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Review Article

Epigallocatechin-3-Gallate in Green Tea: A Promising Neuroprotective Agent Against Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is the second most prevalent neurodegenerative disorder, marked by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies. This neuronal degeneration leads to motor symptoms such as tremors, rigidity, and bradykinesia. Neurochemical alterations, including mitochondrial dysfunction and oxidative stress, are critical in the pathogenesis of PD. With an aging global population, the prevalence of PD is expected to reach 9 million by 2030. Green tea, from Camellia sinensis, is widely consumed for its health benefits, including its neuroprotective properties. Its key component, (-)-epigallocatechin-3-gallate (EGCG), is noted for its potent antioxidant, anti-inflammatory, and neuroprotective activities. EGCG provides significant neuroprotection against MPTP-induced neurotoxicity, a model for Parkinsonism, by inhibiting inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS), reducing nitric oxide (NO)-mediated oxidative stress. It also preserves dopaminergic neurons and maintains dopamine levels in the striatum. Against 6-OHDA-induced neurotoxicity, which mimics PD, EGCG regulates iron metabolism by modulating iron regulatory proteins. It enhances dopaminergic neuron survival and neurite outgrowth by stabilizing mitochondrial function and controlling the ROS-NO pathway. This review mainly focuses on significant neuroprotective effects of EGCG against neurotoxins like MPTP and 6-OHDA, reducing oxidative and nitrosative stress, regulating iron metabolism, and stabilizing mitochondrial function. These findings highlight the potential of green tea and EGCG in developing treatments for PD and other neurodegenerative disorders.

INTRODUCTION

Parkinson's Disease

Parkinson's disease is most common neurodegenerative disorder. PD is generally

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characterized by a progressive loss of dopaminergic neurons in the region of substantia nigra pars compacta and the presence of intracellular proteinaceous inclusion of Lewy bodies. Neurochemicals, PD is marked by dysfunction of mitochondrial complex and increased oxidative stress. Parkinson's disease is characterized by dysfunction in mitochondrial complexes and an increase in oxidative stress. [1] Parkinson's disease (PD) is further recognized by its motor symptoms, including tremors, rigidity, and bradykinesia. These manifestations are among the primary indicators of the disease. Early symptoms of Parkinson's disease arise from the degeneration of dopamine neurons originating in the substantia nigra and projecting to the neostriatum. [2] Parkinsonism ranks as the second most prevalent neurodegenerative ailment associated with aging, impacting over 4 million individuals globally at present. Projections suggest that this number may surge to affect approximately 9 million people worldwide by the year 2030 [3] The pathophysiology of Parkinson's disease encompasses a range of factors, including neurochemical alterations, cellular irregularities, network dysfunction, and molecular pathogenesis. [4] The loss of neurons in the substantia nigra pars compacta results in a deficiency of dopamine in the striatum, which is primarily responsible for the major symptoms observed in Parkinson's disease. [5]

Green tea

Green tea derived from the leaves and buds of the Camellia sinensis plant, stands as the second most consumed beverage globally. It enjoys immense popularity worldwide and is recognized for its various pharmacological properties, including antimutagenic, antiproliferative, and anticarcinogenic effects, as well as its neuroprotective potential in neurodegenerative disorders. [6] Green tea comprises various components, including polyphenols such as catechins, along with minerals, vitamins, and more. Among these, epigallocatechin gallate (EGCG), a catechin, stands out for its potent antioxidant properties. EGCG exhibits antimutagenic, antidiabetic, and anti-inflammatory activities, making it particularly noteworthy among green tea constituents.[7]. Green tea polyphenols are renowned for their numerous health benefits, including antioxidant, anti-inflammatory, and neuroprotective properties. Several studies have indicated that consuming green tea may offer protection against neurodamage, free radicals, and inflammation. [8] Green tea extracts and their isolated components have demonstrated effectiveness in preventing oxidative stress and addressing neurological issues. [9] Green tea polyphenols (GTP) play a pivotal role in these properties, with the four primary components being (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epicatechin (EC). Among these, the major catechin found in green tea is (-)-epigallocatechin-3-gallate (EGCG). The notable health benefits of green tea are largely attributed to the remarkable biological activity of EGCG. [10]

Epigallocatechin -3-Gallate

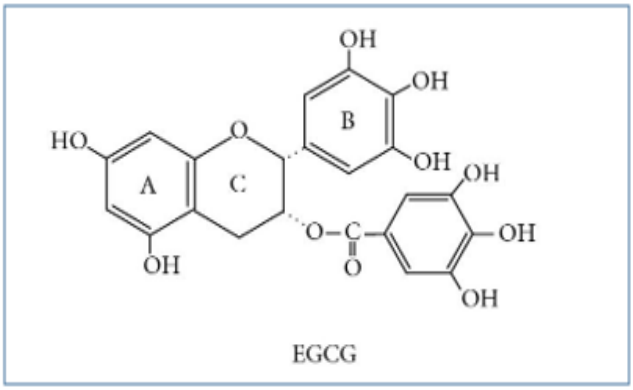

Figure 1: Chemical Structure of EGCG

EGCG is a type of catechin, which is a flavonoid. It consists of a catechin structure with an additional galloyl group attached. This review mainly focusses on the neuroprotective properties of green tea containing epigallocatechin-3-gallate against Parkinson's disease (PD)

Neuroprotective Properties of EGCG against The Parkinson's Disease:

Neuroprotective effect of EGCG in Parkinson's Disease Using MPTP animal model

N-Methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine it is a neurotoxin. In the Pathogenesis of PD the oxidative stress and neuroinflammation play important role. [11]

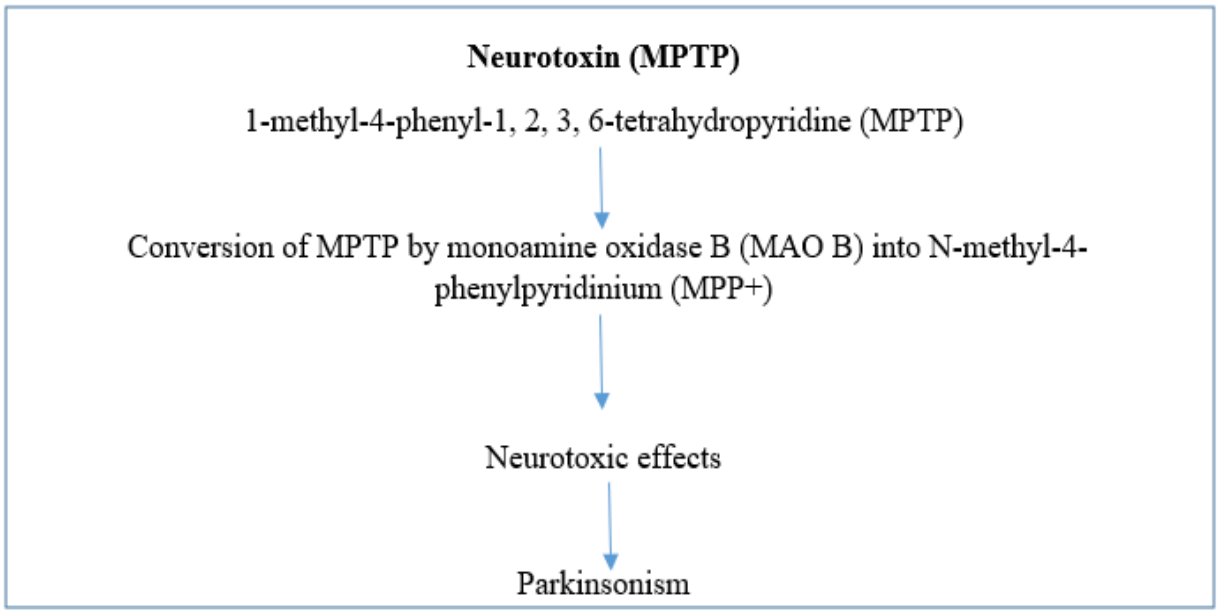

Figure 2: Mechanism of action of MPTP neurotoxin in Parkinson's Disease animal model [12]

It suggests that Parkinson's disease may not be a single disease but rather a group of related conditions. These conditions share common clinical (symptoms observed in patients), pathological (changes in brain structure and function), and biochemical (molecular mechanisms) endpoints. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is noted as the only environmental agent identified so far capable of causing parkinsonism (symptoms similar to Parkinson's disease) rapidly, within 14 days of exposure. This indicates a direct and potent environmental cause. While MPTP is the only confirmed environmental cause of Parkinsonism, other environmental factors such as pesticides and herbicides have been associated with an increased risk of developing Parkinson's disease. [13] Neurotoxin (MPTP) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a compound known for its ability to harm dopaminergic neurons similar to the damage observed in Parkinson's disease, was administered to mice. Following this administration, researchers observed a strong increase in gliosis within the substantia nigra pars compacta, along with a notable rise in the levels of inducible nitric oxide synthase (iNOS). These alterations occurred either before or at the same time as the onset of dopaminergic neurodegeneration induced by MPTP. [14] In research conducted by Ji Seon Kim and others, they explored the potential neuroprotective effects of EGCG using a mouse model of Parkinson's

disease induced by MPTP. They found that inhibiting iNOS could be a crucial mechanism for shielding against MPTP-induced toxicity. Their findings suggest that EGCG could emerge as a promising candidate for safeguarding against the progression of Parkinson's disease. [15] In this study they illustrates the neuroprotective effects of green tea extract and (±)-epigallocatechin-3-gallate (EGCG) in a mouse model of Parkinson's disease induced by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The neurotoxicity of MPTP resulted in the loss of dopamine neurons in the substantia nigra, accompanied by a reduction in striatal dopamine levels and tyrosine hydroxylase protein levels. Polyphenols such as EGCG, with their ability to penetrate the brain, act as antioxidants, and chelate iron, may represent a significant class of compounds for the development of treatments for neurodegenerative diseases characterized by oxidative stress. [16] In fig. 3 shows that the study examines the neuroprotective effects of green tea and its key component, (-)-epigallocatechin 3-gallate (EGCG), in a mouse model of Parkinson's disease (PD) induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP toxicity in these models is primarily mediated by oxidative stress, particularly involving nitric oxide (NO). The study highlights several key findings:

- **Oxidative Stress and Nitric Oxide (NO)**: In Parkinson's disease models, oxidative stress, especially from NO, plays a critical role in neurodegeneration. Inhibiting nitric oxide synthase (NOS) activity, which produces NO, has a neuroprotective effect.
- **Role of EGCG**: EGCG, a major polyphenol in green tea, was tested for its ability to mitigate the effects of MPTP-induced Parkinson's disease.
- **Protection of Dopaminergic Neurons**: Both green tea and EGCG administration prevented the loss of tyrosine hydroxylase (TH)-positive cells in the substantia nigra (SN). TH is an enzyme crucial for dopamine synthesis, indicating that these treatments help preserve dopaminergic neurons.
- **Preservation of Dopamine Levels**: Treatments with green tea and EGCG also maintained striatal levels of dopamine and its metabolites (3, 4-dihydroxyphenylacetic acid and homovanillic acid), which are typically depleted in PD.
- **Inhibition of nNOS Expression**: Both green tea and EGCG reduced the expression of neuronal nitric oxide synthase (nNOS) in the substantia nigra. The reduction in nNOS expression was similar in both tea plus MPTP and EGCG plus MPTP treatments, indicating a specific inhibitory effect on nNOS.
- **Neuroprotective Mechanism**: The study suggests that the neuroprotective effects of green tea and EGCG against MPTP-induced PD can be attributed to the inhibition of nNOS expression in the substantia nigra, thereby reducing NO-mediated oxidative stress. [17]

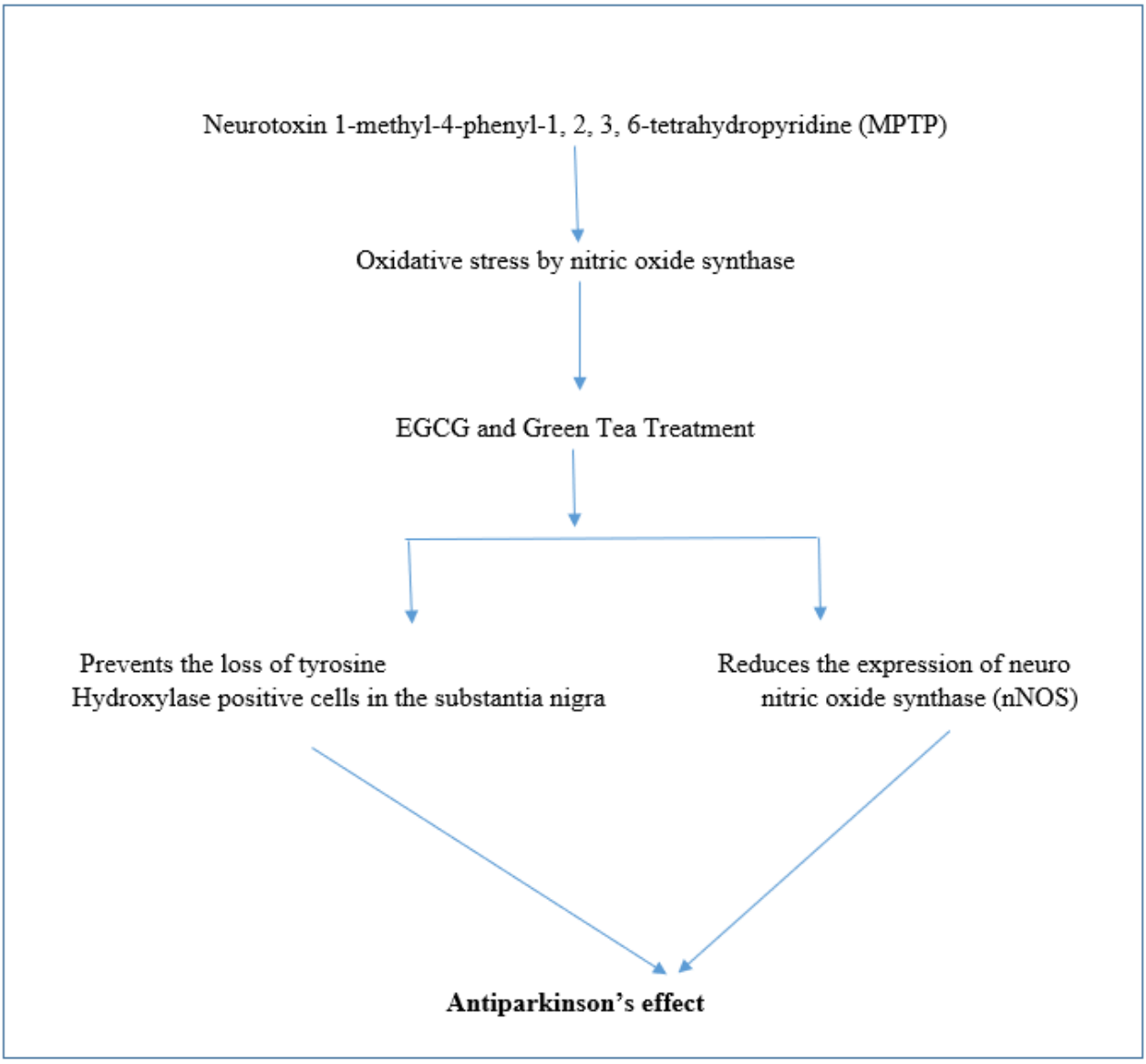

Figure 3: Effect of EGCG and green tea on 1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydropyridin Induced Parkinson's disease [17]

Neuroprotective effect of Epigallocatechin-3-gallate on 6-OHDA (6-Hydroxydopamine) neurotoxin induced parkinsonism animal model

Reactive Oxygen Species (ROS) overproduction is responsible for oxidative stress or oxidative damage in brain. In the region of substantia nigra the increased protein oxidation is apparent in many areas of the brain in Parkinson's Disease [17, 18] 6-OHDA is catecholaminergic neurotoxin which easily forms the free radicals and this free radicals are responsible for the oxidative stress or oxidative damage in the brain. And the most prominent action of 6- OHDA neurotoxin is to inhibit the brain mitochondrial complex I and IV. In neurodegenerative processes 6 OHDA is get easily oxidised and can take part in the reaction of free radical formation [19] Neurotoxicity associated with the 6 OHDA neurotoxin accumulation and uptake by plasma membrane dopamine transport specific for catecholaminergic neurone. The

cytotoxicity of 6 OHDA by its ability to damage the neurons by reactive oxygen species and by inhibition of mitochondrial electron transport chain complex I and IV. [18, 20]

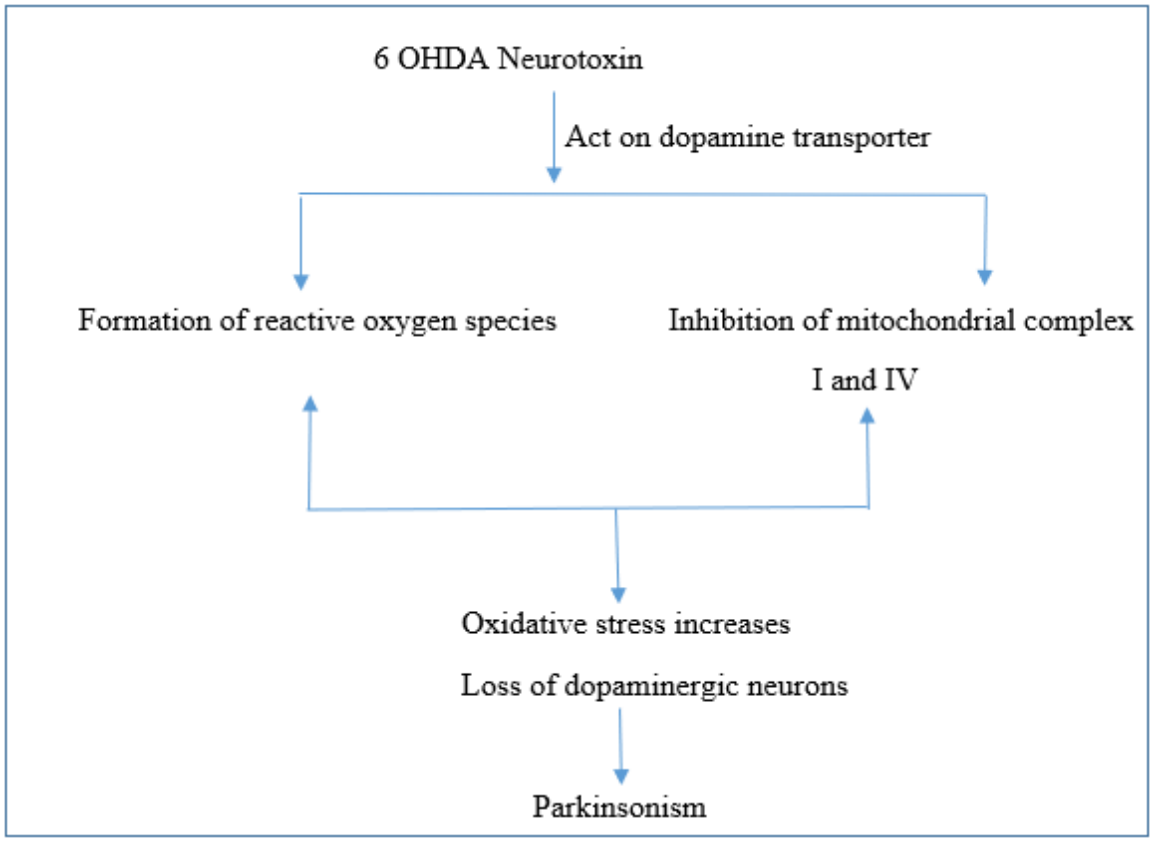

Figure 4: Mechanism of action of 6-OHDA neurotoxin in Parkinson's disease animal model

The study shows that viability of PC12 cells was greatly reduced when it get exposed to 6 OHDA. Induced cytotoxicity greatly inhibited by the green tea polyphenols and EGCG. This study also shows that among all the green tea polyphenols EGCG is the most effective antioxidant and greater activity the other polyphenols. [18] EGCG exerts a protective effect against 6-OHDA-induced neurotoxicity in cell models by regulating iron metabolism. This protection is mediated through the modulation of key iron regulatory proteins and genes, particularly hepcidin, thereby reducing the iron burden in neuronal cells. These findings suggest that EGCG could be a potential therapeutic agent for mitigating neurodegeneration in Parkinson's disease by maintaining proper iron homeostasis in the brain.[21] Parkinson's disease (PD) involves severe dopamine depletion and disrupted iron metabolism. This study tested the protective effects of (-)-epigallocatechin-3-gallate (EGCG) against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in N27 cells. EGCG reduced 6-OHDA-induced toxicity, normalized iron regulatory proteins (DMT1, hepcidin, Fpn1), and decreased iron uptake by 27%. In primary mesencephalic neurons, EGCG significantly increased tyrosine hydroxylase-positive cell count and neurite length. These results suggest EGCG protects against neurotoxicity by regulating brain iron homeostasis, particularly hepcidin levels. [22] The protective effects of Green tea polyphenol like EGCG on SH-SY5Y cells against 6-OHDA-induced apoptosis are mediated by controlling the

ROS-NO pathway. By reducing oxidative and nitrosative stress, stabilizing mitochondrial function, and maintaining calcium homeostasis, GTP demonstrates significant neuroprotective properties, suggesting its potential therapeutic value in neurodegenerative diseases like Parkinson's disease [6OHDA 4] 23

DISCUSSSION:

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to severe dopamine depletion in the brain. The disease's hallmark features include motor symptoms like tremors, rigidity, and bradykinesia, primarily resulting from the loss of dopamine neurons. Neurochemical changes such as mitochondrial dysfunction and increased oxidative stress are crucial in the pathogenesis of PD. As the aging population grows, the incidence of PD is expected to rise significantly, posing a major global health challenge. Green tea, derived from Camellia sinensis, is widely consumed and recognized for its numerous health benefits, including antioxidant, anti-inflammatory, and neuroprotective properties. Among its components, (-)-epigallocatechin-3-gallate (EGCG) stands out due to its potent antioxidant activities. EGCG has been extensively studied for its potential therapeutic effects against neurodegenerative diseases like PD. This review mainly focuses on the Neuroprotective Properties of EGCG. EGCG provides significant neuroprotection against MPTP-induced neurotoxicity, a widely used animal model of PD. MPTP mimics PD by causing oxidative stress and inflammation, leading to the degeneration of dopaminergic neurons. EGCG helps prevent the loss of tyrosine hydroxylase (TH)-positive cells in the substantia nigra and preserves striatal dopamine levels. These protective effects are largely attributed to the inhibition of neuronal nitric oxide synthase (nNOS), reducing nitric oxide (NO)-mediated oxidative stress. EGCG also shows protective effects against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity, another common model for studying PD. 6-OHDA generates reactive oxygen species (ROS) and disrupts iron metabolism, leading to oxidative damage and neuronal death. EGCG mitigates 6-OHDA-induced toxicity by regulating iron regulatory proteins, reducing iron uptake, and maintaining proper iron homeostasis. It also enhances the survival and neurite outgrowth of dopaminergic neurons by stabilizing mitochondrial function and controlling the ROS-NO pathway

CONCLUSION:

EGCG, a major polyphenol in green tea, demonstrates significant neuroprotective effects against neurotoxins like MPTP and 6-OHDA, which model the pathophysiology of Parkinson's disease. By reducing oxidative and nitrosative stress, regulating iron metabolism, and stabilizing mitochondrial function, EGCG emerges as a promising therapeutic candidate for mitigating neurodegeneration in PD. The findings support the potential of green tea and its constituents, especially EGCG, in developing treatments for PD and other neurodegenerative disorders. Future research into Epigallocatechin-3-gallate (EGCG), a major polyphenol in green tea, shows promise in the treatment of Parkinson's disease (PD). EGCG has been found to have neuroprotective properties, potentially reducing disease progression and promoting recovery through various mechanisms, such as antioxidative stress, anti-inflammatory effects, and inhibition of abnormal protein aggregation. Future studies will be crucial in understanding the full potential of EGCG in PD

treatment and its implications for improving patient outcomes.

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