Small Worm, Big Impact: Exploring Neurotoxicant-Induced Parkinsonism in *C. elegans*: A Comprehensive Review

Keerti Mishra, Sneha Verma*, Ramakant

Department of Science, Maharishi School of Science and Humanities, Maharishi University of Information Technology, Lucknow, U.P., India

*Corresponding author email: drsnehaverma@yahoo.com

Abstract

Caenorhabditis elegans has emerged as a robust in vivo platform for modeling Parkinson's disease (PD)-like neurodegeneration triggered by environmental toxicants. Compounds such as rotenone, MPTP (via its active metabolite MPP^+), and 6-hydroxydopamine (6-OHDA) reproduce central pathological features of PD, including dopaminergic (DAergic) neuron loss, mitochondrial impairment, oxidative stress, and behavioral anomalies. This review compiles findings from over 15 key studies, examining the cellular mechanisms of neurotoxicity, genetic influences on vulnerability, and the advantages of *C. elegans* for rapid drug discovery.

Keywords: *Caenorhabditis elegans*, Parkinson's disease, MPTP, Rotenone, dopaminergic neuron.

1. Introduction

Parkinson's disease involves the progressive deterioration of DAergic neurons within the substantia nigra, contributing to characteristic motor and non-motor symptoms. While hereditary factors are important, environmental agents—especially mitochondrial complex I inhibitors like rotenone and MPP^+, as well as catecholaminergic toxins like 6-OHDA—are also implicated. *C. elegans*, with its simple nervous system comprising eight DAergic neurons, optical transparency, and conserved PD-related genes, provides an effective system for studying neurodegeneration and testing neuroprotective compounds. Although there is now no known treatment for Parkinson's disease (PD), research is being done, and drugs or surgery can frequently significantly alleviate motor symptoms.

Patients with Parkinson's disease (PD) have progressive degradation of dopaminergic neurons in the substantia nigra, with many other brain areas also affected. The motor symptoms of Parkinson's disease are exacerbated when neurons in the substantia nigra are destroyed because this lowers the striatal dopaminergic signal. Parkinson disease patients' brains exhibit Lewy bodies, a biological manifestation of the illness that is known to emerge when the protein α-synuclein clumps inside cells (Spillantini MG*et al*., 1998). Parkinson's disease (PD) has an unclear cause, and neuroprotective treatments are not yet available.

It was always thought that Parkinson's disease (PD) was exclusively an idiopathic sickness, however research over the past 20 years has revealed that genetics play a crucial part in the disease.

2. Symptoms of Parkinson's disease

Primary symptoms of PD are:

Tremor:

Tremor, or shaking, usually starts in the hand, however, it can also affect the foot or jaw initially. The typical rhythmic back-and-forth motion of the Parkinson's disease (PD) tremor can encompass the thumb and fingers and is characterized by a "pill rolling" appearance. It is most noticeable when the hand is at

rest or when someone is stressed. Usually, this tremor goes away when you sleep or becomes better when you move with intention and purpose.

Rigidity:

The majority of PD patients have rigidity, often known as muscular stiffness or resistance to movement. The individual has persistent pain or stiffness due to the strained and constricted muscles. When someone attempts to move the stiff person's arm, it only moves in brief, jerky motions that are referred to as "cogwheel" stiffness.

Bradykinesia*:*

Bradykinesia is a disorder that causes spontaneous and automatic movement to slow down. It can be especially annoying because it can make simple tasks challenging. Things that used to be done quickly and effortlessly, like washing or dressing, may now take much longer. Facial expressions tend to decrease (a phenomenon referred to as "masked face").

Postural instability:

Uneven posture and poor balance can raise the chance of falling. Parkinson's disease (PD) does not affect peoples in the same manner. Everyone experiences the symptoms at various stages and with different symptoms. Usually, one side of the body is first affected by PD symptoms. Though symptoms are frequently milder on one side than the other, the illness eventually affects both.

There are many other problems which affect equally, like depression, emotional changes, problem with swallowing and chewing food stuffs, speech change, urinary related issues or constipation in stomach, skin problem, sleep disorder, dementia or other cognitive problems, orthostatic hypotension, muscle pain and dystonia, muscle and joint pain, tiredness and loss of energy, sexual dysfunction, hallucination, delusion and other psychotic symptoms can be caused by the drug prescribed for PD.

3. Causes and Pathophysiology of Parkinson's disease

The number of aged people worldwide is increasing exponentially, and this is leading to a sharp rise in the prevalence of age-related neurodegenerative illnesses, including AD and PD. Devastating progressive motor, cognitive, behavioral, and memory impairment are caused by these disorders. The hunt for a potent treatment for neurodegenerative illnesses has sparked a huge interest in research on medicinal plants in recent years. The human body is exposed to a wide range of contaminants and harmful compounds, which results in the generation of maximum ROS. The latter heavily contributes to mitochondrial dysfunctions and is frequently linked to misfolded proteins like amyloid-β and α-syn (Pandey T, *et al*., 2021, Pandey T, *et al*., 2020, Smita SS, *et al*., 2021, Trivedi S, *et al*., 2020, Uttara B, *et al*., 2009). Aging places a financial strain on the health care system and a social cost on the younger generation because it is the primary cause of many human ailments. It has been calculated that in the USA, delaying the onset of age-related diseases by two years would result in savings of $7.1 trillion over the following fifty years (Goldman D, 2016). Aging-related modifications to the structure and function of bodily organs result in a considerable decrease in motor activity, metabolic rate, and cellular damage. The key to attaining a healthy lifetime is to talk about the cellular and metabolic alterations that occur as we age (Büchter C, *et al*., 2016, Hsu AL *et al*., 2003, Pandey T, *et al*., 2019). The multicellular creature C. elegans has shown to be one of the important species for producing healthy aging and cognitive booster resources for old as well as younger people, as it is not viable to monitor age-dependent changes in higher organisms (Sharma S, *et al*., 2021, Shukla P,*et al*., 2019).Given the previously mentioned aspects of aging and cognition, an investigation was intended to explore thxe potential of plant extracts of specific plant species for their anti-aging, antioxidant, stress-tolerant, and cognitive-boosting properties,

particularly against Parkinson's and Alzheimer's disease, using a variety of biomarkers in Caenorhabditis elegans.

Different causes: ***Dopamine***

Eighty percent of all catecholamines in the brain are found in the neurotransmitter dopamine. Dopamine is synthesised in the SN, CTA, and hypothalamus of the central nervous system and is involved in learning, motivated behavior, and movement regulation (Vallone *et al*., 2000). Dopamine functions via binding to dopamine receptors, which are categorized into five subtypes (D1–D5) and are all members of the G protein coupled receptor (GPCR) superfamily (Beaulieu *et al*., 2015). L-3,4-dihydroxyphenylalanine (L-DOPA) is decarboxylated by aromatic L-amino acid decarboxylase to produce dopamine (Meiser *et al*., 2013). In order to facilitate signal transduction, dopamine is released into the synaptic cleft after being stored in synaptic vesicles. When dopamine has to be released again, vesicular monoamine transporter (VMAT2) loads it back into synaptic vesicles. Dopamine transporter (DAT) pumps released dopamine back into the presynaptic neuron. When DAT is unable to transmit dopamine into the presynaptic neuron, catechol-O-methyl transferase (COMT) breaks it down into 3-methoxytyramine (3-MT), which is then oxidized to homovanillic acid (HVA) by monoamine oxidase-B (MAO-B). DOPA is transformed by MAO-A and MAO-B isoforms inside neurons, but outside synaptic vesicles, to 3,4-dihydroxyphenylacetaldehyde (DOPAL). Aldehyde dehydrogenase (ALDH) quickly oxidizes DOPAL to 3,4-dihydroxyphenylacetic acid (DOPAC). Following DOPAC methylation, COMT produces HVA (Meiser *et al*., 2013). Numerous harmful radical species, including superoxide anions, dopamine-quinone species, and hydroxyl radicals, can be produced when dopamine is metabolized by MAO-B. By creating adducts with hazardous α-syn protofibrils, for instance, these radical species can lead to neurodegeneration (Dias *et al*., 2013). Thus, dopamine leakage into the cytoplasm or extracellular space and its conversion to hazardous metabolites might result from α-syn aggregates inside neurons interfering with dopamine storage in the synaptic vesicles (Dias *et al*., 2013; Lotharius & Brundin, 2002).

Mitochondrial Dysfunction

Multiple Studies has indicated that mitochondrial complex I may be hampered by α-syn oligomers. α-syn oligomers cause harm to complex I's respiratory system by causing ATP synthase to selectively oxidize and mitochondrial lipid peroxidation. This causes the osmotic transition pore (PTP) to open, which causes mitochondria to enlarge and ultimately results in cell death (Ludtmann M.H.R *et al*., 2018). α-syn oligomers can potentially destabilize calcium homeostasis, alter membrane potential, and stimulate cytochrome C release in addition to impairing mitochondrial complex I activity (Luth E.S *et al*., 2014). Furthermore, the α-syn oligomers were also demonstrated to be connected to mitochondrial complex I degradation in an A53T mouse model (Chinta S.J *et al*., 2010).

α-syn oligomers may cause mitochondrial dysfunction by additional means besides breaking down mitochondrial complex I. Reactive oxygen species are elevated and mitochondrial respiration is insufficient due to the major-affinity binding of α-syn oligomers and TOM20 peptide receptors, which prevents TOM20 from attaching to its co-receptor TOM22 (Di Maio R *et al*., 2016). α-syn oligomers cause organelle fragmentation in cultured SH-SY5Y cells by destroying the morphology of the mitochondria (Plotegher N *et al*., 2014). There is a proposal that suggests α-syn oligomers harm mitochondria by triggering cytochrome c oxidase 2 that is encoded in the mitochondria after reaching dopaminergic neurons (Danyu L*et al*., 2019). Microtubule destruction is implicated in the pathophysiology of Parkinson's disease (PD) since A53T α-syn oligomers impede mitochondrial transport, which can be reversed by NAP (davunetide) (Melo T.Q *et al*., 2017). Additionally, by inducing subcellular alterations in the transport regulatory proteins and energy loss, α-syn oligomers can interfere with the anterograde axonal transport of mitochondria (Prots I *et al*.,2018).

Apart from neurons, α-syn oligomers have also been discovered to impact astrocyte mitochondrial activity. Astrocytes have the ability to absorb α-syn oligomers and exhibit neuroprotective properties. On

the other hand, the prolonged retention of α-syn oligomers in astrocytes may compromise their mitochondrial structural integrity and result in neurotoxicity (Lindstrom V*et al*., 2017). It has been demonstrated that in cultured astrocytes, antibodies that target α-syn oligomers can stop α-syn accumulation and mitochondrial damage (Gustafsson G *et al*., 2017). When mouse astrocytes are treated with different forms of α-syn (monomer, oligomer, and fiber), the astrocytes become more active and produce more cytokines and antioxidants. Oligomers are the only substances that may cause mitochondrial dysfunction in astrocytes and dramatically raise the generation of extracellular hydrogen peroxide, in contrast to α-syn monomers and fibers (Chavarria C*et al*., 2018).

ER Stress

The ER is the site of protein synthesis, folding, modification, and transport. Stress arises when the ER's capacity to fold proteins is exceeded. Before Parkinson's disease manifests, α-syn builds up in mitochondria where it forms toxic oligomers and induces ER stress in vivo. This process is ongoing as the pathophysiology of Parkinson's disease advances, suggesting that the ER stress brought on by oligomeric α-syn may have a part in the development of Parkinson's disease. In the transgenic mouse model, treatment with the ER stress inhibitor salubrinal may dramatically lessen the symptoms of Parkinson's disease (Colla E*et al*., 2012, Colla E*et al*., 2012). α-syn oligomers have the unique potential to disrupt cellular functions, including ER function, as evidenced by their ability to activate the protective ER stress response factor XBP1 (X-box binding protein 1), but not monomers or fibers (Castillo-Carranza D.L*et al*., 2012). A multitude of neurological activities are regulated by signal transduction via the VAPB-PTPIP51 route between the mitochondria and the ER. α-syn oligomers have the ability to attach to VAPB, break the tethers between VAPB and PTPIP51, impair the ER mitochondria connections, and ultimately result in ER stress (Paillusson S *et al*., 2017). Additionally, ER stress brought on by α-syn overexpression can raise the quantity of α-syn oligomers (Jiang P *et al*., 2010). These results suggest that PD pathogenesis involves ER stress caused by α-syn oligomers.

Loss of Proteostasis

The accumulation of misfolded proteins might deteriorate due to a vicious cycle caused by the protease inhibitory actions of α-syn oligomers. Soluble α-syn oligomers have been shown to inhibit the activity of the 20S and 26S proteasomes by stoping the entry of new proteasome substrates [43, 44]. In an A53T animal model, overexpression of α-syn led to damage to the 26S proteasome, which therefore resulted in malfunctioning of the UPS. This may hasten the in vivo process of neurodegeneration [45]. Parkin, an E3 ubiquitin ligase, plays a crucial role in ubiquitination. Parkin may nitrosate as a result of oxidation/nitrification stress brought on by the presence of exogenous α-syn oligomers. Reduced parkin levels may result in abnormal protein buildup and cellular death [46].

Synaptic Impairment

α-syn has a physiological role that is uncertain, however it is prevalent in synapses. By attaching to the SNARE-protein synaptobrevin-2/vesicle-associated membrane protein 2 (VAMP2), α-syn normally maintains the normal physiological function of synapses and facilitates SNARE-complex formation. According to additional research, α-syn functions to restrict vesicle mobility and has a tendency to form multimers with an α-helical shape (Bartels T*et al*., 2011). These imply that multiple functions for α-syn in preserving synaptic homeostasis may exist. On the other side, certain conformations of α-syn oligomers may potentially cause synaptic dysfunction. When combined with VAMP2, large α-syn oligomers were favored because they might disrupt the progression of the SNARE complex and prevent dopamine from being released (Choi B.-K*et al*., 2013). Further behavioral impairments were reported in an E57K mutant mouse model that is predisposed to produce oligomeric α-syn, as a result of loss of synapses and dendrites, as well as lower levels of synapsin 1 and synaptic vesicles (Rockenstein E*et al*., 2014). In wild-type α-syn mice, however, these alterations were less noticeable. A mechanism by which α-syn oligomers produce axonal dysfunction was demonstrated by another work employing E46K and

E57K mutant human iPSC-derived neurons. Axon transport disruptions and energy deficits caused by increased α-syn oligomers lead to lower axon density and synaptic degeneration, which in turn causes synapse loss (Prots T *et al*., 2018). This finding aligns with an earlier investigation that found that α-syn oligomers of the E57K form significantly hinder the axon transport mechanism (Prots I*et al*., 2013).

According to several studies, extracellular α-syn oligomers may impair synaptic transmission by selectively binding to the NMDA receptor. Long-term potentiation (LTP), the neurophysiological foundation of learning and brain memory, is hampered in rat hippocampus cells exposed to α-syn oligomers, but baseline synaptic transmission is enhanced via NMDA receptor activation (Diogenes M.J*et al*., 2012). α-syn and cellular prion protein (PrPC) might possibly form a combination that activates the NMDA receptor. The disruption of calcium homeostasis and membrane integrity is the mechanism that causes synaptic injury (Ferreira D.G*et al*., 2017). In addition, by targeting GluN2A-NMDA receptors, α-syn oligomers rather than fibrils might cause synaptic dysfunction and impairment in visual spatial memory in the striatum (Durante V *et al*., 2019). According to these findings, α-syn oligomers block synapses, which causes PD to develop sooner.

Cell Apoptosis

α-syn oligomers have the ability to induce cell death. Reactive oxygen species (ROS) produced by α-syn oligomers are reliant on freely metallic ions and can cause neuronal death and a reduction in endogenous glutathione (Deas E*et al*., 2016). In an iron-dependent way, β-sheet-rich α-syn oligomers interact with the lipid membrane to cause aberrant calcium influx and lipid peroxidation (Angelova P.R*et al*., 2020). Ferroptosis is the term for the process of cell death brought on by lipid peroxidation produced by α-syn. As a result of SH-SY5Y cells absorbing α-syn oligomers, the cell membrane and ion homeostasis are destroyed, activating NOS and S-nitrosylating important proteins. Additionally, the cytoskeletal network, protein folding mechanism, and ubiquitin proteasome system are altered. Cell apoptosis is caused by each of these events (Kumar R*et al*., 2018). Intracellular and extracellular apoptotic pathways can be triggered by externally supplied α-synfibers that attach to the cytoplasmic membrane and function as nucleation sites, hence increasing oligomerization and internalization of α-syn (Mahul-Mellier A.L*et al*., 2015). According to these research, α-syn oligomer has an influence on apoptosis promotion.

Inflammation

In addition to having an impact on neurons, the α-syn pathology also affects glial cells like astrocytes and microglia. Astrocytes are able to absorb α-syn released by neurons and exhibit an inflammatory reaction (Lee H.J*et al*., 2010). Toll-like receptors (TLR) are the primary mechanism through which oligomeric α-syn elicits inflammatory reactions. By activating glial cells via a TLR4-dependent pathway, physiological concentration of α-syn oligomers can result in the release of pro-inflammatory cytokines like TNF-α, which ultimately cause neuronal death (Hughes C.D*et al*., 2019). Additionally, oligomeric α-syn via the TLR1 and TLR2 signaling pathway may cause microglia to change into a pro-inflammatory phenotype (Daniele S.G.*et al*., 2015). Another study also showed that specific conformations of the α-syn oligomer secreted by neurons is an agonist for TLR2 and induces an inflammatory response in microglia cells (Kim C*et al*., 2013).The significant variation in the molecular weight of the α-syn oligomers utilized in these two investigations highlights the wide range of oligomer diversity. Macroglia cells from adult mice have an increased release of TNF-α and a phagocytic deficiency for α-syn oligomers compared to those from younger mice, indicating that α-syn oligomers induced an inflammatory response in the pathology of Parkinson's disease. MPTP treatment in a type 2 diabetes (T2D) model increases oligomeric α-syn levels in the midbrain and pancreas, which in turn activates NLRP3 to increase IL-1β secretion and worsen DA neuron loss. The non-neuronal cells might also be significant players in the pathogenesis of Parkinson's disease (PD), and more investigation is required to elucidate this relationship between the pathology of PD and the inflammatory response. Macroglia cells from adult mice have an enhanced production of TNF-α and a phagocytic deficit for α-syn oligomers compared to those from younger animals, indicating that α-syn oligomers triggered an inflammatory response in the pathophysiology of

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4. Genetic and environmental risk factors

A minority of PD cases (~15%) can be studied by a genetic predisposition, with the majority (~85%) being sporadic and idiopathic (Tran *et al*., 2020). According to Polymeropoulos (1997), the first gene mutation known to cause familial Parkinson's disease (PD) was found in the α-Syn gene SNCA. As of right now, at least 16 loci linked to familial Parkinson's disease have been found in the human genome (Singleton *et al*., 2013; Thomas & Beal, 2007; Tran *et al*., 2020). Genes most commonly associated with PD include:

- SNCA (α-Syn)
- PRKN (parkin E3 ubiquitin ligase) (Poorkaj*et al*., 2004)
- UCHL1 (ubiquitin carboxyl-terminal hydrolase-1) (Leroy *et al*., 1998)
- LRRK2 (leucine-rich repeat kinase 2) (Sanders *et al*., 2014)
- DJ-1 (DJ-1 mitochondrial protein) (Bonifati, 2003)
- PINK1 (phosphatase and tensin homolog-induced putative kinase 1) (Valente, 2004)

The tendency of α-Syn to accumulation can be exacerbated by mutations in the SNCA gene. In addition, mutations affecting the SNCA, UCHL1, and PRKN genes may hinder the activity of the ubiquitin-proteasome system, which eliminates misfolded proteins such as aggregated α-Syn (Dauer &Przedborski, 2003). According to Hauser & Hastings (2013), oxidative stress and mitochondrial insufficiency are linked to the PRKN, LRRK2, DJ-1, and PINK1 genes. Misfolding and aggregation of α-Syn are caused by oxidative stress, and aggregated α-Syn destroys synaptic vesicles, causing dopamine to be secreted into the cytoplasm. Once released, dopamine is transformed into hazardous byproducts that encourage more oxidative stress and α-Syn aggregation, ultimately ending the review loop (Dias *et al*., 2013; Lotharius&Brundin, 2002). Furthermore, α-Syn aggregates are known to stimulate neuroinflammation, and neuroinflammation is known to generate α-Syn aggregation, forming another possible feedback loop in the pathophysiology of Parkinson's disease (PD) (Dias *et al*., 2013; Monahan *et al*., 2008; Tansey & Goldberg, 2010). These findings are supported by preclinical models of the disease. Apoptosis in dopaminergic neurons may eventually result from injury to the mitochondria and cells. Even while the development of idiopathic Parkinson's disease (PD) is probably not variation from that of genetically predetermined Parkinson's disease (PD), mutations are not the only source of the deficiencies in the necessary proteins' functions.

Environmental toxins like rotenone and paraquat pesticides, as well as the recreational drug contaminant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), can also cause α-Syn fibrillation and/or death of dopaminergic neurons (Langston *et al*., 1983; Tanner *et al*., 2011).MPTP's poisonous metabolite shares structural similarities with paraquat; both substances are believed to cause disease by disrupting mitochondrial processes and encouraging the production of reactive oxygen species and free radicals (Dauer &Przedborski, 2003).

C. ELEGANS AS AN ANIMAL MODEL OF PARKINSON'S DISEASE

The nematode C. elegans is a small roundworm that reaches an adult length of 1-2 mm. Under laboratory conditions at 20°C, these animals reach adulthood in just 2 days after hatching. These worms are good for aging research because they have an average lifespan of two to three weeks once they reach adulthood. The important form of C. elegans is a self-fertile hermaphrodite, in which every offspring is genetically identical. Although males make up only <0.1% of the population, it is sure to significantly increase their numbers in the lab in order to enable genetic crosses. This animal contains a completely annotated genome and is genetically tractable, with strong tools for spatiotemporal regulation of gene expression. Fluorescent proteins can be easily seen in a live worm to evaluate the amounts and locations of relevant gene products since C. elegans is transparent. These animals have been used to investigate a number of genetic and cellular issues [11], particularly to learn more about neurodegenerative disease such as Parkinson's disorder [12].

Genetic models of Parkinson's disease

SNCA

α-syn, a protein involved in synaptic vesicle production, is encoded by SNCA/PARK1/PARK4, the first gene to be conclusively linked to familial Parkinson's disease [4]. Autosomal dominant types of Parkinson's disease have been shown to be caused by SNCA mutations as well as gene duplications or triplications [66, 67]. Despite lacking a homolog for SNCA, several worm models have been created by broadly or selectively expressing human wild-type or mutant α-syn in *C. elegans*. Reduced levels of dopamine, deficiencies in behavior dependent on dopamine, and destruction of dopamine neurons are the results of α-syn expression in each neurons or in certain populations of neurons [49, 59, 60, 68–72]. α-syn has been shown in body wall muscle cells for easy form of imaging and coupled to YFP or GFP to analyze aggregation [58, 73, 74]. Apart from congregating, these worms have reduced motility and heightened susceptibility to stress. As α-syn is not routinely expressed by worms, worm models that consistently produce wild-type α-syn from only one copy transgene have also been created.

LRRK2/LRK-1

Autosomal dominant Parkinson disease (PD) has also been demonstrated to be caused by mutations in the leucine rich repeat kinase 2 gene (LRRK2) [6]. The homolog of LRRK2 in *C. elegans*, lrk-1, is widely expressed in these species, including neurons, where it forms an association with the Golgi apparatus [65]. Decreased dopamine levels, deficits in dopamine-dependent behaviors, and a progressive destruction of dopamine neurons are the results of expressing WT or mutant LRRK2 either pan-neuronally using the synaptobrevin promoter [75] or mainly in dopamine neurons by using the dopamine transporter promoter [60, 76, 77] (Table 2). The kinase activity of LRRK2(G2019S) is also crucial for the onset of age-dependent neurodegeneration, as demonstrated by extrachromosomal arrays expressing LRRK2 in dopamine neurons [78].

PRKN/PDR-1

An autosomal recessive variant of Parkinson's disease (PD) with an prior age of onset is brought on by mutations in PRKN/PARK2 [7, 79]. Parkin is an E3 ubiquitin ligase involved in mitophagy and protein degradation that is encoded by pdr-1 in *C. elegans* [80]. Mutants with p dr-1 show deficiencies in dopamine-dependent behavioas well as a loss of dopamine neurons [81, 53, 82]. Furthermore, it has been demonstrated that pdr-1 mutants are more susceptible to a variety of stressors [53, 64, 83]. A pdr-1 in frame deletion enhances susceptibility to proteotoxic stress and resulted the protein to assemble at the cellular level [71]. Lastly, it has been demonstrated that pdr-1 mutations result in the build-up of defective mitochondria [53, 64] and defects in oxidative phosphorylation [53, 84], which are linked to the activation of the mitochondrial unfolded protein response [53]. Pdr-1 mutant animals also create more exophers than wild-type worms, possibly as a way to get rid of their accumulated mitochondria [85].

PINK1/PINK-1

An autosomal recessive variant of Parkinson's disease (PD) with an prior illness start is caused by mutations in PINK1/PARK6 (5, 86). A mitochondrial kinase known as PINK1 (PTEN-induced putative kinase 1) initially recognized as ubiquitin kinase [89] and functions in mitophagy with Parkin [87, 88]. Pink-1, the PINK1 homolog, is more sensitive to various stressors when mutated [64, 65, 83]. Dopamine neurons in pink-1 worm mutants survive in the wild type despite a notable decrease in basal slowness [53]. Age-related accumulation, morphological changes, and deficits in oxidative phosphorylation have been observed in the mitochondria of pink-1 worms [53 and 65–84]. Distinctly more exophers are produced in neurons producing hazardous proteins by worms with defective pink-1, much as in pdr-1 mutants [85].

Gene–Environment Interactions and α-Synuclein Models

Expression of human α-synuclein in *C. elegans* DA neurons heightens susceptibility to toxins. Co-treatment with rotenone, MPTP or 6-OHDA in these transgenic worms amplifies neuronal degeneration, revealing synergistic gene–environment effects.

Rotenone: Mechanism of Action

Rotenone, a hydrophobic pesticide, disrupts mitochondrial complex I function, leading to ATP depletion, increased ROS, and oxidative stress. In nematodes, prolonged exposure to 1–10 µM rotenone results in mitochondrial fragmentation, reduced expression of key mitochondrial genes (e.g., *nduo-1*, *gas-1*), and gradual destrction of DA neurons.

Chronic exposure to low concentrations of rotenone led to a significant loss of dopamine neurons in C. elegans, a hallmark of PD. It also caused a loss in mitochondrial DNA replication and gene expression, particularly for mitochondrial complex IV subunits, before neuron degeneration occurred. A similar effect was observed with Mn2+ exposure. These results suggest that environmental chemicals can suppress mitochondrial biogenesis and gene expression, potentially contributing to neuron degeneration in PD. The study focuses the capacity of C. elegans as a model for exploring the molecular mechanisms of chemical-induced neurodegeneration.

The study investigates the toxic effects of the pesticide rotenone, which mimics Parkinson's disease by inducing dopaminergic degeneration and alpha-synuclein-positive inclusions in rats. By using three model systems, the researchers found that rotenone resulted dose-dependent ATP depletion, oxidative loss, and cell death in human neuroblastoma cells. When cells were infected with a rotenone-insensitive enzyme (NDI1), these toxic effects were prevented, indicating that rotenone's toxicity is linked to its interaction with mitochondrial complex I. While ATP depletion alone wasn't toxic, decreasing oxidative loss with antioxidants or NDI1 transfection protected cells from death. In a chronic midbrain slice culture model, rotenone caused oxidative destruction and dopaminergic cell loss, which was blocked by alpha-tocopherol. Additionally, rotenone-treated animal brains showed oxidative damage in dopaminergic regions. These findings suggest that oxidative damage plays a crucial role in rotenone toxicity and give support antioxidant therapies for Parkinson's disease.

MPTP/MPP$^+$-Induced Neurodegeneration

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a toxin that specifically damages neurons involved in Parkinson's disease, leading to parkinsonian symptoms. It was discovered when drug abusers inadvertently ingested it, resulting in a movement disorder resembling Parkinson’s. MPTP has been used to create animal models for studying Parkinson’s disease and testing potential therapies.

MPTP itself is not toxic, but it is converted into a harmful substance, MPP+, by the enzyme MAO-B in astrocytes and serotonergic neurons. This conversion occurs in acidic organelles, such as lysosomes. MPP+ then enters dopamine (DA) nerve terminals via the DA transporter, causing toxicity. Blocking

MAO-B or the DA transporter can protect against MPTP toxicity, providing insights into Parkinson's disease pathogenesis.

MPTP has provided valuable insights into the pathogenesis of Parkinson's disease, leading to three main hypotheses about its development.

1. **Toxic Substance Hypothesis**: Environmental or brain-produced toxins may contribute to Parkinson's in genetically vulnerable individuals, though the disease's familial occurrence is low.
2. **Oxidative Stress Hypothesis**: Oxidative stress, involving reactive oxygen species like superoxide and hydroxyl radicals, may work as a central role in dopaminergic cell death. This stress could be a consequence or cause of the disease, with evidence of depleted antioxidants and mitochondrial dysfunction in Parkinson's. The imbalance of iron in the substantia nigra may also contribute to radical formation and cell damage.
3. **Immune and Excitatory Pathways Hypothesis**: Immune responses, including microgliosis and the secretion of cytotoxic species like hydroxyl and superoxide radicals, could contribute to regional cell death in Parkinson's. Increased interleukin-6 levels in cerebrospinal fluid further support this immune involvement.

MECHANISM OF ACTION (MPTP)

- MPTP creates an experimental model of Parkinson's disease (PD), replicating most clinical, biochemical, and pathological features of the disease. While it differs from PD in some aspects, experiments to study the molecular mechanisms of MPTP can offer valuable insights into PD's neurodegenerative process. MPTP metabolism involves multiple steps that may predispose individuals to PD. Key factors in MPTP's action include, Such as the extra production of free radicals, nitric oxide involvement, tyrosine nitration, mitochondrial respiration impairment, and apoptosis. These such factors may contribute to the loss of dopaminergic neurons in the MPTP model, suggesting a similar process may underlie neurodegeneration in PD.*PD gene analogs*: Mutants of *pink-1* and *pdr-1* (parkin homologs) show enhanced MPP^+ sensitivity, highlighting conserved mitophagy pathways.

Model Development

MPTP is metabolized to MPP^+ by monoamine oxidase B in glial cells. MPP^+ then enters neurons via the dopamine transporter (DAT-1), disrupting complex I. Braungart et al. first developed this model in *C. elegans*, observing dose-dependent DAergic cell death and locomotor dysfunction with 0.5–1.5 mM MPP^+.

Cellular and Behavioral Impacts

- ***Mitochondrial damage*:** MPP^+ reduces ATP and membrane potential.

- It is commonly known that as animals age, their mitochondrial membrane potential, or $\Delta\Psi m$, decreases. Since artificially increasing $\Delta\Psi m$ in C. elegans enhanced lifespan, it was recently proposed that the lower $\Delta\Psi m$ in aged animals controls mitochondrial bioenergetics and this results a primary driver of aging. In this article, I critically examine research that found that worms and other aged animals had lower $\Delta\Psi m$. I come to the conclusion that most of these such findings are perfectly summarised as proof that the fraction of depolarized mitochondria is higher in aged cells due to increased activation of the mitochondrial permeability transition pore, or mPTP. Degenerative diseases are accelerated when the voltage-gated mPTP is activated because it depolarizes the mitochondria, prevents oxidative phosphorylation, produces a lot of calcium and mROS, and reduces cellular NAD+ aging. The described lifespan extension by artificially created $\Delta\Psi m$ in C. elegans is good described by blockage of the voltage-gated mPTP, since it has been demonstrated to restore $\Delta\Psi m$ and to delay

aging. Similarly, the voltage-gated mPTP is best accounted for as the cause of the observed activation of the mitochondrial unfolded protein response by a decrease in ΔΨm and the preservation of ΔΨm in dietary inhabit treatment in C. elegans.

- ***Oxidative damage*:** Increases ROS and lipid oxidation
- It is believed that oxidative stress is a main factor in the onset and advancement of neurodegenerative illnesses. The intricate web of signaling cascades makes it not easy to fully comprehend the direct function of oxidative stress (OS) in neurodegeneration, despite the fact that it is currently recognized as a characteristic of such diseases. The invertebrate model Caenorhabditis elegans (C. elegans) is widely used as an aging model, but some researchers have also used it to study molecular mediators that either prevent or worsen reactive oxygen species (ROS)-mediated neurodegeneration. The quick creation of C. elegans genetic models can be helpful for researching upstream indicators of oxidative stress within interconnected signaling networks because of their thoroughly described genome and brief life cycle. The roles will be the main emphasis of this paper contains C. elegans homologs for the transcription factor Nrf2, which is linked to oxidative stress, and the autosomal recessive, early-onset proteins Parkin, DJ-1, and PINK1 that are linked to Parkinson's disease (PD) in neurodegenerative processes.

- ***Behavioral signs*:** Worms exhibit coiling, diminished thrashing, and reduced food-seeking. Quantification of DA neurons using GFP tags revealed over 60% cell death after 72 hours of 1 mM MPP^+.
- *Drug screening*: The MPP^+ model facilitates large-scale testing of neuroprotective compounds, including antioxidants and autophagy activators. The neurotoxic MPTP and its active metabolite MPP+ selectively kill dopaminergic neurons in the substantia nigra, resulting in symptoms similar to Parkinson's disease (PD) in vertebrates. To find pharmacologically active substances, rodent MPTP/MPP+ models have been developed. These such animal models for experiments are expensive and time-consuming, and they are not appropriate for chemical library testing on a wide scale. By using the nematode Caenorhabditis elegans, we introduce a unique MPP+-based paradigm for high-throughput screens. Strong symptomatic deficits, such as decreased mobility and higher mortality, were observed when C. elegans were incubated with MPTP or its active metabolite MPP+. These defects are linked to a particular damage of the dopaminergic neurons. For quantification, automated gear and software were used to record the phenotypic effects of MPTP/MPP+ therapies. The MPP+-induced abnormalities were lessened when C. elegans was incubated with a range of pharmacologically active substances used to treat Parkinson's disease. Our findings imply that anti-PD medications can be quantitatively assessed using the C. elegans MPTP/MPP+ model.

ROLE OF MPTP IN NEURODEGENERATION

MPTP, a compound that induces parkinsonism in humans, offers insights into the potential causes of idiopathic Parkinson's disease. While MPTP causes significant damage to the brain's dopamine content and the nigrostriatal system in primates, it does not produce persistent motor deficits in rodents unless administered in high doses. In primates, MPTP leads to a persistent parkinsonian syndrome and selective destrction to the dopamine system, without affecting other neurotransmitter systems. This makes primates an ideal model for testing antiparkinsonian drugs, as they respond to L-DOPA and similar treatments.

MPTP metabolism in the brain produces MPP+, which accumulates in various brain areas. This neurotoxicity can be cure by preventive administration of monoamine oxidase inhibitors, which block the conversion of MPTP to MPP+. The neurotoxic effects are specific to the nigrostriatal system, and while the model mimics many aspects of Parkinson's disease, it remains limited to this region, unlike the more

widespread pathology seen in human Parkinson's. MPTP-induced damage seems primarily confined to dopamine neurons in the nigrostriatal system, highlighting its unique vulnerability to MPTP's effects.

STUDY OF MPTP IN *C.elegans*

The causes of Parkinson's disease (PD) are not completely known, but it is believed to result from a combination of hereditory and environmental factors. The synthetic chemical MPTP, and its metabolite MPP+, mimics major characteristics of PD in human beings and other mammals, providing strong evidence for the role of environmental toxins in the disease. While MPP+ has traditionally been considered unique in its ability to selectively target dopaminergic neurons, recent studies suggest it may be a section of a larger group of similar dopaminergic toxins. In vivo evidence from Caenorhabditis elegans PD models supports this idea and shows that dopaminergic neurons are particularly vulnerable to MPP+ and related toxins due to their tendency to release high oxidative stress. These findings imply that exposure to MPP+ and similar toxins in workplaces or the environment could have serious public health implications.

Parkinson's disease (PD) is a progressive neurodegenerative disorder, primarily characterized by the damage of dopaminergic neurons in the substantia nigra, leading to motor and autonomic dysfunction. Its cause is not fully known, It is supposed to arise from a combination of hereditory and environmental factors, particularly exposure to mitochondrial toxins. People with genetic defects or age-related impairments in mitochondrial function, oxidative stress management, and other cellular systems may be more susceptible to PD. Dopaminergic neurons are especially vulnerable due to their tendency to produce high oxidative stress in response to mitochondrial dysfunction.

The discovery of the synthetic chemical MPTP, which mimics PD pathophysiology, has bolstered the theory that environmental toxins contributing to mitochondrial dysfunction causes PD. MPTP is metabolized in the human brain to MPP+, which selectively destroys dopaminergic neurons. The MPTP/MPP+ model is widely used for studying PD and developing treatments. While MPP+ has been considered a unique mitochondrial toxin, recent studies suggest it may belong to a larger group of similar toxins, which also cause selective dopaminergic toxicity. In vivo studies in C. elegans PD models show that MPP+ and related compounds increase reactive oxygen species (ROS) levels and selectively damage dopaminergic neurons. This toxicity is linked to complex I inhibition in mitochondria and may be influenced by intracellular catecholamines and α-synuclein. These findings support the idea that MPP+ is a part of a broader group of dopaminergic toxins.

6-OHDA-Induced Neurodegeneration

Mechanistic Insights

6-OHDA selectively targets catecholaminergic neurons via DAT-1. It rapidly auto-oxidizes, producing ROS and quinones that cause membrane and mitochondrial damage.

Acute Toxicity and Pathways

Short-term exposure (1 h) to 10–50 mM 6-OHDA selectively degenerates DA neurons (CEP and ADE), as demonstrated by Nass et al. Interestingly, this process occurs independently of canonical apoptotic regulators like *ced-3* and *ced-4*.

Protective Interventions

- *Antioxidants*: Compounds like ascorbic acid and N-acetylcysteine mitigate neuronal damage.
- The occurence and development of neurodegenerative illnesses, such as Parkinson's disease (PD) and Machado-Joseph disease (MJD), are caused by genetic changes and oxidative damage linked to aging. Plant-based natural products are thought to be a significant source of new bioactive substances that can prevent neurodegeneration. Here, using C. elegans models of MJD and PD,

we examined the neuroprotective potential of an ethanolic extract of rapeseed pomace (RSP), a by-product of the manufacturing of rapeseed (canola) oil. In one toxin-induced and two genetic models of Parkinson's disease, the extract, which contains sinapine and other phenolics, inhibited dopaminergic neuron degeneration and restored motor function in mutant ataxin-3 (ATXN3) rats (MJD). Glutathione S-transferase (GST-4) and other phase II detoxification enzymes were shown to be activated with supplementation with RSP extract by whole-organism sensors of antioxidant and xenobiotic response activation.

- Additionally, gst-4 is necessary for the therapeutic impact of RSP extract in the two disease models, according to in vivo pharmacogenetic investigations. The findings validate the value of looking for bioactive chemicals in new sources, including as food and agricultural waste/by-products like RSP, and imply that GST-4-mediated antioxidant pathways may make interesting therapeutic co-targets for neurodegenerative disorders.
- *Stress resistance pathways*: Overexpression of *skn-1* (analogous to Nrf2) and early-life fasting significantly improve resilience.
- The main problem with metabolism is the harmful propensity to produce oxidative stress. Although the exact method and effects of this are yet unknown, the oxidative stress response transcription factor, SKN-1/NRF2, is able to detect and react in variations of metabolic state. In C. elegans, we conducted a genetic screen that focused on amino acid catabolism and found several metabolic pathways that regulate SKN-1 function. We discovered that a distinct subset of SKN-1-regulated genes was activated with knockdown of the conserved amidohydrolase T12A2.1/amdh-1. Remarkably, this transcriptional program requires ELT-3, NHR-49, and MDT-15 but is not dependent on the traditional P38-MAPK signaling components. The upstream histidine catabolism genes HALY-1 and Y51H4A.7/UROC-1 are required for this activation of SKN-1, which can also be brought on by the buildup of the catabolite 4-imidazolone-5-propanoate. Oxidative stress rises when SKN-1 is activated.
- Activating SKN-1 reduces survivability to heat stress but increases resistance to oxidative stress. Our findings collectively imply that SKN-1 influences physiology and stress tolerance by acting downstream of important catabolic pathways.

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