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# Chapter 6: Mechanism of action of PD: Antioxidant, Anti-inflammatory and Neurorestorative pathways

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**Abstract**

Parkinson disease (PD) is a degenerative brain condition that is characterized by the loss of dopaminergic neurons in the substantia nigra portion of the brain and is majorly associated with motor symptoms of this disease that include tremors, rigidity, and bradkinetic movements. Mechanisms that have been known to be involved in the pathogenesis of PD include an intricate network comprising oxidative stress, neuroinflammation, and the weakening of neurorestorative mechanisms. Oxidative stress occurs as a result of higher production of reactive oxygen species (ROS) compared with theory and practice of proton pump inhibition (neutrophilic oxidants) and the antioxidant defense mechanisms of the brain. Dopaminergic neurons are highly metabolic and expose these cells to the oxidative environment by producing a dopamine player that can also auto-oxidize to generate ROS, which puts these cells at high risk of oxidative damage. Protective mechanisms against oxidative stress like superoxide dismutase, glutathione, and catalase are saturated leading to lipid peroxidation and misfolding of proteins, and DNA damage. At the same time, neuroinflammation is very important in the progression of PD. This inflammatory process also interferes with the blood brain barrier and inhales the oxidative destruction. Also, neurorestorative pathways that include neurogenesis, synaptic plasticity, mitochondrial biogenesis are extremely degraded in PD. The decreasing neurotrophic growth factor such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) restricts the brain to repair and regeneration of the damaged neurons. New possibilities of therapy are directed on multi-target targeting combining antioxidants, anti-inflammatory, neurorestorative agents as a complex to reduce tempo of the disease development, stimulate neuronal survival and improve an outcome. Development of these disease-modifying treatments depends on an understanding of these interconnected pathways and how to intervene in the disease pathways rather than focusing solely on symptomatic relief of Parkinson disease.

**Keywords:** *Mitochondrial dysfunction, Neurodegenerative, Neuroinflammation, Neurorestoration, Neuroprotection, oxidative stress, Parkinson disease.*

## 1. Introduction

Parkinson Disease (PD) is a long-lasting disease of the nerves which progressively deteriorates the control of movement since they gradually die, especially the dopaminergic neurons of the substantia nigra pars compacta area of the brain. With the decrease in levels of dopamine, the characteristic motor impairment including tremor at rest, bradykinesia (slowness of movements), muscle rigidity and instability in posture sets in. However, besides motor dysfunction, PD appears to be associated with various non-motor symptoms like cognitive or cognitive decline, sleep disturbance, mood disorders, and autonomic dysfunction [1]. The specific cause of PD is yet to be figured out, however, various sources have been found. These are genetic, environmentally induced mutations (such as SNCA, LRRK2, PARK2), toxins in the environment (such as pesticides), problems in the mitochondria, oxidative stress, neuroinflammation, and abnormal protein aggregation, especially of 1-synuclein, in the form of Lewy bodies in nerve cells in the brain. Parkinson Disease is the second leading neurodegenerative disease next to Alzheimer disease and its occurrence is widespread, with more than 10 million individuals experiencing it and the commonest at an elderly age [2]. At the current time there is no cure and management of the condition is based on the management of symptoms which is mainly by use of dopamine replenishment therapy such as Levodopa. Nevertheless, those therapies are not preventing or reversing the neurodegeneration. As PD is of multifactorial nature, the molecular and cellular mechanisms involving oxidative damage, chronic inflammation, and loss of neurorestorative capacity should be understood so that the less-effective disease-modifying treatment may be developed. Recently, a lot of research has been done on antioxidant, anti-inflammatory and neuroprotective approaches to intervene in these fundamental pathological mechanisms [3].

### 1.1 Pathophysiology of Parkinson s Disease (PD)

The pathophysiology of PD remains a complicated process and includes various interconnected cellular and molecular processes with the ultimate cause being death of dopaminergic neurons especially the SNpc of the midbrain. This type of neuronal loss causes serious decrease in the level of dopamine in striatum part of the brain which plays a major role in controlling activity of the brain [4]. Causes of parkinsons disease that leads to this disease generation and contribute an major role in its pathophysiology are as shown in figure 6.1 are as follows:

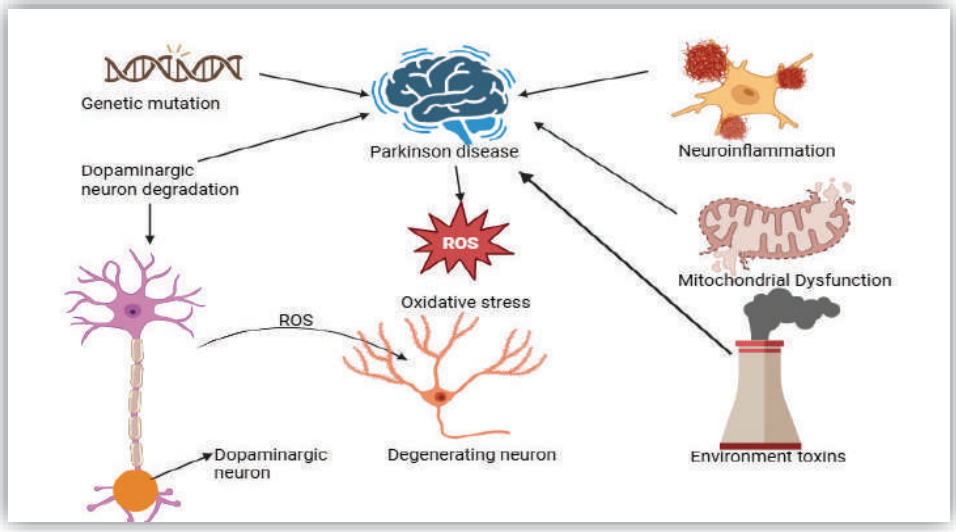


**Figure 6.1: Parkinsons disease Causes**

### 1.1.1 Degeneration of dopaminergic neurons

Dopaminergic neurons are particularly susceptible because they have a high oxidative metabolism, long axons, and several connections in terms of synapses. Their gradual death leads to defects in the transmission of dopamine in the nigrostriatal system, which causes the motor symptoms of PD that are classic: tremor at rest, rigidity, bradykinesia and deterioration of postural balance [5].

### 1.1.2 Aggregation of the α-Synuclein

The main patologic hallmark of patients with PD is the α-,synuclein aggregation and accumulation of a protein in the neurons, with resultant misfolding and intracytoplasmic inclusion, known as Lewy bodies, also seen in the surviving neurons. These aggregates affect the cellular homeostasis, impact the synaptic functionality, and lead to neuronal death [6].

### 1.1.3 Oxidative Stress and Mitochondiral Dysfunction

The abnormalities in mitochondria PD interfere with the production of ATP and generate excessive active oxygen (ROS) that destroy proteins, lipids, and DNA. Failure to neutralize these ROS because of the inadequate antioxidant defenses is a faster way of killing dopaminergic cells [7].

### 1.1.4 Neuroinflammation

Excessive microglial activation, the resident immune cells of the brain, results in pro-inflammatory cytokines secretion (e.g., TNF-a, IL-1b, IL-6). Such inflammatory environment also adds to the neuronal damage and enhances the disease process [8].

### 1.1.5 Defective Deteriorating Protein Systems

Impairments in the ubiquitin-proteasome system (UPS) and autophagy-lysosomal degradation lead to an inefficiency in reducing the levels of misfolded or damaged protein, such as α-synuclein, a driver of toxic accumulation, and dysfunction [9].

### 1.1.6 Hereditary and Environment Causation

Although PD is considered idiopathic in most instances, a number of genetic mutations (i.e., SNCA, LRRK2, PARK2, PINK1, DJ-1) as well as environmental exposures (i.e., pesticides, heavy metals) have been implicated in pathogenicity. These can affect the oxidative stress, mitochondrial performance as well as aggregation of proteins [10].

## 1.2 Why is it Important to Know Mechanism of Action?

The basic mechanism of action with regard to Parkinson Disease (PD) should be understood to proceed with the symptomatic administration of the disease instead of actually correcting the illness proper. The main treatment approaches of traditional therapies like using dopamine replacement therapy using levodopa mainly provide relief of motor symptoms that do not stop or temporarily reverse the gradual deterioration of the dopaminergic neurons. Since PD is a multifactorial disease with the involvement of oxidative stress, neuroinflammation, mitochondrial dysfunction, and aberrant protein aggregation, a mechanistic explanation is essential to target underlying causative factors [11].

Through further clarification regarding the mechanism by which oxidative damage causes injury at the cellular level, how the underlying inflammatory pathways accumulate in chronic stress in neurons and how the neuro-regenerative processes are either compromised or can be ameliorated, researchers and clinicians can devise more powerful interventions. As an example, neuroprotective effects achieved through therapeutic approaches targeting the improvement of antioxidant defenses, inhibition of microglial activation, or stimulation of neurogenesis, may provide neuroprotective effects that are not

available in conventional dopaminergic therapeutic approaches [12]. In addition, a mechanistic scheme can assist in spotting biomarkers that could be used in early detection of diseases, disease progression analysis, and tracking of therapeutic efficiency. It is also used in the finding of repurposing of drugs, particularly those which are multi-target oriented and so, have the propensity to act on multiple pathological pathways at once i.e. natural polyphenols or anti-inflammatory agents which can easily act among a variety of pathological processes [13]. With the advent of personalized medicine, the possibility to tailor the treatment regimen specifically to each patient considering his or her disease specifics, genetic makeup, and response variations offers new hope to treating PD. Thiska is the knowledge that sits between fundamental neuroscience and the clinical practice and eventually positively changes the patient outcome and quality of life [14].

## 2. Parkinson disease (PD) and Oxidative Stress

### 2.1 The role of ROS

Oxidative stress is a central event in the pathogenesis of PD. It can be described as, excess oxidation relative to antioxidants (ROS) and the damage of structures inside cell such as lipids, proteins as well as DNA. This oxidative disequilibrium is especially harmful to dopaminergic nerve cells in the substantia nigrapars compacta, which are more susceptible in nature to have a raised metabolic burden and the ability to metabolize dopamine. Reactive oxygen species consist of a generic collection of extremely reactive compounds the superoxide, $H_2O_2$, (OH). Most of these are produced in byproducts of the process of mitochondrial oxidative phosphorylation. Mitochondrial dysfunction: In PD, production of ROS is dependent on the impairment of mitochondrial complex I [15]. Complex I deficiency overwhelms the cells antioxidant defense mechanisms and results in oxidative damage.Among the dopaminergic neurons of the PD brain, the additional sources of ROS relate to dopamine metabolism per se. Dopamine is enzymatically degraded by monoamine oxidase (MAO) to form hydrogen peroxide that when in the presence of iron can form more damaging hydroxyl radicals in a reaction termed the Fenton reaction. Also, dopamine is potentially auto-oxidized to dopamine quinones which further can promote the oxidative damage and misfolding of proteins, in this case, alpha-synuclein. Superfluous ROS leads to the destruction of the cell membrane by the lipid peroxidation processes, destruction of proteins by protein oxidation, resulting in the structural/functional disability of enzymes and receptors, and destruction of DNA, evoking cell cycle arrest or apoptosis. This domino effect interferes with the neuronal homeostasis, leading to cell death. In addition, ROS serve as signaling agents and initiators of pro-inflammatory mediators and thus connects the oxidative stress to chronic neuronal inflammation which is another principal bio-mark of PD [16].

### 2.2 ROS Production: Mitochondrial malfunction

One of the main pathological characteristics of PD is mitochondrial dysfunction which is directly related to the overproduction of ROS and subsequent oxidative stress which causes injury to neurons. Production of ATP with the help of oxidative phosphorylation takes place in the so-called powerhouses of the cell mitochondria [17]. But in this process, there is a minor percentage of leaking electrons of the ETC specifically at the complex I and complex III which forms superoxide anions a kind of ROS. Studies conducted on the substantia nigra by post-mortem evidence in PD have been found to have the activity of mitochondrial complex I lessened continuously. This deficiency has a negative effect on the electron fluid so that the transfer of electrons is defected and there is leakage of electrons and a high level of ROS generation is observed. The generated oxidative stress destroysmtDNA, proteins and lipids and hinders the mitochondrial functioning in a vicious cycling progress. It is this self-maintaining damage that leads to progressive loss of the dopaminergic neurons [18]. The silver bullet is that

environmental toxins like rotenone and paraquat which inhibit mitochondrial complex I have been demonstrated in animal models to cause Parkinsonian syndromes via increasing ROS production andsimulating mitochondrial dysfunction. Past examples also connect familial PD-linked genetic mutations that include PINK1, Parkin, DJ-1 and LRRK2 to mitochondrial quality control, fission-fusion dynamics and mitophagy [19]. Malfunction of those pathways results in the accumulation of defective mitochondria since they represent key sources of ROS. ROS production also occurs because of dysfunction of mitochondrial calcium handling [20]. There is also autonomous pacemaking activity in the dopaminergic cell bodies in the substantia nigra which is dependent on L-type calcium channels resulting in sustained calcium influx. Mitochondria has a calcium load capacity and too much of it may generate ROS and cause an opening of the mitochondrial permeability transition pore (mPTP) which causes apoptosis. Also, mitochondrial dysfunction influence on the synthesis of ATP, and destabilizes the processes that are dependent on energy, like maintenance of ion transport, the transportation of axons, and recycling of neurotransmitters all of which are relevant in the survival and functioning of neurons [21].

### 2.3 Dopaminergic neural oxidative damage

The biochemical and physiological properties of dopaminergic neurons located in the substantia nigra pars compacta make them very vulnerable to oxidative damage. In Parkinson Disease (PD), overlying oxidative stress as a result of increased reactive oxygen species (ROS) leads to considerable structural and functional deterioration of these neurons which ends up causing them to gradually degenerate. Dopamine metabolism is one big cause of oxidative stress of dopaminergic neurons. The action of the enzyme monoamine oxidase B (MAO-B) breaks down the dopamine into hydrogen peroxide ($H_2O_2$), which in the presence of free iron, reacts by a process known as the Fenton reaction to form highly reactive hydroxyl radical (ORH). These radicals are very toxic and they could destroy cellular macromolecules very quickly. Moreover, dopamine is auto-oxidizable to dopamine quinones, semiquinones, which are capable of binding proteins, including α-synuclein and inducing the formation of its aggregates into Lewy bodies. Such quinones are also capable of damaging proteins/enzymes and impairing mitochondrial functioning further increasing both ROS generation and the overall stress of the cell [22].

Oxidative stress on dopaminergic neurons occurs in many forms:

- Lipid Peroxidation: ROS oxidizes the polyunsaturated fatty acids of the membranes of a neuron and initiates lipid peroxidation. This alters membrane integrity, influences transport of ions and impedes synaptic transmission.
- Protein Oxidation: Oxidative Damage of proteins leads to structural and functional changes and disrupt enzyme action, cytoskeletal integrity and signal transmission. It is also possible to see oxidized proteins that are resistant to degradation, which results in the creation of toxic aggregates.
- DNA Damage: Both nuclear and mitochondrial DNA (mtDNA) strand breaks and base alterations can be caused by the ROS. In dopaminergic cells, mitochondria damage affecting the expression of the mitochondrial genome leads to further degradation of the production of energy and increases oxidative stress.
- Proteasomal and Autophagic Pathway Inhibition: ROS can negatively affect the ubiquitin-proteasome system (UPS) and autophagy, proteins working out proteins on the ground of defectiveness. Their impairment also leads to further neurotoxicity via increased accumulation of misfolded proteins and protein aggregates, including those of α-synuclein [23].

Even more susceptible to the effects of ROS are dopaminergic neurons; their high metabolic activity, massive axonal arborization, and dependence on calcium-dependent pacemaking increase their

vulnerability to ROS and the energy they require. In addition, the substantia nigra is rich in iron that is the facilitator of ROS production and overweight-related oxidative injury [24].

## 3. Mechanisms of Antioxidant in Parkinson Disease (PD)

### 3.1 Intrinsic antioxidant defenses, including (SOD, catalase, glutathione)

The roles of a highly controlled system of endogenous cellular defenses against oxidative stress are to counteract reactive oxygen species (ROS) by their neutralization. Parkinson is a disease (PD) where the balance between production of ROS and antioxidant defense systems is altered causing ROS-driven oxidative damage and development of progressive neuronal degeneration. Among the major endogenous antioxidants that help in the regulation of redox homeostasis today, are SOD, catalase and GSH each of which are critical in the neutralization of certain ROS and safeguarding dopaminergic neurons within the substantia nigra [25].

**Superoxide Dismutase.**

SOD is a vital first line antioxidant enzyme that dismutates the superoxide anion ($O_2$- ) to H $_2$O $_2$ and $O_2$. SOD has three isoforms:

- The cytoplasmic lcSOD1 (Cu/Zn-SOD),
- Mitochondrial SOD2 (Mn-SOD), and
- The extracellular SOD3.

Mitochondrial SOD2 is of importance especially in cases of PD because of the role of mitochondria in creating ROS. It can lead to the onset of oxidative stress and the destruction of the mitochondria by the accumulation of superoxide radicals should there be deficiency or failure of SOD [26].

**Catalase**

In addition to SOD, another important antioxidant enzyme is catalase which breaks down $H_2O_2$ produced both by SOD and by the degradation of dopamine into water and oxygen in the process halting the production of hydroxyl radicals (OH ) through the Fenton reaction. Catalase is mainly localized to peroxisomes and is critical in $H_2O_2$ detoxification of different tissues such as the brain. Catalase activity is frequently impaired in PD and this weakens the cells to remove oxidative hydrogen peroxide and predisposes it to oxidative damage [27].

**Glutathione**

Glutathione is a tripeptide (glutamate, cysteine and glycine) and the most prevalent non-enzymatic antioxidant in the brain. It takes the form of reduced (GSH) and oxidized (GSSG). GSH also eliminates ROS directly as well as acting as a catalyst of the glutathione peroxidase (GPx) enzyme, which breaks down hydrogen peroxide and lipid peroxides into harmless molecules. It also participates in detoxification reaction and also replenishment of other antioxidants like vitamin C and E. Interestingly, it has also been demonstrated that the level of GSH in patients with PD decreased significantly in the substantia nigra even at an early stage of PD development. This depletion is discussed as a one of the first biochemical changes of PD and it is used as a sensitive marker of oxidative stress. Damage of glutathione does not only diminish antioxidant power, but also reduces the performance of mitochondria and increases aggregates of alpha-synuclein [28].

### 3.2 Vitamin, Polyphenols, and Natural Compound Therapies: Antioxidants

Oxidative stress has a prominent role in dopaminergic neurons degeneration, which occurs across Parkinson Disease (PD). As endogenous antioxidant mechanisms such as superoxide dismutase (SOD), catalase, as well as glutathione (GSH) get compromised in the development of the disease, exogenous antioxidant interventions have become under consideration as one of the possible neuroprotective measures. Of particular interest among these are vitamins, polyphenols, and other naturally occurring compounds that have antioxidant ability to scavenge free radicals, chelating metals, their redox refiner direction and sustenance of mitochondrial action. Figure 6.1 indicates some examples of antioxidants that prevent PD [29].

**Antioxidant Vitamins**

**Vitamin E (alpha Tocopherol):**

A cell membrane protective antioxidant lipid-soluble that prevents oxidation of lipids by lipid peroxidation. It stops the free radical chain processes particularly within the membranes of the neurons which contain high levels of poly unsaturated fatty acids. A delay progression of the disease appears in some clinical studies on the use of vitamin E supplementation but they are mixed [29].

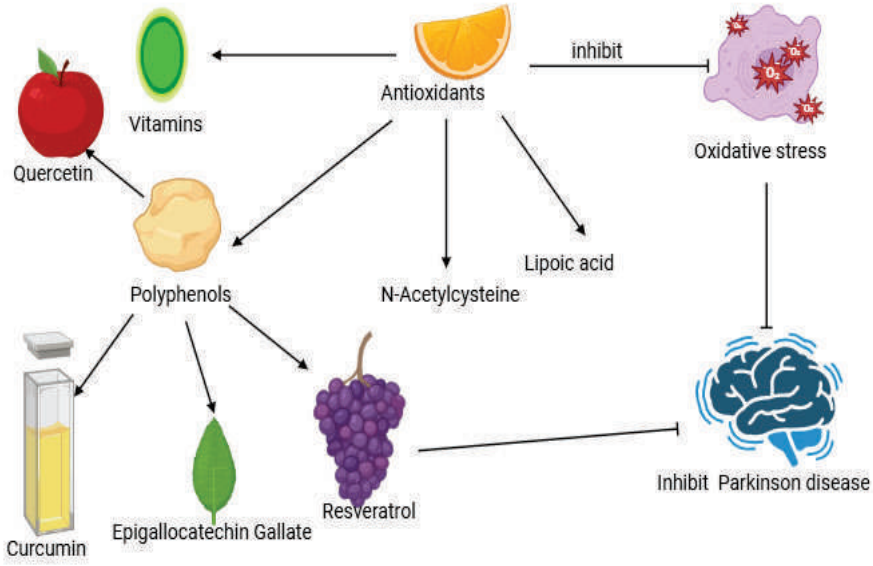


**Figure 6.1: Antioxidants inhibit Parkinson disease**

**Asorbic Acid (Vitamin C):**

An antioxidant, water-soluble, which reacts directly with ROS including superoxide and hydroxyl radicals. It also recycles oxidized vitamin E and is a contributing factor in keeping glutathione within the body. Vitamin C is also associated with the build-up of the vitamin in the brain, which can safeguard the oxidative damage to dopaminergic neurons [30].

**Carotenoids and Vitamin A:**

Antioxidant compounds such as beta-carotene have the ability to regulate oxidative losses and inflammation. Their protective effects on the nervous system have yet to be fully examined but a few *in vitro* and animal trials have proven their neuroprotective worth [31].

**Vitamin B**

This vitamins do not represent classical antioxidants, but they reduce homocysteine, also a pro-oxidant and neurotoxic molecule, raised in PD. They also protect mitochondria and mechanisms of repair of DNA [32].

**Polyphenols**

Polyphenols Contain compounds of a plant origin, with a high anti-inflammatory and antioxidant effect. They either directly scavenge free radicals, chelate metals and induce endogenous defense mechanisms like Nrf2 [33].

**Resveratrol:**

Resveratrol is found in grapes and red wine and can use the SIRT1 and Nrf2 pathways to activate an improved mitochondrial response as well as epicrisis of inborn-antioxidant boundaries. It has provided promising results in PD models to reduce 66-synuclein aggregation and death of neurons (apoptosis) [34].

**Curcumin:**

This is a turmeric polyphenol that has high ROS-scavenging and anti-inflammatory and anti-aggregatory activity. Curcumin has been found to regulate some of the major signaling pathways in apoptosis and mitochondrial protection which makes it an ideal neuroprotective drug in PD studies [35].

**Quercetin:**

Occurring in apples, onions and berries, quercetin is able to cross the blood-brain barrier as well as having antioxidant, anti-inflammatory, and iron-chelation activities. It is also useful in replenishing glutathione level and preventing dopaminergic neuronal death [36].

**Epigallocatechin Gallate**

EGCG (found in green tea) is a strong antioxidant, it protects neurons by: decreasing oxidative stress, preventing mitochondrial dysfunction and preventing protein misfolding [37].

**Natural Compounds**

**Coenzyme Q10**

CoQ10 is a mitochondrial coenzyme that increases the production of ATP and diminishes ROS production. Clinical PD trials have had mixed successes, although high doses are judged as rather safe with the possible positive effect [38].

**N-Acetylcysteine:**

NAC also serves as a precursor of glutathione that resupply the intracellular GSH levels and minimise oxidative damage. It also regulates metabolism of dopamine and guards against dysfunction of mitochondrial in the PD models [39].

**Melatonin:**

One of the neurohormones with high antioxidant and anti-apoptotic activity. Melatonin is able to penetrate the blood-brain barrier, reduce ROS, and increase mitochondrial activity, as well as the inhibition of young synuclein toxicity [40].

**Lipoic Acid:**

A thiol antioxidant which recycles other antioxidants like vitamins C, and E. It also binds with metal ions and aids in the energy metabolism of the mitochondria [41].

## 4. PD neuroinflammation

Table 6.1 indicates role of Microglia and Astrocytes in Neuroinflammation and Neuronal Degeneration in PD are as follows [42]:

**Table 6.1: Role of Microglia and Astrocytes in Neuroinflammation and Neuronal Degeneration in PD**

| Cell Type | Physiological Role | Activation Trigger | Pathological Outcome in PD | Key Molecules Involved |
|---|---|---|---|---|
| **Microglia** | - Immune surveillance- Removal of dead cells and pathogens | - Neuronal injury- Neuroinflammation- DAMPs- Misfolded α-synuclein via TLRs | - Chronic inflammation- Release of pro-inflammatory cytokines, ROS, NO- Dopaminergic neuron degeneration | TNF-α, IL-1β, IL-6, ROS, NO, DAMPs, TLRs, α-synuclein |
| **Astrocytes** | - Maintenance of neuronal homeostasis- Support for blood-brain barrier- Nutrient regulation | - Pro-inflammatory signals- Neuronal stress signals | - Reactive gliosis- Amplification of microglial response- Disruption of neuronal-glial communication | GFAP, S100β, IL-1β, cytokines |

### 4.1 Microglia and astrocytes activation

Neuroinflammation is a defining feature of Parkinson Disease (PD) with an important role in the subsequent dopaminergic neuronal loss of the substantia nigra pars compacta. Microglia and astrocytes are the two principal types of glial cells of the central nervous system (CNS) interacting with the central functions of inflammation in the nervous system [42]. Although they are initially protective, they become chronic and harmful inducing prolonged neuron injury and chronic diseases. Microglial Activation [43]. Microglia are immune cells present in the brain and serve as the initial defense against invasion and cell injury. Microglia in a healthy brain are in a so-called resting mode and continuously survey their surroundings. Microglia however respond to injury to the neurons and upon such reception of neuronal injury; microglia are transformed into a reactive phase. Microglia activated by neuroinflammation and/or neurotransmitters simultaneously release various pro-inflammatory cytokines (e.g., TNF-alpha, IL-1beta, IL-6), chemokines, reactive oxygen species (ROS), and nitric oxide (NO). These factors serve the purpose of removing damaged cells and pathogens, but long-term and excessive microglial activation results in a toxic microenvironment that leads to rapid deterioration of neurons [44]. This becomes an ongoing cycle of inflammation and cell death, with dying dopaminergic neurons in PD releasing damage-associated molecular pattern molecules (DAMPs) that then, in turn, activate more microglia, creating a vicious circle. In addition, microglia have receptors (including TLR) which are activated by misfolded ions of alpha-synuclein that are released by degenerating neurons, inducing innate immunity measures. Not only does it enhance cytokine release,

but also facilitating the uptake and processing of α-synuclein, there is a possibility of distributing pathological aggregates to other parts of the brain [45].

### 4.2 Pro-inflammatory cytokines (TNF-alpha, IL-1-beta, IL-6)

Such pro-inflammatory cytokines are essential elements of neurodegenerative mechanisms related to Parkinsons Disease (PD). The most studied neuroinflammation mediators include the tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1-beta) and interleukin-6 (IL-6) which play a crucial role in the development of neuroinflammation and they are the causative mechanism of neuronal destruction in the substantia nigra [46]. Neuronal stress or damage prompts rapid upregulation of TNF-a which is released mainly by activated microglia. It is able to also initiate apoptosis through binding to its receptors (TNFR1/TNFR2) which causes downstream intracellular signaling events like the activation of caspases, NF-kB translocation as well as the malfunction of the mitochondrium [47]. During PD, TNF-alpha in the CSF and post mortem human brain tissues have been found to be raised hinting its involvement in direct dopaminergic neurodegeneration. Another essential cytokine is IL-1, which has its inactive form, IL-1, and their transformation is activated through the inflammasome complex, including NLRP3 [48]. When IL-1beta is released it causes cell recruitment and activation of other immune cells, continuing the circle of inflammation. It can also mitigate with the synaptic plasticity and can break the blood-brain barrier (BBB), which lets peripheral immune cells enter the brain and boost the CNS inflammation. IL-6 is also bipolar as it is both a pro and anti-inflammation agent during its situation [49]. Increased IL-6 levels have been linked with progression of the disease in PD. It can boost the inflammatory processes with enhancing the acute-phase proteins production and differentiation into Th17 cells. Persistent IL-6 exceeds the activation of glia and oxidation and neuronal death. Taken together, these cytokines produce an inflammatory microenvironment that is self-sustaining and will worsen the increased production of oxidative stress, impair neuronal homeostasis, and promote the rate of dopaminergic neuronal depletion. Inhibiting these molecules or their signalizing activity can be viewed as an effective approach to chronic PD management and preserve the physiology of the neurons in the disease [50].

### 4.3 Chronic Inflammation and Development of the Disease

It is now known that chronic inflammation is a major driver of the manifestation of Parkinson Disease (PD). Unlike acute inflammation that is a limited response that protects the organism, chronic neuroinflammation has persisting effects and plays a role in producing chronic neuronal damage. Chronic activation of glial cells (microglia and astrocytes, specifically) cause a chronic signal linked to the release of pro-inflammatory cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide (NO) which all have the potential to worsen the dysfunction and death of neurons in PD. It is proposed that the onset of this chronic inflammatory state occurs many years earlier in the development of motor symptoms. It can result in the initiation of inflammatory responses related to the presence of environmental toxins, genetic mutations (e.g., SNCA, LRRK2, or PINK1), the buildup of misfolded proteins, and especially α-synuclein. Such stimulation, nevertheless, persists over time, keeping microglia activated and, hence, establishing a vicious circle in which inflammation leads to neuronal damage which, in turn, causes more inflammation [51].

The abnormalities in the brain in terms of the regulation of the immune system is one of the most important points of chronic inflammation in PD. Through post-inflammatory glial we normally achieve a recuperating state of glial cells following an episode of inflammation. In Pd, however, such resolution process is unsuccessful resulting in prolonged generation of harmful mediators and lack of efficient repair processes. In addition, the blood-brain barrier (BBB) can be compromised and peripheral immune cells can infiltrate into the CNS providing the inflammatory milieu. Noticeably, chronic inflammation

is not discerned in a single brain area (substantia nigra), but can extend to other areas of the brain: this is consistent with the non-motor symptoms of PD, including cognitive, mood, and sleep disorders. The gradual advance of inflammation might even be the cause of the sequential manner of the worsening of the symptoms as time passed. A focused attack on chronic inflammation by anti-inflammatory drugs, immunomodulators, or lifestyle changes, i.e., diet and physical activity, is a potential means of stabilizing the disease by reducing progression, enhancing quality of life, and postponing more serious clinical manifestations in PD patients [52].

## 5. Anti-inflammatory Mechanisms in PD

### 5.1 Prevention of microglial activation

In Parkinson Disease (PD), chronic neuroinflammation is mediated by the microglial activation leading to degeneration of dopaminergic neurons. Microglial inhibition may be a useful approach toward preventing or retarding PD. The neuroinflammatory cycle can be calmed down by avoiding unwarranted microglial responses, by lessening the generation of damaging mediators and safeguarding the dopaminergic nerve cells in the substantia nigra [53].

**Myriad strategies have been pursued towards preventing microglial activation:**

Various pharmacological interventions like NSAID, Pioglitazone and Minocycline have demonstrated capacity to diminish microglia activation in Parkinsonians disease. More specifically, minocycline can reduce apoptosis of the neurons. Flavonoids (e.g., quercetin, luteolin) and polyphenols (e.g., curcumin, resveratrol) also have anti-inflammatory and neuroprotective actions by regulating the activity of microglia using several pathways, such as NF-κB, MAPK, Nrf2. Toll-like receptor (TLR) or CD200/CD200R-based immunomodulatory interventions can be used to regulate microglia and change it to an anti-inflammatory phenotype (M2) where possible. New methods that utilize gene therapy are also studied to suppress the activities of the inflammatory mediators or increase production of anti-inflammatory molecules in microglia. Altogether, microglial activation inhibition has a two-fold effect in the case of PD: it can save neurons against the toxicity of inflammation and leave the homeostatic microglial role intact. Further studies on the molecular nature of microglial activation and the regulation thereof promise to help establish more specific and successful treatment approaches towards PD [54].

### 5.2 Inhibition of Signaling of Inflammatory Cytokine

Pro-inflammatory cytokines especially (TNF- a ), interleukin-1 beta (IL-1 b ) and ( IL-6 ) are the critical factors contributing to neuroinflammation and gradual loss of dopaminergic neurons in(PD). Mainly secreted by microglia and astrocytes when activated, these cytokines trigger and maintain pathological signaling cascades of inflammation to the detriment of neuronal survival and functionality. In the treatment of neuroinflammation, modulation of inflammatory cytokine signaling is one way that the pro-inflammatory mediators as well as related intracellular pathways are targeted to alleviate their neurotoxic mediators. A number of mechanisms and therapeutic approaches have been approached [55]:

**1. Cytokine production inhibition**

Other anti-inflammatory drugs interfere with the production and secretion of TNF-a, IL-1b and IL-6. As an example, NSAIDs such as ibuprofen or celecoxib block (COX-2) and hence reduce the synthesis of prostaglandins and subsequent cytokine expression. There is mixed clinical evidence, but epidemiological studies provide evidence that the long-term intake of NSAIDs can decrease the likelihood of developing PD [56].

**2. Cytokine Receptor Blockade**

It also includes another approach of preventing the interaction between cytokines and their corresponding receptors on target cells. The development of monoclonal antibodies and receptor antagonists that can act as inhibitors to the cytokine-receptor interactions has taken place. As an example, TNF-alpha inhibitor etanercept has demonstrated neuroprotective effects in preclinical models through the mediation of decreases in inflammation and death of dopaminergic cells [57].

**3. Inhibition of Inflammatory Signal Pathways**

Big transcription factors activated downstream are nuclear factor-kappa B (NF-kappa B) and signal transducer and activator of transcription 3 (STAT3) following cytokine signaling. These lead to increased stimulus of other inflammatory genes increasing the neuroinflammatory response. These pathways can be suppressed by natural compounds such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) thus lowering neuronal injury caused by the cytokines [58].

**4. Anti-inflammatory Cytokines Promotion**

Increasing production of anti-inflammatory cytokines like IL-10 and (TGF- through their production, restores homeostasis in the immune system in the brain. These beneficial cytokines have been reported to be upregulated by some neuroprotective agents as well as certain lifestyle alterations i.e. exercise, dietary polyphenols etc [59].

**5. RNA Interference and gene therapy**

New strategies would encompass the use of gene silencing reagents (such as siRNA or CRISPR/Cas9) to silence genes that encode pro-inflammatory cytokines/signaling proteins. The advantage of this strategy is that it provides extreme specificity and prolonged control of inflammatory reactions. Table 6.1 indicates Key Inflammatory Pathways Implicated in PD are as follows [60]:

**Table 6.1 indicates Key Inflammatory Pathways Implicated in PD are as follows:**

| Pathway | Involved Molecules/Cells | Role in PD Pathogenesis | Mechanistic Outcome |
|---|---|---|---|
| **NF-κB Pathway** | TNF-α, IL-1β, Microglia | Activates pro-inflammatory cytokine expression | Neuronal death, oxidative stress |
| **NLRP3 Inflammasome** | Caspase-1, IL-18, IL-1β | Amplifies neuroinflammation | Promotes dopaminergic neuron degeneration |
| **MAPK Pathway** | JNK, p38 MAPK, ERK | Mediates stress-induced signaling | Enhances glial activation and neurotoxicity |
| **JAK/STAT Pathway** | STAT1/3, IL-6 | Drives inflammatory gene transcription | Chronic inflammation in the substantia nigra |
| **TLR Signaling (TLR2/4)** | Toll-like receptors on microglia | Recognizes α-synuclein aggregates | Induces innate immune response and neurodegeneration |

**5.3 Drugs and Natural Anti-inflammatory**

Based on their ability to adjust neuroinflammation, which is a major characteristic of Parkinson Disease (PD) progression, natural anti-inflammatory compounds as well as pharmacological agents have become a focus of research in Parkinson Disease. These agents inhibit pro-inflammatory mediators, prevent microglial activation and the recovery of cellular homeostasis in the central nervous system. Table 6.1 indicates Anti-inflammatory Agents and Natural Compounds in PD Therapy are as follows [61]-

**Table 6.1 Anti-inflammatory Agents and Natural Compounds in PD Therapy**

| Agent/Compound | Source | Target Pathway | Anti-inflammatory Action | Status |
|---|---|---|---|---|
| **Chrysin** | Flavonoid (honey, propolis) | NF-κB, MAPK | Inhibits cytokine release and microglial activation | Preclinical studies |
| **Curcumin** | Turmeric (*Curcuma longa*) | NF-κB, JAK/STAT | Suppresses inflammatory mediators | Clinical trials ongoing |
| **Baicalein** | Scutellaria baicalensis root | NLRP3, TLR4 | Downregulates inflammasome and TLR signaling | Preclinical evidence |
| **Resveratrol** | Grapes, berries | SIRT1/NF-κB | Reduces microglial activation and oxidative inflammation | Clinical trials ongoing |
| **Non-steroidal Drugs** | Ibuprofen, Aspirin | COX, NF-κB | Suppresses prostaglandin synthesis and cytokines | Mixed results in PD |

**A. Herbal Anti-inflammatory**

The natural compounds, especially those of botanical origin and dietary sources, have strong anti-inflammatory activity and mechanisms of action that are multi-targeted:

**1. Curcumin (turmeric)**

Curcumin is a *Curcuma longa* polyphenol and there have been a lot of investigations on its neuroprotective effect. It suppresses NF-kB activation and pro-inflammatory cytokines including TNF-alpha, IL-1-Beta and IL-6. Moreover, curcumin can minimize oxidative pressure and reinforce neuronal survival by managing pathways of an indication such as MAPK and PI3K/Akt.

**2. Grapes and berries (resveratrol)**

Resveratrol can induce the SIRT1 that is a deacetylase and controller of inflammation and oxidative stress. It prevents the activation of the microglia and reduction of pro-inflammatory enzymes (e.g. iNOS, COX-2) and downregulation of the release of cytokines helps to preserve the dopaminergic neurons.

**3. Epigallocatechin Gallate (EGCG, green Tea)**

EGCG decreases neuroinflammation: inhibition of the activities of NF-κB and JNK. It also removes reactive oxygen species (ROS), reduces microglial activation and inhibits the release of IL-6 and TNF-alpha.

**4. Quercetin (in apples, onions and tea)**

Quercetin is an antioxidant, anti-inflammatory flavonoid. It regulates inflammatory genes in part by disrupting NF- and AP-1 signals and exerted neuroprotective properties in PD animal models.

**5. The Omega-3 Fatty Acids**

Fish oil contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which have anti-inflammatory properties, because they decrease production of pro-inflammatory eicosanoids and cytokines. Omega-3s also aid the integrity and the functioning of neuronal membranes [62].

**B. Anti-inflammatory medication.**

A number of anti-inflammatory pharmacological agents are under consideration with the view to use in PD treatment:

**1. Non Steroidal Anti Inflammatory Drugs (NSAIDs)**

COX enzymes are inhibited by NSAIDs such as ibuprofen and aspirin, which decreases the production of prostaglandins that are involved in creating inflammation. Epidemiological reports indicate that chronic use of NSAIDs can reduce the risk of PD but clinical responses are inconsistent.

**2. Glucocorticoids**

Anti-inflammatory drugs such as dexamethasone and prednisone act on pro-inflammatory transcriptional factors and pro-inflammatory cytokines. However, they have little applications in the long run due to side effects, including; immunosuppression and metabolic imbalance.

**3. Minocycline**

Minocycline is an antiinflammatory antibiotic that suppresses activation of the microglia, decreases TNF-alpha and IL-1beta. It has shown neuroprotective properties in preclinical models of PD but the clinical trials disappoint.

**4. TNF-α Inhibitors**

Biologic agents (such as etanercept and infliximab) have direct inhibitory effects on TNF-alpha. These have been promising in shielding dopaminergic cells and diminishing neuroinflammation in testing PD models.

**5. Statins**

Statins are mainly used in the treatment of high cholesterol and have anti-inflammatory activity. They prevent the activation of microglia and inhibit the formation of oxidative stress and cytokines and this provides possible neuroprotective effects of PD [63].

### 5.4 The NF-κB and MAPK Pathways Role

NF-kB and MAPK signaling pathways are vital in the control of inflammation, cell survival and microbial dysfunction in PD. Activation of each of these pathways as a result of environmental toxins, oxidative stress, and protein misfolding in PD, has the end result of upregulation of inflammatory genes and cytokines, which include TNF-a and IL-1-b and IL-6. In particular, NF-kB translocation into the nucleus commences in event of degradation of inhibitory IkB proteins (hence) enabling its translocation into the nucleus and activation of transcription of pro-inflammatory mediators [64]. At the same time, the MAPK family MAPKs, which includes ERK, JNK, and p38, react to apoptotic signals and help in the generation of inflammatory reactions and apoptosis. Excessive activation of these pathways also occur in microglia and astrocyte that contribute to neuroinflammation and death of dopaminergic neurons. Specific compounds such as curcumin, resveratrol, and flavonoids, and natural products are NF-kB and MAPK inhibitors that have been shown to minimize neuroinflammation and neuronal protection in PD models. The regulation of such signaling cascades, therefore, can be one of the therapeutic options to delay the progression of PD and enhance the survival of the neurons [65].

## 6. Neurorestorative Pathways

### 6.1 Neural Stem Cells and Neurogenesis

Originally, neurogenesis is a phenomenon that enables the production of new neurons in the neural stem cells to build brain plasticity and repair. From a perspective of Parkinson Disease, a condition that is associated with progressive atrophy of dopaminergic cells of the substantia nigra, neurogenesis is a potential line of neurorestitution. Even though adult neurogenesis is actively taking place in SVZ and

hippocampal dentate gyrus, research demonstrated that the stem/precursor nerve cells may migrate towards damaged tissue (e.g., substantia nigra) in case of brain injury [66].

Nevertheless, PD is linked with dysfunctional neurogenesis, which partly occurs because of the chronic inflammation, oxidative stress, and toxic microenvironment of the brain in the case of this illness. The factors lower the survival, differentiation potentials, and propagation of NSCs. The approaches to prevent degeneration, or stimulate neurogenesis, involve administration of neurotrophic factors and the use of gene therapy, cell replacement therapy, and pharmacological agents promoting activity of endogenous stem cells. White compounds such as curcumin, resveratrol, and ginsenosides have also been documented to induce neurogenesis through signaling pathway regulation and suppression of inflammatory factors. In the end, the therapeutic approaches that aim at stimulating neurogenesis and awaking of resident neural stem cells hold promise of fixing dopaminergic circuitry and better clinical performance in patients with PD [67].

**6.2 Neurotrophic Factors**

BDNF is notably present in the CNS and promotes survival of neurons, synaptic plasticity and neurogenesis. In PD, the impairment in the expression level of BDNF leads to neuronal vulnerability in the dopaminergic neurons. Increasing levels of BDNF (directly or indirectly) by means of pharmacological agents, gene therapy or physical exercise has been promising in providing neuronal protection and enhancing motor system in animal experimental models of PD [68]. When it comes to stimulating the survival of the dopaminergic neurons, GDNF comes out as quite powerful. It does that by using the GFRalpha1 receptor, and the Ret tyrosine kinase in order to provoke the survival pathways and the stimulation of the regeneration in the neurons. GDNF has been demonstrated to increase the release of dopamine, protect against neurotoxic challenge (e.g. MPTP, 6-OHDA) and ameliorate motor deficits in animal models of PD. Delivery via intercerebral infusion GDNF or viral vectors: Clinical trials with GDNF delivery through intracerebral infusion or viral vectors have been mixed and encouraging in nature with the significance of delivery methods and patient selection in mind [69]. The combination of BDNF and GDNF is important therapeutic targets to interfere with neurodegeneration in PD. Research that is currently going on includes how best to deliver them, as well as strategies combining them with other neuroprotective strategies to develop maximum therapeutic benefits [70].

**6.3 Cellular repair and mitochondrial biogenesis**

Parkinson Disease (PD) is characterized by the mitochondrial dysfunction, causing oxidative stress, failure of energy production, and death of the neurons. Consequently, mitochondrial biogenesis and cell repair enhancement is yet another potentially neurorestorative solution to the management of PD. Mitochondrial biogenesis is a process whereby fresh mitochondrion in the cell is formed in order to have sufficient production of energy and maintenance of metabolism. PGC-1alpha has been shown to be often down-regulated in PD as a factor that leads to reduced function of mitochondria. Pharmacologic or lifestyle (e.g., exercise, caloric restriction) improvement of PGC-1 activity has been found to have neuroprotective properties by increasing the number and function of mitochondria in dopaminergic neurons [71].

The repair processes by cells such as the autophagy mechanism, mitophagy, also play a vital role in ensuring neuronal health. The removal of broken proteins and organelles occurs through autophagy, whereas only the malfunctioning ones are targeted by mitophagy. Mutations in other mitophagy-regulating genes like Parkin and PINK1 that are known to promote neurodegeneration in PD interfere with mitochondrial quality control. The improvement of mitophagy by using pharmacological methods

or transgenics prevents mitochondrion disintegration, alleviates the oxidative stress, and aids cell survival [72].

### 6.4 Strategies to Regenerate dopaminergic Neurons

Since available treatment solutions mainly focus on the symptoms rather than regaining the lost neurons, DA neuronal regeneration has become the hotpoint of interest in neurorestorative treatment. Most promising is stem cell-based treatment especially stem cells derived embryonic (ESCs), induced pluripotent (iPSCs) and mesenchymal (MSCs). Such stem cells could be expanded into dopaminergic neuron-like cells in culture and implanted into the striatum or substantia nigra. iPSCs are particularly useful, since they could be grown out of the patient themselves by using their somatic cells, eliminating immune rejection [73]. Treatment with iPSCs-derived dopaminergic progenitors have illustrated promising results in clinical trials in terms of safety and functionality, but the long-term risks and benefits are unexplored. The other regeneration approach is gene therapy which is intended to increase the production of dopamine or survival of dopaminergic neurons. This involves provision of genes coding tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC) or GTP cyclohydrolase I (GCH1) used in production of dopamine. Also, viral vectors have been used to introduce neuroprotective genes, including GDNF (glial cell-derived neurotrophic factor), neurturin, in an attempt to improve the survival and activity of remaining DA neurons [74].

Delivery of neurotrophic factors aids survival as well as regeneration. However, other trophic factors such as FGF20 (fibroblast growth factor 20) and IGF-1 (insulin-like growth factor 1) have also been shown to be promising in preclinical research using PD models other than GDNF and BDNF (brain-derived neurotrophic factor). Further, this process is also promoted by other mechanisms, including Nrf2 activation, which is partially related to antioxidant defense and acute repair of the mitochondrion. Nrf2 increases production of antioxidant enzymes and mitochondrial proteins thus countering ROS and enhancing cellular resistance [75].

## 7. Integrative Approach: Antioxidant and an Anti-inflammatory Interaction Neurorestorative Interaction

Parkinson disease (PD) is a non-infectious multifactorial neurodegenerative disease that is catalyzed by overlapping mechanisms, which include oxidative stress, neuroinflammation, altered mitochondrial function, and dopaminergic down-trodden. Thus, the effectiveness of single-target therapies to stop or even turn around the release of the disease does not always work. A comprehensive treatment that includes treatment of oxidative damage, inflammation, and neuronal loss at once is vital in the modification of the disease. The addition of antioxidant, anti-inflammatory and neurorestorative approaches provides a complete way of defending and restoring the dopaminergic system [76].

### 7.1 Multi-target Therapy Multi-target therapies (MTTs) have synergistic effects.

The opportunity of targeting the inter-relatedness of the pathogenic pathways in PD leads to the synergistic therapies. As an example, the microglial cells may be activated under oxidative stress and cause neuroinflammation, which in its turn contributes to increased oxidative damage. Combining the two pathways simultaneously increases neuroprotection. Use of antioxidants like Coenzyme Q10 or N-acetylcysteine (NAC) has been proven capable of suppressing the levels of reactive oxygen species (ROS), thus inhibiting NF-OB manifestations of inflammation. In parallel, use of anti-inflammatory therapy in combination with neurotrophic support (e.g. GDNF or BDNF delivery) may not only prevent neuronal loss but actually promote repair and regeneration [77]. Trophic factors and antioxidants together with stem cell therapies have increased cell survival, integration, and functional recovery in

models of PD. The fact that the pathways are synergistic implies that alteration of one mechanism usually has a positive impact on others complicating development of mono-target based treatment affecting the PD progression compared to multi-target treatment [78].

### 7.2 Multi-functional Acting Natural Compounds

Natural substances are characterized by their pleiotropic effect, and several substances are reported to have antioxidant, anti-inflammatory, and neuroprotective effects in one molecule. As an example, curcumin scavenges free radicals, suppresses NF-kB and MAPK inflammatory pathway, and stimulates neurogenesis. Resveratrol recruits SIRT1 signaling which boosts mitochondrial biogenesis and neuronal survival as well as decreasing inflammation. Baicalein is isolated ingredient of Scutellaria baicalensis, which has been identified to protect dopaminergic neurons through inhibition of ROS generation, pro-inflammatory cytokine downregulation and deactivation of the apoptotic cascade. Ginsenoside is active ingredients of ginseng and increases expression of BDNF and promotes differentiation of nerve cells. Such natural agents have the potential as alternative or combinations with synthetic drugs because of their safety and multi-activity. They are specially important in early or preventive approaches, where the key to success is slowing the multifaceted development of PD [79].

### 7.3 Current polypharmacology in PD

Polypharmacology describes either the design or application of drugs which have multiple targets, or drug actions on several disease processes. Polypharmacology has the goal of finding single compounds or combinations of agents that would help in the concomitant prevention of oxidative stress, inflammation and neuronal loss. Advances Current advances include the preparation of hybrid compounds that have features of both antioxidant and anti-inflammatory in a single molecule, including dual COX-2 inhibitors and free-radical scavengers [80]. Drug repurposing includes further investigation of the existing drugs based on their multi-target effects in PD, such as riluzole, pioglitazone, or minocycline, due to their properties of being neuroprotective and anti-inflammatory drugs. More so, nanotechnology and targeted delivery systems are also being applied in the delivery of antioxidants and neurotrophic agents directly to CNS, mainly to enhance efficacy and decrease systemic toxicity. Identification of the candidate molecules with multi-target functions is also proceeding due to artificial intelligence (AI) and computational modeling to enhance the drug discovery and personalized medicine in PD [81].

## Conclusion

The presence of intricate combinations of oxidative stress, chronic inflammation, and neurodegeneration including dopaminergic cell death in the substantia nigra sums up PK. Antioxidant pathway prevents reactive oxygen species (ROS) that will aggravate the damage of the cells and anti-inflammatory reduces excessive excitation and/or production of pro- inflammatory cytokines by the microglia. Neurorestorative efforts strive to fix/interchange indisposed neurons, encourage neurogenesis, and improve the synaptic plasticity. All these processes are not merely essential independently but also inter-dependent and thus form a triad which is the key to the process of development and the possible cure of PD. These mechanisms have been discovered and a wide range of therapeutic targets has been identified. Although some traditional therapies have majorly targeted the relief of symptoms (e.g., dopamine replacement therapy with levodopa), mechanism-based therapies go a step further to target the prevention or deceleration of disease progression. Natural compounds, gene therapies, growth factor delivery and cell-based methods have prospective potential as translational research. Antioxidants and anti-inflammatory agents have entered the clinical trial stage in different studies, albeit with minimal success because of the difficulties associated with this type of medication in terms of bioavailability and heterogeneity of patients. However, these investigations have formed the basis of individualized and preventive measures which are the potential solution to transform PD care. PD treatment is in the future of multi-targeted and personalized neuroprotective neurorestorative therapy. Drug targeting and efficacy has the potential to be solved by innovations in nanotechnology, progress with biomarker discovery, and delivery-type (e.g., intranasal and nanoparticle-based devices). In addition, the system polypharmacology, or the creation of drugs the action of which affects several pathological pathways at the same time, is becoming popular. This could improve with integrative strategies--e.g., the use of combination pharmacologic treatments with lifestyle transditions (e.g., diet, exercise, stress management). Exquisite clinical trials that are longitudinal are needed to confirm the effectiveness of these therapies. Finally, symptomatic treatment to disease modification will be the next milestone in the treatment of PD.

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