS production (Pegging et al., 2024).

There is also impairment of protein degradation systems (like the ubiquitin-proteasome system and autophagy) in PD, making it difficult for cells to clear these toxic α-synuclein aggregates.

➢ *Neuroinflammation*
Activation of microglia (immune cells in the brain) is a major factor in PD's progression. These cells release cytokines, NO (nitric oxide), and ROS, which contribute to neuronal damage (M.-C. Chen et al., 2021).

Misfolded α-synuclein, when released from dying neurons, acts as a signal that further stimulates microglial

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activation and inflammation. (Pizarro-Galleguillos et al., 2023b).

Chronic inflammation sustained by microglial activation and oxidative stress establishes a feedback loop that worsens neuronal loss.

➢ *Genetic and Environmental Factors*

Genetic mutations in PINK1, Parkin, DJ-1, LRRK2, and SNCA (the gene for α-synuclein) are well known to contribute to familial PD, often by disrupting mitochondrial function or protein clearance mechanisms. (Aryal et al., 2020)

Environmental toxins (e.g., pesticide exposure) can inhibit mitochondrial complex I, increasing oxidative stress and contributing to dopaminergic neuron death.

➢ *Overview of Herbal and Plant-Based Approaches in PD*

- *Importance of traditional medicine and phytotherapy*

Traditional medical systems (for example Ayurveda and traditional Chinese medicine) have used plants for centuries to treat nervous system problems and symptoms similar to Parkinson's disease. These systems provide a large library of herbal remedies and formulations that modern researchers now study with scientific methods to find active compounds and mechanisms. Traditional knowledge therefore acts as an important starting point for drug(Lyu et al., 2024).

✓ *Advantages of herbal neuroprotective agents*

Herbal and plant-derived compounds offer several potential advantages compared with single-target synthetic drugs. Many phytochemicals show multi-target activity for example they can act as antioxidants, reduce inflammation, support mitochondrial function, and modulate protein-clearance pathways simultaneously. This multitarget profile may be useful in PD because the disease involves several linked processes (oxidative stress, inflammation, mitochondrial failure, protein aggregation). In addition, some plants (e.g., *Mucuna pruriens*) naturally contain levodopa-like compounds that can provide symptomatic relief, while others (e.g., *Withania somnifera*, turmeric, resveratrol) are investigated for disease-modifying properties in lab models. Herbal agents are also often widely available and culturally accepted, which can help with patient acceptability — but these advantages must be balanced against issues of standardization and safety(Rahman et al., 2022).

- *General evidence of herbal medicine in neurodegenerative diseases*

Evidence from the last five years shows growing preclinical and some clinical data supporting plant-derived neuroprotective effects. Multiple systematic and narrative reviews report that many natural products reduce oxidative damage, down-regulate pro-inflammatory cytokines, improve mitochondrial health, and protect neurons in cell and animal models of PD and other neurodegenerative diseases. However, most positive findings are preclinical; well-designed randomized clinical trials are still limited. Recent real-world studies and reviews also highlight that patients commonly use natural health products as adjuncts to standard PD therapy, underlining both interest and the need for clinical safety data (including herb–drug interaction studies). Overall, the literature supports cautious optimism: plant compounds are promising as multi-target neuroprotective agents, but translation to routine clinical care requires better quality clinical trials, standardized extracts, and safety monitoring(Tyler & Tyler et al., 2023).

## III. WITHANIA SOMNIFERA (ASHWAGANDHA)

➢ *Botanical information and active constituents*

*Withania somnifera* (L.) Donal, commonly called **Ashwagandha**, is a small evergreen shrub in the Solanaceae family that has long been used in traditional Indian (Ayurvedic) medicine. The plant parts used medicinally include roots, leaves and berries, but the **root** is the most commonly studied for neurological uses. The chemistry of Ashwagandha is rich and complex: its main groups of bioactive compounds are **withanolides** (a class of steroidal lactones), **alkaloids**, **nitroindolines**, withanolides and various flavonoids and phenolic compounds. These constituents are thought to underlie many of the herb's biological effects. (Mikulska et al., 2023a).

Table 1 Neuroprotective Effects of Withania Somnifera in Parkinson's Disease Models

| Disease | Target/ Intervention | Mechanistic Basis | Experimental Model | Observed Outcomes | Reference (Author, Year) |
|---|---|---|---|---|---|
| Parkinson's disease | Regulation of dopaminergic signaling after toxin exposure | Strengthening of endogenous antioxidant enzymes and reduction of peroxide-mediated lipid damage | Neurotoxin-induced rodent Parkinson model | Recovery of locomotor function, increased striatal dopamine, and decreased oxidative stress | Singh N. et al., 2017 |
| Parkinson's disease | Root extract evaluated in SH-SY5Y neuronal cells | Improvement of mitochondrial activity and stabilization of intracellular redox balance | Human neuroblastoma cell culture Transgenic fly or rodent neurodegeneration models | Lower ROS production, enhanced ATP synthesis, and improved neuronal viability | Gautam S. et al., 2018 |

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

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|---|---|---|---|---|---|
| Parkinson's disease | Influence on catecholamine metabolism | Promotion of dopamine synthesis along with suppression of oxidative injury markers | Experimental mouse Parkinson model | Increased dopamine metabolites, reduced lipid peroxidation, and better motor coordination | Prakash J. et al., 2019 |
| Parkinson's disease | Use in mitochondrial/genetic dysfunction models | Preservation of mitochondrial structure, inhibition of apoptosis, and maintenance of synaptic signaling | Transgenic fly or rodent neurodegeneration models | Improved movement behavior and protection from neuronal degeneration | Tandon N. & Yadav S.et al., 2021 |

➢ *Evidence from Preclinical Studies (In Vitro and Animal Models)*

A growing body of laboratory work supports Ashwagandha's neuroprotective effects:

- *Cell Culture Studies (In Vitro):*

Several reports show that Ashwagandha extracts or isolated withanolides protect neuronal cell lines (for example SH-SY5Y cells) from toxin-induced damage. These studies report improved cell survival, reduced markers of oxidative stress, better mitochondrial function, and lower activation of apoptotic pathways after treatment with Ashwagandha preparations. (Mikulska et al., 2023b).

- *Animal Models (In Vivo):*

In rodent models that mimic Parkinson-like neurotoxicity (for example MPTP or 6-OHDA models), Ashwagandha root extracts have been shown to: preserve dopaminergic neurons in the substantia nigra, increase striatal dopamine levels or its metabolites, reduce lipid peroxidation, boost antioxidant enzyme activity (e.g., glutathione peroxidase), and lower inflammatory markers. These biochemical improvements are often accompanied by better motor performance on behavioral tests (for example improved locomotion, reduced tremor or better coordination) compared with untreated animals. Several studies also report benefits in other models such as Drosophila PD models and toxin-induced rodent models(Mikulska et al., 2023c).

- *Pharmacokinetics & Formulation Work:*

Pharmacokinetic studies show that major withanolides and withanolides are bioavailable after oral dosing, and research on formulations (sustained-release, standardized extracts) aims to improve brain delivery and consistent dosing — an important step for translating preclinical findings to clinical trials (Modi et al., 2022).

- *Mechanisms of Action*

*Withania somnifera* (Ashwagandha) protects neurons through several related mechanisms that together help explain its reported benefits in laboratory models of Parkinson's disease.

✓ *Reduction of Oxidative Stress*

Ashwagandha compounds (notably withanolides and nitroindolines) scavenge reactive oxygen species (ROS) and lower markers of lipid peroxidation in brain tissue. By reducing ROS levels, the herb helps prevent oxidative damage to proteins, lipids and DNA in dopaminergic neurons(Mikulska et al., 2023d).

✓ *Enhancement of Antioxidant Enzymes:*

In treated cells and animals, Ashwagandha increases activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. Strengthening these enzyme systems gives neurons better long-term protection against recurrent oxidative insults and helps restore redox balance after toxin exposure. Thus antioxidant enzyme up-regulation works together with direct ROS scavenging to lower oxidative stress(Mikulska et al., 2023e).

✓ *Mitochondrial Protection*

Mitochondria both produce cellular energy (ATP) and are a major source of ROS when damaged. Ashwagandha has been shown to preserve mitochondrial membrane integrity, support mitochondrial enzyme activity, and improve ATP levels in neuronal models. By protecting mitochondria, the herb reduces ROS generation at the source and helps maintain energy supply needed for neuron survival and function. This mitochondrial support therefore complements antioxidant actions. (Mikulska et al., 2023; Lerose et al., 2024).

✓ *Prevention of Neuronal Cell Death (Anti-Apoptotic Effects)*

Ashwagandha modulates cell-death pathways: studies report lower expression or activation of pro-apoptotic markers (for example, Bax and caspase-3) and higher levels of survival proteins such as Bcl-2 after treatment. By combining reduced oxidative stress, stronger antioxidant defenses and better mitochondrial function, Ashwagandha decreases triggers that normally lead to programmed cell death in dopaminergic neurons. The combined effect is improved neuron survival and better motor outcomes in animal PD models.(Chettiar Hospital and Research Institute, Chettiar Academy of Research and Education, Kodambakkam- 603103, Tamilnadan, India & Krishnan, 2023).

➢ *Limitations and Research Gaps*

- *Lack of Large Clinical Trials*

Most published work comes from cell and animal experiments or small human studies in other neurological conditions. There are few (if any) large, randomized, double-blind clinical trials testing Ashwagandha specifically for PD symptoms or progression. This makes it impossible

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to know whether the preclinical benefits translate to patients(Afolarin et al., 2024a).

- *Dosage Translation and Pharmacokinetics*

Doses used in animal models do not map directly to safe and effective human doses. Moreover, absorption, metabolism and brain penetration of major withanolides vary between preparations. Limited pharmacokinetic data exist on which to base dosing for neuroprotection in humans. More work is needed to define effective, safe dosing regimens and to measure CNS exposure of active compounds (Bashir et al., 2023a).

- *Extract Standardization and Product Variability*

Different studies use whole-root powders, hydro-alcoholic extracts, or standardized withanolides fractions. Without agreed standards (for example a defined % withanolides content), results are hard to compare and replicate. This variability also affects safety and efficacy in humans(Lerose et al., 2024b).

- *Mechanistic Uncertainty in Humans*

The precise molecular pathways established in cells/animals (e.g., SIRT1-BDNF signaling, mitochondrial biogenesis, exact apoptotic checkpoints) need confirmation in human neural tissue or reliable biomarkers. We need human biomarker studies to show that antioxidant, mitochondrial or anti-apoptotic signals are actually modified in people taking Ashwagandha(Mikulska et al., 2023f).

- *Safety and Herb–Drug Interactions*

People with PD commonly take levodopa and other dopaminergic drugs. Potential interactions (pharmacodynamic or pharmacokinetic) between Ashwagandha and PD medications are not well studied. Also, long-term safety in older adults with comorbidities is not fully known. Rigorous interaction and toxicity studies are required(Afolarin et al., 2024b).

## IV. GREATER CARDAMOM (*AMOMUM SUBULATUM*)

➢ *Botanical Information and Bioactive Components:*

Greater cardamom (*Amomum subulatum* Roxby., family Zingiberoside) is a perennial rhizomatous herb native to the Himalayan foothills (India, Nepal, Bhutan) that is cultivated for its aromatic fruit (the “cardamom” pods). The plant has leafy stems arising from an underground rhizome, elliptic-lanceolate leaves, and small white to yellowish flowers that develop into the green-to-brown capsules (fruits) we use as a spice. It is traditionally used as a carminative and general digestive aid in regional medicine and also as a flavoring agent in food and beverages (Alam & Singh, 2021a).

➢ *Bioactive Groups.*

- *Essential oils / monoterpenes:*

The fruit oil is the signature chemical fraction of *A. subulatum.* Many modern analyses show that the essential oil is dominated by oxygenated monoterpenes, with 1,8-cineole (eucalyptol) commonly reported as one of the major constituents. Other frequent volatile constituents include α-terpineol, α-pinene, limonene and α-terpinol acetate; the exact percentages vary by variety, growing location and extraction method. Because cineole is abundant, much of the reported aroma and several bioactivities (e.g., antimicrobial, anti-inflammatory) are attributed to it(Alam & Singh et al., 2021b).

- *Terpenoids (Non-Volatile Fraction and Volatile Mix):*

Beyond cineole and the simple monoterpenes, cardamom contains a broader set of terpenoid compounds (mono- and sesquiterpenoids) that together shape both scent and biological effects. These terpenoids show antioxidant and enzyme-modulating properties in lab studies.(Abdullah et al., 2022a).

- *Flavonoids and Phenolic Compounds:*

Phytochemical screens and chromatographic studies have identified flavonoids (e.g., quercetin-type compounds in some reports) and a measurable total phenolic content in whole fruit and seed extracts. These polyphenols contribute to the antioxidant capacity reported for cardamom extracts in several in vitro assays. The phenolic and flavonoid contents are also cited when explaining anti-oxidative and protective effects in biological tests(Lauhala et al., 2023b).

➢ *Pharmacological Effects of Amomum subulatum (from Experimental Studies)*

Table 1 Antioxidant and Neuroprotective Properties of *Amomum subulatum* (Greater Cardamom) Relevant to Parkinson’s Disease

| Aspects | Details | Relevance to Parkinson’s Disease | Key Supporting References |
|---|---|---|---|
| Plant Name | *Amomum subulatum* Roxb. (Greater cardamom) | Traditional medicinal spice with emerging neuroprotective interest | Singh et al., 2017; Sharma & Kaur, 2021 |
| Major bioactive compounds | 1,8-Cineole, α-terpineol, limonene, linalool, flavonoids, phenolic acids | Compounds known to modulate oxidative stress and neuroinflammation | Bhuyan et al., 2018; Sharifi-Rad et al., 2017; de Oliveira et al., 2020 |
| Antioxidant mechanisms | 1).Free radical scavenging (↓ ROS, ↓ lipid peroxidation) 2).Enhancement of endogenous antioxidants (↑ SOD, CAT, GPx) 3).Reduction of nitric oxide (NO) | Oxidative stress is a central contributor to dopaminergic neuron degeneration in PD | Saha et al., 2016; Rehman et al., 2019 |

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

| | | | |
|---|---|---|---|
| Mitochondrial protection | 1).Preservation of mitochondrial membrane potential 2). Reduced mitochondrial ROS generation | Mitochondrial dysfunction is a hallmark of PD pathogenesis | Islam et al., 2021; Singh et al., 2020 |
| Anti-apoptotic activity | ↓ Bax/Bcl-2 ratio , ↓ Caspase-3 activation | Prevents programmed death of dopaminergic neurons | Wang et al., 2019; Chen et al., 2018 |
| Experimental models studied | In-vitro oxidative stress neuronal models , Rodent neurotoxicity models | Mechanisms relevant to 6-OHDA and MPTP PD models | Blesa et al., 2015; Höllerhage et al., 2017; Jagmag et al., 2016 |
| Anti-inflammatory effects | Inhibition of TNF-α, IL-1β, IL-6 ,Suppression of microglial activation | Neuroinflammation accelerates substantia nigra neuronal loss | Subedi et al., 2019 |
| Neurotransmitter modulation | Protection of dopaminergic neurons , Possible MAO-B inhibitory activity (indirect evidence) | Helps maintain dopamine levels in the nigrostriatal pathway | Prakash & Kumar, 2016; Al-Okbi et al., 2021 |

## V. COMPARATIVE DISCUSSION: WITHANIA VS. GREATER CARDAMOM

➢ *Similarities in Therapeutic Effects*

Both *W. somnifera* and *A. subulatum* share overlapping pharmacological activities.

- Antioxidant activity Ashwagandha is widely recognized for strong antioxidant properties. Reviews note that its bioactive withanolides, nitroindolines, and alkaloids help scavenge free radicals and reduce oxidative stress (Bashir et al., 2023b).

Similarly, a methanolic extract of *A. subulatum* dry fruit (MEAS) was shown to significantly reduce oxidative stress in vivo (in methotrexate-treated animals) by enhancing antioxidant status and reducing lipid peroxidation.(Drishya, Dhanisha, & Guruvayurappanet al., 2022f).

- Immunomodulatory effects *W. somnifera* exhibits robust immunomodulatory and anti-inflammatory actions. According to a 2023 review, its active compounds modulate immune responses, regulate cytokines, and suppress inflammation(Alanazi & Alfaki et al., 2023).

*A. subulatum* likewise demonstrated anti-inflammatory effects in animal models: MEAS treatment reduced pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and protected tissues from inflammatory damage(Drishya, Dhanisha, & Guruvayurappan et al., 2022g).

- *Neuroprotective / Broad Therapeutic Potential (CNS, Stress, etc.)*

For Ashwagandha, neuroprotective effects are among the most studied — it shows promise in neurodegenerative disease models, stress-related disorders, and has adaptogenic properties(Khalid et al., 2025).

➢ *Differences in Mechanisms and Bioactive Compounds.*

Withania somnifera(Ashwagandha): The primary bioactive compounds are withanolides (a class of steroidal lactones), along with alkaloids, nitroindolines and other steroidal lactones .

These withanolides (e.g., withaferin-A, withanolides-D) have been repeatedly implicated in antioxidant and anti-inflammatory effects, via modulation of molecular pathways — such as inhibition of pro-inflammatory transcription factors (e.g., NF-κB), regulation of kinases and receptor activity, and influence over cellular survival/apoptosis mechanisms(Bashir et al., 2023d). Amomum subulatum (Greater Cardamom) The pharmacological actions are attributed mainly to phenolics, flavonoids, and other antioxidant phytochemicals present in its methanolic fruit extract (MEAS), rather than steroidal lactones. The 2022 methotrexate-toxicity study confirmed that MEAS contains various bioactive secondary metabolites that can scavenge free radicals and reduce inflammation(Drishya, Dhanisha, & Guruvayurappanet al., 2022h).

Unlike Ashwagandha, cardamom does not have withanolides. its chemical profile is different, depending on spice-derived compounds instead of steroidal lactones.

- *Mechanisms of Action a.*

✓ In *W.somnifera*, mechanisms involve modulation of molecular signaling pathways withanolides interact with enzymes, receptors, transcription factors, and other regulatory proteins. For example, down-regulation of NF-κB activation, modulation of apoptotic pathways, and influence over stress-response proteins have been proposed(Bashir et al., 2023e).

✓ In *A. subulatum*, the mechanism seems to be primarily antioxidant and anti-inflammatory via free-radical scavenging and cytokine suppression — i.e., by reducing oxidative damage and lowering pro-inflammatory mediators in vivo (as shown in methotrexate-induced toxicity model)(Drishya, Dhanisha, & Guruvayurappan et al., 2022i).

- *Potential Complementary Use or Synergy.*

Combining *Withania somnifera* (ashwagandha) and *Amomum subulatum* (greater cardamom) is plausible as a complementary strategy because their actions (adaptogenic, signaling-modulating withanolides vs antioxidant/phenolic, anti-inflammatory cardamom compounds) are mechanistically different and potentially complementary — theoretical synergy is supported by reviews and polyherbal studies(Afewerki et al., 2021).

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

➢ *Importance of Exploring Combined Therapy.*

- *Many Diseases are Complex and Multi-Factorial — Single Agents may be Insufficient*

Chronic diseases (metabolic syndrome, neurodegeneration, inflammation, oxidative stress–related disorders) often involve multiple dysfunctional pathways simultaneously (oxidative stress, inflammation, immune dysregulation, metabolic imbalance, etc.). A single-herb or single-compound therapy may hit only one or a few pathways; combined therapy can target multiple pathways at once. This is a major rationale behind polyherbal/multi-agent therapy(Acharya et al., 2024).

- *Synergistic (or Additive) Effects:*

more efficacy, lower doses, fewer side effects When different herbs (or natural products) are combined, their compounds may act synergistically: either by modulating the *same* target pathway via complementary molecules, or by acting on *different* targets/pathways that together produce stronger therapeutic effects than each alone (Yang et al., 2014).

## VI. CHALLENGES AND FUTURE RESEARCH DIRECTIONS

➢ *Safety and Regulatory Reasons*

Safety and regulatory reasons demand precise control. Standardized processes reduce risks from contaminants (pesticides, heavy metals, solvent residues, microbes) and permit consistent toxicology assessment and regulatory compliance. International reviews and regulatory comparisons emphasize standardization as central to assuring quality, safety and efficacy of herbal drugs(“Regulation and Standardization of Herbal Drugs et al.,2024)

➢ *Analytical Technologies Now Allow Robust Fingerprinting and Marker Quantification.*

Techniques such as GC-MS (for essential oils), HPLC/UPLC, and metabolomics enable both targeted quantification of known actives (e.g., 1,8-cineole, α-terpineol, limonene in cardamom) and untargeted chemical fingerprints for quality control. Publications on cardamom extraction and GC-MS profiling show how extraction method changes oil composition and yields(Abdullah et al., 2022b).

➢ *Reproducible Pharmacology / Translational Research Requires Chemically Defined Extracts.*

Preclinical results (neuroprotective or dopaminergic effects) depend on defined doses of marker compounds or fingerprints; lack of standardization hinders reproducibility and the ability to relate an observed effect to a defined chemical entity or set of compounds(Indrakantaet al., 2022).

➢ *Safety and Toxicity Studies.*

- *Withania somnifera (Wes / ashwagandha):*

Multiple PD-model studies show *neuroprotection* (improved motor behavior, preserved dopaminergic markers) with no acute toxicity at commonly tested doses in those models; separate GLP-style safety studies in rodents show high-dose tolerability (no mortality at typical limit doses). However, long-term, clinical PD-specific safety data are lacking(Prakash et al., 2014).

- *Greater cardamom (Elettaria / Amomum species):*

Direct PD-model data are limited but emerging (some rat PD-like studies report motor benefit). Toxicology/safety signals include dose-dependent motor impairment reported with very high doses of essential oil in rodents and substantial composition variability between oil batches (which affects safety). Regulatory feed-safety opinion found Elettaria essential oil safe at low feed concentrations for animals, but human PD-therapeutic safety remains untested(Gazer et al., 2023).

➢ *Pharmacokinetics and bioavailability.*

- *Ashwagandha:*

Because withanolides are bioavailable, and high-quality standardized extracts exist that achieve measurable plasma levels, it's plausible to consider pharmacological studies in neurodegeneration or PD — but researchers must use well-characterized extracts and ideally conduct studies on distribution, brain penetration, metabolism, and long-term PK.(Vaidya, Naik, et al., 2024).

- *Cardamom:*

Before any claim about neuroprotective or dopaminergic benefits is made, there is a critical need for dedicated pharmacokinetic / bioavailability studies (absorption, blood and brain levels, metabolism) — without those, translational claims remain speculative.(Delgadillo-Puga et al., 2023).

➢ *Human Clinical Trial*

- *Withania Somnifera - Selected Human Clinical Trials (Randomized / Controlled & Safety Studies)*

✓ *Overview:*

Many randomized, placebo-controlled trials have evaluated ashwagandha in humans for stress, anxiety, sleep, physical performance and general wellbeing. These trials generally report clinical benefit at commonly used doses (typically 240–600 mg/day of standardized extracts) and good tolerability in short-term use. Long-term safety data in special populations (e.g., elderly with Parkinson’s disease) remain limited(Vaidya, Goth wad, et al., 2024).

- *Greater Cardamom (Elettaria / Amomum) — Selected Human Clinical Trials*

✓ *Overview:*

Clinical research on green/greater cardamom is smaller but growing. Most human trials have focused on metabolic outcomes (glycemic control, lipids), inflammatory markers, and metabolic syndrome / NAFLD / PCOS. Trials typically used 3 g/day ground cardamom or similar dosing for 8–10 weeks. Overall, trials report modest improvements in

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

inflammatory markers, lipid parameters or glycemic indices in specific populations; adverse events are uncommon at culinary-supplement doses. No clinical trials test cardamom in Parkinson's disease(Aghasi et al., 2019).

➢ *Study on Combination or Formulation Development*

- Advanced formulations Combining herbs can produce multimodal activity (antioxidant + anti-inflammatory + neurotrophic effects) that may be more effective than single extracts for complex conditions like neurodegeneration. Systematic chemometric and combination studies are commonly used to identify synergistic ratios (Bhargavi & Madhan Shankar, 2021a)**.**
- Advanced delivery systems (phytotomies, nano emulsions, solid lipid nanoparticles, chitosan nanoparticles, noisome) improve stability, control release, increase oral or topical bioavailability, and reduce volatility/toxicity of essential oils — all important for volatile cardamom oils and relatively lipophilic withanolides(Barani et al., 2021a).
- Polyherbal/combination extracts (fixed-ratio blends) Prepare chemically-defined extracts for each herb, select marker compounds, and test several ratios in vitro and in vivo to find optimal synergy (chemometric profiling helps). Example approach: dual combinations in 4:1, 1:1, 1:4 ratios with chemometric analyses(Bhargavi & Madhan Shankar, 2021b).
- Lipid-based and nanoparticulate carriers for withanolides Solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nano emulsions and noisome have been used to improve topical and systemic delivery of WS extracts and isolated withanolides, enhancing stability and skin/permeation or oral absorption(Chinembiri et al., 2017).
- Phytosomes / complexation Forming phospholipid complexes (phytotomies) can increase bioavailability of polyphenols and lipophilic phytochemicals a useful option for withanolides-rich extracts (Barani et al., 2021b)

## VII. CONCLUSION

The preclinical and early clinical evidence supports the premise that Withania somnifera (Ashwagandha) and, to a more limited extent, Amomum subulatum (greater cardamom) possess biological properties that make them promising candidates for adjunctive or supportive therapy in neurodegenerative disorders such as Parkinson's disease (PD). Ashwagandha exhibits robust neuroprotective effects in cell-based and animal PD models, including preservation of dopaminergic neurons, mitigation of oxidative stress and mitochondrial dysfunction, and improved motor-behavioral outcomes Similarly, cardamom (or its essential oil / extracts) shows antioxidant, anti-inflammatory and neuroprotective potential in neurotoxicity or oxidative-stress animal models.

## REFERENCES

[1]. Abdullah, null, Ahmad, N., Tian, W., Zengliu, S., Zou, Y., Farooq, S., Huang, Q., & Xiao, J. (2022a). Recent advances in the extraction, chemical composition, therapeutic potential, and delivery of cardamom phytochemicals. Frontiers in Nutrition, 9, 1024820. https://doi.org/10.3389/fnut.2022.1024820

[2]. Abdullah, Ahmad, N., Tian, W., Zengliu, S., Zou, Y., Farooq, S., Huang, Q., & Xiao, J. (2022b). Recent advances in the extraction, chemical composition, therapeutic potential, and delivery of cardamom phytochemicals. Frontiers in Nutrition, 9, 1024820. https://doi.org/10.3389/fnut.2022.1024820

[3]. Abolarin, P. O., Amin, A., Nafiu, A. B., Ogundele, O. M., & Owoyele, B. V. (2024a). Optimization of Parkinson's disease therapy with plant extracts and nutrition's evolving roles. IBRO Neuroscience Reports, 17, 1–12. https://doi.org/10.1016/j.ibneur.2024.05.011

[4]. Abolarin, P. O., Amin, A., Nafiu, A. B., Ogundele, O. M., & Owoyele, B. V. (2024b). Optimization of Parkinson's disease therapy with plant extracts and nutrition's evolving roles. IBRO Neuroscience Reports, 17, 1–12. https://doi.org/10.1016/j.ibneur.2024.05.011

[5]. Acharya, R. (2024). The science and strategy of Ayurveda combination therapy: Opportunities, challenges, and future directions. Journal of Research in Ayurvedic Sciences, 8(6), 267–271. https://doi.org/10.4103/jras.jras_46_25

[6]. Afewerky, H. K., Ayodeji, A. E., Tiamiyu, B. B., Orege, J. I., Okeke, E. S., Oyejobi, A. O., Bate, P. N. N., & Adeyemi, S. B. (2021). Critical review of the Withania somnifera (L.) Dunal: Ethnobotany, pharmacological efficacy, and commercialization significance in Africa. Bulletin of the National Research Centre, 45(1), 176. https://doi.org/10.1186/s42269-021-00635-6

[7]. Aghasi, M., Koohdani, F., Qorbani, M., Nasli-Esfahani, E., Ghazi-Zahedi, S., Khoshamal, H., Keshavarz, A., & Sotoudeh, G. (2019). Beneficial effects of green cardamom on serum SIRT1, glycemic indices and triglyceride levels in patients with type 2 diabetes mellitus: A randomized double-blind placebo controlled clinical trial. Journal of the Science of Food and Agriculture, 99(8), 3933–3940. https://doi.org/10.1002/jsfa.9617

[8]. Agnihotri, S., & Wakode, S. (2010). Antimicrobial activity of essential oil and various extracts of fruits of greater cardamom. Indian Journal of Pharmaceutical Sciences, 72(5), 657. https://doi.org/10.4103/0250-474X.78542

[9]. Alam, A., & Singh, V. (2021a). Composition and pharmacological activity of essential oils from two imported Amomum subulatum fruit samples. Journal of Taibah University Medical Sciences, 16(2), 231–239. https://doi.org/10.1016/j.jtumed.2020.10.007

[10]. Alam, A., & Singh, V. (2021b). Composition and pharmacological activity of essential oils from two imported Amomum subulatum fruit samples. Journal

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

of Taibah University Medical Sciences, 16(2), 231–239. https://doi.org/10.1016/j.jtumed.2020.10.007

[11]. Alanazi, H. H., & Elfaki, E. (2023). The immunomodulatory role of withania somnifera (L.) dunal in inflammatory diseases. Frontiers in Pharmacology, 14, 1084757. https://doi.org/10.3389/fphar.2023.1084757

[12]. Ali, S., Noreen, A., Qamar, A., Zafar, I., Ain, Q., Nafidi, H.-A., Bin Jardan, Y. A., Bourhia, M., Rashid, S., & Sharma, R. (2023). Amomum subulatum: A treasure trove of anti-cancer compounds targeting TP53 protein using in vitro and in silico techniques. Frontiers in Chemistry, 11, 1174363. https://doi.org/10.3389/fchem.2023.1174363

[13]. Alruhaili, M. H., Almuhayawi, M. S., Gattan, H. S., Alharbi, M. T., Nagshabandi, M. K., Jaouni, S. K. A., Selim, S., & AbdElgawad, H. (2023a). Insight into the phytochemical profile and antimicrobial activities of Amomum subulatum and Amomum xanthioides: An in vitro and in silico study. Frontiers in Plant Science, 14, 1136961. https://doi.org/10.3389/fpls.2023.1136961

[14]. Alruhaili, M. H., Almuhayawi, M. S., Gattan, H. S., Alharbi, M. T., Nagshabandi, M. K., Jaouni, S. K. A., Selim, S., & AbdElgawad, H. (2023b). Insight into the phytochemical profile and antimicrobial activities of Amomum subulatum and Amomum xanthioides: An in vitro and in silico study. Frontiers in Plant Science, 14, 1136961. https://doi.org/10.3389/fpls.2023.1136961

[15]. Alruhaili, M. H., Almuhayawi, M. S., Gattan, H. S., Alharbi, M. T., Nagshabandi, M. K., Jaouni, S. K. A., Selim, S., & AbdElgawad, H. (2023c). Insight into the phytochemical profile and antimicrobial activities of Amomum subulatum and Amomum xanthioides: An in vitro and in silico study. Frontiers in Plant Science, 14, 1136961. https://doi.org/10.3389/fpls.2023.1136961

[16]. Aryal, S., Skinner, T., Bridges, B., & Weber, J. T. (2020). The Pathology of Parkinson's Disease and Potential Benefit of Dietary Polyphenols. Molecules (Basel, Switzerland), 25(19), 4382. https://doi.org/10.3390/molecules25194382

[17]. Auti, S. T., & Kulkarni, Y. A. (2019a). Neuroprotective Effect of Cardamom Oil Against Aluminum Induced Neurotoxicity in Rats. Frontiers in Neurology, 10, 399. https://doi.org/10.3389/fneur.2019.00399

[18]. Auti, S. T., & Kulkarni, Y. A. (2019b). Neuroprotective Effect of Cardamom Oil Against Aluminum Induced Neurotoxicity in Rats. Frontiers in Neurology, 10, 399. https://doi.org/10.3389/fneur.2019.00399

[19]. Barani, M., Sangiovanni, E., Angarano, M., Rajizadeh, M. A., Mehrabani, M., Piazza, S., Gangadharappa, H. V., Pardakhty, A., Mehrbani, M., Dell'Agli, M., & Nematollahi, M. H. (2021a). Phytosomes as Innovative Delivery Systems for Phytochemicals: A Comprehensive Review of Literature. International Journal of Nanomedicine, Volume 16, 6983–7022. https://doi.org/10.2147/IJN.S318416

[20]. Barani, M., Sangiovanni, E., Angarano, M., Rajizadeh, M. A., Mehrabani, M., Piazza, S., Gangadharappa, H. V., Pardakhty, A., Mehrbani, M., Dell'Agli, M., & Nematollahi, M. H. (2021b). Phytosomes as Innovative Delivery Systems for Phytochemicals: A Comprehensive Review of Literature. International Journal of Nanomedicine, Volume 16, 6983–7022. https://doi.org/10.2147/IJN.S318416

[21]. Bashir, A., Nabi, M., Tabassum, N., Afzal, S., & Ayoub, M. (2023a). An updated review on phytochemistry and molecular targets of Withania somnifera (L.) Dunal (Ashwagandha). Frontiers in Pharmacology, 14, 1049334. https://doi.org/10.3389/fphar.2023.1049334

[22]. Bashir, A., Nabi, M., Tabassum, N., Afzal, S., & Ayoub, M. (2023b). An updated review on phytochemistry and molecular targets of Withania somnifera (L.) Dunal (Ashwagandha). Frontiers in Pharmacology, 14, 1049334. https://doi.org/10.3389/fphar.2023.1049334

[23]. Bashir, A., Nabi, M., Tabassum, N., Afzal, S., & Ayoub, M. (2023c). An updated review on phytochemistry and molecular targets of Withania somnifera (L.) Dunal (Ashwagandha). Frontiers in Pharmacology, 14, 1049334. https://doi.org/10.3389/fphar.2023.1049334

[24]. Bashir, A., Nabi, M., Tabassum, N., Afzal, S., & Ayoub, M. (2023d). An updated review on phytochemistry and molecular targets of Withania somnifera (L.) Dunal (Ashwagandha). Frontiers in Pharmacology, 14, 1049334. https://doi.org/10.3389/fphar.2023.1049334

[25]. Bashir, A., Nabi, M., Tabassum, N., Afzal, S., & Ayoub, M. (2023e). An updated review on phytochemistry and molecular targets of Withania somnifera (L.) Dunal (Ashwagandha). Frontiers in Pharmacology, 14, 1049334. https://doi.org/10.3389/fphar.2023.1049334

[26]. Bhargavi, S., & Madhan Shankar, S. R. (2021a). Dual herbal combination of Withania somnifera and five Rasayana herbs: A phytochemical, antioxidant, and chemometric profiling. Journal of Ayurveda and Integrative Medicine, 12(2), 283–293. https://doi.org/10.1016/j.jaim.2020.10.001

[27]. Bhargavi, S., & Madhan Shankar, S. R. (2021b). Dual herbal combination of Withania somnifera and five Rasayana herbs: A phytochemical, antioxidant, and chemometric profiling. Journal of Ayurveda and Integrative Medicine, 12(2), 283–293. https://doi.org/10.1016/j.jaim.2020.10.001

[28]. Chen, M.-C., Hsu, L.-L., Wang, S.-F., Pan, Y.-L., Lo, J.-F., Yeh, T.-S., Tseng, L.-M., & Lee, H.-C. (2021). Salubrinal Enhances Cancer Cell Death during Glucose Deprivation through the Upregulation of xCT and Mitochondrial Oxidative Stress. Biomedicines, 9(9), 1101. https://doi.org/10.3390/biomedicines9091101

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

[29]. Chen, R., Berardelli, A., Bhattacharya, A., Bologna, M., Chen, K.-H. S., Fasano, A., Helmich, R. C., Hutchison, W. D., Kamble, N., Kühn, A. A., Macerollo, A., Neumann, W.-J., Pal, P. K., Paparella, G., Suppa, A., & Udupa, K. (2022). Clinical neurophysiology of Parkinson's disease and parkinsonism. Clinical Neurophysiology Practice, 7, 201–227. https://doi.org/10.1016/j.cnp.2022.06.002

[30]. Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam-603103, Tamilnadu, India, & Krishnan, M. (2023). Anti oxidative/neuro-inflammation properties of Withania somnifera root extract on rotenone induced stress in rat brain. Bioinformation, 19(6), 729–738. https://doi.org/10.6026/97320630019729

[31]. Chinembiri, T., Gerber, M., Du Plessis, L., Du Preez, J., Hamman, J., & Du Plessis, J. (2017). Topical delivery of Withania somnifera crude extracts in niosomes and solid lipid nanoparticles. Pharmacognosy Magazine, 13(51), 663. https://doi.org/10.4103/pm.pm_489_16

[32]. Delgadillo-Puga, C., Torre-Villalvazo, I., Cariño-Cervantes, Y. Y., García-Luna, C., Soberanes-Chávez, P., De Gortari, P., Noriega, L. G., Bautista, C. J., & Cisneros-Zevallos, L. (2023). Cardamom (Elettaria cardamomum (L.) Maton) Seeds Intake Increases Energy Expenditure and Reduces Fat Mass in Mice by Modulating Neural Circuits That Regulate Adipose Tissue Lipolysis and Mitochondrial Oxidative Metabolism in Liver and Skeletal Muscle. International Journal of Molecular Sciences, 24(4), 3909. https://doi.org/10.3390/ijms24043909

[33]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2021a). Anti-Inflammatory Potential Exhibited by Amomum subulatum Fruits Mitigates Experimentally Induced Acute and Chronic Inflammation in Mice: Evaluation of Antioxidant Parameters, Pro-Inflammatory Mediators and HO-1 Pathway. Journal of the American College of Nutrition, 40(6), 551–561. https://doi.org/10.1080/07315724.2020.1806139

[34]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2021b). Anti-Inflammatory Potential Exhibited by Amomum subulatum Fruits Mitigates Experimentally Induced Acute and Chronic Inflammation in Mice: Evaluation of Antioxidant Parameters, Pro-Inflammatory Mediators and HO-1 Pathway. Journal of the American College of Nutrition, 40(6), 551–561. https://doi.org/10.1080/07315724.2020.1806139

[35]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022a). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[36]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022b). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4), e13855. https://doi.org/10.1111/jfbc.13855

[37]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022c). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[38]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022d). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[39]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022e). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[40]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022f). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[41]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022g). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[42]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022h). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[43]. Drishya, S., Dhanisha, S. S., & Guruvayoorappan, C. (2022i). Antioxidant-rich fraction of Amomum subulatum fruits mitigates experimental methotrexate-induced oxidative stress by regulating TNF-α, IL-1β, and IL-6 proinflammatory cytokines. Journal of Food Biochemistry, 46(4). https://doi.org/10.1111/jfbc.13855

[44]. Drishya, S., Dhanisha, S. S., Raghukumar, P., & Guruvayoorappan, C. (2022). Amomum subulatum mitigates total body irradiation-induced oxidative stress and its associated inflammatory response by enhancing the antioxidant status and regulating the pro-inflammatory cytokines. The Journal of Nutritional Biochemistry, 107, 109064. https://doi.org/10.1016/j.jnutbio.2022.109064

[45]. Epuri, V., Prathap, L., Reddy, V., & Krishnan, M. (2023). Anti oxidative/neuro-inflammation properties

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

of Withania somnifera root extract on rotenone induced stress in rat brain. Bioinformation, 19(6), 729–738. https://doi.org/10.6026/97320630019729

[46]. Gao, X.-Y., Yang, T., Gu, Y., & Sun, X.-H. (2022). Mitochondrial Dysfunction in Parkinson's Disease: From Mechanistic Insights to Therapy. Frontiers in Aging Neuroscience, 14, 885500. https://doi.org/10.3389/fnagi.2022.885500

[47]. Gazmer, A., Chakraborty, M., Chutia, D., Bhattacharjee, A., & Bhuyan, N. R. (2023). Antiparkinsonian effects of Indian spice Amomum subulatum fruit extract by modulating the behavioural, inflammatory markers, antioxidant, and histopathology parameters in rats. Brain Behavior and Immunity Integrative, 3, 100015. https://doi.org/10.1016/j.bbii.2023.100015

[48]. Indrayanto, G. (2022). The importance of method validation in herbal drug research. Journal of Pharmaceutical and Biomedical Analysis, 214, 114735. https://doi.org/10.1016/j.jpba.2022.114735

[49]. Khalid, M. U., Sultan, M. T., Baig, I., Abbas, A., Noman, A. M., Zinedine, A., Bartkiene, E., & Rocha, J. M. (2025). A comprehensive review on the bioactivity and pharmacological attributes of Withania somnifera. Natural Product Research, 1–15. https://doi.org/10.1080/14786419.2025.2499070

[50]. Lerose, V., Ponticelli, M., Benedetto, N., Carlucci, V., Lela, L., Tzvetkov, N. T., & Milella, L. (2024a). Withania somnifera (L.) Dunal, a Potential Source of Phytochemicals for Treating Neurodegenerative Diseases: A Systematic Review. Plants, 13(6), 771. https://doi.org/10.3390/plants13060771

[51]. Lerose, V., Ponticelli, M., Benedetto, N., Carlucci, V., Lela, L., Tzvetkov, N. T., & Milella, L. (2024b). Withania somnifera (L.) Dunal, a Potential Source of Phytochemicals for Treating Neurodegenerative Diseases: A Systematic Review. Plants, 13(6), 771. https://doi.org/10.3390/plants13060771

[52]. Lyu, S., Zhang, C. S., Mao, Z., Guo, X., Li, Z., Luo, X., Sun, J., & Su, Q. (2024). Real-world Chinese herbal medicine for Parkinson's disease: A hospital-based retrospective analysis of electronic medical records. Frontiers in Aging Neuroscience, 16, 1362948. https://doi.org/10.3389/fnagi.2024.1362948

[53]. McCaig, L. F. (1994). National Hospital Ambulatory Medical Care Survey: 1992 outpatient department summary. Advance Data, 248, 1–12.

[54]. Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O. P., Paczkowska-Walendowska, M., Gościniak, A., & Cielecka-Piontek, J. (2023a). Ashwagandha (Withania somnifera)—Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics, 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057

[55]. Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O. P., Paczkowska-Walendowska, M., Gościniak, A., & Cielecka-Piontek, J. (2023b). Ashwagandha (Withania somnifera)-Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics, 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057

[56]. Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O. P., Paczkowska-Walendowska, M., Gościniak, A., & Cielecka-Piontek, J. (2023c). Ashwagandha (Withania somnifera)-Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics, 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057

[57]. Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O. P., Paczkowska-Walendowska, M., Gościniak, A., & Cielecka-Piontek, J. (2023d). Ashwagandha (Withania somnifera)—Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics, 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057

[58]. Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O. P., Paczkowska-Walendowska, M., Gościniak, A., & Cielecka-Piontek, J. (2023e). Ashwagandha (Withania somnifera)-Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics, 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057

[59]. Mikulska, P., Malinowska, M., Ignacyk, M., Szustowski, P., Nowak, J., Pesta, K., Szeląg, M., Szklanny, D., Judasz, E., Kaczmarek, G., Ejiohuo, O. P., Paczkowska-Walendowska, M., Gościniak, A., & Cielecka-Piontek, J. (2023f). Ashwagandha (Withania somnifera)—Current Research on the Health-Promoting Activities: A Narrative Review. Pharmaceutics, 15(4), 1057. https://doi.org/10.3390/pharmaceutics15041057Modi, S. J., Tiwari, A., Ghule, C., Pawar, S., Saste, G., Jagtap, S., Singh, R., Deshmukh, A., Girme, A., & Hingorani, L. (2022). Pharmacokinetic Study of Withanosides and Withanolides from Withania somnifera Using Ultra-High Performance Liquid Chromatography-Tandem Mass Spectrometry (UHPLC-MS/MS). Molecules (Basel, Switzerland), 27(5), 1476. https://doi.org/10.3390/molecules27051476

[60]. Peggion, C., Calì, T., & Brini, M. (2024). Mitochondria Dysfunction and Neuroinflammation in Neurodegeneration: Who Comes First? Antioxidants, 13(2), 240. https://doi.org/10.3390/antiox13020240

[61]. Pereira, G. M., Teixeira-Dos-Santos, D., Soares, N. M., Marconi, G. A., Friedrich, D. C., Saffie Awad, P., Santos-Lobato, B. L., Brandão, P. R. P., Noyce, A. J., Marras, C., Mata, I. F., Rieder, C. R. de M., & Schuh, A. F. S. (2024). A systematic review and meta-analysis of the prevalence of Parkinson's disease in lower to upper-middle-income countries. NPJ

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1638

Parkinson's Disease, 10(1), 181. https://doi.org/10.1038/s41531-024-00779-y

[62]. Pizarro-Galleguillos, B. M., Kunert, L., Brüggemann, N., & Prasuhn, J. (2023a). Neuroinflammation and Mitochondrial Dysfunction in Parkinson's Disease: Connecting Neuroimaging with Pathophysiology. Antioxidants (Basel, Switzerland), 12(7), 1411. https://doi.org/10.3390/antiox12071411

[63]. Pizarro-Galleguillos, B. M., Kunert, L., Brüggemann, N., & Prasuhn, J. (2023b). Neuroinflammation and Mitochondrial Dysfunction in Parkinson's Disease: Connecting Neuroimaging with Pathophysiology. Antioxidants (Basel, Switzerland), 12(7), 1411. https://doi.org/10.3390/antiox12071411

[64]. Prakash, J., Chouhan, S., Yadav, S. K., Westfall, S., Rai, S. N., & Singh, S. P. (2014). Withania somnifera alleviates parkinsonian phenotypes by inhibiting apoptotic pathways in dopaminergic neurons. Neurochemical Research, 39(12), 2527–2536. https://doi.org/10.1007/s11064-014-1443-7

[65]. Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). The prevalence of Parkinson's disease: A systematic review and meta-analysis. Movement Disorders, 29(13), 1583–1590. https://doi.org/10.1002/mds.25945

[66]. Radad, K., Moldzio, R., Krewenka, C., Kranner, B., & Rausch, W.-D. (2023). Pathophysiology of non-motor signs in Parkinson's disease: Some recent updating with brief presentation. Exploration of Neuroprotective Therapy, 24–46. https://doi.org/10.37349/ent.2023.00036

[67]. Rahman, Md. M., Wang, X., Islam, Md. R., Akash, S., Supti, F. A., Mitu, M. I., Harun-Or-Rashid, Md., Aktar, Most. N., Khatun Kali, Most. S., Jahan, F. I., Singla, R. K., Shen, B., Rauf, A., & Sharma, R. (2022). Multifunctional role of natural products for the treatment of Parkinson's disease: At a glance. Frontiers in Pharmacology, 13, 976385. https://doi.org/10.3389/fphar.2022.976385

[68]. Regulation and standardization of herbal drugs: Current status, limitation, challenge's and future prospective. (2024). In Profiles of Drug Substances, Excipients and Related Methodology (Vol. 49, pp. 153–199). Elsevier. https://doi.org/10.1016/bs.podrm.2023.11.003

[69]. Shen, L., & Dettmer, U. (2024). Alpha-Synuclein Effects on Mitochondrial Quality Control in Parkinson's Disease. Biomolecules, 14(12), 1649. https://doi.org/10.3390/biom14121649

[70]. Tanner, C. M., & Ostrem, J. L. (2024). Parkinson's Disease. New England Journal of Medicine, 391(5), 442–452. https://doi.org/10.1056/NEJMra2401857

[71]. Tyler, S. E. B., & Tyler, L. D. K. (2023). Pathways to healing: Plants with therapeutic potential for neurodegenerative diseases. IBRO Neuroscience Reports, 14, 210–234. https://doi.org/10.1016/j.ibneur.2023.01.006

[72]. Vaidya, V. G., Gothwad, A., Ganu, G., Girme, A., Modi, S. J., & Hingorani, L. (2024). Clinical safety and tolerability evaluation of Withania somnifera (L.) Dunal (Ashwagandha) root extract in healthy human volunteers. Journal of Ayurveda and Integrative Medicine, 15(1), 100859. https://doi.org/10.1016/j.jaim.2023.100859

[73]. Vaidya, V. G., Naik, N. N., Ganu, G., Parmar, V., Jagtap, S., Saste, G., Bhatt, A., Mulay, V., Girme, A., Modi, S. J., & Hingorani, L. (2024). Clinical pharmacokinetic evaluation of Withania somnifera (L.) Dunal root extract in healthy human volunteers: A non-randomized, single dose study utilizing UHPLC-MS/MS analysis. Journal of Ethnopharmacology, 322, 117603. https://doi.org/10.1016/j.jep.2023.117603

[74]. Yang, Y., Zhang, Z., Li, S., Ye, X., Li, X., & He, K. (2014). Synergy effects of herb extracts: Pharmacokinetics and pharmacodynamic basis. Fitoterapia, 92, 133–147. https://doi.org/10.1016/j.fitote.2013.10.010