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A Review Of Oxidative Stress Induced Parkinsonism And The Potentials Of Antioxidants In Treating Parkinson's Diseases

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ABSTRACT
Parkinson's disease (PD) is brought on by an aberrant build-up of α-synuclein in the substantia nigra (SN) and progressive neurodegeneration of dopaminergic neurones.An imbalance between antioxidants and free radicals in your body causes oxidative stress, which damages cells. Numerous illnesses, including cancer, Parkinson's disease, and Alzheimer's disease are impacted by it. Oxidative stress can be brought on by toxins such as cigarette smoke and pollution. Antioxidant-rich foods can aid in its reduction. Numerous proteins, including α-synuclein and amyloid β, as well as signalling pathways, including extracellular signal-regulated kinases, phosphoinositide 3-kinase/protein kinase B pathway, and extracellular signal-regulated protein kinases, are closely linked to neural damage and play a critical role in the pathogenesis of neurodegenerative diseases due to oxidative stress. The altered oxidative stress and mitochondrial dysfunctions are the two important cellular stress parameters playing important role in PD pathogenesis.

Keywords: Oxidative stress, Mitochondria, Reactive oxygen species, Neurodegenerative disease, Anti oxidants,

INTRODUCTION

A prevalent neurodegenerative disease, Parkinson's disease (PD) is primarily caused by a progressive loss of dopaminergic (DAergic) neurones together with a buildup of α-synuclein in the ventral midbrain's substantia nigra (SN). Dopamine (DA) is secreted by these neurones, which are essential for regulating how easy and balanced motions are. Moreover, Parkinson's disease (PD) is associated with olfactory deficiencies, sleep difficulties involving rapid eye movement (REM), depression, constipation, and impairments in cognitive functioning, which may be mediated through the cholinergic, serotonergic, and noradrenergic systems [1]. Approximately 1% of those over 65 suffer from the condition. Levodopa, carbidopa, apomorphine, amantadine, orphenadrine, benzhexol, benztropine, selegeline, pergola, and many other medications are among the possible treatments. These medications effectively increase dopamine levels and reverse Parkinson's disease symptoms. The medications used to treat Parkinson's disease (PD) have a number of side effects, including dyskinesia, arrhythmia, mydriasis, depression, respiratory problems, hallucinations, mania, convulsions, nausea, and vomiting. When taken long-term, it can lead to postural hypotension, peripheral vasospasm, ankle oedema, anxiety, insomnia, constipation, sore throat, dry mouth, momentary dizziness, diarrhoea, and abdominal pain, as well as increased appetite and sleepiness. The wearing off phenomena, on-off phenomenon, and dyskinesia are the main adverse consequences of long-term levodopa medication [2]. About 7–10 million people worldwide suffer with Parkinson's disease (PD), the second most common neuro degenerative ailment. Dopamine deficit leads to the degradation of dopaminergic nigro-striatal neurones in the corpus striatum, which is the primary cause of Parkinson's disease (PD).

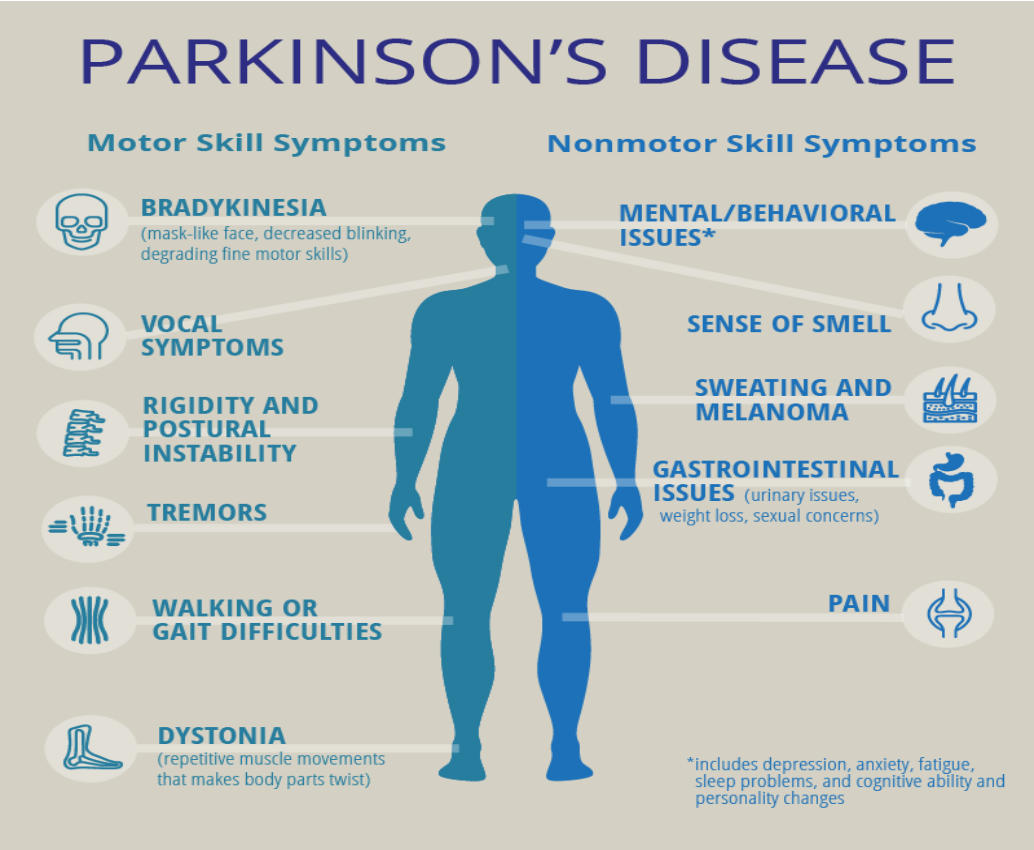
The cause of neuronal loss in Parkinson's disease is yet unknown. Free radical production, oxidative stress, mitochondrial dysfunction, excitotoxicity, trophic factor deficiency, inflammatory processes, genetic factors, environmental factors, the toxic action of nitric oxide, and apoptosis are some of the mechanisms of neuronal degeneration in Parkinson's disease (PD) that have been proposed. The interplay of these variables results in a toxic cycle that damages neurones, atrophyes, and ultimately kills cells [3].

The primary thought to be responsible for the typical classical motor symptoms as well as non-motor symptoms is the degeneration of dopaminergic neurons[4]. Age, gender, ethnicity, environment, and genetic component are some of these risk factors [5]. Studies have shown that two critical cellular stress parameters that are significant in the aetiology of Parkinson's disease are altered oxidative stress and mitochondrial dysfunction [6, 7]. This is seen in animal models and the brain postmortem samples from Parkinson's disease patients, where it was discovered that complex I activity, or mitochondrial function, was reduced [8].

Clinical features of Parkinson's Disease

Each person may experience Parkinson's disease symptoms differently. Early symptoms could not be seen or be moderate. Tremor, or rhythmic shaking, generally starts in a leg; bradykinesia, or slower movement of the hand or fingers; rigid muscles; poor posture and balance; loss of automatic movements; altered speech; altered writing; etc. In addition,

individuals exhibit non-motor symptoms include behavioural and cognitive issues, in addition to sensory deficits. They might, however, also experience autonomic dysfunction or sleep disturbances.



Reactive Oxygen Species (ROS)

ROS encompass hydroxyl radicals (•OH), superoxide anion radicals (O2•−), and nonradical hydrogen peroxide (H2O2). Reactive nitrogen intermediates (RNI) are considered significant radicals because they play a role in controlling necrotic or apoptotic cell death. These consist of various nitric oxide (NO•) forms, peroxynitrite (ONOO−), nitroxyl anion (NO−), and nitrosonium cation (NO+).Byproducts of regular oxygen metabolism are ROS. ROS play a part in homeostasis and cell signalling. ROS are essential to the operation of cells and are found in normal cells at low, stable concentrations. Because ROS oxidise and change certain cellular components and prevent them from fulfilling their natural activities, they have the potential to cause irreparable damage to DNA.

Reactive Oxygen Species			
Sl. No.	Species	Physiological Role	Pathological role
01	Superoxide ($O_2^{\bullet-}$)	• Contributes to the oxygen-dependent innate immune system's ability to destroy invasive infections. • Induce pain, chemotaxis, leukocyte adhesion, vasodilation, and regulation of gene expression, ageing, and apoptosis	• Generates peroxynitrites; • Oxidises biomolecules, including proteins, lipids, and DNA; • Causes damage to the cell membrane, modifies the signal transduction pathway, and reduces the capacity of DNA repair

		● Control over the differentiation of cells	
02	Hydroxyl radical ($HO^{\bullet-}$)	● Control of autophagy; ● control of cellular differentiation; ● control of hypoxic adaption	● Oxidises biomolecules, including proteins, lipids, and DNA ● Damages signal transduction pathways, cell membranes, and the capacity to repair DNA.
03	Hydrogen Peroxides (H_2O_2)	Modification of proteins post-translationally ● Control of certain enzyme activity ● control of signalling pathways ● control of cellular differentiation	Oxidises biological molecules, including DNA, proteins, and lipids. ● Impairs DNA repair capabilities, damages the cell membrane, and signal transmission mechanisms

This implies that ROS have two roles: the balance between their synthesis and appropriate disposal at the appropriate time and location determines whether they will function as detrimental, protective, or signalling components. Put another way, the antioxidant system's ineffective removal of ROS can lead to oxygen toxicity as well as unchecked creation.

ROS levels can rise sharply during periods of environmental stress (such as exposure to heat or UV light). Cell structures may sustain serious harm as a result of this. This is collectively referred to as oxidative stress.

Oxidative stress in Parkinsonism

Oxidative stress is characterised by an imbalance between the amount of reactive oxygen species (ROS) generated and the biological system's capacity to eliminate the reactive intermediates, resulting in a dangerous condition that can harm cells. It is distinguished by a notable rise in the proportion of oxidised constituents. One important ageing process mechanism that can directly harm the central nervous system (CNS) is OS. In fact, due to their high oxygen demand and comparatively low antioxidant levels, neurones are highly susceptible to OS [9,10,11]. Reactive oxygen species (ROS), also known as free radicals, are unstable and potentially harmful chemicals that are created by the organism under normal physiological conditions. These molecules are essential for host defence, gene transcription, control of synaptic plasticity, and programmed cell death (apoptosis) [12].

Numerous mechanisms can produce reactive oxygen species (ROS), including direct interactions between redox-active metals and oxygen species through reactions like the Fenton and Haber-Weiss reactions, or indirect mechanisms involving the activation of enzymes like NADPH oxidases or nitric oxide synthase (NOS). Generally speaking, most free radicals have a chemical genesis that requires molecular oxygen to be activated [13]. Superoxide anion radical (O22−), hydroxyl radical (•OH), and hydrogen peroxide (H2O2) are a few examples of ROS.

The electron transport chain's mitochondrial complexes I and III are the primary producers of superoxide anion, which is extremely reactive and permeable to the inner mitochondrial membrane, where it can be reduced to H2O2. Peroxisomes can produce H2O2 from sources other than mitochondria [14]. Catalase, which is present in peroxisomes, converts H2O2 into water, preventing its buildup. However, H2O2 is released into the cytosol and contributes to oxidative stress when peroxisomes are damaged and their enzymes are down-regulated. The most dangerous ROS of all, the highly reactive hydroxyl radical, can be created from H2O2 by the Fenton reaction when reduced metals, such as ferrous iron (Fe2+), are present [15].

In Parkinson's disease (PD), dopamine metabolism itself can potentially lead to oxidative stress through enzymatic and chemical pathways. Semiquinones, which are produced when dopamine undergoes autoxidation, are hazardous by themselves and have the potential to produce reactive oxygen species [16, 17].

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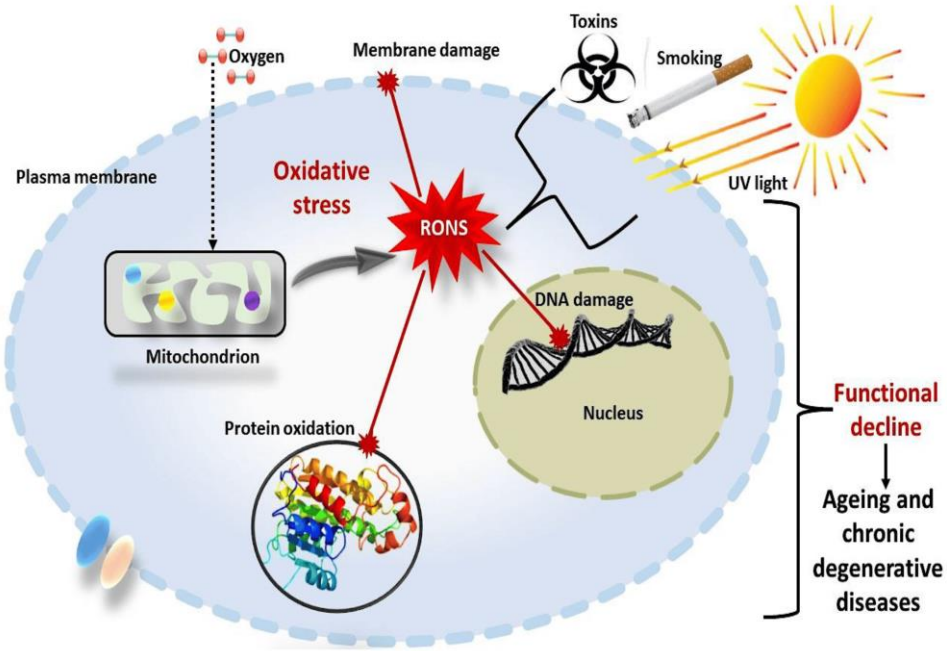

Mitochondrial Disfunction

There are several possible causes of the mitochondrial malfunction linked to Parkinson's disease (PD). Loss of mitochondrial biogenesis, excessive ROS production, impaired trafficking, impaired ETC activity, altered dynamics of the mitochondria, calcium imbalances, and other issues are among them. One of the main causes of Parkinsonism is mitochondrial dysfunction, particularly in the electron transport chain (ETC) [18, 19]. In fact, complex I of the ETC is frequently linked to issues with this condition. This complex is essential for the production of energy in mitochondria, a process that is critical to neurone health. Most of the unfavourable neuronal degradation in Parkinson's disease is caused by complex I deficits of the respiratory chain[20].

Antioxidants used for the treatment of Parkinsonism

Antioxidants are substances that can be sparingly given to other substances in order to stop them from interacting with atmospheric oxygen. They go by the names stabilisers and oxidation inhibitors as well. Natural or artificial antioxidants have the ability to stop or slow down some forms of cell damage. Fruits and vegetables are among the many foods that contain antioxidants. Additionally, they can aid in shielding your body from free radicals, which are chemicals that can harm cells and cause long-term ailments.

By giving up some of their own electrons, they neutralise free radicals and stop a chain reaction that may harm other body cells and substances. In fact, a number of studies reveal that the brains of PD patients have high levels of iron, enhanced dopamine oxidation, low levels of endogenous antioxidants like glutathione and coenzyme Q10 (CoQ10))[21], and low levels of endogenous antioxidants like glutathione. These findings imply that oxidative stress is a major factor in the pathophysiology of PD. Low GSH levels and enhanced lipid peroxidation and nucleic acid oxidation are expected given the higher iron content of certain brain regions. Antioxidants include, for instance,

1. Uric Acid

Strong antioxidant uric acid has potential anti-PD properties [22]. Uric acid inhibits the death of dopaminergic neurones brought on by H2O2 or MPP+ in mouse SN neurones that have been cultivated [22, 23]. In 6-OHDA-lesioned animals, elevated cerebral uric acid ameliorates Parkinsonian phenotypes [24, 25]. Higher serum uric acid levels are consistently linked to a slower rate of Parkinson's disease progression, according to two clinical trials [26, 27]. Reduced changes in universal PD rating scale (UPDRS) ratings [27] and a slower pace of clinical progression [26, 27] are also associated with high amounts of uric acid in CSF. In addition, uric acid levels in the serum are lower in PD patients with cognitive problems than in those without [28]. The findings point to uric acid as a PD protective biomarker[29].

2. Retinoic Acid (RA) and Carotenoids

In animal and cell models of Parkinson's disease (PD), RA and carotenoids exhibit antioxidant properties. In SH-SY5Y cells, RA reduces the neurotoxicity caused by 6-OHDA and MPP+ [30, 31]. In rat midbrain slice cultures, administration of a RA agonist inhibits the loss of dopaminergic neurones produced by interferon (IFN)-γ/LPS [32]. PD patients' plasma has lower amounts of RA [33]. Patients with Parkinson's disease also have decreased serum levels of lycopene, α- and β-

carotenes, and both of these factors have an inverse relationship with the motor portion of UPDRS scores as well as Hoehn and Yahr stage [34].

3. Vitamin C

Water-soluble vitamin C, sometimes referred to as L-ascorbic acid, is added to certain foods, found naturally in others, and accessible as a dietary supplement. Since humans, unlike the majority of animals, cannot produce vitamin C on their own, it must be obtained from diet. It aids in shielding cells from free radicals created by radiation, tobacco smoke, and the digestion of food by the body.

4. Vitamin E

Lower plasma levels of vitamin E [35]. But according to other research, there is no difference in vitamin E levels in theserum or plasma between those with Parkinson's disease and healthy controls [35–38].

5. Glutathione Peroxidase (GSH-Px), Superoxide Dismutase (SOD) and Xanthine Oxidase

Two significant antioxidative enzymes are SOD and GSH-Px [39]. Current findings of GSH-Px activities in PD patients show wide diversity; they may be elevated in serum [43,44], reduced [40,41] or not changed in erythrocytes [42]. There are reports of higher or stable SOD activities in PD patients' plasma or serum, while fewer research show decreased SOD activities in PD patients' erythrocytes [45, 46]. O2 and H2O2 are produced when xanthine oxidase catalyses the conversion of hypoxanthine to xanthine. Natural antioxidants, which are abundant in herbal remedies, may improve GSH-Px or SOD activity to have neuroprotective effects in Parkinson's disease (PD). For instance, gypenosides from Gynostemma pentaphyllum have been shown to be able to counteract MPTP-induced decreases in GSH and SOD activity in mouse SN [45].

In a rotenone-treated PD mouse model, nerolidol, which is included in plant essential oils, increases SOD and GSH levels [47]. In the striatum of 6-OHDA-treated rats, quercetin, which is widely present in fruits, vegetables, red wine, and olive oil, raises GSH levels. In the SN of MPTP-treated rats, kaempferol, a flavonoid found in tea, apples, grapefruits, and broccoli, increases SOD and GSH-Px activity [48]. In the SN of 6-OHDA-treated rats, resveratrol and hesperetin up-regulate GSH levels as well as GSH-Px and SOD activity. To confirm the use of these natural antioxidants in the treatment of Parkinson's disease, clinical investigations will be necessary.

As an irreversible MAO-B inhibitor, deprenyl, also known as selegiline, has been shown to shield animals from the toxicity of MPTP by preventing MPTP from being converted to MPP [49]. It would lessen the oxidative deamination of DA to DOPAC and hydrogen peroxide as an MAO-B inhibitor, which would lessen the production of oxyradicals from hydrogen peroxide. Alpha-tocopherol, or vitamin E, an antioxidant, was tried in conjunction with selegiline.

6. Melatonin.

Melatonin, a naturally occurring antioxidant that can lower oxidative stress in cells, safeguards mitochondrial processes in vitro. Patients with Parkinson's disease had low melatonin levels [50]. A study that showed melatonin treatment to cultured cells restored α-synuclein damage to mitochondria was inspired by Zampol and Barros [51]. Furthermore, Patki and Lau looked into the possibility of melatonin reversing neurobehavioral impairments and mitochondrial problems in an experimental model of Parkinson's disease (PD)[52], indicating that melatonin may eventually protect neurones as well as mitochondria in an animal model of chronic PD. Because of this, melatonin may be useful in lowering respiratory chain inhibition and oxidative stress in several mitochondrial disorders as well as in decreasing the progression of idiopathic Parkinson's disease.

7. Coenzyme Q

CoQ10, a mitochondrial electron carrier that also helps to avoid oxidative damage, is an example of another significant antioxidant mechanism [53,54]. Moreover, it functions as an activator and cofactor for mitochondrial coupling proteins [55]. Though it is known that PD patients who have lower levels of CoQ10 have altered ATP production and mitochondrial membrane damage, the exact processes by which CoQ10 shields dopaminergic neurones from degeneration remain unclear [64]. This is why oral CoQ10 supplementation reduced mitochondrial dysfunction in both animal models and PD patients [56,57], prevented dopamine and dopaminergic axon loss [58], shielded dopaminergic neurones from excite toxin-induced neurodegeneration in PD [59,60], and partially improved motor function. [61]. However, a subsequent meta-analysis [63] confirmed the findings of a clinical study including 600 patients, which found no indication of benefit for CoQ10 supplementation [62].

CONCLUSIONS

Maintaining the physiological level and regular functioning of the organism requires a balance between the generation and removal of ROS. ROS are produced throughout the cell, but mostly in the mitochondria. To keep ROS levels steady, there are enzymatic and non-enzymatic methods available. By modifying signalling pathways, such as the activation of protein kinases and the deactivation of phosphatases for LTP development, normal levels of ROS can influence

physiological function. It is detrimental to upset the ROS equilibrium. Certain physiological tasks of a living organism cannot be performed at low ROS conditions. On the other hand, a live organism experiences oxidative stress when there are excessive quantities of ROS, either from overproduction or restricted removal.
The most human-like models we can assess are those used for animal screening. To fully understand the pathophysiology of the disease and investigate potential new treatments, a number of animal models for Parkinson's disease have been developed. Every model has a unique set of advantages and disadvantages. Furthermore, the development of a disease is mediated differently by each toxin and medication.

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