

Neuroprotective Potential of *Ocimum basilicum*: Insight into Mechanisms and Therapeutic Applications

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Abstract: Sweet basil, or *Ocimum basilicum*, is a popular therapeutic herb with potent neuroprotective properties that are enhanced by phenolics, flavonoids, and essential oils. An increasing body of research indicates that its bioactive components, including linalool, eugenol, rosmarinic acid, and ursolic acid, are essential in preventing oxidative stress, neuroinflammation, and mitochondrial dysfunction—all of which are key components of many neurodegenerative diseases. The activation of the Nrf2 antioxidant pathway, regulation of NF-κB-mediated inflammatory signaling, inhibition of acetylcholinesterase, and augmentation of neuronal survival pathways are among the molecular mechanisms by which *O. basilicum* exerts its protective benefits. Its relevance as a promising herbal neurotherapeutic agent is shown by preclinical studies that show its potential advantages in models of Parkinson's illness, Alzheimer's disease, epilepsy, and cognitive impairment. Clinical evidence is still scarce despite promising results, and further research is needed to determine standardized formulations, ideal dosages, and safety profiles. All things considered, *O. basilicum* shows itself to be a versatile herb with substantial therapeutic potential, meriting more research for its potential use in treating neurological conditions.

Keywords: Nrf2 Pathway; Neuroprotection; Antioxidant Activity; *Ocimum Basilicum*.

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I. INTRODUCTION

A class of illnesses known as neurodegenerative disorders (NDs) causes nerve cells to progressively deteriorate or die over time. Memory loss, poor motor coordination, and other neurological symptoms are caused by this gradual and ongoing loss of neurons. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are some of the most well-known conditions in this group. Even though all these disorders fall under the same group, each one has its own clinical features, affected brain regions, and disease mechanisms. For example, AD mainly causes memory loss and difficulties in thinking, and it is linked with the build-up of beta-amyloid plaques and tau tangles in the brain. PD is recognized by symptoms such as tremors, slow movements, and rigidity, caused by the loss of dopamine-producing neurons. HD develops due to a genetic mutation (CAG repeat expansion in the HTT gene) and leads to involuntary movements along with cognitive decline. ALS, on the other hand, damages motor neurons, resulting in progressive muscle weakness and eventually paralysis⁽¹⁾ These disorders are a major cause of long-term

disability around the world and affect more than 15% of the global population. Their numbers have been rising rapidly over the last few decades and are expected to increase even more in the coming years. AD and PD are the two most common neurological disorder⁽²⁾ In 2023, around 6.7 million Americans aged 65 and above were living with Alzheimer's disease, and this number may rise to nearly 14 million by 2060 if no effective treatments are developed. Similarly, the number of people diagnosed with PD is expected to double by 2040. According to the Parkinson's Foundation, nearly one million Americans currently live with PD, and around 90,000 new cases are diagnosed each year—much higher than the earlier estimate of 60,000⁽³⁾

The most prevalent neurodegenerative disease, Alzheimer's disease (AD), is primarily identified by a progressive loss of memory, particularly of recent events and recently acquired knowledge. The "amyloid cascade hypothesis" has long been the most popular theory explaining how AD starts. According to this idea, the accumulation of amyloid-beta (Aβ) proteins in the brain initiates a series of detrimental processes, including the production of aberrant tau proteins, loss of neuronal

connections, inflammation, and ultimately the death of brain cells(4) However, several recent clinical trials targeting amyloid alone have not shown the expected improvements in patients. As a result, researchers are now considering AD from a wider angle. Instead of focusing on a single cause, most recent theories emphasize tau pathology, issues with brain metabolism, and the existence of several overlapping alterations. This change indicates that AD is far more complicated than previously believed.. According to long-term brain imaging research, the molecular alterations linked to AD actually start years or even decades before symptoms like memory loss manifest. (Duyckaerts et al., 2015) The brain's amyloid levels progressively rise early in the illness. Following this, tau disease becomes more apparent, causing some areas of the brain to shrivel (atrophy). Knowing this schedule has inspired scientists and medical professionals to investigate therapies that begin much earlier in order to slow or stop the disease before significant symptoms appear(5)

II. PARKINSON DISEASE

The primary symptoms of Parkinson's disease are associated with movement. Bradykinesia (slow movements), tremors (shaking at rest), and rigidity (stiffness) are common symptoms in people with this illness. As the disease progresses, these symptoms make everyday tasks—like dressing, walking, or eating—more difficult, eventually affecting a person's independence and overall quality of life. Although these motor symptoms appear early and are important for diagnosis, problems such as poor balance, difficulty walking, speech changes, and trouble swallowing tend to worsen over time and greatly add to the disability(6) Non-motor symptoms can appear very early, sometimes even years before the motor symptoms begin. In many patients, they start out mild but gradually become more noticeable as the disease progresses. These symptoms add a significant burden on patients and families, reduce quality of life, and greatly increase the cost of care. In later stages of Parkinson's disease, issues like worsening memory, difficulty thinking, and hallucinations become common and are major reasons why patients may require hospitalisation or long-term care(7)

III. GENERAL INTRODUCTION TO OCIMUM BASILICUM (SWEET BASIL) TRADITIONAL USES AND CHEMICAL RICHNESS

Ocimum basilicum L. , commonly known as sweet basil, is known by many local names across different regions and has been widely used in several traditional medical systems. Plants of *O. basilicum* used in the referenced study were collected from a local plantation in Gombak, Kuala Lumpur, Malaysia, and a voucher specimen (HF100) was authenticated and stored at the Herbarium in Bangi.(8)

Sweet basil is well recognized for its broad range of pharmacological activities. Research has shown that it possesses anti-ulcer, anti-inflammatory, and antimicrobial

properties. In addition, it has been reported to have anti-asthmatic, anti-carcinogenic/chemopreventive, analgesic, antipyretic, and anti-diabetic/hypolipidemic effects. The plant is also known for supporting digestion, offering hepatoprotective benefits, and demonstrating anti-stress, immunomodulatory, lipid-lowering, and hypoglycemic actions. These diverse therapeutic potentials are summarized(9)

➤ *Bioactive Principles and Chemical Composition of O. basilicum* L.

Many research studies have shown that *Ocimum basilicum* (sweet basil) contains a wide variety of natural chemicals that contribute to its medicinal value. When scientists tested the leaves through preliminary phytochemical screening, they found several important groups of compounds such as alkaloids, glycosides, gums, mucilage, planteose, polysaccharides, proteins, amino acids, tannins, phenolic compounds, triterpenoids, steroids, sterols, saponins, flavones, and flavonoids. Apart from this, different extraction techniques and plant parts also revealed the presence of similar classes of compounds, including tannins, saponins, alkaloids, phenolics, flavonoids, glycosides, steroids, proteins, and amino acids. These results clearly show that basil is a chemically rich plant, and its composition can slightly change depending on factors like the solvent used for extraction, the stage of plant growth, and environmental conditions(10) Studies on *Ocimum basilicum* have found a wide range of phytochemicals, though the presence of phenolic compounds has been reported more frequently than other groups. This chemical richness is one of the main reasons why *O. basilicum* exhibits so many beneficial activities, particularly antioxidant, anti-inflammatory, antimicrobial, and even neuroprotective effects that support brain health. It is crucial to stress that the process utilized to extract, isolate, and identify these molecules has a significant impact on what components are found. diverse extraction methods frequently produce diverse chemical profiles, and the active chemicals that are recovered can even be influenced by the particular plant portion that was employed.(11)

For instance, GC/MS analysis has found substantial concentrations of linalool, one of the main aromatic components of basil, whereas hydro-distillation or n-hexane leaf extracts have shown the existence of eugenol derivatives. Essential oils (EO) are mostly responsible for *O. basilicum* species' distinctive scent. Large amounts of oil and major fatty acids, including about 50% linoleic acid, 22% linolenic acid, 15% oleic acid, and 8% other unsaturated fatty acids, are found in basil seeds(12)



Fig 1 *Ocimum basilicum* Linn.

Several essential oil components frequently reported in basil include α -terpineol, linalool, β -elemene, germacrene D, α -bergamotene, α -guaiene, eucalyptol, cubenol, τ -cadinol, eugenol, methyl eugenol, camphor, bornyl acetate, α -caryophyllene, β -caryophyllene, elixen, and β -cadinene. The leaves also contain residues of ursolic acid and oleanolic acid in lower quantities. In addition to being abundant in essential oils, dried leaves and flower tops also include proteins (14%), carbohydrates (61%), high concentrations of vitamins A and C, and phenolic substances such xanthomicrol and rosmarinic acid(13). Along with some flavones including eriodictyol, eriodictyol-7-glucoside, and vicenin-2, the plant also includes a variety of flavonoid glycosides and aglycones. According to one study, the amounts of phenolic compounds change according to the stage of the plant's growth, however rosmarinic acid and caffeic acid are always present. The most prevalent phenolic component of *O. basilicum* among these is rosmarinic acid. Because it has high antiviral, antibacterial, anti-inflammatory, and antioxidant properties, this molecule is especially important and contributes significantly to the medicinal potential of basil. There have also been reports of other components such β -sitosterol, tannins, and polyphenols (2.2–2.3%). The molecular structure of rosmarinic acid, a typical bioactive component of *O. basilicum*.(14)

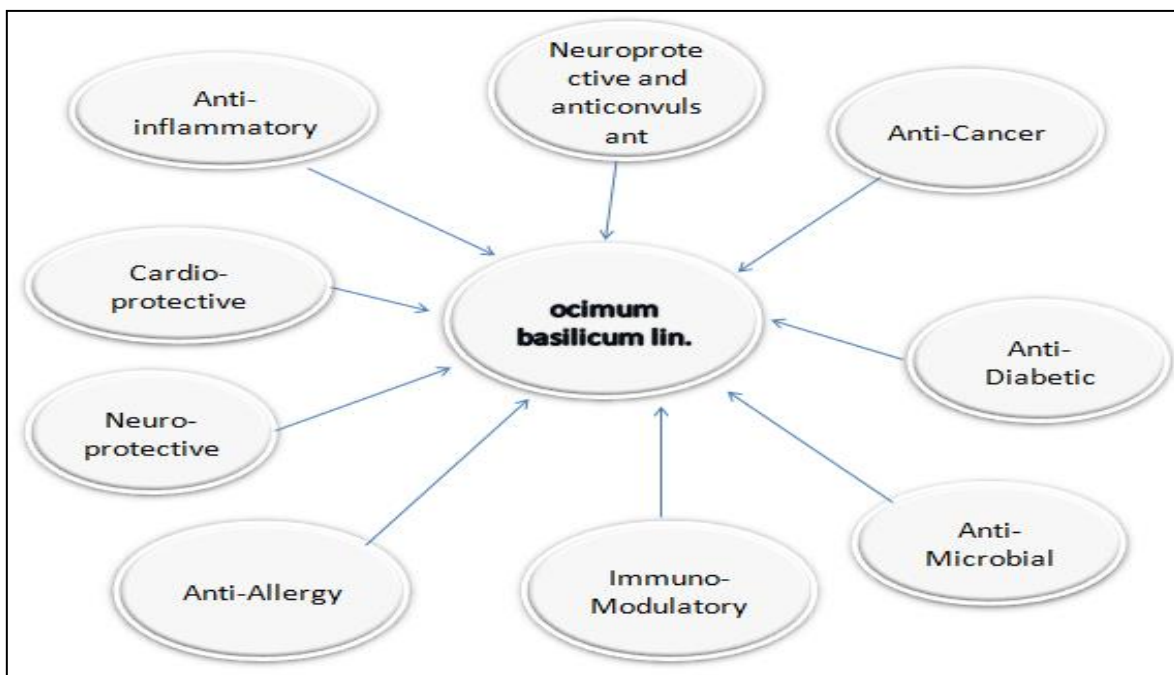


Fig 2 Phytochemical Profile of *Ocimum basilicum*

Polyphenols are essential natural substances that are commonly present in fruits and vegetables. They give plants their flavor, color, and many health advantages. Similarly, the amount of polyphenols and aromatic chemicals found in *Ocimum basilicum*, or basil, is the main source of its health benefits. The plant's antioxidant, anti-allergic, anti-inflammatory, immune-boosting, and even antiviral properties are made possible by these bioactive compounds.(15). Basil's chemical composition can vary. The location of the plant's growth, the climate, the kind of

soil, and agricultural practices can all have an impact on this variability. Generally speaking, there are three main types of constituents in basil essential oil.(16):• Methyl cinnamate, eugenol, methyl eugenol, and methyl chavicol are examples of phenylpropanoids. Ocimenes, linalool, 1,8-cineole, citral, camphor, geraniol, and thymol are examples of monoterpenoids. Sesquiterpenoids such trans- α -bergamotene, β -caryophyllene, β -elemene, and β -bisaboleneMed(17)

Table 1 Phytochemical Constituents of *Ocimum basilicum* Relevant to Neuroprotection

Phytochemical	Chemical class	Neuroprotective role
Rosmarinic acid	Phenolic acid	Antioxidant anti inflammatory anti apoptotic
Caffeic acid	Phenolic acid	ROS scavenging, mitochondrial protection
Orientin	Flavonoid	Neuroprotection against oxidative stress
Vecnin	Flavonoid	Anti inflammatory and neuronal servival
Eugenol	Phenylpropanoid	Anti inflammatory and neuro modulatory
linalool	Monoterpene	Anti oxidant neurocalming effect

(18–20) Phytochemical Content-Relating Factors *Ocimum basilicum*'s active phytochemical content and concentration can differ based on a number of parameters, including: Chemotype/Variety Sweet basil, holy basil, clove basil, and lemon basil all have unique chemical signatures. While some have higher quantities of eugenol or methyl chavicol, others are rich in linalool.(21)climate and conditions for cultivation Volatile oil output and phenolic content are strongly influenced by temperature, sunshine exposure, soil nutrients, altitude, and water availability. Plant Part and Stage of Growth In general, leaves have the largest concentrations of phenolics and essential oils.

Antioxidant content is frequently higher in younger leaves. Extraction Technique Essential oil output and volatile content are impacted by steam distillation and hydrodistillation.(22)More polyphenols (flavonoids, rosmarinic acid) are captured by ethanolic or methanolic extracts. Supercritical CO2 extraction is one example of an advanced technique that can increase yield and purity. Phenolics and volatile chemicals can be broken down by post-harvest handling, drying techniques, storage, and processing temperatures.(23)

➤ Pathophysiology of Parkinson's Disease

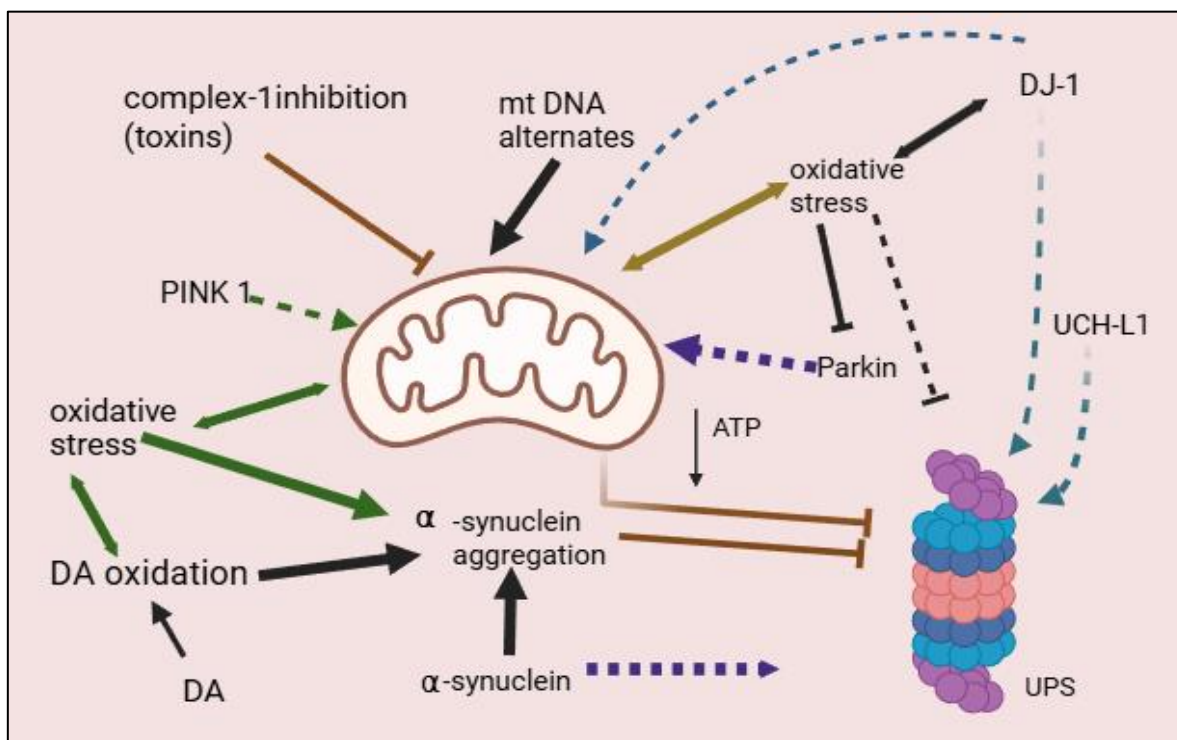


Fig 3 Pathogenesis of Parkinson ((24))

Both oxidative stress and mitochondrial dysfunction were thought to have a significant role in the pathogenesis of sporadic Parkinson's disease (PD) until the genes causing monogenic variants of the disease were discovered. These pathways have been further linked by both genetic and non-genetic research, but they have also shown that protein mishandling brought on by UPS malfunction is a significant route causing neuronal degeneration in Parkinson's disease. This section examines mounting data that suggests oxidative stress, mitochondrial malfunction, and UPS impairment may be the main molecular pathways that frequently underlie the pathogenesis of both familial and sporadic types of Parkinson's disease. (25)

Oxidative stress and dysfunction of the mitochondria Oxidative damage to lipids, proteins, and DNA has been found in the SNc of sporadic PD brains, and post-mortem investigations have repeatedly linked oxidative damage to the pathophysiology of Parkinson's disease. It is believed that oxidative stress contributes to neuronal degeneration by compromising the integrity of susceptible neurons. Although the exact cause of this elevated oxidative stress is unknown, potential causes include mitochondrial malfunction, elevated dopamine metabolism, which can produce excess hydrogen peroxide and other ROS, elevated reactive iron, and compromised antioxidant defense pathways.(26) . The process of oxidative phosphorylation is linked to the generation of ROS, and mitochondria are subjected to a highly oxidative environment. There is ample evidence that mitochondrial malfunction, specifically abnormalities in mitochondrial complex-I (complex-I) of the respiratory chain, plays a significant role in the pathogenesis of Parkinson's disease. The most evident way that a complex-I defect could contribute to neuronal degeneration in Parkinson's disease (PD) is through reduced ATP synthesis and damage from excessive ROS production. The source of the consistent findings of decreased complex-I activity in

the SNc of patients with sporadic Parkinson's disease (PD) is unknown. Additionally, cytoplasmic hybrid (cybrid) cell lines containing mitochondrial DNA (mtDNA) from sporadic Parkinson's disease (PD) patients have decreased complex-I activity, suggesting that complex-I deficiencies can be stably transmitted, while it's unclear if somatic or inherited mutations cause these mtDNA abnormalities.

➤ *Pathophysiology of Neurodegenerative Disease*

The pathophysiology of ND is significantly influenced by ROS, which are collections of atoms with an odd, unpaired number of electrons that cause OS. Reduced expression of antioxidant genes or mitochondrial malfunction may make this worse. Superoxide, oxygen, hydroxyl, alkoxy, and peroxy radicals, as well as nitric oxide and nitrogen dioxide, are examples of free radicals (Rs) Non-radical ROS include hydrogen peroxide, hypochlorous acid, and other nitrogen compounds. Immunofluorescence is one of the OS biomarker detection methods that can be used to study ND. One detection technique is the use of nitro-tyrosine, 4-hydroxynoneal, and 8-hydroxyguanine in hippocampal slices. Protein carbonyls are additional indicators that could be helpful as diagnostic tools.

The primary source of highly active endogenous biological ROS is the mitochondria, where superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals are produced during mitochondrial electron transport of four electron reduction of O₂ to H₂O₂ (Fig. 2).11,12 Endogenous ROS are also produced by immune cell activation, inflammation, mental stress, excessive exercise, ischaemia, infection, cancer, and aging, while exogenous sources include pollution, alcohol, tobacco, smoke, industrial solvents, pesticides, radiation, and some medications.(27)

Table 2 Mechanisms of Neuroprotective Action of *Ocimum basilicum*

Mechanism	Molecular Effect	Outcome in Parkinson's Disease
Antioxidant activity	↑ SOD, CAT, GSH; ↓ MDA	Reduced oxidative neuronal damage
Anti-inflammatory	↓ TNF-α, IL-1β, NF-κB	Reduced microglial activation
Mitochondrial protection	Stabilized membrane potential	Improved ATP production
Anti-apoptotic	↓ Bax, caspase-3; ↑ Bcl-2	Prevention of neuronal apoptosis
Dopaminergic protection	Preservation of TH-positive neurons	Improved motor behavior

➤ *Activation of Nrf2-ARE Antioxidant Pathway*

Transcriptional regulation plays a major role in the induction of several cytoprotective enzymes in response to reactive chemical stress. A cis-acting element known as ARE,2, which was first discovered in the promoters of the genes encoding the two main detoxication enzymes, GSTA2

(glutathione S-transferase A2) and NQO1 (NADPH: quinone oxidoreductase 1), mediates this transcriptional response. The ARE's distinct reaction to oxidative stress is characterized by structural and biochemical characteristics. It is especially triggered by chemical substances that have the ability to either undergo redox cycling or be

metabolically converted into a reactive or electrophilic intermediate, in addition to H₂O₂. Moreover, strong inducers of ARE activity include substances like diethyl maleate, isothiocyanates, and dithiothiones that have a tendency to react with sulfhydryl groups. Therefore, a key signal for initiating the transcriptional response mediated by this enhancer appears to be a change in the cellular redox status brought on by increased quantities of ROS and electrophilic species and/or a decreased antioxidant capacity (such as glutathione).(28)

➤ *Modulation of PI3K/Akt Cell Survival Pathway*

Conversely, the PI3K/AKT pathway regulates biological processes such as brain cell migration, proliferation, and plasticity. The cytoprotective phenotype of PI3K/AKT offers a crucial signal for neuroprotection, but it requires that the pathway be optimally activated in Parkinson's disease (PD) brains. This could potentially counteract the negative effects of p38 MAPK activation in degenerating DA neurons and help create a neuro-protective environment in damaged brains. While SAPKs, c-Jun N-terminal kinases (JNKs), and the p38 MAPK moderate cell mortality, the activation of ERK or p42/p44 MAP kinase and the PI3K/AKT pathway often promote cell survival (cytoprotective pathways). However, a number of possible cyto-dynamics involving P38 MAPK-PI3K/AKT and their subtle contribution to progressive neurodegenerative disease continue to be of interest for Parkinson's disease study. Furthermore, neuroprotection in PD-affected brains may be greatly enhanced by active biomolecules that target the compromised p38-PI3K/AKT balance. The p38 MAPK and PI3K pathways' potential contributions to preserving neuronal dynamics in Parkinson's disease (PD) brains will be the exclusive focus of this review. Later on, we have listed a number of potential neurotherapeutic compounds that can provide neuroprotection through mechanisms involving the

likely targeting of the cell survival (PI3K/AKT) and death pathways (p38 MAPK). These compounds can actually lessen or prevent neurodegenerative symptoms linked to Parkinson's disease (PD) brains in the future. (29)

IV. EXPERIMENTAL EVIDENCE SUPPORTING NEUROPROTECTIVE EFFECTS

➤ *Experimental Studies on Ocimum basilicum in Parkinson's Disease Models (In vitro and In vivo)*

The Animal Division of the International Centre for Diarrheal Diseases and Research in Bangladesh (ICDDR) provided Swiss albino adult mice aged 4 to 5 weeks and weighed 25 to 30 g. Prior to the animal research, these mice were kept in polypropylene cages under conventional climatic settings such as a 55% relative humidity level, 25°C ambient temperature, and a 12-hour light-dark cycle. Prior to the beginning of the experiments, the animals were allotted a week to acclimate to their new environment. During this time, the animals were fed a standard laboratory diet and had unlimited access to water. Their care and handling followed the guidelines set by the Swiss Academy of Medical Sciences (SAMS) and the Swiss Academy of Sciences. The study also complied with the latest Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines.(30)The protocols for animal handling and procedures involved in the animal studies were thoroughly reviewed and approved by the Committee on Ethical The study included 3 different doses of the methanol extract of *C. reticulata* (MECR) at concentrations of 100, 200, and 400 mg/kg body weight, designated as ME-100, ME-200, and ME-400, respectively. The animal subjects were divided into 5 groups, each consisting of 4 mice (n = 4). This sample size was estimated by using the "resource equation" method which was clear(31).

Table 3 Experimental Studies on Neuroprotective Effects of *Ocimum basilicum* Leaf Extract in Parkinson's Disease Models (*In vitro* and *In vivo*)(32,33)

in vivo	Neurotoxin-induced oxidative stress model	Hydroalcoholic extract	100–300 mg/kg	Reduced lipid peroxidation, enhanced GSH levels	ROS scavenging, antioxidant defense
In vitro	SH-SY5Y human neuroblastoma cells	Aqueous leaf extract	25–50 µg/mL	Increased cell viability under oxidative stress	↓ ROS generation, mitochondrial stabilization
In vitro	PC12 neuronal cell line	Rosmarinic acid (isolated compound)	10–50 µM	Protection against H ₂ O ₂ -induced neurotoxicity	Nrf2 activation, anti-apoptotic effect
In vitro	Neuronal oxidative stress model	Flavonoid-rich fraction	20–100 µg/mL	Reduced neuronal cell death	NF-κB inhibition, anti-inflammatory effect

➤ *Therapeutic Applications of Ocimum basilicum in Neurodegenerative Disorders*

Neurodegenerative illnesses such as Parkinson's disease (PD), Alzheimer's disease (AD), and other age-related neurological conditions are characterized by progressive loss of neurons due to oxidative stress, neuroinflammation, mitochondrial failure, and apoptosis. Due to the complexity of these disorders, plant-based therapies with multi target effects have garnered significant attention. Because of its many neuroprotective properties, sweet basil, or *Ocimum basilicum* Linn., has emerged as a promising therapeutic herb. The Therapeutic Applications of *Ocimum basilicum* in Neurodegenerative Disorders Parkinson's disease (PD) and other age-related neurological conditions are characterized by progressive neuronal loss brought on by oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis. Due to the complexity of these disorders, plant-based therapies with multiple target effects have garnered significant attention. Due to its many uses, sweet basil has emerged as a promising therapeutic herb.

• *Antioxidant Activities:*

The antioxidant properties of *Ocimum basilicum* polyphenols were well-known. Two phenolic compounds, rosmarinic and caffeic acids, were found to be potent antioxidant components of sweet basil. In one study, polyphenols of *O. basilicum* were separated from methanol extract and tested for antioxidant activities. The results showed the best antioxidant activity as well as an excellent synergistic effect against α -tocopherol²⁷.⁽³⁴⁾ have documented the antioxidant potential of essential oils extracted by steam hydrodistillation from five species of *Ocimum*: *O. basilicum*, *O. gratissimum*, *O. micranthum*, *O. tenuiflorum* (syn. *O. sanctum*), and *O. basilicum* var. *purpurascens*. All of the oils shown substantial antioxidant capacity in the hypoxanthine/xanthine oxidase experiment, however *O. tenuiflorum*'s (IC₅₀ = 0.46 μ L/mL) was stronger than *O. basilicum* var. *purpurascens*' (IC₅₀ = 1.84 μ L/mL). Using several in vitro assay model systems, the antioxidant activity of a methanolic extract of *O. basilicum* was investigated.⁽³⁵⁾The antioxidant activity of each fraction was assessed using the DPPH scavenging assay technique and the oxidation of the soy phosphatidylcholine liposome model system. The most active fraction was fraction IV, which was followed by fractions V and VI. Atmospheric pressure and chemical ionization liquid chromatography-mass spectrometry were used to identify the phenolic chemicals responsible for the fractions' antioxidative activity. Additionally, rosmarinic acid's natural antioxidant activity in the liposome system was investigated. The findings shown that 1.52 radicals may be captured by one rosmarinic acid, and they also demonstrated that α -tocopherol and rosmarinic acid have a synergistic effect. state that several antioxidant techniques were used to examine the potential radical scavenging and antioxidant activities of the water and ethanol extracts of basil.1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radical scavenging, reducing power, hydrogen peroxide scavenging, ferric thiocyanate technique, and scavenging of superoxide anion radical-generated non-enzymatic system. Experiments

showed that basil extracts in ethanol and water exhibit concentration-dependent antioxidant properties. The ferric thiocyanate technique was used to measure the total antioxidant activity. Furthermore, BHA, BHT, and α -tocopherol were used as reference antioxidants to compare these antioxidant properties. These basil extracts' increased total phenolic content was calculated as the gallic acid equivalent, and the results showed that they were equivalent..⁽³⁶⁾

• *Anti-inflammatory Activity:-*

Twenty-five years ago, it was first noted that activated microglia may be found in PD patients' brains after autopsy. Since then, inflammatory mechanisms have been linked to the onset and progression of nigral dopaminergic neuron loss in both human and animal models of parkinsonism [for a thorough review].The most notable is the recent suggestion that neuroinflammation may be a major factor in the "prion-like" spread of misfolded α -syn (α -synuclein) in Parkinson's disease.⁽³⁷⁾ In this review, we suggest and address the hypothesis that, during Parkinson's disease (PD), the initially protecting microglia become toxic to dopamine (DA) neurons due to an excess of cytokines and ROS/RNS (reactive oxygen species and reactive nitrogen species). We also investigate the idea that microglia activate peripheral immune cells to influence the brain concurrently with these processes, leading to a dynamic cross-regulation of their individual phenotypes..⁽³⁸⁾

In the PD brain, increased microglia activity is probably taking place concurrently with neuronal dysfunction and loss of DA terminals, as well as before nigral DA neurons die. This theory is supported by in vivo imaging studies of microglial activation using the peripheral benzodiazepine receptor binding ligand [11C]-(R) PK11195 using PET (positron-emission tomography), which revealed that patients with idiopathic Parkinson's disease (PD) have significantly increased neuroinflammation in the pons, basal ganglia, striatum, and frontal and temporal cortical regions compared with age-matched healthy controls.⁽³⁹⁾ Therefore microglia that become activated early in the disease process (by triggers discussed in other sections of this review) may remain primed, leaving them poised to respond robustly and/or aberrantly to subsequent stimuli (including dying neurons) thereby enhancing inflammation-induced oxidative stress in vulnerable brain regions. Indeed, phagocytic activity of microglia during debris removal is associated with respiratory bursts and would be expected to further enhance oxidative stress for the remaining population of DA neurons, while homeostatic 'nibbling' of synapses by microglia are known to regulate neuronal transmission and maintain neuronal health⁽⁴⁰⁾. Importantly, microglia-derived factors and/or release of chemoattractants by the dying DA neurons are likely to play a role in recruitment of peripheral immune cells and influence PD progression. The protective compared with detrimental role of the peripheral immune system in PD pathophysiology is an area of investigation that we will discuss in this review⁽⁴¹⁾.

V. INFLAMMATORY SIGNS IN PD PATIENTS

A number of characteristics in the brain and peripheral blood point to the immune system's involvement in Parkinson's disease. Microglia are active in all brain regions linked to Parkinson's disease (PD), including the SN (substantia nigra), according to PET imaging of PD patients. (42). The post-mortem immunohistological examination of PD brains, which reveals morphological alterations in microglia and up-regulation of certain proteins like HLA-DR+ (human leucocyte antigen type DR), which are linked to variations in function/activation, supports this. (43) Since up-regulation of HLA-DR expression seems to represent an early pathological event in the disease process, this final observation raises the prospect that microglia activation could serve as a surrogate marker for early PD pathology. The phagocytic receptor CD68, also called macrophage, is another activation marker that is up-regulated in the brains of Parkinson's disease (PD) patients and frequently utilized in animal models of PD. Upon microglia activation, it is frequently seen in cytoplasmic vesicles. (44). The brains of Parkinson's disease patients also contain higher levels of other proteins linked to microglia-induced neuroinflammation, such as COX (cyclooxygenase) and iNOS (inducible nitric oxide synthase). (45). Because CD4/CD8 T-cells infiltrate the SN of PD patients and may contribute to vascular alterations during the disease, the adaptive immune system has also been linked to the pathophysiology of PD. Furthermore, it seems that PD also modifies the peripheral T-cell pool. (46). Specifically, it has been seen that the CD4+ population is declining. Although the causes of this decrease are unknown, they most likely stem from increased oxidative damage to DNA and apoptosis induction. The fact that CD4+ $\gamma\delta$ T-cells, which are mostly activated locally rather than in secondary lymphoid organs, are elevated in the peripheral and CSF (cerebrospinal fluid) of Parkinson's disease patients, where they exhibit an activated phenotype, is of particular interest to our research. (47). Humoral immunity has also been linked to the development of Parkinson's disease. About one-third of SN DA neurons have surface immunoreactivity for IgG, and LB (Lewy body) in PD brains has significant immunolabelling for IgG (immunoglobulin G). It's interesting to note that the percentage of IgG immunopositive neurons in SN had a negative correlation with the surviving DA neurons and a positive correlation with the amount of HLA-DR+ microglia. (48) indicating that DA neurons may be targeted for destruction early in the disease process if their surface is coated with IgG. Additionally, people with specific types of familial Parkinson's disease have been reported to have antibodies against α -syn in their serum and CSF. According to a recent study, antibodies from PD patients' CSF were cross-reactive with rat neurons and proteins altered by DA oxidation, while sera from patients with sporadic PD included disease-specific auto-antibodies. (49).

Researchers studying Parkinson's disease (PD) have known for twenty years that post-mortem SN from PD patients has increased levels of cytokines, including as TNF

(tumor necrosis factor), IL (interleukin)-1 β , IL-2, IL-4, and IL-6. The most straightforward explanation for these findings was that the neuroinflammatory reaction was the final consequence of microglia activation after neuronal loss. They did, however, also raise the potential that the local environment produced by cytokine signaling affected nigral DA neuron survival and might have an impact on how Parkinson's disease develops. Particularly (50) levels of TNF in the healthy adult brain are generally very low and produced primarily by neurons (51) However, PD patients have much higher levels of TNF, IL-1 β , and IFN γ (interferon γ) than normal controls at the area of maximal damage where the susceptible melanized DA-producing neurons are located in the ventral midbrain. There have also been reports of increased cytokine levels in the peripheral circulation of Parkinson's disease (PD) patients, in addition to increased CNS (central nervous system) levels. (52) It could be the cause of some non-motor PD symptoms. In particular, it was discovered that patients with more severe symptoms of depression and exhaustion had higher serum levels of TNF. (53) as well as impaired cognition and sleep disturbances (54). Although high levels of IL-1 β have been found in the CSF of PD patients, this finding is not specific because the brains of patients with AD (Alzheimer's disease) and LB dementia also show IL-1 β -expressing microglia surrounding neurons that were highly immunoreactive for β APP (β -amyloid precursor protein) and contained both LBs and neurofibrillary tangles. (55). Indeed, our findings suggest that IL-1 β may facilitate the neuropathological and clinical overlap between AD and PD. (56). Increased levels of other cytokines with anti-inflammatory or repair functions, such IL-10, have also been documented in PD patients, despite the large body of research linking pro-inflammatory cytokines to the disease's progression. (57). Anti-TNF biologics have already been successfully used to treat psoriasis, inflammatory bowel disease, and rheumatoid arthritis, so it is reasonable to assume that patients with Parkinson's disease (PD) or other neurological conditions marked by persistent neuroinflammation could benefit therapeutically from CNS delivery of these drugs. (58).

Overall, patient data points to a complicated role for the immune system and inflammatory variables in Parkinson's disease (PD); microglia, in particular, are likely actively involved in multiple disease processes rather than being merely scavengers of cellular detritus. Furthermore, a multi-target immunomodulatory approach is likely to be necessary for a successful intervention to protect the nigrostriatal pathway from death-inducing inflammatory insults and/or treat non-motor symptoms resulting from chronic neuroinflammation due to the complexity of the human disease and the interactions of inflammatory pathways. (59). Furthermore, these immunomodulatory treatments are probably more effective in the early stages of Parkinson's disease (PD) in promoting an M2 microglia phenotype over an M1 phenotype and raising protective cytokine levels while lowering cytotoxic pro-inflammatory cytokine levels. (60)

The brain's potential for oxidation is high, but its capacity to combat oxidative stress is restricted. In a number

of disease conditions of the brain, including neurodegenerative disorders, oxidative stress has been linked to mechanisms causing damage to neuronal cells. The brain uses around 20% of the oxygen that is available through respiration, but making up less than 2% of the body weight. Consequently, the brain is the organ most vulnerable to oxidative injury due to its high oxygen requirement.(61) Due to their therapeutic potential, phytopharmaceuticals are becoming more and more important in both traditional and modern medicine. New antioxidants may provide a safe and efficient way to strengthen the body's fight against free radicals. Vitamins, bioactive compounds, lipoic acid, antioxidant enzymes, and redox-sensitive protein transcriptional factors are some of the few resources that central nervous system cells can use to fight oxidative stress. However, nutritional antioxidants including polyphenols, flavonoids, terpenoids, fatty acids, and others can activate or modify this defensive system. People's food and drink choices have been influenced by plant-derived alternative antioxidants (AOX), which are thought to be helpful in mitigating the consequences of oxidative damage.(62) The use of antioxidants to treat neurodegenerative diseases is supported by a wealth of empirical and scientific data. Herbal medicine, with its four pillars of phytochemistry, phytopharmacy, phytopharmacology, and phytotherapy, is

being considered as a revival of ancient human tradition as the focus of medicine moves from treating manifest disease to prevention. Antioxidants derived from phytochemicals may play neuroprotective (avoiding apoptosis) and neuroregenerative activities. (63) via lowering the rate of neuronal cell death and minimizing or stopping cellular damage. AOX are classified as either endogenous or exogenous in nature. The endogenous group consists of proteins including albumin, transferrin, ceruloplasmin, metallothionein, and haptoglobin as well as enzymes (including trace elements) such glutathione peroxidase (selenium), catalase, and superoxidase dismutase (zinc, manganese, and copper). Dietary phytochemicals (polyphenols, quinones, flavonoids, catechins, coumarins, terpenoids) and smaller molecules like ascorbic acid (Vitamin C), alpha-tocopherol (Vitamin E), beta-carotene (Vitamin E), and supplements are the most significant exogenous AOX.(64) AOX offer a promising strategy for controlling or slowing the progression of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and ischemic and hemorrhagic stroke, despite the fact that their exact mode of action is still unknown and there are still relatively few clinical trials involving them..(65)

Table 4 Therapeutic Applications of *Ocimum basilicum* in Neurodegenerative Disorders

Sr. No	Application	Therapeutic Significance
1	Adjunct therapy in PD	Enhances neuroprotection with standard drugs
2	Preventive antioxidant	Delays progression of neurodegeneration
3	Nutraceutical use	Safe long-term neuronal support
4	Drug discovery	Source of lead neuroprotective compound

Despite the fact that *Ocimum basilicum* leaf extract and other phytochemicals derived from plants have shown notable neuroprotective effects in preclinical models of neurodegenerative disorders, there has been little use of these discoveries in clinical settings. The majority of the information that is now accessible comes from animal research and in vitro tests that demonstrate antioxidant, anti-inflammatory, anti-apoptotic, and signaling-modulating activities, including interactions with pathways including

Nrf2, PI3K/Akt, and MAPKs. These molecular targets are essential for cellular stress responses and neuronal survival, and plant polyphenols have been shown to modulate them in a variety of experimental contexts..(66)

The absence of standardized extracts and clearly defined phytochemical profiles is a significant obstacle to the advancement of *Ocimum basilicum* toward therapeutic application. It is often challenging to compare results or

establish dose-response associations due to uneven biological activity among research caused by variations in extraction techniques, plant chemotypes, and bioactive content. Additionally, safety evaluation, dose optimization, and reproducibility—all necessary for regulatory approval—are made more difficult by this heterogeneity problem.(67)

The lack of pharmacokinetic and bioavailability information for basil phytochemicals is another drawback. Numerous natural substances, such as flavonoids and phenolics, have restricted blood–brain barrier permeability, fast metabolism, and poor gastrointestinal absorption, which may drastically lower their therapeutic efficiency in humans when compared to preclinical models. These elements have been identified as obstacles in phytochemical studies on neurodegenerative diseases, where transport to the central nervous system is crucial.(68)

➤ *Standardization of Extracts:*

For repeatability and regulatory compliance, create and verify standardized *Ocimum basilicum* leaf extracts with constant quantities of important bioactive constituents.

➤ *Bioactive Marker Identification:*

Determine and measure the active phytochemicals that have neuroprotective effects using sophisticated analytical methods (HPLC, LC-MS/MS).

➤ *Pharmacokinetics and Bioavailability:*

Perform thorough pharmacokinetic investigations to comprehend the distribution, metabolism, and absorption of basil phytochemicals, including evaluation of blood-brain barrier penetration.(69)

VI. CONCLUSION

Growing preclinical evidence supports *Ocimum basilicum*'s potential as a multi-targeted neuroprotective herbal agent. Strong antioxidant, anti-inflammatory, and neuromodulatory qualities are displayed by its bioactive components, including linalool, eugenol, rosmarinic acid, and other polyphenols, which directly combat important pathological processes linked to neurodegenerative illnesses. *O. basilicum* can modulate important molecular pathways, such as activation of the Nrf2/ARE antioxidant defense, inhibition of NF-κB-mediated neuroinflammation, reduction of oxidative stress, mitochondrial protection, and attenuation of excitotoxicity, according to a significant number of in-vitro and in-vivo studies. In models of Alzheimer's disease, Parkinson's disease, epilepsy, and stress-induced neurotoxicity, these processes collectively support its involvement in moderating cognitive impairment, lowering neuronal degeneration, and improving behavioral outcomes.

Despite encouraging outcomes, limitations including inconsistent plant composition, a lack of standardized extraction, insufficient pharmacokinetic data, and a dearth of carefully planned human trials continue to restrict translation to clinical practice. By increasing brain bioavailability and targeting efficiency, innovations in innovative delivery methods such liposomes, phytosomes,

and nanoemulsions provide intriguing alternatives. To establish *O. basilicum* as a dependable therapeutic or adjuvant approach for neurodegenerative and cognitive illnesses, future research must concentrate on standardized formulations, mechanistic validation, and well-structured clinical investigations. *Ocimum basilicum* is a promising contender in herbal neuroprotection, with broad therapeutic applicability and solid mechanistic support, according to the available data. It has a great deal of promise for incorporation into contemporary neurotherapeutic strategies with further scientific development.

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