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Neurotoxin models and treatments of Parkinson's disease: A review

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***Abstract*---**Parkinson's disease (PD) is a prevalent neurological illness that manifests itself sporadically. The destruction of dopaminergic neuronal cells in the substantia nigra is the primary cause of PD. The cause of PD is unknown, while its pathogenesis is becoming to be recognized as a complex cascade of harmful elements. The majority of insights regarding PD pathogenesis reported evidence of experimental PD models, particularly those caused by neurotoxins. Although many natural and synthetic chemicals have negative effects on neuronal cells of the dopaminergic region, only a few are employed in living animal studies to mimic some of the symptoms of PD. Therefore, more studies are required to better understand the causes of PD and select better neurotoxin models in animals. In this review, we discussed the treatment drugs and animal induced model (neurotoxin model) including MPTP, rotenone,6-hydroxydopamine (6-OHDA), manganese, and paraquat for Parkinson's disease. We also discussed the neuropathological disease stages and telemedicine current status for PD.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disease that affected the CNS with tremors-like symptoms. Dr. James Parkinson initially discovered PD in 1817 (Dick 2006). He described the main characteristics of PD and gave historical cases of six patients, one of whom was a gardener (Singh, Pillay, and Choonara 2007). It affects the largest population in the United States i.e. 1 million people and 1 out of every 100 individuals over the age of 60 (Sukendar, Sutarni, and Subagya 2016). It is the oldest and second-largest degeneration of neuronal disease afterward Alzheimer's disease (AD) (Aswath and Vignesh 2019). It is a long-lasting and advanced neurological problem that founds a deficiency of neurons from a definite portion of the brain (Sukendar, Sutarni, and Subagya 2016). Approximately, 2% of people in old age (above 80 years) are exposed to PD globally (Oluwole et al. 2019). It is present with four important cardinal motor appearances: rigidity, tremors, bradykinesia, posture instability, and some non-motor signs, including insomnia, olfactory abnormal function, dysautonomia, and constipation. This type of symptom is not shown in all types of PD patients and its shown due to the loss of neurons in many specific regions of the brain (Zhao et al. 2020). These symptoms are produced by some factors including aging, genetics, and environmental because of the loss of dopaminergic neuronal cells in PD patients (Zhao et al. 2020). Improper functioning of the mitochondria, free radical generation, and protein mismanagement have the main characteristics of PD. This process is induced by non-genetic factors (Aswath and Vignesh 2019). The clinical analysis of PD is dependent on a hospital's records and a neurological check-up and no laboratory blood test or experiment is used to determine the PD (Sukendar, Sutarni, and Subagya 2016). It is determined by historical examination study, and neuroimaging of the brain. With the help of this study, the estimate of dopamine loss and this method is too expansive to be routinely used for diagnosis and also failed in histopathology upon autopsy to determine the PD (Sukendar, Sutarni, and Subagya 2016). Tremor is the main characteristic of PD. These symptoms occur in 70% of patients with PD. In many cases, tremor symptoms are absent. Rigidity is a motor sign and it is examined by physicians in patients. Bradykinesia is another main symptom that produces slowly, scarcity of movement, and loss of expression of the face. If the bradykinesia disturbs the oropharynx, it can face problems in swallowing that turn into aspirational pneumonia disorder. Postural uncertainty is the most common dangerous problem of PD and can cause a fracture in the bone (Sveinbjornsdottir 2016). This disease has distinctive neuropathological brain changes. They have developed abnormal proteinaceous spherical bodies in the stomata of the involving nerve cells and in 2003, they examined Parkinson's disease. Dopaminergic neurons and Lewy bodies degeneration are associated with the neuropathology of motor loss in PD, but GABAergic, glutamatergic, noradrenergic, tryptominergic, and adrenergic nerves may express impairment in their cytoskeleton (Braak and Braak 2000). The deficiency of DA neuronal cells in the SN region is a defining diseased indication of PD and is expected for its pathologic determination. PD patients have lost DA neurons around 60% by the time they die along with likely the

leftover neurons, which accounts for the corpus striatum's DA loss of generally 80% (Kordower et al. 2013). When the terminals of DA neurons degenerate decreases high-affinity DA absorption. This, in combination with some natural overt repetitiveness in DA receptors and DA terminals, appears to permit striatal volume to go on without interference or dynamic remuneration all through the beginning phases of neurodegeneration. The enduring DA terminals seem to improve the amount of transmitter delivered and provided to the extracellular fluid after fairly greater injuries. This gives off an impression of being inferable, in some measure partially, to a net expansion in how much DA is delivered because of terminal depolarization, which is an after effect of the beset frameworks' short-unsettling influence of homeostatic directing components (Zigmond 1994). Since there are not many high-partiality DA assimilation destinations in the extracellular district, a piece of the DA seems to be wordy out of the neurotransmitter and into the outside the cell, where its exercises are widened. These cycles accept, and allow the SNpc to keep up with dopaminergic command above striatal cell movement until a few DA terminals remain. Expanded DA union and delivery, then again, may increase receptive metabolites created from DA, adding to sickness advancement. When the availability of DA falls under the sum essential for rapid remuneration, or when the outline is presented to specific pharmacological, natural, or physiological burdens, neurologic impedances show up. If subsequent, continuously increasing remunerations are made, these can be reduced (Simon, Tanner, and Brundin 2020). Extra DA receptors are created and included; excitation of tyrosine hydroxylase (TH) combination; growth; and recovery all occur at a faster pace than basic neurodegeneration. This has been observed in creature models, where recovery occurs even after 90 percent striatal DA loss, which is common in most creature models. However, such a recovery is unlikely to occur quickly in those whose degenerative disease is progressing (Charvin et al. 2018). Nonetheless, one main suggestion of the cerebrum's capability to recompense for DA neuron loss midway in these ways is that, when shortages occur, therapy just has to address the far less basic nigrostriatal projection. In any case, one significant ramification of the mind's capacity to create for slight destruction of DA neuronal cells in these traditions is that, when deficits occur, medication's errand need not be to re-establish the whole nigrostriatal projection but rather to re-establish DA accessibility to the level expected to accomplish the animal study state. Even though the focal sensory system (CNS) contains various kinds of dopaminergic neurons, it is the deficiency of DA cells in the region of SNpc that is supposed to be liable for PD's engine side effects in general. The way that MPTP is particular to DA neuronal cells in the SNpc region in people and monkeys upholds this clinicopathologic link (William Langston et al. 1983b). Moreover, not all SNpc DA neurons give off an impression of being embroiled in Parkinson's illness. The ventral-horizontal level is extra dangerously affected than the dorsal level, which represents more prominent damage of DA in the putamen portion, which might be just about as high as 95% dorsally contrasted with the caudate, which can be essentially as low as 60% ventrally (Kish, Shannak, and Hornykiewicz 1988). The ventral tegmental region and hypothalamic system are fairly saved, but the dopaminergic system in the plummeting spinal cord is saved. Although some dopaminergic neuronal cells are saved in Parkinson's infection, neuron misfortune is boundless. Other catecholaminergic cell bunches ensnared incorporate the locus coeruleus, sympathoadrenal system cells, and raphe core serotoninergic neurons. In the core

basalis of Meynert, there is additionally a lack of cholinergic neurons, which in certain conditions might be halfway responsible for dementia (Chan-Palay 1988; Whitehouse et al. 1983). Stages of the PD is an important to understand the clinical and preclinical symptoms that affected the larger portion of the brain given in Table 1.

The 6 neuropathological disease stages are given in Table 1:

Table 1. The 6 neuropathological disease stages

S. No.	Stages	Characteristics	Reference
1.	1-2	Pre-symptomatic affects- pontine tegmentums, olfactory blub, anterior portion of olfactory nucleus and medulla oblongata.	(Braak and Braak 2000)
2.	3-4	Clinical symptoms: Substantia nigra, midbrain, forebrain.	
3.	5-6	End-stage – Arrives the neocortex and exhibits a widespread range of clinical appearances.	

Rotenone, MPTP, 6-Hydroxydopamine (6-OHDA) Manganese (Mn), and Paraquat-Induced Models of Parkinson's Disease

A drug causes a drug-induced state or reaction. Several drug-related deaths are caused by narcotic overdoses. A kind of psychosis generated by the use of medications is known as drug-induced psychosis. A drug causes a drug-induced state or reaction. Drug-induced parkinsonism (DIP), dyskinesia, tardive ataxia, akathisia, myoclonic seizures, and tremor are all examples of drug-induced parkinsonism. The most frequent movement problem caused by medicines that alter dopamine receptors is DIP (Marti-Massó, Poza, and Lopez De Munain 1996; Montastruc et al. 1994). Patients with DIP are commonly misdiagnosed as getting PD because clinical signs of DIP being extremely similar to those of PD (Esper and Factor 2008). Antiparkinsonian medicines are frequently prescribed unnecessarily for lengthy periods in these patients, even though recovery is attainable merely by stopping the offending drugs. Dopamine transporter scanning can help with the diagnosis of a variety of parkinsonism etiologies, including DIP (Shin and Chung 2012).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

It is a neurotoxin compound that is extensively utilized in preclinical studies of PD. It is a lipid-soluble peptide, which permits it to cross the brain with ease. Upon systemic administration, MPTP can be transformed via MAO-B in astrocyte cells into the potent dopaminergic neurotoxic 1-methyl-4-phenylpyridinium ion (MPP+), which is a dangerous metabolite that is easily taken by neuronal cells via neurotransmitter dopamine because to its structural similarities to the dopamine transporter (Sayre, Wang, and Hoppel 1989). MPP+ promotes a continuously loss of neurons in the SN and also a reduction in striatal levels of dopamine [38]. Neuronal death is caused by the suppression of mitochondrial complex I function

by MPP+. This causes a fast drop in ATP level in the SN and striatum, accompanied by DA neuron necrosis and apoptosis (Sayre, Wang, and Hoppel 1989). The poisonous substance MPTP resembles a variety of well-known ecological compounds, such as herbicides like paraquat and the lawn insecticide/fish poison rotenone (Di Monte et al. 1986; Storch et al. 2000). Both have been found to cause dopaminergic neurons degeneration (Betarbet et al. 2000; Thiruchelvam et al. 2000). In 1976, a chemistry student was attempting to make synthetic heroin when he accidentally created MPTP, which kills dopaminergic neurons (Davis et al. 1979). MPTP is hydrophobic and easily traverses the blood-brain barrier, in which it engages primarily in astrocyte lysosomes, where glial are assumed to change MPTP to its lethal derivative MPP+ (Lau et al. 1991). MPP+ does not affect basal DAergic neurons when given systemically as of its charge, which prevents it from crossing the blood-brain barrier. The DAergic substantia nigra pathway is completely suppressed by unilateral perfusion into the brain (Yazdani et al. 2006). The dopamine transporter (DAT) prefers MPP+ as a substrate, thus underlies their DAergic neuron specificity. The mechanics underlying MPP+-induced apoptosis are now being explored. MPP+ was shown to suppress respiration in mitochondrial complex I (Nicklas, Vyas, and Heikkila 1985; Ramsay et al. 1986). As a result, adenosine triphosphate (ATP) levels decline rapidly in the SNpc and striatum, the brain areas most prone to neurotoxicity that induced by MPTP (Chan et al. 1991). Surprisingly, even a 25% obstruction of complex I can cause considerable ATP suppression (Davey, Peuchen, and Clark 1998). Depending on the regimen, DA neurons may die by apoptosis or necrosis. The hydro pyridine or its metabolite is eliminated out of the brain in 12 hours after being subjected to MPTP and ATP shortage is no longer noticeable later 24 hours (Irwin, DeLanney, and Langston 1993; Jackson-Lewis et al. 1995), are entirely to blame for the neurodegeneration. MPTP easily crosses the barrier of brain by the systemic administration and is changed to MPP^+ by the MAO-B enzyme outside the dopaminergic cell. This MPP^+ crosses the dopaminergic neuronal cells by the transporter of dopamine in the dopaminergic neuron (Mounayar et al. 2007). MPP^+ blocks mitochondrial complex 1 enzyme in the mitochondria of dopaminergic neurons, ensuing in ATP deficiency and elevation of superoxide leakage through the respiratory chain of mitochondria. iNOS and nNOS generated the NO^- exterior of the dopaminergic cell and diffuses in the nearby dopaminergic neurons (Vila, Wu, and Przedborski 2001). If superoxide levels in the nearby cell are high, there's a higher chance to generate peroxynitrite through NO^- react with superoxide which has the potential to harm proteins, DNA, and lipids. MPP+ may induce cytochrome c to be released from the mitochondria to cytosol, where it activates a cascade after caspase stimulation. It released proinflammatory cytokines, enzymes, and increased calcium influx through the glutamate binding for the generation of free radicals that cause neuronal cell death (Figure 1) (Przedborski and Vila 2001).

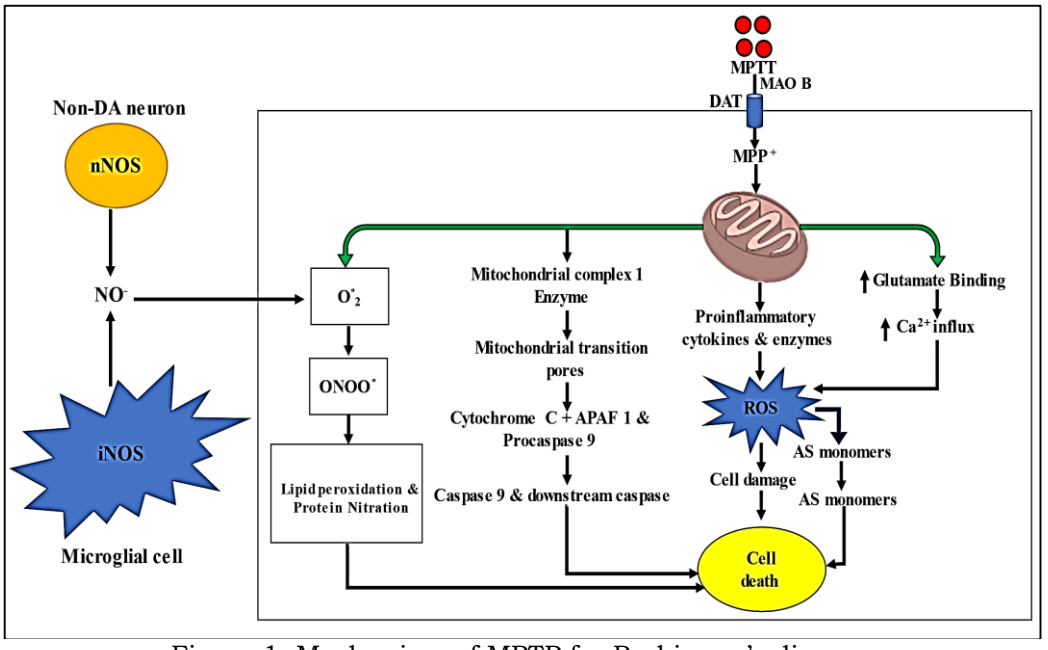

Figure 1. Mechanism of MPTP for Parkinson's disease

The usage of a synthetic drug, 'new heroin,' manufactured by a clandestine laboratory, and the MPTP identified in faulty batches of the street drug were connected to the Newstart of parkinsonism in extremely new sufferers in the San Francisco Bay Area during 1982. It was discovered that MPTP is hazardous to humans (William Langston et al. 1983a). MPP+ was found to be the neurotoxic form of MPTP, causing degradation of dopaminergic neuronal cells. The 4-e oxygenation of MPTP in brain mitochondria yields MPP+ (1-methyl-4-phenylpyridinium), which was revealed (Chiba, Trevor, and Castagnoli 1984). Soon after, it was revealed that the protein required to process MPTP in astrocytes, where it is an optimal substrate, is a monoamine oxidase (MAO B), and that MAO-A can also oxidize MPTP, albeit much more slowly (Salach et al. 1984). As shown in 1987, deprenyl, a metabolic pathway MAO B inhibitor, stopped pure MAO B from oxidizing MPTP and protected experimental animals against MPTP's neurotoxic effects and MPTP's passage through the blood-brain barrier. The combustion of dihydropyridine (MPDP+) by MAO B in brain glial, which is then reduced partly through these enzymes and then in portion non-enzymatically to a pyridinium form, MPP+, is the initial phase in the evolution of neurodegeneration (T. P. Singer et al. 1986). MPP+ is particularly taken up by the reuptake process at dopamine synapses and pushed through into the lamina of the neuronal cells. The inner membrane's electrochemical gradient concentrates MPP + from the cytoplasm into the mitochondrial matrix, where it mixes with NADH dehydrogenase, most likely at the dehydrogenase-Q junction, limiting electron transport (Nicklas, Vyas, and Heikkila 1985). This results in the cessation of ATP production, nigrostriatal cellular damage, and Parkinson's disease neurological problems. Some questions remained, like whether MPP was the sole neurotoxin product generated from MPTP or perhaps even the principal neurotoxic product (Ramsay et al. 1986). The mitochondrial theory, which assumes that hydroxide ions & superoxide radicals, despite their unique

structures, caused striatal cell damage, vs the cellular oxidative theory, which claims that the effects of hydroxide and superoxide's triggered striatum apoptosis. The actual question was whether the similarities between MPTP and its congeners' neural injuries and neuropathies as well as those observed in unexplained Parkinson's disease imply that environmental substances with similar structures might be the origin of human Parkinson's disease (Thomas P. Singer et al. 1987). In the cell, the process by which MPDP, MPTP's principal oxidation product, is further oxidized to MPP is unknown. MPDP is disproportionate to MPP and MPTP at perhaps high levels and a more basic pH, although the reactions are anticipated to be substantial at the subcellular concentrations reported in MPTP-treated animals. It has also been shown that molecule O_2 undergoes slow non-enzymic oxidation. Both MAO-A and B oxidize MPDP and its analogs at a sluggish pace, with each rate being two orders of magnitude slower. The oxidation of brain mitochondria is susceptible to MAO B inhibitors. However, it has been observed that it is not in hepatocytes. Perhaps as a result of the various catabolic events that take place in the liver but not in the brain (Di Monte et al. 1987).

Paraquat

The paraquat quaternary nitrogen herbicide (1,1-dimethyl-4,4'-bipyridinium dichloride) has been used for the suppression of broadleaf weeds. It's a non-selective, fast-acting chemical that kills green plant tissues on contact and by translocation. These are some of the primary benefits of using paraquat as an herbicide but it has good compatibility to adhesion on sand grains and chemical molecules, limiting their bioavailability to plants and bacteria (Eddleston 2017). On the other hand, paraquat is an extremely hazardous chemical for human beings and wildlife creatures, with numerous incidents of severe toxicity associated with mortality stated in recent decades. The paraquat contact knowingly or suddenly to individuals and animals is by ingestion or direct skin contact (Klinkenberg et al. 2020). When paraquat is consumed, it causes a burning feeling in the respiratory and buccal regions, which is accompanied by gastric annoyance, which causes abdominal pain, loss of appetite, nausea, vomiting, and diarrhea. Solutions of Paraquat can induce dermal lesions and bruises if they come into direct contact with the skin. Contact with paraquat might irritate the eyes, burn and cause corneal damage and scarring of the eyes. Elevated plasma contents are connected to a burning pain in the extremities, which is a significant predictor of mortality. Paraquat may have a suppressive activity of cell-mediated and autoimmune immunity at high dosages. T-cell stimulation and division are influenced by paraquat, and humoral immune system response attenuation may be a side consequence of T-cell cytotoxicity (Hatcher, Pennell, and Miller 2008). Lung impairment and emphysema, which are the most prevalent injuries and main causes of mortality, have been related to inhaling paraquat in restricted environments, including a greenhouse. As a result, it's classified as extremely hazardous by inhaling (EPA toxicity class I), moderate toxic by oral route (class II), and minimally toxic by topical route (EPA toxicity class III) (Yan et al. 2018). MPTP's active metabolite is neurotoxic that causes PO-like symptoms in rats, nonhuman apes, and people. Atypically, MPP+ was studied as a pesticide in the 1960s under the trade name cyperquat. Those people due to paraquat exposure killed had significant brain damage (GRANT, LANTOS, and

PARKINSON 1980). Epidemiological studies in agricultural areas have connections between paraquat use & PO-related risk, suggesting that paraquat is a toxin that causes Parkinson's disease in the environment. Paraquat does, in fact, cause movement problems in certain mammals (Somayajulu-Nițu et al. 2009).

PQ-induced difficulties were revealed to be involved in the JNK phosphorylation and induction of caspase-3 caused neuronal death of dopaminergic cells in exposed organisms, which was predominantly driven by the formation of free radicals like $O2^-$ and $ONOO^-$ (Figure 2) (Shukla et al. 2014).

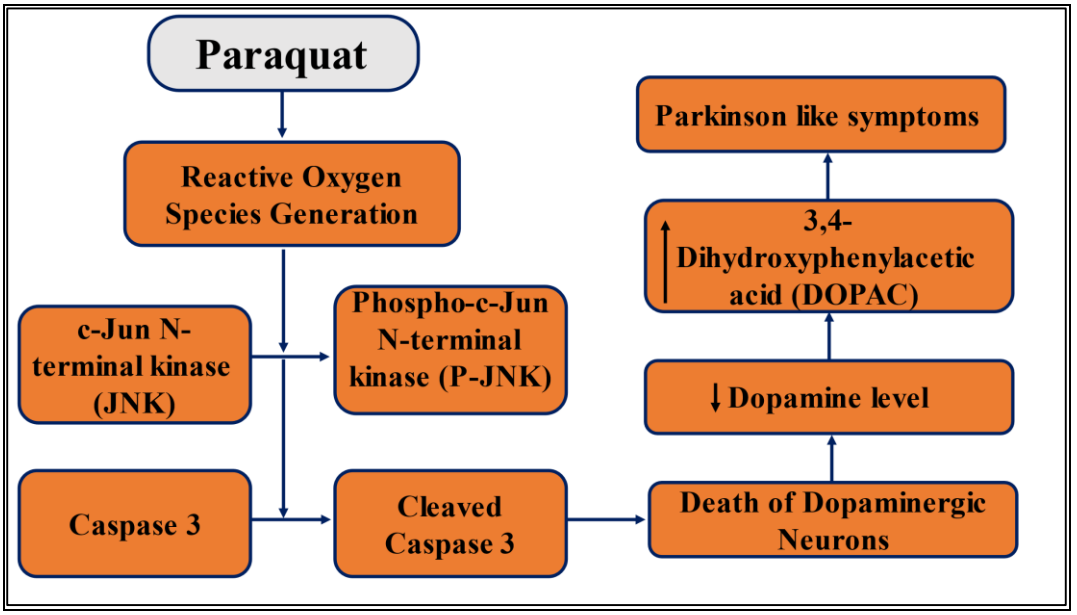

Figure 2. Schematic representation of PQ-induced ROS production leading to caspase-3 and JNK stimulation, which resulted in the neuronal death of dopaminergic cells and PD-like manifestations in the exposed creature

The xanthine oxidase enzyme initiates lipid peroxidation activity and provided the framework for paraquat-induced peroxidation. The enzyme superoxide dismutase, which hunts down the superoxide anion, was employed (Adams and Wilkinson 1972). They concluded that superoxide radicals were involved in xanthine oxidase-induced lipid peroxidation in vitro using a singlet oxygen-trapping chemical, 1,3-diphenylisobenzofuran (Keele, McCord, and Fridovich 1971). Nonenzymatically, highly reactive singlet oxygen was produced from superoxide radicals, which then reacted with unsaturated fatty acids to form fatty acid hydroperoxides, triggering lipid peroxidation (Salokhiddinov, Byteva, and Gurinovich 1981). The redox cycle of paraquat is principally responsible for its oxidative stress, which comprises a very well chain of events that result in NADPH consumption and the formation of ROS, predominantly H2O2 and hydroxyl radicals (HO), which have cellular harmful effects. Indeed, following *in vivo* and *in vitro* exposure to paraquat, lipid peroxidation has been proposed as a possible cause of harm (Burk, Lawrence, and Lane 1980). The herbicide's function in PD neurotoxicity appears to be supported by evidence that

increased production of ROS is connected to the etiology of Parkinson's disease and that ROS is inexorably tied to the mechanisms by which paraquat destroys neuronal cells (Burk, Lawrence, and Lane 1980). Paraquat induces cell apoptosis in rat brain cerebral cortex cultured neurons, which is compatible with the specific and temporary inhibition of aconitase triggered by superoxide oxidative stress (Patel et al. 1996). Paraquat can cause intraneuronal aggregates to develop, which can be stained using anti-alpha-synuclein antibodies and thioflavin S (Manning-Bog et al. 2002). Though, other study shows that paraquat-induced nigral deterioration did not result in significant dopamine depletion or behavioral abnormalities (McCormack et al. 2002). According to numerous data, apoptosis seems to important role in neuronal cell death in parkinsonian patients. Paraquat regulates genes that are related to apoptosis and belongs to the BCL2 family, the TNF-α receptor and the cell death-inducing DFF45-like effector (CIDE) family, ligand family, and the caspase family at gaining a better understanding of gene-toxicant interactions (Móran et al. 2008). Paraquat activates the endogenous apoptosis cycle, including Bak-dependent nuclear outer sheath destabilization, cytochrome c ejection, caspase-3, and c-Jun-N-terminal kinase (JNK) stimulation, as well as finally tissue destruction (Peng et al. 2004).

Rotenone

Rotenone is a phytochemical that has historically been used as a plant pesticide. It's indeed lipid-soluble and therefore can penetrate the blood-brain barrier, avoiding the inactivation of mitochondrial compounds. MPTP is one of my favorites. Rotenone, on the other hand, generates systemic inhibition, whereas MPTP targets neurons of catecholamines (Bisbal and Sanchez 2019). The first Rotenone theory was established by stereotaxic implantation of extremely high concentrations of Rotenone into the parenchyma, leading to significant drops in subcortical dopamine and serotonin levels (Heikkila et al. 1985). However, it's thought that the effects of such high concentrations aren't limited to dopaminergic neurons. Rotenone at high concentrations has caused liquefactive necrosis in the striatal area. Rotenone has also been linked to selective cell deterioration in the nigrostriatal region when given chronically at a lower dose (Inden et al. 2011). Rotenone is an insecticide derived from *Leguminosae* and *Fabaceae* plants that are extensively used in organic food production limitedly. It is always mostly used as an insecticide and to rid lakes and reservoirs of nuisance fish. Even when sprayed over huge expanses of agricultural land, rotenone biodegrades in a couple of days, which is one of its most significant benefits as a pesticide. Because of its limited environmental usage, short half-life, and low bioavailability, rotenone is unlikely to have a significant influence on PD. The most prevalent route for humans to be exposed to rotenone is ingestion. However, absorption is slow and incomplete in the stomach and intestines, and the chemical is successfully broken down by the liver. Inhaling or ingesting rotenone for a long time does not create parkinsonian manifestations. Rotenone is a very potent dopamine toxic agonist. It quickly crosses the BBB because of its high lipophilicity, and unlike many other dangerous chemicals, it enters cells without using the dopamine transporter (OAT). It collects in subcellular organelles, especially the mitochondria, once inside the cell (Talpade et al. 2000). It binds to complex I in particular.

Molecular mechanisms of rotenone toxicity

Iron homeostasis impairment has been linked to PD. Various transporters, such as transferrin1, help to maintain iron homeostasis (Tsf1). Low iron levels are caused by rotenone-induced ROS production, which inhibits transferrin1 (Tsf1) development in the CNS. Increased levels of ROS in the brain degrade complex I activity and reduce ATP production (Figure 3) (Xue, Wang, and Xiao 2020).

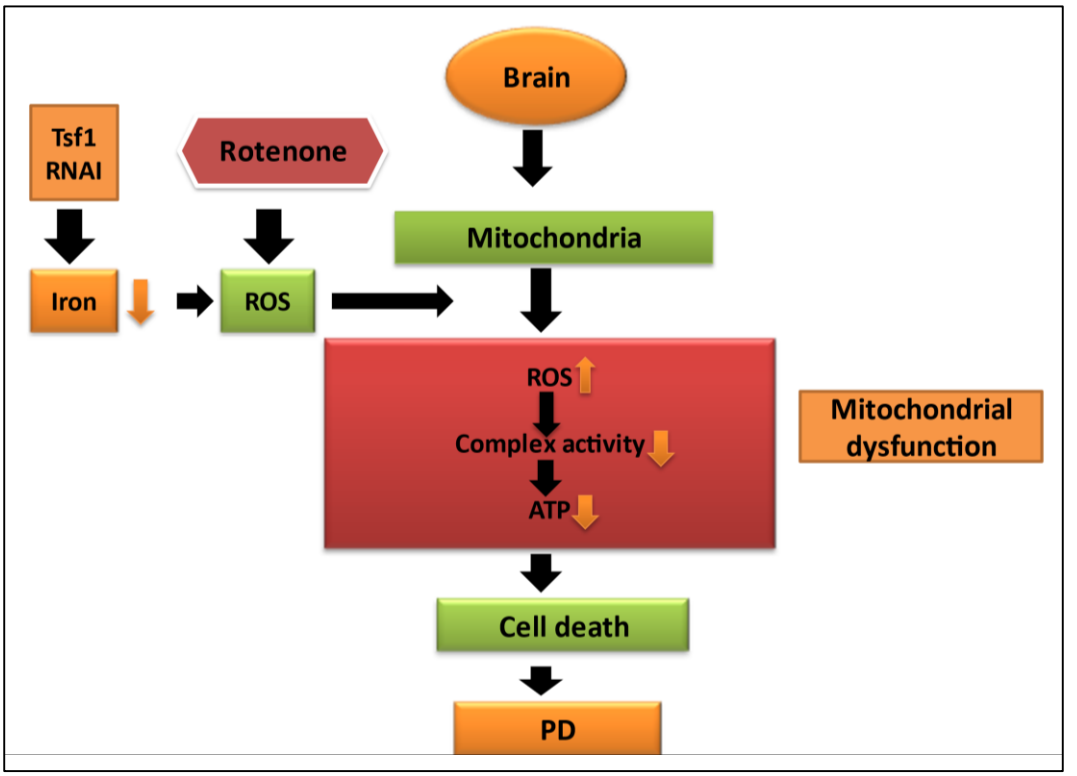

Figure 3. Schematic representation of Rotenone-induced ROS production leading to cell death, which resulted in Parkinson's disease

Rotenone is a famous electron-transport chain complex I regulator with a high affinity. Complex-I malfunction lowers Energy transfer, induces mitochondrial excitability, and leads to calcium imbalance. They can also result in an excess of ROS, causing severe peroxidation. As shown in PD, a combination of these factors can cause apoptosis (Seo et al. 2000, 2002; Sherer et al. 2003). Complex I blockers have been proven to be effective upon dopamine neurons. It thus paved way for designing PO models involved in the complex I inhibition in the somatic sensory circuit. And though the rotenone model proposes that complex I dysfunction may play a role in PO etiology, the mechanisms by which it induces neurotoxicity are unclear. Much research reveals that rotenone's toxicity is multifaceted. As a result, while reducing the generation of complex I and ROS, this herbicide activates microglia, causes oxidative damage to peptides, triglycerides, and Genetic material, induction of apoptosis, also speeds up alpha-synuclein accumulation with fibrillation. All of these characteristics trigger

selective dopamine neuronal degeneration produced by rotenone (Uversky 2004). Compared to paraquat, greater information on the rotenone's electrophysiological effects of single neurons has been collected. This neurotoxicant has been shown to augment NMDA currents in dopaminergic cells while not affecting AMPA-induced responses (Y. N. Wu and Johnson 2009). Rotenone additionally hyperpolarizes as well as inhibits the nerve impulses of suddenly separated rat SNc neuron, which is blocked by tolbutamide and glibenclamide (Röper and Ashcroft 1995). This toxin interferes with mitochondrial activity at a micromolar level, resulting in an energy failure by generating mitochondrial membrane depolarization. Mitochondrial failure causes the activation of KATP-sensitive gates in mesodermal slices, resulting in hyperpolarization of the plasma membrane of dopamine neurons and the formation of ROS (Sherer et al. 2003; J. Wu et al. 2006). Rotenone has also been shown to inhibit/hyperpolarize DAergic neurons in previous studies utilizing perforated patch-clamp recordings. The cells' early protective response could be viewed as the activation of KATP channels. The metabolic requirement (oxygen consumption) sustained by spontaneous neural activity could be reduced by hyperpolarization. However, there is experimental evidence that KATP channels contribute to neuronal degeneration. Rotenone-induced DAergic tissue necrosis has been reduced significantly in Kir 6.2 mutant mice, suggesting restriction instead of initiation of the KATP channels would contribute to neuroprotection (Liss et al. 2005).

6-Hydroxydopamine (6-OHDA)

A first Parkinson's mouse model was produced with 6-OHDA therapy. It has been frequently employed in PD investigations owing to its predictor phenotype in this model and expectable atrophy in dopamine neurons. 6-OHDA must be given intracerebrally since it does not cross the brain (U. Ungerstedt, Ljungberg, and Steg 1974). 6-OHDA oxidizes efficiently within the cell, yielding free radicals such as H2O2, superoxide anion radical, & reactive species, all of which add to endothelial dysfunction. When 6-OHDA is given to various parts of the brain, it causes a diverse pattern of neuron degeneration. The axon endings in the hippocampus are destroyed by the first 6-OHDA injections, accompanied by neuronal cell destruction in the substantia nigra (Perese et al. 1989). When 6-OHDA is administered to the SN, it kills a lot of dopaminergic neurons. As a result, the latter strategy exhibits more severe symptoms. Numerous research using 6-OHDA models have been undertaken to investigate the neuroprotective properties of various substances. Antioxidants and iron chelators have been demonstrated to be effective in mitigating 6-OHDA neurotoxicity (Haleagrahara, Siew, and Ponnusamy 2013).

The accumulation of toxins and then conversion into catecholaminergic neurons are the mechanisms by which 6-OHDA works. Because 6-OHDA and dopamine have similar patterns, transporter of the dopamine picks up the 6-OHDA and causes poisoning (Hernandez-Baltazar, Zavala-Flores, and Villanueva-Olivo 2017). The generation of free radicals by the extra hydroxyl group inside the neurotoxin's structure causes these toxic effects (Prasad and Hung 2020). Oxidative stress is also present, which is caused by the restriction of the cell's complex I of mitochondria, that results in the production of ROS and a reduction or reduction of respiratory function. Furthermore, the mechanism of oxidative stress-

producing neuroinflammation has been hypothesized (Figure 4) (Blesa et al. 2012).

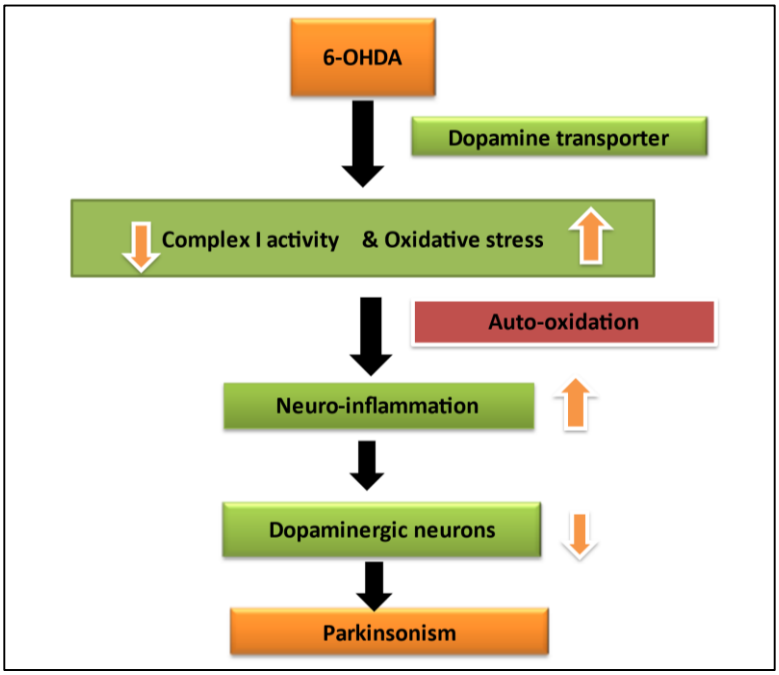

Figure 4. Mechanism of 6-OHDA to induce Parkinson's disease

6-OHDA is toxic both peripherally and centrally; however, because the neurotoxins cannot cross the blood-brain barrier, Neurological toxicity will only be generated by administering the cytotoxic deep brain by the stereotaxic procedure (Urban Ungerstedt 1968). 6-OHDA neurotoxicity effects are caused by a 2-step process that involves the buildup of the toxin in neurons possessed catecholamine, accompanied by homeostasis at cellular level disruption and neuron destruction. The noradrenaline or dopamine membrane transporters are responsible for intracellular storage of 6-OHDA, which detects and absorb 6-OHDA because it is an analog of endogenic catecholamines. Downregulation, and biological deactivation of any NAT or DAT, stops 6-OHDA-induced neurodegeneration, demonstrating that deposition of a catecholaminergic neuron is a key stage under this mechanism (Luthman et al. 1997). Several sets of evidence imply that free radicals act a crucial role in endocellular events leading to 6-OHDA-induced neuronal injury. 6-OHDA causes cytotoxicity in the brain by enzyme and without enzymatic processes, that are enhanced by intracellular micro compounds including iron and manganese (Cadet et al. 1989; Cadet and Brannock 1997). Thus, when monoamine oxidase (MAO-A) oxidizes 6-OHDA produces H_2O_2, which is very cytotoxic, and also causes the generation of oxygen radicals (Cohen 1984). Consequently, 6-OHDA involves extensive auto-oxidation, yielding fatal H2O2, ROS, and dopaminergic quinones, particularly targeting endocellular electrophilic groups (Padiglia et al. 1997). 6-OHDA-induced increases in free radicals cause fast destruction of intracellular non-oxidative enzymes, resulting in enhanced neurotoxicity, metabolism, abnormal cell structure and finally neuronal death (Blum et al. 2001). In the rat, 6-OHDA infusion changed

the levels of free radical scavengers, indicating that antioxidants can reduce neurotoxicity that induced by 6-OHDA (Cadet et al. 1989). Transgenic animals and cultured cells overexpressing the enzymes glutathione peroxidase and superoxide dismutase also showed a significant reduction in 6-OHDA toxicity (Callio, Oury, and Chu 2005). 6-OHDA, in addition to worsening endocellular oxidative stress, may cause neurotoxicity by affecting the function of mitochondria, since it has been revealed to disrupt complex I activity in separated mitochondria from the brain. Surprisingly, this latter impact was unaffected by oxidative stress and was unaffected by antioxidants (Y. Glinka, Tipton, and Youdim 1996; Y. Y. Glinka and Youdim 1995). Experiments on entire cells failed to corroborate these findings and resolve the debate over whether mitochondrial damage plays a role in neurotoxicity by 6-OHDA (Y. Wu et al. 1996).

Manganese (Mn)

Manganese (Mn) is found naturally in the environment, including soil, water, oil, and food. It acts as a co-factor and supports in production & digestion of neurotransmitters. Over absorption of Mn within the brain tissues can induce manganism, a form of extrapyramidal motor dysfunction similar to Parkinsonism (Harischandra et al. 2019). Mn can build up in the globus pallidus and sub-thalamic nucleus, which are involved in motor and without-motor function control. The locomotor function can be harmed by intraperitoneal injection at the dose of 10 mg $MnCl_2$ for 35 days. After Mn toxicity, there are changes in the rate of firing and structure of basal ganglion, as well as decreased levels of serotonergic and norepinephrine systems. Mn can alter dopaminergic neurons in the brain depending on how it is given and how much it is given. Mn increases dopamine concentration in drinking water but decreases it after intrathecal injection (Sun, Sukumaran, and Singh 2020).

A reported animal study of neurotoxin models to induced Parkinson's disease: Neurotoxin models were used in preclinical studies for an ancient time to understanding the better toxic compounds that have well toxic results without given adverse lethal effects. The drug dose, route, time, animal model, and evaluated results in each neurotoxin-induced PD animal model are summarized in Table 2.

Table 2

Model	Dose	Route	Time	Animal model	Result	References
MPTP	14 mg/kg	IP	7 Days	Mice	Striatal dopamine depletion after dopaminergic neurodegeneration	(Jackson-Lewis et al. 1995)
	20 mg/kg					
	30 mg/kg		5 Days		Causes apoptosis and depletes striatal dopamine	(Tatton and Kish 1997)
		SC			More than 80%	(Meredith and

Model	Dose	Route	Time	Animal model	Result	References
		IP	21 Days		losses the DA later 1 day and more than 40% losses later 30 days. Acute: >90% losses DA on 7 days. Subchronic: >90% losses DA on 7 days, Chronic: 95 to 98% DA losses later 3 weeks.	Rademacher 2011)
	46 mg/kg	IP/SC	42 Days	Rat	loss of dopaminergic neurodegeneration in SN.	
6-OHDA	10 µl	MFB Infusion	14 Days		Akinesia, sensorimotor deficits, rotational behavior & improper movement.	(Perese et al. 1989)
		MFB Infusion			Dyskinetic behavior & akinesia	(Haleagrahara, Siew, and Ponnusamy 2013)
		VLS Infusion			Deficits in fine motor control, Jaw tremor, cognitive deficits	
	10 mg/kg	MFB Infusion or striatum		Mouse	Akinesia, sensorimotor deficits, rotational behavior & improper movement.	(Haleagrahara, Siew, and Ponnusamy 2013)(Bonito-Oliva, Masini, and Fisone 2014)
	2 mg/kg	SNc or A8 dopaminergic mesencephalic infusion	8 Days	Cat	Aphagia, akinesia, bradykinesia & reduced attention	(Simola, Morelli, and Carta 2007) (Beleslin, Samardžić, and Stefanović-Denić 1981)
Paraquat	3 mg/kg	IP	20 Days	Rat	The ipsilateral striatal dopamine	(Liou et al. 1996; Vegh et

Model	Dose	Route	Time	Animal model	Result	References
					level was decreased, Nissl substances losses & protuberant glial reaction in the substantia nigra region caused a severe neuronal Loss.	al. 2021)
	0.2 mg/ml	Inhalation	28 Days	Mice	Oxidative stress-induced hippocampal neurocytes that injured in mitochondria	(Chen et al. 2010), (Anderson et al. 2021)
Rotenone	30 mg/kg	Oral			Specific nigrostriatal DA neurodegeneration, and loss of t*yrosine hydroxylase* - neurons, damage the behavioral characteristics	(Inden et al. 2011)
	100 mg/kg		56 Days		Loss of t*yrosine hydroxylase* positive nerve cell amid distinct mice	
	2.5 mg/kg	IP	60 Days	Rat	The hanging wire and rotarod test shows brain impairment and declines in tyrosine hydroxylase in the nigrostriatal region	(Wrangel et al. 2015)
Manganese	1.5 mg/kg	Inhalation	13 Weeks	Rat	Decreased in hypothalamic DA, whereas PRL and Pit-1 mRNA levels increased	(Hyeon et al. 2009)
	1.3 mg/kg	IP	60 Days	Mice pups	Generation of oxidative stress	(Chepukosi et al. 2021) (Okada et al. 2016)

IP: Intraperitoneal, SC: Subcutaneous, MFB: Medial Forebrain Bundle, VLS: Ventrolateral Striatum, DMS: Dorsomedial Striatum

Telemedicine Current Status for PD in Japan

Telemedicine can help people with PD have easier access to specialists; nevertheless, it is not frequently utilized in Japan. A questionnaire survey was used to inspect the efficacy of telemedicine in PD. From October 2017 to November 2018, we emailed a questionnaire to 52 individuals with Parkinson's disease who volunteered to participate after using telemedicine services at Juntendo University Hospital. Caregivers were asked to answer one question at a time. The questionnaire was completed by 38 patients. The majority of patients (7.8±1.9) were happy with the telemedicine consultation that helped minimize their trip time. 21-patients participated in telemedicine as a consultant throughout their careers, and they were very satisfied (8.4 ±1.8). PD patients and their caretakers in a specific cohort in Japan were largely happy with the telemedicine service (Ogawa et al. 2022). Many of today's intriguing new clinical trials, technologies, and medication therapies have their roots in research from the last decade. Physicians, scientists, and patients alike hope that today's advances will lead to cures and prevention in the future. Parkinson's disease research covers a wide range of topics (Demiya-Dillenburger, Isshiki, and Mahlich 2022). Some researchers are looking at the functioning and structure of the motor system, as well as how it regulates movement and interacts with the brain's major command centers. Scientists inspecting the aetiology of PD will continue to explore environmental or other variables that may trigger the disease, such as toxins, as well as genetic factors to see if one or more faulty genes are involved. Although Parkinson's disease is not passed down the generations, likely, some people are genetically predisposed to it. Other researchers are researching novel protective medications that could help to postpone, prevent, or reverse the disease. When taken with the investigational medication R0 40-7592 for the PD treatment, levodopa-carbidopa symptoms are reduced by 60%. This new promising medication prevents the breakdown of dopamine. Scientists are still working on the dose of this medicine (Jiménez-Delgado et al. 2021), therefore it is still in the experimental stage. Additional control released formulations and an implantable pump that provides a constant supply of Levodopa to regulate the problem of fluctuating levels in patients are two PD medications under investigation. The implementing capsule, which contains dopamine and is encased with a biologically inert membrane that permits the medicine to flow into the brain, is also a viable treatment. Nerve cell replacement or neural grafting is an experimental treatment for treating the disorder (Omboni et al. 2022). Treatment involves replacing missing or injured dopamine-producing neurons with healthy fetal neurons, resulting in improved movement and drug response. The use of genetically modified cells as a therapy option appears to be promising. A genetically engineered cell is a modified skin cell that does not come from the nervous system but is generated in tissue culture and has the same beneficial effects as the nervous system's cells. Skin cell harvesting is significantly easier, and this patient may be his or her donor (Mirzaei et al. 2021; Tamtaji et al. 2020).

Treatment of Parkinson Disease

Many drugs are available that provide some relief from Parkinson's disease symptoms but do not cure the disease completely. Surgery may be recommended in some later situations.

Levodopa-Carbidopa: Levodopa is a prodrug that passes the blood-brain barrier and is changed to dopamine, a highly effective Parkinson's drug. When taken with levodopa, carbidopa protects levodopa from being converted to dopamine outside the brain and reduces adverse effects like nausea and light-headedness. The benefit of levodopa may become less sustained as the disease worsens over time. Involuntary movements may occur after taking a high dose of Levodopa (Hernando et al. 2016).

Dopamine agonists: Dopamine antagonists are drugs that mimic the effects of dopamine in the brain. They are not as effective as dopamine, but they can help manage illness symptoms. They can be combined with Levodopa to smooth out the drug's on-and-off effects (Stowe et al. 2008).

Dopamine agonists: Pramipexole, ropinirole, and rotigotine are a few examples. Hallucinations, drowsiness, and compulsive behaviors such as hypersexuality, gambling, and eating are some of the negative effects of dopamine (Clarke and Guttman 2002).

Monoamine oxidase-B (MAO-B Inhibitors): They are included Rasagiline and Selegiline which stop dopamine from being broken down in the brain by inhibiting monoamine oxidase B, a brain enzyme that breaks down dopamine. These medications can cause nausea and sleeplessness as side effects. When combined with other drugs, the risk of hallucination may increase (Maliyakkal et al. 2022).
Catechol-O-methyltransferase (COMT) inhibitors: Entacapone is the most common medicine in this class. Because this medicine blocks an enzyme that breaks down dopamine, the effect of levodopa therapy is moderately prolonged. Side effects include an increased incidence of involuntary movements and diarrhea. Tolcapone is another medicine in this class that is rarely prescribed due to the risk of major liver damage and failure (Waters 2000).

Anticholinergic: This medicine has been used for many years to manage the tremor associated with Parkinson's disease. Benztropine or trihexyphenidyl are two medications that can be used. Side effects include impaired memory, disorientation, hallucination, constipation, dry mouth, and impaired urination (Ehrt et al. 2010).

Future perspectives

Parkinson's disease (AD) is a neurodegenerative disease that mostly affected the substantia nigra portion of the brain that usually starts slowly destroying memory and thinking skills. If it affected a larger population then more studies will be required. In this review, we completed studies on inducing models including 6-OHDA, MPTP, rotenone, paraquat, and manganese. 6-OHDA, MPTP, and other neurotoxin models will be a better option with any novel drug combination for inducing PD. Administration of 2-3 neurotoxin models at minimum dose or neurotoxin model with the treatment drug will be the future option for PD. Animal inducing models have shown a better positive result in a previous preclinical study, but very less studies were conducted on them, so the larger studies on animal models and they are combined with treatment drugs will be the best opportunity for PD.

Conclusion

PD is the most frequent neurodegenerative ailment with a high fatality rate despite contemporary therapy. Because there are no good diagnostic biomarkers, clinical criteria are used to diagnose Parkinson's disease throughout time. Therefore, chemicals including 6-OHDA, MPTP, rotenone, paraquat, and manganese are routinely employed in the neurotoxic model to cause PD-like symptoms in animals**.** The most important characteristics of the most prevalent toxic models of PD were outlined in this review. MPTP causes PD-like disease in cells that target the mitochondria, making it a good model for reviewing mitochondria' abnormal function in Parkinsonism. Key hallmarks of Parkinsonism have been generated in the rotenone model, such as motor impairments, nigral dopamine destruction, catecholamine reduction, and, most crucially, the development of Lewy bodies. This review evaluated the key features of the most common toxic models and treatment drugs of Parkinson's disease. Even though some neurotoxins covered here are considered to destroy dopaminergic neurons, they all cause distinct neuropathological or clinical problems. Before commencing research utilizing a model of PD, we must constantly question ourselves which neurotoxin model and treatment drug is most suited to the situation.

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Conflict of Interest

The authors declare no conflict of interest.

Credit Author Statement

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Wasim Akram and Vishal Kumar: Writing- Reviewing and Editing.
Sanjar Alam, Swamita Arora and Rohit Kumar: Visualization, Investigation.
Wasim Akram: Conceptualization, Visualization, Investigation, Supervision, Writing-Reviewing and Editing.

Abbreviation List

PD - Parkinson's disease,
DA - Dopamine,
SNc - Substantia nigra pars compacta,
6-OHDA - 6-Hydroxydopamine,
MPTP - 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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