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REVIEW

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A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson's disease with insights into screening models

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Abstract

Background Parkinson's disease is a neurodegenerative disorder of the central nervous system that is one of the mental disorders that cause tremors, rigidity, and bradykinesia. Many factors determine the development of disease. A comprehensive physical examination and medical history of the patient should be part of the differential diagnosis for Parkinson's disease (PD). According to epidemiology, Parkinson's disease majorly affects elderly persons and frequency of affecting men is more as compared to women where the worldwide burden of Parkinson's disease (PD) increased more than twice in the past 20 years.

Main body of the abstract In this review paper, we discussed screening models, recent clinical trials, cellular and molecular pathways, and genetic variants (mutations) responsible for induction of Parkinson's disease. The paper also aims to study the pathophysiology, epidemiology, general mechanism of action, risk factors, neurotoxin models, cellular and molecular pathway, clinical trials genetic variants of Parkinson's disease. These models correspond to our research into the pathogenesis of Parkinson's disease. The collected data for the review have been obtained by studying the combination of research and review papers from different databases such as PubMed, Elsevier, Web of Science, Medline, Science Direct, Medica Database, Elton B. Stephens Company (EBSCO), and Google open-access publications from the years 2017–2023, using search keywords such as "Cellular and molecular pathways, Clinical trials, Genetic mutation, Genetic models, Neurotoxin, Parkinson's disease, Pathophysiology."

Short Conclusion Microglia and astrocytes can cause neuroinflammation, which can speed the course of pathogenic damage to substantia nigra (SN). The mechanism of Parkinson's disease (PD) that causes tremors, rigidity, and bradykinesia is a decrease in striatal dopamine. Genes prominently CYP1A2 (Cytochrome P450 A2), *GRIN2A*, and *SNCA* are Parkinson's disease (PD) hazard factor modifiers. The most well-known neurotoxin is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which destroys dopaminergic neurons, resulting in the development of Parkinson's disease (PD). Dopamine auto-oxidation in dopaminergic (DA) neurons is a significant source of reactive oxygen species (ROS) that causes neuronal oxidative stress. Most common genes which when affected by mutation lead to development and progression of Parkinson's disease (PD) are *LRRK2*, *SNCA* (alpha-synuclein protein), *DJ-1*, *PRKN* (Parkin protein), *PINK1*, *GBA1*, and *VPS35*. The commonly used neurotoxin models for inducing Parkinson's disease are

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6-hydroxydopamine (6-OHDA), rotenone, paraquat, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and genetic models. Anti-apoptic drugs, gene mutation therapy, cell-based therapy, and plasma therapy were all discontinued due to insufficient efficacy. Because it is unclear how aging affects these molecular pathways and cellular functions, future research into these pathways and their interactions with one another in healthy and diseased states is essential to creating disease-specific therapeutics.

Keywords Cellular and molecular pathways, Clinical trials, Genetic mutation, Genetic models, Neurotoxin, Pathophysiology, Parkinson's disease

Background

A neurodegenerative condition known as Parkinson's disease (PD) causes tremors, stiffness, and lack of motion. As the patient becomes older, molecular changes in the substantia nigra (SN) exhibit signs of increasing neuronal loss. Particularly in the late stage of PD, non-motor symptoms are very rare, such as confusion and dysautonomia. Some individuals utilize time as a precise scientific diagnostic and can get distinctive pathologic substrates underlying the condition. Some people will reserve the word for people who suffer from idiopathic Parkinsonism brought on by Lewy body (LB) framework inclusion in SN and cells from other parts of the brain. The diagnosis of PD responds to dopaminergic medication because decreases in dopamine levels and LB are present within the remaining neurons. Those suffering with the typical fundamental signs have an incredible response to levodopa for the clinical diagnosis of PD. However, there are different types of PD in the early stage of the disease. Motor signs are challenging. There is a 24% error rate in clinical and pathological series. The difficulties in detecting this PD in its initial stages are highlighted by two studies. Researchers found that the first clinical diagnosis was appropriate in 65% of patients within 5 years of the disease's development in a prospective clinical and pathological study. Like this, 8–9% of 800 individuals with mild early-onset PD were later found to have an alternate diagnosis based on multidimensional, clinical diagnostic criteria in the tocopherol potent antioxidant treatment for PD analysis (Tolosa et al. 2021). The UK PD brain bank criteria are the standard clinical criteria that will increase the specificity greatly of a clinical diagnosis of the disease. However, up to 10% of people who are diagnosed with the disease during their lifetime may still require categorization at the time of death (Sonustun et al. 2022).

Population-dependent research has found that about 20% of PD patients who have already received treatment have not yet been diagnosed with the condition, while about 15% of patients diagnosed with PD within a community don't know the criteria which will be strong for a diagnosis for the disease (Bai et al. 2021 May). The most frequent misdiagnosis in clinical morphological research concerns different types of degenerative Parkinsonism, such as multisystem atrophy or degeneration, degenerative supranuclear palsy. Recent studies in clinical PD have shown that extensive tremors, (visual) hallucinations, and cognitive fluctuations are among the other common features to distinguish between dementia and PD with LB (Perren et al. 2020).

Here, we critically evaluate the capability of further investigation for the diagnosis and therapy for patient's with PD by reviewing published data on the clinical differential diagnosis for different types of Parkinsonism. Further, craniocerebral trauma and exposure to pesticide and fungicides, which include paraquat and rotenone, as well as imperative frightening device infection seem to be related to the pathogenic nature of PD (Senturk 2020).

However, we have recognized that nearly 10% of genetic cases lead to the development of PD. We have also discussed some of the more common genetic PD rodent models in this paper. Since numerous scientists thought herbicides and pesticides could increase the symptoms of PD, lots of research was conducted to evaluate several elements of paraquat and rotenone in animal models (Liu et al. 2020). Levodopa is the gold-standard medication for treating PD. It is a precursor for dopamine that can cross the blood–brain barrier (BBB). There are several medications that are frequently used in combination with L-dopa, and they are classified based on how they work to increase dopamine production; these medications include monoamine oxidase-B (MAO-B), catechol-O-methyl transferase (COMT) inhibitors as well as dopaminergic agonists, such as amantadine (Koga et al. 2021). The motor symptoms of PD can be recovered through pharmacological treatment. However, in addition to several motor control elements being resistant to pharmacological treatment, the effectiveness of dopaminergic medicines diminishes with time (Mylius et al. 2021). Moreover, current therapies only work to relieve symptoms and cannot prevent the further development of disease (Pereira et al. 2019).

Main text

In recent years, neurotrophic element therapy and cellular transplantation have become innovative therapies for those suffering from PD. However, the common of these methods involves extremely invasive localization surgery, which has risks. Neuropharmacological remedies and workout are complementary, and it generates more interest as a PD method of treatment. Ultimately, a slew of large-scale epidemiological research indicated that exercise is good for PD. Lau et al. revealed that workout might reduce chances of developing neurological impairments in PD (Feng et al. 2020). Exercise can improve motor and nonmotor signs of individuals with PD as a supplementary and alternative therapy. Different types of workout training have been included in scientific research, including gait training, cardio exercise, complementary exercise, innovative resistance training, and balance training. This might slow the disease's course and enhance its quality of life, helping a growing number of PD patients (Silva et al. 2021).

Materials and methods

In this paper, we have studied recent research on PD, neurotoxicity-induced models, techniques for the induction of disease, molecular pathways, therapeutic clinical trials, genetic mutation for PD. We thoroughly used search engines like PubMed, Elsevier, Web Science, Google Scholar, Science Direct, Medline Plus, Google Open Access, Europe PMC, Hub Med, Scopus, Semantic Scholar, Shodhaganga, Science Open, and ScienceDirect. Keywords search during the review were "Parkinson's disease, Neurotoxicity models, Pathophysiology in PD, Clinical trials in PD, Genetic mutation in PD, Cellular and molecular pathways in PD, Neurodegenerative disease, Epidemiology of PD, Central nervous system, Oxidative stress in PD, Diagnosis of PD." In addition, articles were also obtained from authentic online websites and official magazines. The review contained information from published sources on PD and its models.

Data abstraction and analysis

Literature research was made on database abstractions like PubMed and Medline Plus by using keywords like "Cellular and molecular pathways, Clinical trials, Neurotoxin and genetic models, PD, Pathophysiology." We have attempted to review the published research and reviews on PD, including its pathophysiology, epidemiology, risk factors, mechanism of action, models observed, and cellular and molecular pathways, genetic mutation. This paper also focuses on the research conducted from 2017 to 2023 on patients suffering from PD.

Epidemiology

Since the early 1800s, PD has become widely recognized and, when the disease is reported, physicians gave PD its name (Skidmore et al. 2022). Sometimes PD, known as "paralysis agitans," is rare in young adults, particularly individuals under 40 (Xu et al. 2020 Feb). Around 60,000 new instances of PD are reported each year, with an estimated one million Americans suffering from the condition. According to estimates, 7–10 million people worldwide have PD, which affects men 1.5 times more frequently than women. In accordance with a population-based analysis of Medicare users, those 65 and older had an average frequency of PD of 1.6% (Draoui et al. 2020).

Pathophysiology of Parkinson's disease and role of Lewy bodies in dopaminergic neurons

Pathophysiology

Lewy body (LB), a pathologic characteristic of dopaminergic neurons, is improved in PD, which is described as pathophysiological as degradation or dopaminergic neuronal loss located in the SN. Several years may pass before there is any sign of a pathologic change. This lack of dopamine-producing neurons impairs motor function significantly. Aggregation of LB contains a wide range of proteins including ubiquitin alpha-synuclein and ubiquitin, which impair optimal neuron function. Aging and environmental stress, according to new guidelines, both contribute to neuropathology. Environmental contamination (e.g., pesticides), the strain of the growing-old process, or misuse of pills causes a low-stage illness inside the mind ("inflammation"), persistent. Cellular aging in neurons in the brain over time is caused by this inflammatory process (Crowley et al. 2019). Details about the pathophysiology of PD are shown in Fig. 1.

Degradation of neurons is triggered by gene mutations that encode for central nervous system (CNS) proteins. In particular, *SNCA* (alpha-synuclein protein) turns self-aggregates and abnormal. This inflexible alpha-synuclein is a crucial element of LB, the cellular accumulation that characterizes PD (Sun and Armstrong 2021). Atypical protein-disrupting systems, like the ubiquitin–proteasome device, are also made more difficult. PD can result from a variety of dysfunctional processes, such as mitochondrial disease or unique oxidative stress caused by reactive oxygen species (ROS), which results in neuronal degeneration (Roeh et al. 2019).

Role of substantia nigra, dopaminergic transmission, and D1, D2 receptors in Parkinson's disease

A dopaminergic imbalance causes the novel neurodegenerative disease PD to cause mobility deficits (inhibitory D2 and excitatory D1 receptors). However, K + channels

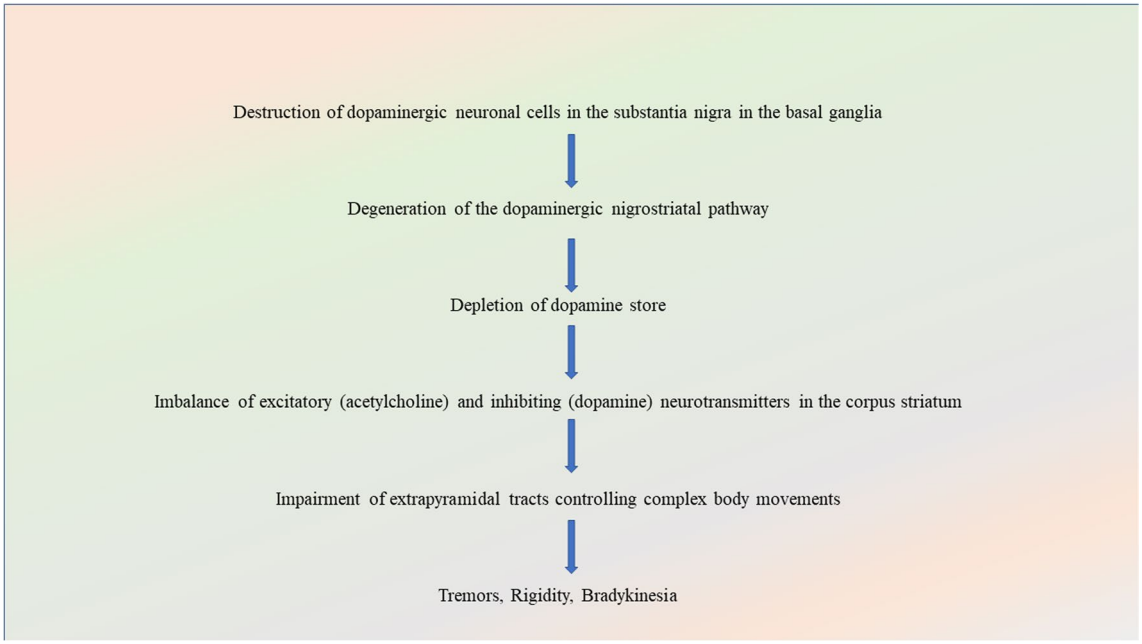

Fig. 1 Pathophysiology PD. (Parkinson's disease is mainly characterized by the neuronal loss within the SN of the brain, which causes motor and non-motor signs such as tremors, bradykinesia, and stiffness.) (Feng et al. 2020)

enhance these. Dopamine: In PD, the substantia nigra degenerates, destroying the nigrostriatal pathway. The neurochemical basis of PD is the ensuing reduction in striatal dopamine. The impairment in striatal dopaminergic transmission seems to depend on and be sufficient for the emergence of PD motor symptoms. Dopamine is the precursor of levodopa. Individual dopamine does not cross the BBB. Levodopa is actively transported into the brain, where levodopa is converted into dopamine in the brain. In the periphery of the brain, medication decarboxylated dopamine. Because of that, it requires a large dose of levodopa (Ishiguro et al. 2021). In the peripheral tissues and gastrointestinal tract (GIT), the metabolism of levodopa decreases and enhances with carbidopa and increases the bioavailability of levodopa in the CNS. Because of that, levodopa administered with carbidopa should enhance the effect of levodopa on the CNS (Jaiswal et al. 2021).

Clinical features in the development and progression of Parkinson's disease

Since James PD in the nineteenth century, the important component of the disease has been motor symptoms of PD, which was later improved by Jean-Martin Charcot (Flynn et al. 2023). These PD signs encompass molecular stress, bradykinesia, rest tremor, gait, and postural impairment. The patients are categorized as a subtype of disease which, in having patients with PD motor actions, are heterogeneous (Marchetti 2020). The average time between the beginning of Parkinsonian and Parkinsonian motor signs occurrence is 12–14 years. It is an example of how that premature stage can be increased (Greener 2021). The pathology of PD is thought to be ongoing throughout the motor period, including dopaminergic neurons as well as the CNS and peripheral system areas in the substantia nigra paras compacta (SNpc) (Wuthrich and Rapee 2019).

The development of PD is described by impairment of motor function, which can primarily be treated with symptomatic treatment options. However, headaches associated with prolonged durations of symptomatic therapy, like dyskinesia, fluctuations, psychosis, motor and non-motor symptoms, dyskinesia, and psychosis, may arise as the disease progresses (Islam et al. 2021). Treatment-resist motor and non-motor symptoms in the last stage of PD are differentiated, with axial motor signs including movement problems, falls, gait freezing, speech difficulties, and swallowing. In the last stage of PD, non-motor signs such as symptomatic postural hypotension are frequent, constipation needing regular laxatives and urine incontinence (Neag et al. 2020). After 20 years with the disease, 83% of PD patients have dementia. These levodopa-resistant late-stage PD signs and symptoms significantly increase impairment and are reliable indicators of death and the necessity for hospitalization (Bjørklund et al. 2019).

Role of environmental, genetic, and epigenetic factors in causing Parkinson's disease

Age is the potential risk of PD. This pattern has significant implications for public health: By 2030, the number of patients of PD is predicted to rise by more than 50% because of an aging population, as well as a rise in life expectancy globally (Masato et al. 2021). Environmental exposures are also risk factors for PD. These factors have been demonstrated that significantly alter the risk of PD in a meta-analysis of individual capability threat elements (Borghammer et al. 2022). The hypothesis that smoking may provide protection against the disease has arisen because of the factors that lower the risk of PD with smoking. The results of extensive case–control research and modern research, however, indicated that PD patients can avoid smoking more rapidly and that the correlations with smoking may be brought on by a reduced reactivity to nicotine during the prodromal stage of PD. The consequences of at least five potential population-based studies showed a negative correlation between blood urate attention and PD risk, a finding that is possibly more resolute in men than in women (Gao et al. 2020). Heating and manganese exposures were not related to an elevated risk of PD, according to a comparable meta-analysis. Single epidemiologic results show that exposure to solvents, especially trichloroethylene, and the use of antipsychotics by elderly people, particularly benzamides, phenothiazines, risperidone, or haloperidol, would likely increase the risk of PD (Smeyne et al. 2021).

Although there are multiple factors that might increase the possibility of developing PD, their complex interactions are increasing to be recognized. For instance, circumstantial findings of this study showed that exposure to brain trauma and Paraquat both increased the chances of PD (Xicoy et al. 2021). Further research has found genetic factors on environmental risk factors. For example, single-nucleotide polymorphisms in CYP1A2, that encode the isoform of Cytochrome P450 that causes metabolism of *GRIN2A*, that codes for a component of the N-methyl-D-aspartate (NMDA) receptor, affect the threat caused by drinking coffee. Moreover, the shape of a polymorphism blended with a repeat dinucleotide within the gene promoter of *SNCA* (alpha-synuclein protein) affects the risk of PD correlated with head trauma (Rocha et al. 2022). Environmental, genetic, epigenetic, and other risk factors for PD are shown in Fig. 2.

Screening rodent models for induction of Parkinson's disease

Many neurotoxin animal models are currently used in rodents and mice, such as 6-Hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), but pesticides are primarily used. They have increased some events and symptoms that may

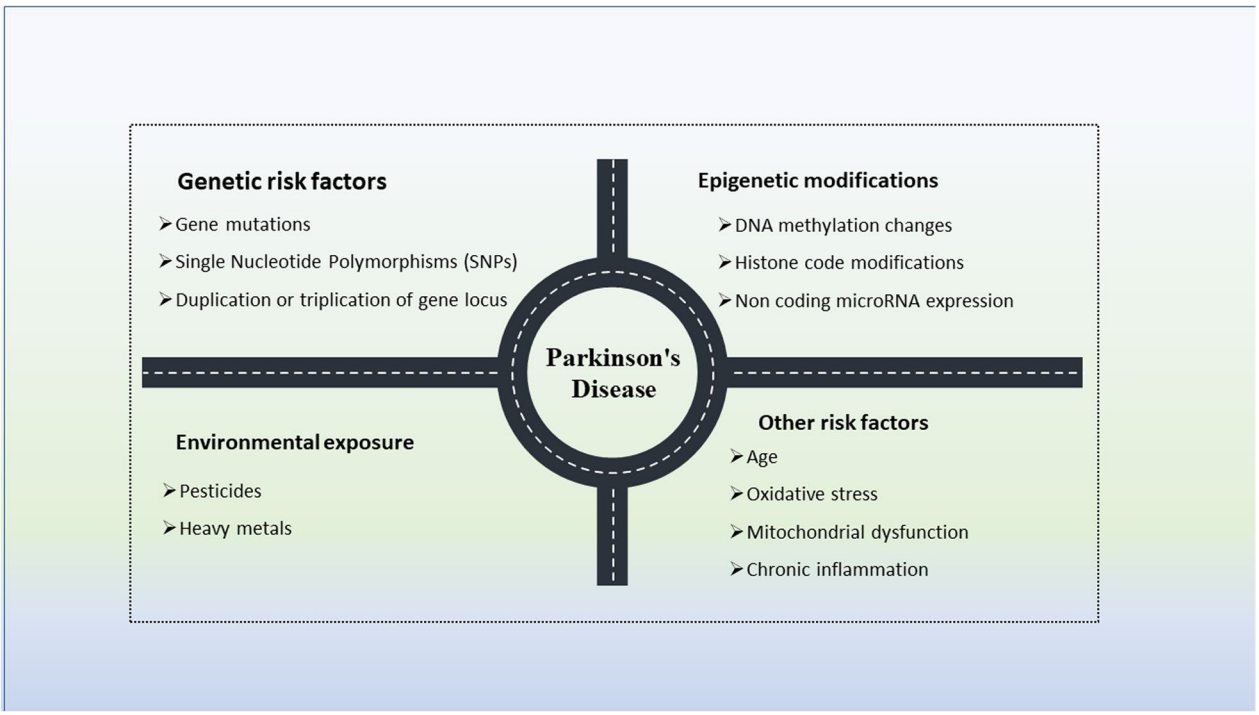

Fig. 2 Risk factors for PD (Parkinson's disease is a central nervous system disorder that affects the movement, often including tremors, bradykinesia, and rigidity.) (Adams et al. 2023)

result in PD by inducing neurotoxicity. These toxin-based PD models have some advantages and disadvantages (Tran et al. 2021). Table 1 shows the required dose and route of administration of neurotoxin.

Conventional 6-hydroxydopamine model in induction of Parkinson's disease

6-Hydroxydopamine (6-OHDA) is a conventional and classical animal model for PD. Inject 6- 6-OHDA directly into the SNpc of the brain because this compound does not cross the BBB (Kayis et al. 2023). In the region of the mouse or rat brain, it has approximately 60% of the tyrosine hydroxylase-containing neurons present, with the lack of striatum containing the tyrosine hydroxylase-positive terminals. It is widely believed and has been tested that the tyrosine hydroxylase-advantageous terminals were dead before the tyrosine hydroxylase-advantageous neuronal cells within the SNpc, which reflect PD symptoms. Hence, most researchers have injected this 6-OHDA immediately within the SN to observe retrograde of degeneration (Belvisi et al. 2022). 6-OHDA enters the cytosol via the dopaminergic neuron transporter, where it may self-oxidize and induce oxidative pressure inside the cell. It has been shown the 6-OHDA and interaction, although neither leading to nor producing clumps or LB clusters like those found in PD (Fabbri et al. 2019). The bilateral injection of 6-OHDA into the SNpc causes not only the most severe aphasia, seizures; moreover, it is more common for people to turn to apomorphine or amphetamine after unilateral 6-OHDA can measure the severity of the precipitated striatal loss or SNpc, and this behavior to enhance the efficacy of treatments for PD (Kambey et al. 2021). 6-OHDA is produced in the metabolism of endogenous dopamine; hence, 6-OHDA is a neurotoxin compound; it causes lesions within the dopaminergic neurons which makes it potential for the endogenous toxin in the initiation of the PD neurodegeneration (Park et al. 2019). 6-OHDA induced neurotoxicity produces symptoms of PD, as shown in Fig. 3.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-based model for inducing oxidative stress

Originally, MPTP became an unintentional visitor in the catalytic process, and while it may cause some concern in certain areas, it turned into ROS. Oxidative pressure, energy failure, infection, and energy failure have been are shown symptoms of PD (Dumurgier and Tzourio 2020). MPTP is the popular animal model of PD. MPTP has induced neurotoxicity in PD and shows all of the symptoms of PD in guinea pigs, monkeys, and other animal models, as well as a specific range of signs and symptoms observed in mice models, but there is no longer in rodents because rats were resistant to the MPTP (Neshige et al. 2021).

Role of Rotenone in Parkinson's disease induction by inducing the synthesis of Lewy bodies, inflammation, and alpha-synuclein aggregation

Rotenone is an insecticide as well as herbicide; as compared to paraquat it is a pure herbicide. It easily crosses BBB as well as is also highly lipophilic. Rotenone induces all the symptoms of PD, including behavioral changes, inflammation, complex-I blockage, α-synuclein aggregation, development of LB, digestive issues, and oxidative stress (Jia et al. 2020). This model's apparent strength is that it has been shown to produce α-synuclein aggregation and LB formation. While using rotenone as a PD model enhances dopaminergic neuron (DA) oxidation, there is little proof that it leads to

Table 1 Drug-induced neurotoxicity in Parkinson's disease (PD) (SNC: substantia nigra compacta; MFB: medial forebrain bundle; IC: intracerebral injection; IP: intraperitoneal injection; SC: subcutaneous injection) (Vaccari et al. 2019)

Sr. no	Neurotoxin	Dose	Animal species	Route of administration
1	6-OHDA	0.032 mg/kg	Rat or mice	I.C. into SNC
		0.05 mg/kg	Rat	I.C. into MFB
		0.02–0.16 mg/kg	Mice	I.C. into MFB
		0.05–0.32 mg/kg	Rat or mice	I.C. into striatum
2	MPTP	33 nmol/24 h	Rat	I.C. into SNC/striatum
		15–20 mg/kg	Mice	I.P
		46 mg/kg	Mice	I.P. infusion
		23 mg/kg	Mice	S.C
3	Paraquat	10 mg/kg	Mice	Oral
		10–15 mg/kg	Rat or mice	I.P
4	Rotenone	2–3 mg/kg	Rat	S.C. infusion
		5.0 µg	Rat	I.C
		2.75–3.0 mg/kg	Rat	I.P
		50 mg/kg	Mice	oral

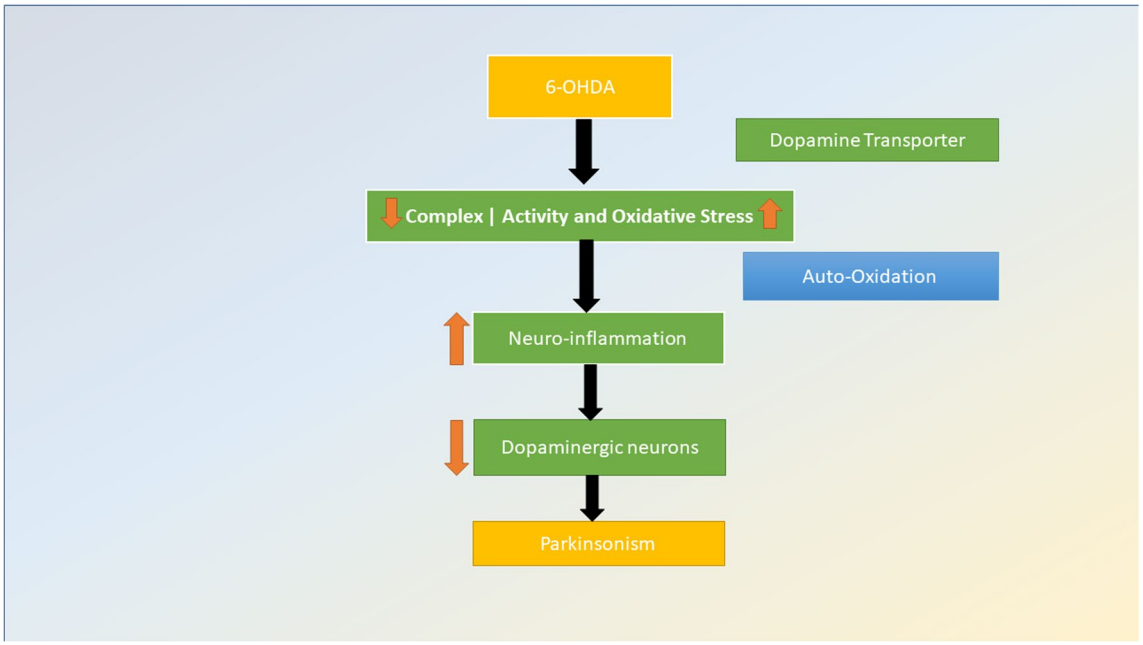

Fig. 3 6-OHDA induced PD in a specific way. It has been suggested that oxidative stress causes neuroinflammation (Luca et al. 2020)

degradation of the dopaminergic pathway (Yin et al. 2021). The mechanism of rotenone as a neurotoxicity inducer in PD is shown in Fig. 4.

Methamphetamine in substantia nigra paras compacta neurodegeneration

Methamphetamine is a derivative of amphetamine; some effects such as induced neurotoxic effects on the CNS lead to some structural changes. Numerous

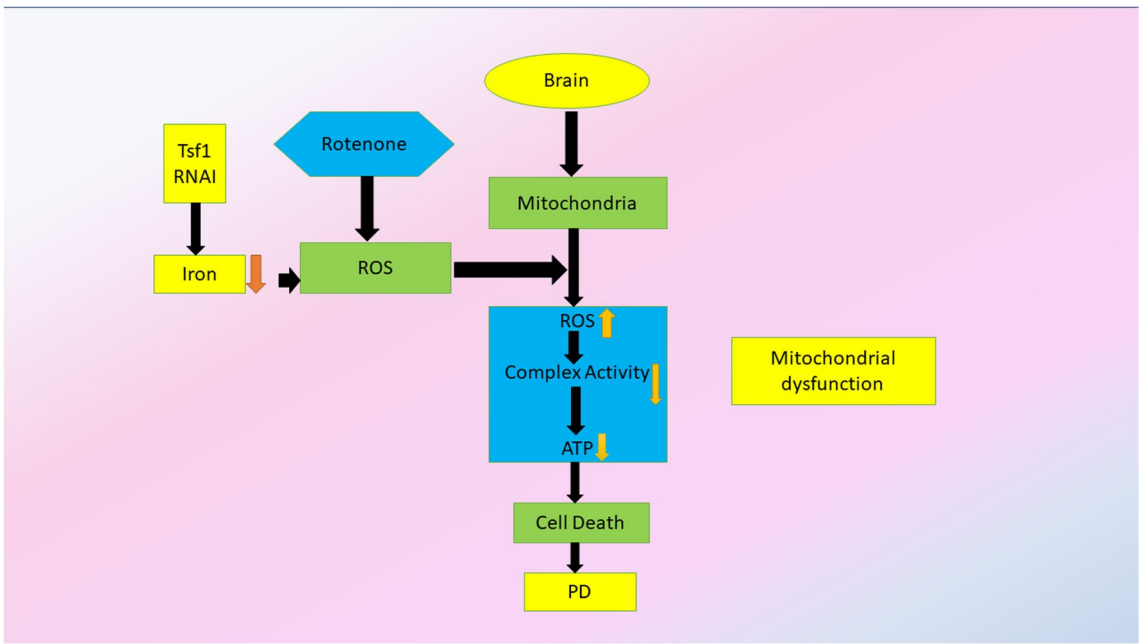

Fig. 4 Rotenone-induced ROS generation and cell death are depicted schematically as the causes of PD (Adamson et al. 2022)

research studies have shown that selective damage to serotonergic nerves or dopaminergic nerve endings leads to neuronal loss in rodents after hypothermia (Guo et al. 2022) though it was not a universally accepted hypothesis. These genes (*LRRK2* and *SNCA*, autosomal-dominant PD; *PRKN, PINK1, DJ-1*, and autosomal–recessive PD) are potential and prominent therapeutic targets in animal models. We first need to understand how these animal models work to that extent. For example, neither of the above mutations are knocked out or overexpressed in humans (Hamed et al. 2019). In accordance with this approach, a protein's degree of expression might contain the key to understanding the nature of that protein. Research has demonstrated that wiping out alpha-synuclein has no effect on DA retention or development (Sitzia 2022).

Autosomal–recessive PD is caused by several mutations. These are *PINK1* (mitochondrial-localized enzyme and new kinase 1 that are stimulated by tensin isoforms), Parkin (20% of individuals with early-onset PD and about 50% of gene mutations of PD), and *DJ-1* (an oxidation–reduction reaction-sensitive antioxidant regulator and molecular stress). Rodent models of these genes do not show neurodegeneration. Recent reports show that exogenous Parkin depletion within adult mice is associated with the SNpc neurodegeneration. Therefore, the lack of neurotoxicity in rodents may be because rodents may have protective mechanisms that prevent the development of PD symptoms in these models (Palasz et al. 2019).

Pesticide paraquat and its damage to DNA

Epidemiological studies indicate that using pesticides increases the symptoms of PD, but since only 95 cases of PD have been associated with paraquat poisoning, this association may be very hypothetical in the case of paraquat (Agnihotri and Aruoma 2020). In agriculture, paraquat is frequently employed. Pesticide is used as a weed killer because paraquat causes damage to deoxyribonucleic acid (DNA), proteins, ribonucleic acid (RNA), and lipids through oxidative stress caused by redox reaction. This process also produces ROS, including the superoxide radical, hydrogen peroxide, and radical. Recent research on paraquat's effects on the nigrostriatal DA system is somewhat contradictory (Martínez-Chacón et al. 2021). Diagrammatic illustration mechanism of induction of neurotoxicity by paraquat in PD is shown in Fig. 5.

Mutation-based genetic models for inducing Parkinson's disease

The "new kids on the block" are certainly genetic models of PD. Even though PD was once thought to be a "sporadic" non-genetic condition, genetic alterations are uncommon and only account for roughly 10% of PD patients. Furthermore, *DJ-1*, alpha-synuclein, *LRRK2* autosomal-dominant PD and *PINK1*-recessive PD, are significant genes which undergo mutations to cause

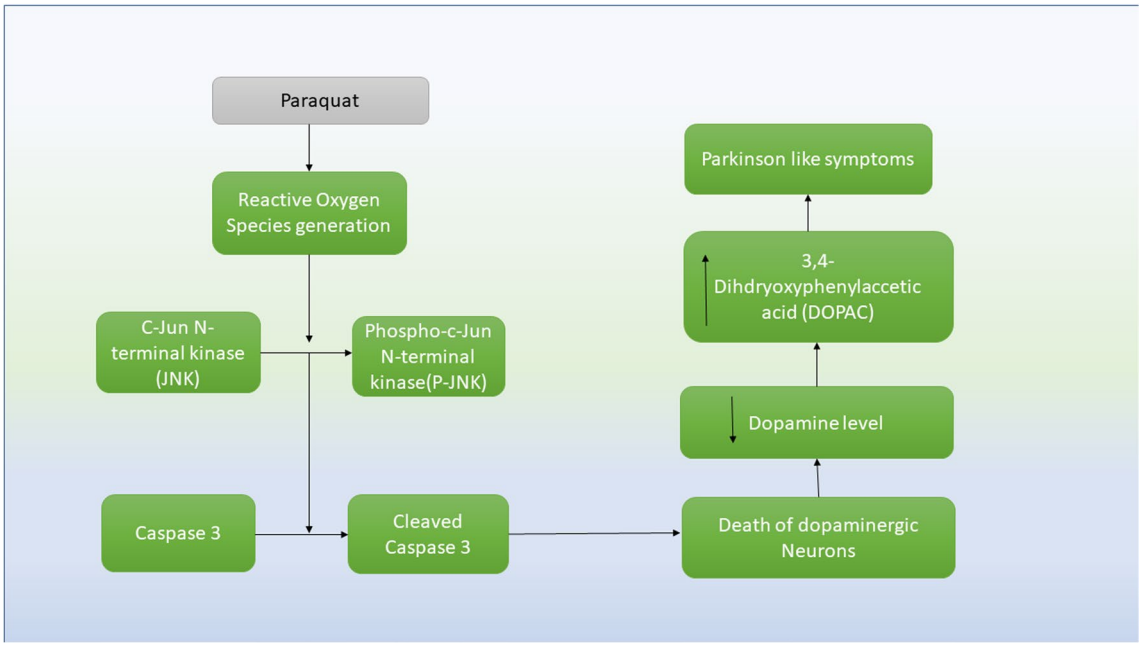

Fig. 5 Illustration of the paraquat-induced neurotoxicity, ROS production, and c-Jun N-terminal kinase (JNK) activation that led to the dopaminergic cells' neuronal loss and PD-like symptoms (Colle and Farina 2021)

PD thus are potential targets for therapy. The complexity of this PD is becoming more apparent, so we must first comprehend how these animal models function. For example, neither of the mentioned mutations above are completely absent or overexpressed within humans. However, model of PD in animals use overexpression and knockout techniques. The idea behind this is that understanding a protein's behavior may depend on how much of it is expressed. Consider alpha-synuclein as an example. Moreover, it was demonstrated that knocking down alpha-synuclein does not have an impact on dopaminergic neuron development or maintenance (Calabresi et al. 2023).

This suggests that the degradation of dopaminergic neurons found in PD is not likely to be caused by the loss of alpha-synuclein. The precise role of alpha-synuclein, however, is unknown; it is difficult to determine its relationship to PD. *LRRK2* is restricted to mucosal tissue, in contrast with the ubiquitous alpha-synuclein. Moreover, although *LRRK2* knockout mice have been shown to not affect the *LRRK2* animal model, it is not particularly useful in investigating DA nerve cell development and preservation. Melanogaster models have limited generalizability for the human state. Autosomal–recessive PD is caused by several mutations. These include *PRKN* (20% of instances of onset of PD and 50% cases of familial), *DJ-1* (a redox-sensitive regulator of antioxidants and molecular chaperone) and *PINK1* (phosphatase and tensin homolog-induced kinase 1; confined to the mitochondria). Animal models of these genes that are constitutively knocked out do not exhibit neurodegeneration. Meanwhile, a scientific study demonstrates that SNpc neurodegeneration is correlated with Parkin conditional deletion in adult mice (Aryal and Lee 2019).

Genetic studies on PD have shown a variety of monogenic variants of the disease and several genetic risk factors that raise the possibility of developing neuron degeneration (Tran et al. 2020). The most often advised method for people to diagnose the disease is molecular testing. Few genes that are significant in both the autosomal–recessive forms and autosomal dominant of PD have been reported in the last ten years (Jia et al. 2022). It has determined that mutations in the loci *PARK1* to *PARK13* (loci on 13 chromosomes) indicate linkage to PD by whole genome linkage screening to differentiate between chromosomal areas linked to the risk of PD or the period of PD onset (Selvaraj and Piramanayagam 2019).

Monogenic forms, which are pervasive but only make up around 30% of related cases, were brought on by a single mutation in a gene that was passed down either recessively or dominantly. Most of the gene mutations leading to increased ROS production, mitochondrial DNA damage (mtDNA damage), reduced mitochondrial membrane potential (MMP), decreased ATP levels, structural defects in the organelle, and mitochondrial network are related to mitochondrial dysfunction; these various phases of mitochondrial dysfunction have been responsible for of the development of PD (Liu et al. 2017). Parkinsonism is caused by the autosomal-dominant gene transformation of the *UCHL1*, *SNCA*, *LRRK2*, and *GIGYF2*, and mutations in the, *DJ-1*, *PRKN*, *PINK1*, *FBXO7*, *PLA2G6*, and *ATP13A2*, genes. **(**Table 2**)** About 27% of those with early-onset PD (EOPD) have a mutation in one of the three genes (*LRRK2*, *glucocerebrosidase* or *Parkin*)(Papagiannakis et al. 2018).

Cellular and molecular pathways involved in the initiation and progression of Parkinson's disease

Different genetic, epigenetic, environmental, molecular, cellular, and intracellular dysfunctional symptoms can be seen in this condition. The main molecule that makes up the LB at the molecular level is alpha-synuclein. Significant pathogenic correlation, pathogenesis of Ca^{2+}, is linked to an oxidation–reduction imbalance in cells and an increment in reactive oxygen species (ROS) generation. There are seven most common PD-related genes (*VPS35*, *DJ-1*, *GBA1*, *LRRK2*, *PINK1*, *PRKN* and *SNCA*). In the cerebral cortex of PD patients, various cellular and molecular biomarkers,

Table 2 Genes and susceptibility genes involved in Parkinson's disease (PD) (Chia et al. 2020)

Sr.no	Gene symbol	Locus name	Type of mutation	Protein product	Mode of inheritance
1	*PINK1*	*PARK6*	Missense, frameshift, splice site, point, truncating	PTEN-induced putative kinase 1	AR
2	*SNCA*	*PARK1*	Missense, point	Alpha-synuclein	AD
3	*PRKN*	*PARK2*	Missense, frameshift, splice site, point, nonsense	Parkin	AR
4	*ATP13A2*	*PARK9*	Frameshift	ATPase 13A2	AR
5	*DJ-1*	*PARK7*	Point, missense, frameshift, exon deletion, and slice site frameshift	Protein DJ-1	AR
6	*LRRK2*	*PARK8*	Missense	Leucin-rich protein kinase 2	AD

such as neuroinflammation, autophagy, and oxidative stress, were detected. Factors that cause oxidative stress promote alpha-synuclein aggregation. In the nigrostriatal neuronal cell, in which it initially aggregates alpha-synuclein deposited, it appears in the GIT or enteric nervous system (ENS), olfactory bulb, and the LB (Fraint et al. 2018).

The earliest symptoms of PD are mitochondrial dysfunction and mitophagy. Melanin-concentrating hormone is essential for ATP synthesis, but it also affects calcium storage, cellular metabolism, the generation of damage-associated molecular patterns, damaged associated molecular pathways (DAMPs), the balance of ROS, programmed cell death, inflammatory processes, and immunity to programmed cell death. The loss of dopamine pathways by i) loss of the dopaminergic neuronal cells currently available for synaptic transmission in the SNpc is neuropathological characteristics of PD. ii) Alpha-synuclein, LB, clumps containing neurofibrillary tangles that contain microfibrils are developing (Camargo et al. 2019). Lack of dopamine neurotransmitters in the SNpc disrupts the circuitry that controls posture and movement, resulting in symptoms consisting of relaxed shaking and sluggish movement. PD non-motor symptoms include difficulties with sleep, anxiety, memory, autonomic nervous system, and the senses (Zampese and Surmeier 2020).

Buildup of oxidative stress due of presence of reactive oxygen species and its effects on generation of Parkinson's disease

Reactive oxygen species in PD such as hydroxyl radical (OH•), superoxide anion (O_2), and hydrogen peroxide (H_2O_2) are synthesized because within the mitochondria there is physiological metabolism of molecular oxygen. In ETS (electron transport chain) the mitochondrial complexes I and III produce Superoxide anion which are very reactive and can easily cross the mitochondrial membrane where it is reduced to H_2O_2. Additionally, various nitric oxide synthases (NOS) create nitric oxide (NO), a transient reactive nitrogen species (RNS), which combines with thiols and reduced glutathione (GSH) to form disulfides, sulfenic, sulfonic, and s-nitrosothiols. Additionally, peroxynitrite (ONOO) can be created when oxygen (O_2) and nitric oxide (NO) are combined (Hollville et al. 2020) shown in Fig. 6. An increase in ROS production in PD has shown failure in mitochondrial complex I, according to studies utilizing the paraquat and MPTP-like toxins, which are known to cause PD-like symptoms including dopaminergic neuronal cells to die and protein clusters are produced. A complex I impairment can result in a decrease in energy production as well as an increase in the synthesis of free radicals (Mailloux 2020).

Although the specific causes of mitochondrial complex-I failure in PD are not fully recognized yet, it is

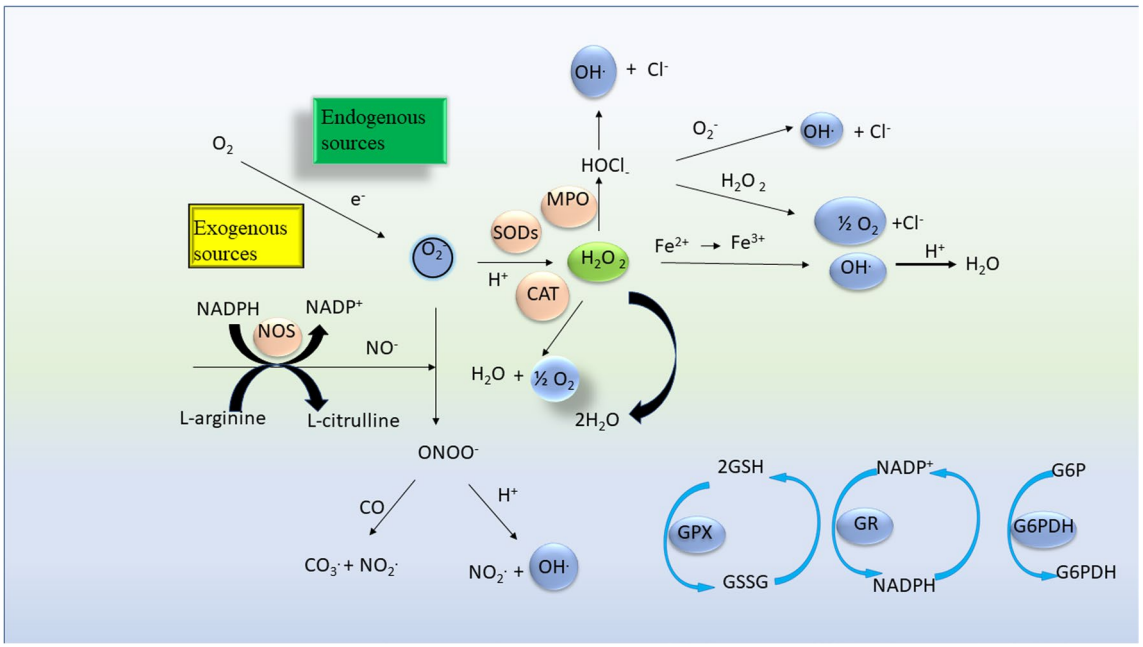

Fig. 6 Radical species development. ROS are produced by a variety of metabolic processes, including oxidative phosphorylation, superoxide anion (O_2 •), Singlet oxygen (O_2), hydrogen peroxide (H_2O_2), hydroxyl radical (OH•) nitric oxide (NO•) and mitochondrial-derived reactive oxygen species (mtROS), hydroxyl ion (OH-) (Trist et al. 2019)

reported that a GSH-to-oxidized glutathione (GSSG) ratio increases the formation of RNS as well as ROS species. However, the pathway by which the highest levels of GSSG might rise RNS as well as ROS generation was not discovered; it was demonstrated that glutathione redox state is necessary for the opening of the transition pore of mitochondrial permeability. For instance, GSSG causes the MPTP to open, which then triggers a Ca^{2+} basis reduction within the potential of the inner membrane of Wang and Kang (2020). The reduced glutathione/ oxidized glutathione ratio can increase the generation of ROS or RNS by preventing mitochondrial complex-I from functioning and lowering the potential of the mitochondria. The protein's sulfhydryl portion of the enzymes having thiol oxidation, which are involved in electron transport of mitochondria, is another way that low amounts of GSH may harm mitochondrial complex-I. In addition, high quantities of these reactive species can also damage crucial complex I residues and decrease the activity of the enzyme glutathione reductase, which is responsible for decreasing GSSG (Teleanu et al. 2022).

Recent clinical trials involved in evaluation of possible treatments for Parkinson's disease

Clinical studies closely monitor the evaluation of novel medications. The US Food and Drug Administration states that the objective of phase-I is dose as well as safety; about 70% of drugs and therapies advance to phase II. About 33% of medications transfer to phase III after completing phase II, which examines the efficacy as well as adverse effects. Phase III is used to monitor adverse effects and investigate their potency. The 'United States National Library of Medicine' established the 'web-based' registry "clinical trials. gov" for ease in availability of data and information related to the clinical trials, such as the methodology, study design, outcomes, anticipated finish dates, etc. Worldwide sponsors of trial update and maintain the data (Nakamura et al. 2021). Clinical trial endpoints are related to the subject of comparing the impact of research, and results may be obtained by a number of means, including behavioral tests, positron emission tomography, magnetic resonance imaging (MRI), biological biomarkers, or electrophysiological monitoring (Jiménez-Gómez et al. 2023; Choudhury et al. 2022). Each clinical trial is assessed and planned for the advancement to reduce the possibility of negative outcomes (Bouchez and Devin 2019). For comparison research in clinical trials, post-approval is necessary. This allows safety, tolerance, and better quality of life, to be taken into account when obtaining effective data from a broader patient group (Nunes and Laranjinha 2021). In clinical trials, primary endpoints are necessary and sufficient to determine a drug's or therapy's effectiveness. The primary endpoints serve as the foundation for secondary endpoints, which are sufficient for claiming the efficacy of clinical trial study, and the tertiary endpoints, which provide detailed information (Braidy et al. 2019). To investigate PD treatments, we have searched for "clinical trials.gov" clinical trial pipeline data. These clinical studies are shown below among those identified (Table 3).

Based on the recent study status, which indicates updated/ongoing or stopped as of 2023, we selected 10 registered intervention clinical trials in phases I, II, and III as novel PD medicines after reviewing the data gathered from "clinical trials.gov." The phase I/II or phase II/III trials in clinical trials.gov are regarded as being in phase I and II, respectively. The 10 trials, (41%) were in phase I and in phase II (53%), (6%) were in phase III in Fig. 7. Stem cells have shown the potential of providing a huge supply of dopaminergic neurons which could be beneficial in treatment. Stem cells have also shown differentiation into dopaminergic neurons which will benefit post their transplantation in models of PD (Asemi-Rad et al. 2022).

Neurological disorders have been popularly being treated using herbal and ayurvedic remedies since ages. Hence, it is crucial to isolate bioactive compounds to potentially alleviate these conditions (Staff et al. 2019; Saraswat et al. 2020a, 2020b). In our current research by our laboratory, we are focusing on herbal extracts and their bioactive active compounds for treating PD in animal models (Sachan et al. 2022).

Conclusions

Parkinson's disease is a progressive neurodegenerative disease condition that develops both motor and non-motor symptoms. The motor signs like tremors, resting, bradykinesia, and stiffness which have been determined to be striatal dopamine deficiency and nonmotor symptoms include disorders of sleep, sadness, and cognitive abnormalities. Unfortunately, there are no conclusive tests to support a Parkinson's disease diagnosis, but identifying conditions with symptoms like Parkinson's disease is a crucial first step in the diagnostic process.

In this paper, we reviewed recent researches and came to following conclusions. Improvement in both motor and non-motor symptoms for enhancing the lifestyle of patients is the main objective of the Parkinson's disease treatment.

In the pathophysiology, it was concluded that the slow degradation of dopaminergic neuronal cells in the brain's substantia nigra is Parkinson's disease main pathophysiological cause. There are many other risk factors associated with Parkinson's disease, including age-related, genetic, epigenetic, and environmental variables. Single-nucleotide polymorphism in *CYP1A2* (Cytochrome P450

Table 3 Small molecules being tested in phase I, II, or III clinical studies to treat PD. Information depends on clinical trials. gov (https://clinicaltrials.gov) trial statuses as of 2022 (ongoing, updated, or discontinued) (Masato et al. 2019; Millichap et al. 2021; 2021; Merkow et al. 2020; Merchant et al. 2019; Ivanova 2020; Mullin et al. 2020; Parker et al. 2020; Barker 2019; Ghosh et al. 2021)

Therapeutic strategy	Classification	Name of compound	PD subjects	Trial status	Reasons for discontinuation	Sponsor	Clinical trial numbers and references
Convalescing plasma therapy	Infusion of young plasma	Infusion of young plasma	Moderate stage of PD	Phase I	–	Stanford University	NCT02968433 (Trist et al. 2019)
Cell-based therapy	Injection of cultured human retinal pigment epithelial cells within both hemispheres	Spheramine/ BAY86-5280	Advanced stage of PD	Phase II discontinued	The trial was completed, and only the follow-up phase was discontinued after 12 years	Bayer	NCT00206687 (Nakamura et al. 2021)
Gene therapy	Small molecular glucocerebrosidase (GBA) gene mutating therapy	GZ/SAR402671	Early stage of PD	Phase II discontinued	Terminated due to not meeting the primary and secondary endpoints	Genzyme	NCT02906020 (Jiménez-Gómez et al. 2023)
Serotonin receptors agonists or antagonists	Small molecular selective 5-HT1A agonist and D2 antagonist	Sarizotan	Idiopathic PD	Phase III	–	EMD Serono	NCT00105508 (Choudhury et al. 2022)
Anti-apoptotic drugs	Small molecular synthetic tetracycline derivative	Minocycline	Early stage untreated	PD Phase II	–	University of Rochester	NCT00063193 (Bouchez and Devin 2019)
Kinase inhibitor	Small molecular Semisynthetic inhibitor of the mixed lineage kinase family	CEP-1347 (KT7515)]	Early stage of PD	PD phase II/III discontinued	Terminated due to insufficient efficacy	Cephalon	NCT00040404 (Nunes and Laranjinha 2021)
Gene therapy	Surgical infusion of AAV-GAD into the subthalamic nucleus	Glutamic acid decarboxylase (GAD) gene therapy	Advanced stage of PD	Phase-I	–	Neurologix, Inc	NCT00195143(Braidy et al. 2019)
Cell-based therapy	Embryonic dopamine cell implant	Embryonic dopamine cell implant surgery	Idiopathic PD	Phase-III	–	University of Colorado, Denver	NCT00038116(Masato et al. 2019)
Dopamine receptor agonists	Small molecular dopamine D_1 partial agonist	PF-06669571	Idiopathic PD	Phase-I	–	Pfizer	NCT02565628(Millichap et al. 2021)
Gene therapy	AAV2-neurturin gene therapy	CERE-120	Idiopathic PD	Phase-II	–	Sangamo Therapeutics (Ceregene	NCT00400634(Clinical Research. 2021)

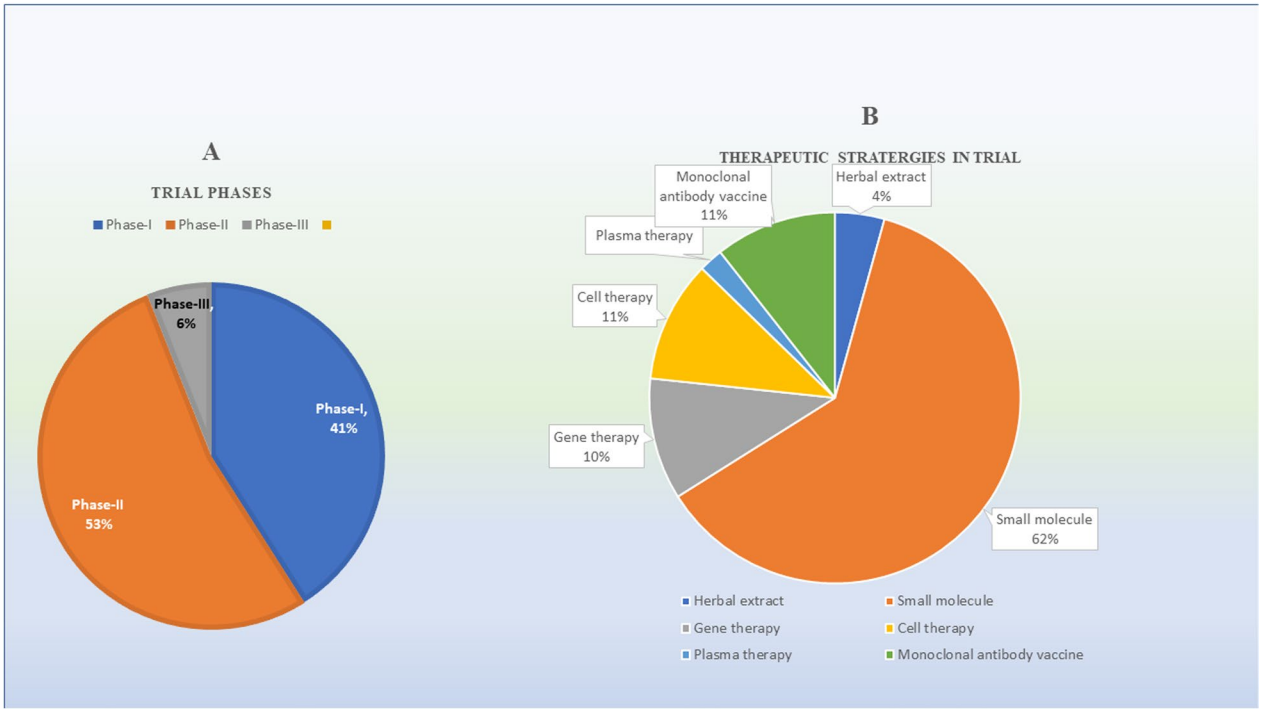

Fig. 7 Clinical trial phases and treatment plans for treating PD. The relative contribution of phase I, phase II, and phase III trials to the total is depicted in (**A**) using a pie chart. In Clinical trials. gov, the phase I or phase II trials, respectively, are displayed. **B** A pie chart showing the percentages of every therapeutic approach to all the clinical trials for PD (Masato et al. 2019; Millichap et al. 2021; Clinical Research 2021; Merkow et al. 2020; Merchant et al. 2019; Ivanova 2020; Mullin et al. 2020; Parker et al. 2020; Barker 2019; Ghosh et al. 2021; Asemi-Rad et al. 2022; Desai et al. 2021; Bryson 2020)

A2) or *GRIN2A* strikes the major threat for Parkinson's disease which is associated with coffee consumption and falls into the category of genetic modifiers for the environmental risks.

Parkinson's disease has a significant mortality rate and is the widespread neurodegenerative disease. Induction of the disease by various models has been successfully studied for understanding the genesis, propagation and treatment. Hence, substances like 6-hydroxydopamine, paraquat, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone, and methamphetamine are successfully used for inducing neurotoxicity to develop signs and symptoms like Parkinson's disease as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine targets mitochondrial cells and serves as an excellent model for how aberrant mitochondrial function can result in symptoms like those of Parkinson's disease. Rotenone impairs motor function, depletes catecholamines, destroys nigral dopamine, and develops Lewy bodies. Among the neurotoxin models discussed in this review paper, pesticides like parquet and rotenone are commercially available and exhibit many of the symptoms of Parkinson's disease, including motor impairment, a reduction in Lewy bodies, and the destruction of dopaminergic neurons.

Several geographically specific cellular and molecular mechanisms are actively involved in the development of Parkinson's disease. In comparison with previous clinical trials for the treatment of Parkinson's disease, small molecule such as alpha-synuclein aggregation therapy, and monoclonal antibody gene therapy, may show promise in the future. Dopamine auto-oxidation in dopaminergic neurons is a significant source of reactive oxygen species that causes neuronal oxidative stress. *LRRK2*, *SNCA* (alpha-synuclein protein), *DJ-1*, *PRKN* (Parkin protein), *PINK1*, *GBA1*, and *VPS35* are the seven most common Parkinson's disease-related genes which when affected by mutations leads to development and progression of disease.

According to our opinion, the purpose of clinical studies should be to postpone motor difficulties before they manifest ever lasting effects. Finding new multitarget medications or therapies without side effects is becoming more difficult, whereas the rate of Parkinson's disease occurrence globally is rising quickly. Future investigations

of these molecular pathways will be essential for designing disease-specific therapeutics.

Abbreviations

BBB	Blood–brain barrier
CMP	Cellular and molecular pathway
CNS	Central nervous system
COMT	Catechol-o-methyltransferase
CYP1A2	Cytochrome P450A2
DA	Dopamine
DAMP	Damaged associated molecular pathway
ENS	Enteric nervous system
GAD	Glutamic acid decarboxylase
GBA	Glucocerebrosidase
GRIN2A	*Glutamate ionotropic receptor NMDA type subunit 2A*
GSSG	Oxidized glutathione
H_2O_2	Hydrogen peroxide
IC	Intracerebral route
IP	Intraperitoneal route
JNK	C-Jun N-terminal kinase
LB	Lewy body
L-DOPA	Levodopa
LRRK2	Leucine-rich repeat kinase
MAO-B	Monoamine oxidase-B
MOA	Mechanism of action
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADH	Nicotinamide adenine dinucleotide hydrogen
NO	Nitric oxide
NOS	Nitric oxide synthase
O_2	Superoxide anion
6-OHDA	6-Hydroxydopamine
OH	Hydroxyl radical
PD	Parkinson's disease
PQ	Paraquat
ROS	Reactive oxygen species
SC	Subcutaneous route
SNpc	Substantia nigra paras compacta
TH	Tyrosine hydroxylase

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Author contributions
AS complied the paper, worked on English, grammar, and collected information regarding genetic studies. NS was responsible for filtering the useful information and mechanisms enlisted. NV contributed in the basic idea of paper and collected all data regarding recent clinical trials with their interpretations. AK was responsible for all high-quality diagrams, epidemiological data, and information regarding risk factors.

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Declarations

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No ethical approval or consent to participate was required for this manuscript.

Consent for publication
Yes, all the researches studied have been duly cited and we have all the open access rights to access these studies.

Competing interests
No, the authors declare that they have no competing interests.

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References

Adams C, Suescun J, Haque A, Block K, Chandra S, Ellmore TM, Schiess MC (2023) Updated Parkinson's disease motor subtypes classification and correlation to cerebrospinal homovanillic acid and 5-hydroxyindoleacetic acid levels. Clin Parkinsonism Related Disord 8:100187

Adamson A, Buck SA, Freyberg Z, De Miranda BR (2022) Sex differences in dopaminergic vulnerability to environmental toxicants—implications for Parkinson's disease. Curr Environ Health Rep 9(4):563–573

Agnihotri A, Aruoma OI (2020) Alzheimer's disease and Parkinson's disease: a nutritional toxicology perspective of the impact of oxidative stress, mitochondrial dysfunction, nutrigenomics and environmental chemicals. J Am Coll Nutr 39(1):16–27

Aryal B, Lee Y (2019) Disease model organism for Parkinson disease: drosophila melanogaster. BMB Rep 52(4):250

Asemi-Rad A, Moafi M, Aliaghaei A, Abbaszadeh HA, Abdollahifar MA, Ebrahimi MJ, Heidari MH, Sadeghi Y (2022) The effect of dopaminergic neuron transplantation and melatonin co-administration on oxidative stress-induced cell death in Parkinson's disease. Metab Brain Dis 37(8):2677–2685

Bai X, Liu X, Li X, Li W, Xie A (2021) Association between VPS13C rs2414739 polymorphism and Parkinson's disease risk: A meta-analysis. Neurosci Lett 29(754):135879

Barker RA (2019) Designing stem-cell-based dopamine cell replacement trials for Parkinson's disease. Nat Med 25(7):1045–1053

Belvisi D, Pellicciari R, Fabbrini A, Costanzo M, Ressa G, Pietracupa S, De Lucia M, Modugno N, Magrinelli F, Dallocchio C, Ercoli T (2022) Relationship between risk and protective factors and clinical features of Parkinson's disease. Parkinsonism Relat Disord 98:80–85

Bjørklund G, Hofer T, Nurchi VM, Aaseth J (2019) Iron and other metals in the pathogenesis of Parkinson's disease: toxic effects and possible detoxification. J Inorg Biochem 199:110717

Borghammer P, Just MK, Horsager J, Skjærbæk C, Raunio A, Kok EH, Savola S, Murayama S, Saito Y, Myllykangas L, Van Den Berge N (2022) A postmortem study suggests a revision of the dual-hit hypothesis of Parkinson's disease. NPJ Parkinson's Disease 8(1):166

Bouchez C, Devin A (2019) Mitochondrial biogenesis and mitochondrial reactive oxygen species (ROS): a complex relationship regulated by the cAMP/PKA signaling pathway. Cells 8(4):287

Braidy N, Zarka M, Jugder BE, Welch J, Jayasena T, Chan DK, Sachdev P, Bridge W (2019) The precursor to glutathione (GSH), γ-Glutamylcysteine (GGC), can ameliorate oxidative damage and neuroinflammation induced by Aβ40 oligomers in human astrocytes. Front Aging Neurosci 11:177

Bryson S (2020) Gene therapy trial patients, in death, helping show what did and didn't work. Parkinson's News Today

Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G, Ghiglieri V (2023) Alpha-synuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction. Cell Death Dis 14(3):176

Camargo CH, Della-Coletta MV, da Silva DJ, Teive HA (2019) Alpha-synucleinopathies: Parkinson's disease, dementia with lewy bodies, and multiple system atrophy. In: Handbook of research on critical examinations of neurodegenerative disorders 2019. IGI Global, pp 274–297

Chia SJ, Tan EK, Chao YX (2020) Historical perspective: models of Parkinson's disease. Int J Mol Sci 21(7):2464

Choudhury SP, Bano S, Sen S, Suchal K, Kumar S, Nikolajeff F, Dey SK, Sharma V (2022) Altered neural cell junctions and ion-channels leading to disrupted neuron communication in Parkinson's disease. NPJ Parkinson's Disease. 8(1):66

Clinical Research. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research. Accessed 26 Jan 2021.

Colle D, Farina M (2021) Oxidative stress in paraquat-induced damage to nervous tissues. In: Toxicology. Academic Press, pp 69–78
Crowley EK, Nolan YM, Sullivan AM (2019) Exercise as a therapeutic intervention for motor and non-motor symptoms in Parkinson's disease: evidence from rodent models. Prog Neurobiol 172:2–22
da Silva WA, Oliveira KF, Vitorino LC, Romão LF, Allodi S, Correa CL (2021) Physical exercise increases the production of tyrosine hydroxylase and CDNF in the spinal cord of a Parkinson's disease mouse model. Neurosci Lett 760:136089
Desai A, Benner L, Wu R, Gertsik L, Maruff P, Light GA, Uz T, Marek GJ, Zhu T (2021) Phase 1 randomized study on the safety, tolerability, and pharmacodynamic cognitive and electrophysiological effects of a dopamine D1 receptor positive allosteric modulator in patients with schizophrenia. Neuropsychopharmacology 46(6):1145–1151
Di Luca DG, Feldman M, Jimsheleishvili S, Margolesky J, Cordeiro JG, Diaz A, Shpiner DS, Moore HP, Singer C, Li H, Luca C (2020) Trends of inpatient palliative care use among hospitalized patients with Parkinson's disease. Parkinsonism Relat Disord 77:13–17
Draoui A, El Hiba O, Aimrane A, El Khiat A, Gamrani H (2020) Parkinson's disease: from bench to bedside. Revue Neurol 176(7–8):543–559
Dumurgier J, Tzourio C (2020) Epidemiology of neurological diseases in older adults. Revue Neurol 176(9):642–648
Fabbri M, Coelho M, Abreu D, Guedes LC, Rosa MM, Godinho C, Cardoso R, Guimaraes I, Antonini A, Zibetti M, Lopiano L (2019) Dysphagia predicts poor outcome in late-stage Parkinson's disease. Parkinsonism Relat Disord 64:73–81
Feng YS, Yang SD, Tan ZX, Wang MM, Xing Y, Dong F, Zhang F (2020) The benefits and mechanisms of exercise training for Parkinson's disease. Life Sci 245:117345
Flynn MS, Robinson C, Patel S, Liu B, Green C, Pavlis M (2023) Clinicopathologic characteristics of melanoma in patients with parkinson disease. JID Innovations 3(2):100173
Fraint A, Pal DG, Tam E, et al (2018) Interest in genetic testing in Parkinson's disease patients with deep brain stimulation. Neurology 90(15 Supplement):P4.069
Gao C, Liu J, Tan Y, Chen S (2020) Freezing of gait in Parkinson's disease: pathophysiology, risk factors and treatments. Trans Neurodegener 9:1–22
Ghosh S, Won SJ, Wang J, Fong R, Butler NJM, Moss A, Wong C, Pan J, Sanchez J, Huynh A et al (2021) α-Synuclein aggregates induce c-Abl activation and dopaminergic neuronal loss by a feed-forward redox stress mechanism. Prog Neurobiol 202:102070
Greener M (2021) Parkinson's disease: is pharmacotherapy on the move? Prescriber 32(8–9):26–31
Guo Z, Ruan Z, Zhang D, Liu X, Hou L, Wang Q (2022) Rotenone impairs learning and memory in mice through microglia-mediated blood brain barrier disruption and neuronal apoptosis. Chemosphere 291:132982
Hamed MA, Mohammed MA, Aboul Naser AF, Matloub AA, Fayed DB, Ali SA, Khalil WK (2019) Optimization of curcuminoids extraction for evaluation against Parkinson's disease in rats. J Biological Act Products Nat 9(5):335–351
Hollville E, Joers V, Nakamura A, Swahari V, Tansey MG, Moy SS, Deshmukh M (2020) Characterization of a Cul9–Parkin double knockout mouse model for Parkinson's disease. Sci Rep 10(1):1–3
Ishiguro M, Li Y, Yoshino H, Daida K, Ishiguro Y, Oyama G, Saiki S, Funayama M, Hattori N, Nishioka K (2021) Clinical manifestations of Parkinson's disease harboring VPS35 retromer complex component p D620N with long-term follow-up. Parkinsonism Relat Disord 84:139–143
Islam MS, Azim F, Saju H, Zargaran A, Shirzad M, Kamal M, Fatema K, Rehman S, Azad MM, Ebrahimi-Barough S (2021) Pesticides and Parkinson's disease: current and future perspective. J Chem Neuroanat 115:101966
Ivanova M (2020) Altered sphingolipids metabolism damaged mitochondrial functions: lessons learned from Gaucher and Fabry diseases. J Clin Med 9(4):1116
Jaiswal V, Alquraish D, Sarfraz Z, Sarfraz A, Nagpal S, Singh Shrestha P, Mukherjee D, Guntipalli P, Sánchez Velazco DF, Bhatnagar A, Savani S (2021) The influence of coronavirus disease-2019 (COVID-19) on Parkinson's disease: an updated systematic review. J Prim Care Commun Health 12:21501327211039708
Jia F, Fellner A, Kumar KR (2022) Monogenic Parkinson's disease: genotype, phenotype, pathophysiology, and genetic testing. Genes 13(3):471
Jia Y, Tan W, Zhou Y (2020) Transfer RNA-derived small RNAs: potential applications as novel biomarkers for disease diagnosis and prognosis. Ann Transl Med 8(17):1092
Jiménez-Gómez B, Ortega-Sáenz P, Gao L, González-Rodríguez P, García-Flores P, Chandel N, López-Barneo J (2023) Transgenic NADH dehydrogenase restores oxygen regulation of breathing in mitochondrial complex I-deficient mice. Nat Commun 14(1):1172
Kambey PA, Chengcheng M, Xiaoxiao G, Abdulrahman AA, Kanwore K, Nadeem I, Jiao W, Gao D (2021) The orphan nuclear receptor Nurr1 agonist amodiaquine mediates neuroprotective effects in 6-OHDA Parkinson's disease animal model by enhancing the phosphorylation of P38 mitogen-activated kinase but not PI3K/AKT signaling pathway. Metab Brain Dis 36:609–625
Kayis G, Yilmaz R, Arda B, Akbostancı MC (2023) Risk disclosure in prodromal Parkinson's disease—a survey of neurologists. Parkinsonism Relat Disord 106:105240
Koga S, Zhou X, Dickson DW (2021) Machine learning-based decision tree classifier for the diagnosis of progressive supranuclear palsy and corticobasal degeneration. Neuropathol Appl Neurobiol 47(7):931–941
Liu C, Liu Z, Zhang Z, Li Y, Fang R, Li F, Zhang J (2020) A scientometric analysis and visualization of research on Parkinson's disease associated with pesticide exposure. Front Public Health 8:91
Liu H, Liu H, Li T, Cui J, Fu Y, Ren J, Sun X, Jiang P, Yu S, Li C (2017) NR4A2 genetic variation and Parkinson's disease: evidence from a systematic review and meta-analysis. Neurosci Lett 650:25–32
Mailloux RJ (2020) An update on mitochondrial reactive oxygen species production. Antioxidants 9(6):472
Marchetti B (2020) Nrf2/Wnt resilience orchestrates rejuvenation of glia-neuron dialogue in Parkinson's disease. Redox Biol 36:101664
Martínez-Chacón G, Yakhine-Diop SM, González-Polo RA, Bravo-San Pedro JM, Pizarro-Estrella E, Niso-Santano M, Fuentes JM (2021) Links between paraquat and Parkinson's disease. Handbook of Neurotoxicity, pp 1–9
Masato A, Plotegher N, Boassa D, Bubacco L (2019) Impaired dopamine metabolism in Parkinson's disease pathogenesis. Mol Neurodegener 14(1):1–21
Masato A, Sandre M, Antonini A, Bubacco L (2021) Patients stratification strategies to optimize the effectiveness of scavenging biogenic aldehydes: towards a neuroprotective approach for Parkinson's disease. Curr Neuropharmacol 19(10):1618
Merchant KM, Cedarbaum JM, Brundin P, Dave KD, Eberling J, Espay AJ, Hutten SJ, Javidnia M, Luthman J, Maetzler W et al (2019) A proposed roadmap for Parkinson's disease proof of concept clinical trials investigating compounds targeting alpha-synuclein. J Parkinson's Dis 9:31–61
Merkow RP, Schwartz TA, Nathens AB (2020) Practical guide to comparative effectiveness research using observational data. JAMA Surg 155(4):349–350
Millichap LE, Damiani E, Tiano L, Hargreaves IP (2021) Targetable pathways for alleviating mitochondrial dysfunction in neurodegeneration of metabolic and non-metabolic diseases. Int J Mol Sci 22(21):11444
Mullin S, Smith L, Lee K, D'Souza G, Woodgate P, Elflein J, Hällqvist J, Toffoli M, Streeter A, Hosking J et al (2020) Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, non controlled trial. JAMA Neurol 77:427–434
Mylius V, Möller JC, Bohlhalter S, Ciampi-de-Andrade D, Perez-Lloret S (2021) Diagnosis and management of pain in Parkinson's disease: a new approach. Drugs Aging 38:559–577
Nakamura T, Oh CK, Zhang X, Lipton SA (2021) Protein S-nitrosylation and oxidation contribute to protein misfolding in neurodegeneration. Free Radical Biol Med 172:562–577
Neag MA, Mitre AO, Catinean A, Mitre CI (2020) An overview on the mechanisms of neuroprotection and neurotoxicity of isoflurane and sevoflurane in experimental studies. Brain Res Bull 165:281–289
Neshige S, Ohshita T, Neshige R, Maruyama H (2021) Influence of current and previous smoking on current phenotype in Parkinson's disease. J Neurol Sci 427:117534
Nunes C, Laranjinha J (2021) Nitric oxide and dopamine metabolism converge via mitochondrial dysfunction in the mechanisms of neurodegeneration in Parkinson's disease. Arch Biochem Biophys 704:108877
Palasz E, Niewiadomski W, Gasiorowska A, Mietelska-Porowska A, Niewiadomska G (2019) Neuroplasticity and neuroprotective effect of treadmill

training in the chronic mouse model of Parkinson's disease. Neural Plasticity 2019:8215017
Papagiannakis N, Koros C, Stamelou M et al (2018) Alpha-synuclein dimerization in erythrocytes of patients with genetic and nongenetic forms of Parkinson's Disease. Neurosci Lett 672:145–149
Park JH, Kim DH, Kwon DY, Choi M, Kim S, Jung JH, Han K, Park YG (2019) Trends in the incidence and prevalence of Parkinson's disease in Korea: a nationwide, population-based study. BMC Geriatr 19:1
Parker JE, Martinez A, Deutsch GK, Prabhakar V, Listing M, Kapphahn KI, Anidi CM, Neuville R, Coburn M, Shah N, Bronte-Stewart HM (2020) Safety of plasma infusions in Parkinson's disease. Mon Disord 35(11):1905–1913
Pereira AP, Marinho V, Gupta D, Magalhães F, Ayres C, Teixeira S (2019) Music therapy and dance as gait rehabilitation in patients with Parkinson disease: a review of evidence. J Geriatr Psychiatry Neurol 32(1):49–56
Rocha EM, Keeney MT, Di Maio R, De Miranda BR, Greenamyre JT (2022) LRRK2 and idiopathic Parkinson's disease. Trends Neurosci 45(3):224–236
Roeh A, Kirchner SK, Malchow B, Maurus I, Schmitt A, Falkai P, Hasan A (2019) Depression in somatic disorders: is there a beneficial effect of exercise? Front Psychol 10:141
Sachan N, Saraswat N, Chandra P, Khalid M, Kabra A (2022) Isolation of Thymol from Trachyspermum ammi Fruits for Treatment of Diabetes and Diabetic Neuropathy in STZ-Induced Rats. BioMed Res Int 2022:8263999
Saraswat N, Sachan N, Chandra P (2020a) A review on ethnobotanical, phytochemical, pharmacological and traditional aspects of indigenous Indian herb *Trachyspermum ammi* (L). Curr Tradit Med 6(3):172–187
Saraswat N, Sachan N, Chandra P (2020b) Anti-diabetic, diabetic neuropathy protective action and mechanism of action involving oxidative pathway of chlorogenic acid isolated from Selinum vaginatum roots in rats. Heliyon 6(10):e05137
Selvaraj S, Piramanayagam S (2019) Impact of gene mutation in the development of Parkinson's disease. Genes Diseases 6(2):120–128
Senturk ZK (2020) Early diagnosis of Parkinson's disease using machine learning algorithms. Med Hypotheses 138:109603
Sitzia G (2022) The circuit and synaptic organization of the basal ganglia output: mechanistic insights on movement disorders and action control
Skidmore FM, Monroe WS, Hurt CP, Nicholas AP, Gerstenecker A, Anthony T, Jololian L, Cutter G, Bashir A, Denny T, Standaert D (2022) The emerging postural instability phenotype in idiopathic Parkinson disease. NPJ Parkinson's Disease 8(1):28
Smeyne RJ, Noyce AJ, Byrne M, Savica R, Marras C (2021) Infection and risk of Parkinson's disease. J Parkinsons Dis 11(1):31–43
Sonustun B, Altay MF, Strand C, Ebanks K, Hondhamuni G, Warner TT, Lashuel HA, Bandopadhyay R (2022) Pathological relevance of post-translationally modified alpha-synuclein (pSer87, pSer129, nTyr39) in idiopathic Parkinson's disease and Multiple System Atrophy. Cells 11(5):906
Staff NP, Jones DT, Singer W (2019) Mesenchymal stromal cell therapies for neurodegenerative diseases. Mayo Clinic proceedings. Retrieved January 26, 2022.
Sun C, Armstrong MJ (2021) Treatment of Parkinson's disease with cognitive impairment: current approaches and future directions. Behav Sci 11(4):54
Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladâcenco O, Roza E, Costăchescu B, Grumezescu AM, Teleanu RI (2022) An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. Int J Mol Sci 23(11):5938
Tolosa E, Garrido A, Scholz SW, Poewe W (2021) Challenges in the diagnosis of Parkinson's disease. Lancet Neurol 20(5):385–397
Tran J, Anastacio H, Bardy C (2020) Genetic predispositions of Parkinson's disease revealed in patient-derived brain cells. NPJ Parkinson's Disease 6(1):8
Tran TN, Le Ha UN, Nguyen TM, Nguyen TD, Vo KN, Dang TH, Trinh PM, Truong D (2021) The effect of non-motor symptoms on health-related quality of life in patients with young onset Parkinson's disease: a single center vietnamese cross-sectional study. Clin Parkinsonism Related Disord 5:100118
Trist BG, Hare DJ, Double KL (2019) Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Aging Cell 18(6):e13031
Vaccari C, El Dib R, Gomaa H, Lopes LC, de Camargo JL (2019) Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies. J Toxicol Environ Health Part B 22(5–6):172–202
Van der Perren A, Gelders G, Fenyi A, Bousset L, Brito F, Peelaerts W, Van den Haute C, Gentleman S, Melki R, Baekelandt V (2020) The structural differences between patient-derived α-synuclein strains dictate characteristics of Parkinson's disease, multiple system atrophy and dementia with lewy bodies. Acta Neuropathol 139:977–1000
Wang W, Kang PM (2020) Oxidative stress and antioxidant treatments in cardiovascular diseases. Antioxidants 9(12):1292
Wuthrich VM, Rapee RM (2019) Telephone-delivered cognitive behavioural therapy for treating symptoms of anxiety and depression in Parkinson's disease: a pilot trial. Clin Gerontol 42(4):444–453
Xicoy H, Klemann CJ, De Witte W, Martens MB, Martens GJ, Poelmans G (2021) Shared genetic etiology between Parkinson's disease and blood levels of specific lipids. NPJ Parkinson's Disease 7(1):23
Xu Y, Cai X, Qu S, Zhang J, Zhang Z, Yao Z, Huang Y, Zhong Z (2020) Madopar combined with acupuncture improves motor and non-motor symptoms in Parkinson's disease patients: a multicenter randomized controlled trial. Eur J Integr Med 1(34):101049
Yin R, Xue J, Tan Y, Fang C, Hu C, Yang Q, Mei X, Qi D (2021) The positive role and mechanism of herbal medicine in Parkinson's disease. Oxid Med Cell Longevity 2021:9923331
Zampese E, Surmeier DJ (2020) Calcium, bioenergetics, and Parkinson's disease. Cells 9(9):2045

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