



REVIEW

Rotenone-Induced Mitochondrial Dysfunction, Neuroinflammation, Oxidative Stress, and Glial Activation in Parkinson's and Alzheimer's Diseases

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ABSTRACT: Rotenone is a lipophilic herbicide extensively utilized in experimental neurodegenerative models because of its capacity to disrupt complex I of the mitochondrial electron transport chain. This inhibition results in reduced ATP synthesis, elevated reactive oxygen species (ROS) formation, and mitochondrial malfunction, which instigates oxidative stress and cellular damage, critical elements in neurodegenerative disorders like Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD). In addition to causing direct neuronal injury, rotenone significantly contributes to the activation of glial cells, specifically microglia and astrocytes. Activated microglia assumes a proinflammatory (M1) phenotype, distinguished by the secretion of inflammatory cytokines including tumor necrosis factor alpha (TNF- α), interleukin 1 beta (IL-1 β), and interleukin 6 (IL-6), with the generation of nitric oxide and ROS, which exacerbate the neuronal injury. Astrocytes can intensify neuroinflammation by secreting proinflammatory molecules and impairing their neuroprotective roles. Our hypothesis is that rotenone is posited to elicit a neuroinflammatory response via mitochondrial malfunction, ROS generation, and the activation of proinflammatory pathways in microglia and astrocytes. This mechanism leads to accelerated neuronal impairment, promoting neurodegeneration. Comprehending the inflammatory pathways activated by rotenone is crucial for pinpointing therapeutic targets to regulate glial responses and mitigate the advancement of neurodegenerative disorders linked to mitochondrial malfunction and chronic inflammation. This review examines the function of glial cells and critical inflammatory pathways, namely Nuclear factor kappa β (NF- κ B), Phosphoinositide 3-kinase/Protein kinase B/Mammalian target of rapamycin (PI3K/AKT/mTOR), and Wnt/ β -catenin signaling pathway in Parkinson's disease, Alzheimer's disease, and ALS, emphasizing illness-specific responses and the translational constraints of rotenone-based models. The objective is to consolidate existing understanding regarding the role of rotenone-induced mitochondrial failure in promoting glial activation and neuroinflammation, highlighting the necessity for additional research into these pathways. Despite the prevalent application of rotenone in experimental models, its specific effects on glial-mediated inflammation are inadequately comprehended, necessitating further investigation to guide the formulation of targeted therapeutic strategies.

KEYWORDS: Rotenone; neuroinflammation; mitochondrial dysfunction; glial activation; neurodegenerative disorders



1 Introduction

Mitochondria are vital organelles for cellular homeostasis, they are pivotal for energy production, metabolic regulation, cellular signaling, and apoptosis [1]. Their main role is to produce adenosine triphosphate (ATP) via oxidative phosphorylation, a process that takes place in the electron transport chain situated in the inner mitochondrial membrane [2]. Electrons are conveyed through protein complexes to molecular oxygen, creating an electrochemical gradient that facilitates ATP synthesis through ATP synthase [3]. Mitochondrial failure can undermine cell viability and contribute to numerous illnesses, including neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) [4]. Rotenone is a naturally occurring insecticide extensively utilized in experimental neurodegenerative models because of its capacity to specifically block complex I of the mitochondrial electron transport chain [5,6]. This inhibition obstructs the flow of electrons from reduced nicotinamide adenine dinucleotide (NADH) to ubiquinone, impeding ATP synthesis and fostering a pro-oxidative milieu [7]. As a result, the generation of ROS escalates, causing damage to lipids, proteins, and mitochondrial DNA, which finally results in cellular malfunction and neuronal demise [8].

Moreover, owing to its lipophilic characteristics, rotenone readily traverses the blood-brain barrier, facilitating its dissemination inside the central nervous system [9]. This trait renders it an effective instrument for eliciting neurodegeneration in animal models and investigating neurodegenerative disorders [10]. Investigations utilizing these models have shown that rotenone-induced mitochondrial dysfunction impacts cellular bioenergetics, activates inflammatory pathways, disrupts calcium equilibrium, and facilitates the aggregation of misfolded proteins, thereby exacerbating the advancement of neurodegenerative diseases [11,12]. A crucial element of rotenone-induced neurotoxicity is its effect on glial function, specifically the activation of microglia and the malfunctioning of astrocytes [13,14]. Exposure to rotenone induces an amplified inflammatory response in microglia, facilitating the secretion of pro-inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), which exacerbate neuronal injury via chronic neuroinflammation mechanisms [10,15]. The activation of microglia is partially facilitated via the Toll-like receptor 4 (TLR4) pathway and the activation of the NF- κ B transcription factor, promoting a prolonged neurotoxic condition that jeopardizes neuronal survival [16].

Conversely, rotenone-induced astrocytic impairment disrupts glutamate homeostasis, energy metabolism, and neuronal trophic support [17]. Inhibition of mitochondrial complex I in astrocytes diminishes glutamate uptake by the EAAT2 transporter, resulting in neurotransmitter buildup at the synapse and exacerbating neuronal excitotoxicity [18]. Mitochondrial failure in astrocytes diminishes lactate synthesis, an essential energy substrate for neurons, thus hindering neuronal metabolism and heightening vulnerability to oxidative injury [19]. Microglia-mediated neuroinflammation and astrocytic metabolic dysfunction create a pathogenic circuit that intensifies neuronal degeneration in rotenone-induced neurodegenerative models [16,20,21]. Previous findings highlight the essential significance of glial cells in the etiology of neurodegenerative illnesses and indicate that modifying their activity may serve as a viable therapeutic approach to alleviate neuronal damage linked to mitochondrial malfunction [22]. Furthermore, rotenone-induced mitochondrial dysfunction impairs intracellular calcium homeostasis, resulting in elevated cytosolic calcium levels [23]. The increase in calcium levels induces excitotoxicity, a condition where excessive calcium accumulation in neurons leads to the hyperactivation of ion channels and glutamatergic receptors, including N-methyl-D-aspartate (NMDA) receptors [24]. Excitotoxicity leads to irreversible neuronal injury, worsening neurodegeneration, and hastening the advancement of conditions such as PD and AD [25]. Rotenone administration has been demonstrated to raise intracellular calcium concentrations in dopaminergic neurons, leading to compromised neurogenesis and heightened excitotoxicity in experimental settings [23,26]. Most investigations utilizing rotenone-induced

neurodegenerative models have predominantly been performed on male rats or mice. Emerging research indicates that sex-related characteristics may affect susceptibility to rotenone toxicity, including variances in oxidative stress response, glial activation, and mitochondrial function. These findings underscore the imperative of including sex as a biological variable in experimental designs and analysis. Rotenone-induced mitochondrial impairment facilitates neurodegeneration via a multifaceted pathway encompassing oxidative stress, glial dysfunction, intracellular calcium dysregulation, and excitotoxicity. This study seeks to examine the cellular and molecular mechanisms involved in this process, emphasizing oxidative stress, glial activation, calcium dysregulation, and excitotoxicity, to improve our comprehension of their contributions to the pathogenesis of neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis.

2 Methods

A comprehensive search was performed on Google to locate pertinent publications regarding rotenone and its correlation with mitochondrial dysfunction in neurodegenerative illnesses, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. The inquiry employed several combinations of keywords, including rotenone, mitochondrial malfunction, oxidative stress, glial activation, calcium dysregulation, neuroinflammation, and specified disorders. Articles published were chosen based on scientific rigor, methodological excellence, and relevance.

A review of experimental investigations on rotenone induced neurotoxicity emphasized its involvement in mitochondrial malfunction, oxidative damage, glial activation (microglia and astrocytes), calcium dysregulation, protein aggregation, and neuroinflammation. The results were consolidated to emphasize shared and disease-specific causes of neurotoxicity in different neurodegenerative diseases.

3 Model of Parkinson's Disease Induced by Rotenone

Rotenone is utilized experimentally in Parkinson's disease (PD) research [27–31]. This neurodegenerative disorder is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra, leading to motor dysfunction due to diminished dopamine levels in the brain [32]. Despite its prevalent use and reputation as a gold standard in experimental models of Parkinson's disease due to its selective toxicity towards dopaminergic neurons, rotenone unlike 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), lacks genuine neurotoxic selectivity [33]. Rather, it functions as a broad-spectrum mitochondrial toxin that elicits nonspecific systemic toxicity, impacting nearly all cell types within the organism. Nonetheless, the clinical and neuropathological signs evident in the central nervous system are chiefly ascribed to the heightened vulnerability of certain brain areas, notably the substantia nigra and the locus coeruleus, to mitochondrial complex I inhibition [34]. This persistent inhibition results in significant and frequently permanent neurodegeneration of nigrostriatal dopaminergic neurons, correlated with classical motor symptoms like as bradykinesia and rigidity, closely resembling human PD [35]. Rotenone administration in rats and other animal models selectively induces degeneration of dopaminergic neurons in the substantia nigra, closely resembling the neuropathological features observed in human Parkinson's disease [33]. This model is particularly beneficial for investigating the underlying causes of neuronal loss in PD and evaluating prospective therapeutic methods [36]. The rotenone-induced model of Parkinson's disease in rats well mimics the motor impairments associated with the condition, such as stiffness and bradykinesia [37]. Furthermore, microglial activation and the formation of protein inclusions indicative of the illness were observed [38–40]. This model illustrates the aggregation of proteins, such as α -synuclein, in structures resembling Lewy bodies [41]. Protein aggregates are a clinical hallmark of Parkinson's disease, and their formation in animal models provides a robust framework for examining the mechanisms of neurodegeneration [40]. Rotenone

induces α -synuclein aggregation in neuronal cells, triggering a neuroinflammatory response similar to that observed in patients with PD [42–44]. Neuroinflammation is pivotal in the etiology of Parkinson's disease, and elucidating the role of rotenone in this process may provide essential insights into the disease start. Injection of rotenone in mice has been demonstrated to elevate pro-inflammatory cytokines and activate microglia, thereby facilitating neurodegeneration in the Parkinson's disease model [9,45,46], (Fig. 1). The behavioral manifestations and extent of cellular damage caused by rotenone are markedly affected by the route of delivery, dosage, and duration of exposure. Fleming et al. (2004) demonstrated that alterations in the delivery method (subcutaneous, intraperitoneal, or intravenous) at doses of 2–3 mg/kg produced significant variations in rearing behavior and tyrosine hydroxylase optical density [47]. Notably, although α -synuclein aggregation typically occurs after six weeks of continuous MPTP therapy, rotenone induces the formation of these deposits within approximately 10 days of exposure, underscoring its efficacy and swift neurotoxic impact [48,49].

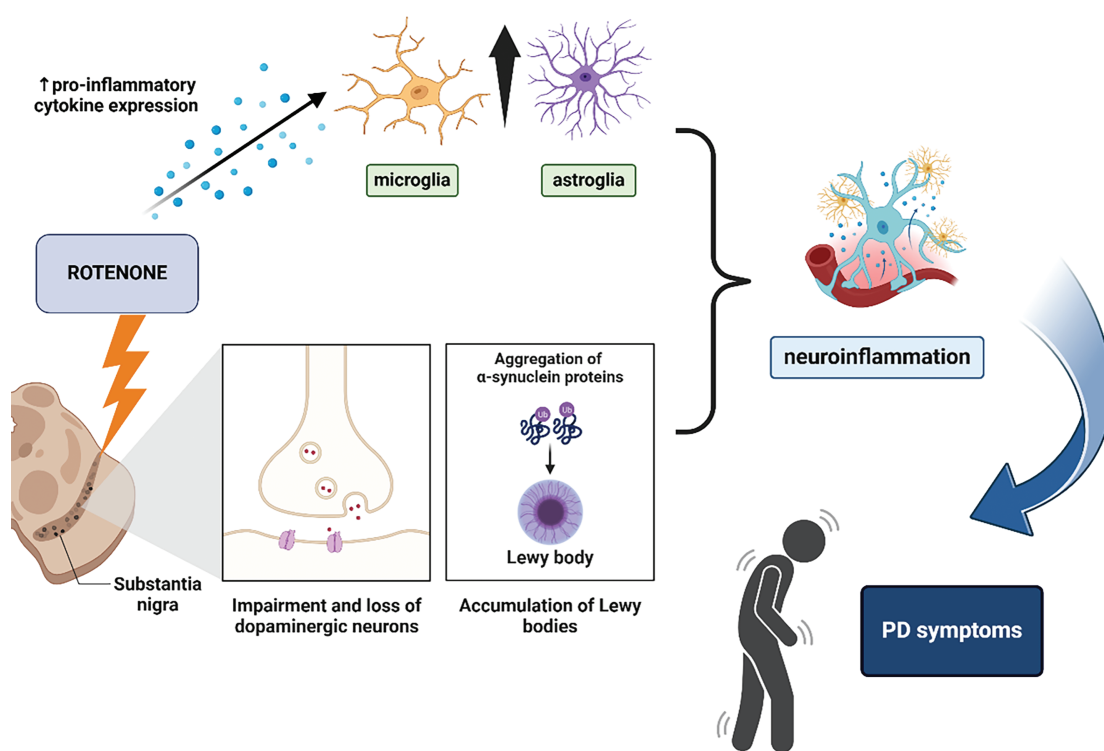


Figure 1: Schematic representation of the mechanisms underlying rotenone-induced Parkinson's disease (PD) models. Rotenone exposure leads to mitochondrial dysfunction in the substantia nigra, resulting in the impairment and loss of dopaminergic neurons. This is accompanied by the aggregation of α -synuclein proteins and the formation of Lewy bodies. Additionally, rotenone promotes neuroinflammation by increasing pro-inflammatory cytokine expression, activating microglia and astroglia. These processes contribute to neuronal damage and ultimately lead to PD-related motor symptoms (Created using [biorender.com](https://www.biorender.com))

4 The Function of Rotenone in Alzheimer's Disease

Rotenone, a powerful inhibitor of mitochondrial complex I [42], impairs the electron transport chain, resulting in less ATP synthesis and increased ROS. This oxidative imbalance inflicts damage on lipids, proteins, and DNA, ultimately inducing apoptosis [50]. Cholinergic neurons are significantly impacted by rotenone, leading to compromised synaptic function and reduced levels of acetylcholine, a crucial

neurotransmitter for cognition and memory [51,52]. A significant reduction of cholinergic neurons in the hippocampus was noted in rats treated with rotenone, corresponding with cognitive impairments characteristic of AD [53]. Furthermore, rotenone-induced mitochondrial impairment activates stress-related kinases, including p38 mitogen-activated protein kinase (MAPK) and Jun N-terminal kinase (JNK), intensifying neuroinflammation and neuronal degeneration [54]. Tau hyperphosphorylation, a significant clinical characteristic of AD [55], is facilitated by rotenone through oxidative stress and the activation of glycogen synthase kinase-3 beta (GSK-3 β), an essential enzyme in aberrant tau processing [56]. The aggregation of hyperphosphorylated tau destabilizes microtubules, disrupts axonal transport, and results in synaptic degeneration [57]. Moreover, rotenone affects β -amyloid (A β) metabolism by modifying the processing of amyloid precursor protein (APP). This amplifies β -secretase (BACE1) activity, hence elevating A β synthesis and plaque formation [58]. The accumulation of A β exacerbates mitochondrial dysfunction and oxidative stress, establishing a detrimental cycle of neurotoxicity that hastens the onset of Alzheimer's disease [57,59]. In addition to neuronal damage, rotenone stimulates glial cells, leading to the secretion of pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6, which exacerbate synaptic injury [60]. Microglial activation induced by rotenone has been associated with increased inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) generation, resulting in further oxidative damage [16,61]. These findings collectively underscore the significance of rotenone in mimicking essential pathogenic mechanisms of AD, such as mitochondrial failure, oxidative damage, neuroinflammation, tau pathology, and A β buildup [58,60]. Consequently, it functions as an essential model for investigating the molecular and cellular foundations of AD (Fig. 2).

5 Neurodegeneration Induced by Rotenone in Amyotrophic Lateral Sclerosis

In the context of amyotrophic lateral sclerosis (ALS), rotenone is capable of simulating neurodegeneration chiefly via mitochondrial dysfunction, oxidative stress, and neuroinflammation fundamental components of ALS pathogenesis [62]. Rotenone inhibits complex I of the electron transport cycle, so diminishing ATP synthesis and elevating ROS, resulting in oxidative damage to both motor neurons and glial cells [6,63]. This stress triggers apoptosis-related pathways, including Bax and caspase-3, leading to motor neuron death [15,64]. Furthermore, rotenone interferes with calcium homeostasis, intensifying glutamate excitotoxicity and endoplasmic reticulum stress [23,65]. In ALS models, rotenone enhances the activation of microglia and astrocytes, promoting the release of cytokines such as TNF- α and IL-1 β , which further exacerbate neuronal degradation [10,66]. It also hinders the elimination of misfolded proteins, such as mutant superoxide dismutase 1 (SOD1), exacerbating proteotoxic stress and protein aggregation in ALS [67,68]. Rotenone exposure hastens motor dysfunction and the loss of spinal cord motor neurons in animal models, highlighting its relevance for investigating disease causes and evaluating neuroprotective therapies (Fig. 3) [69,70]. The intensification of motor symptoms and neurodegeneration noted in rotenone-treated mice validates the significance of this paradigm in ALS research [71].

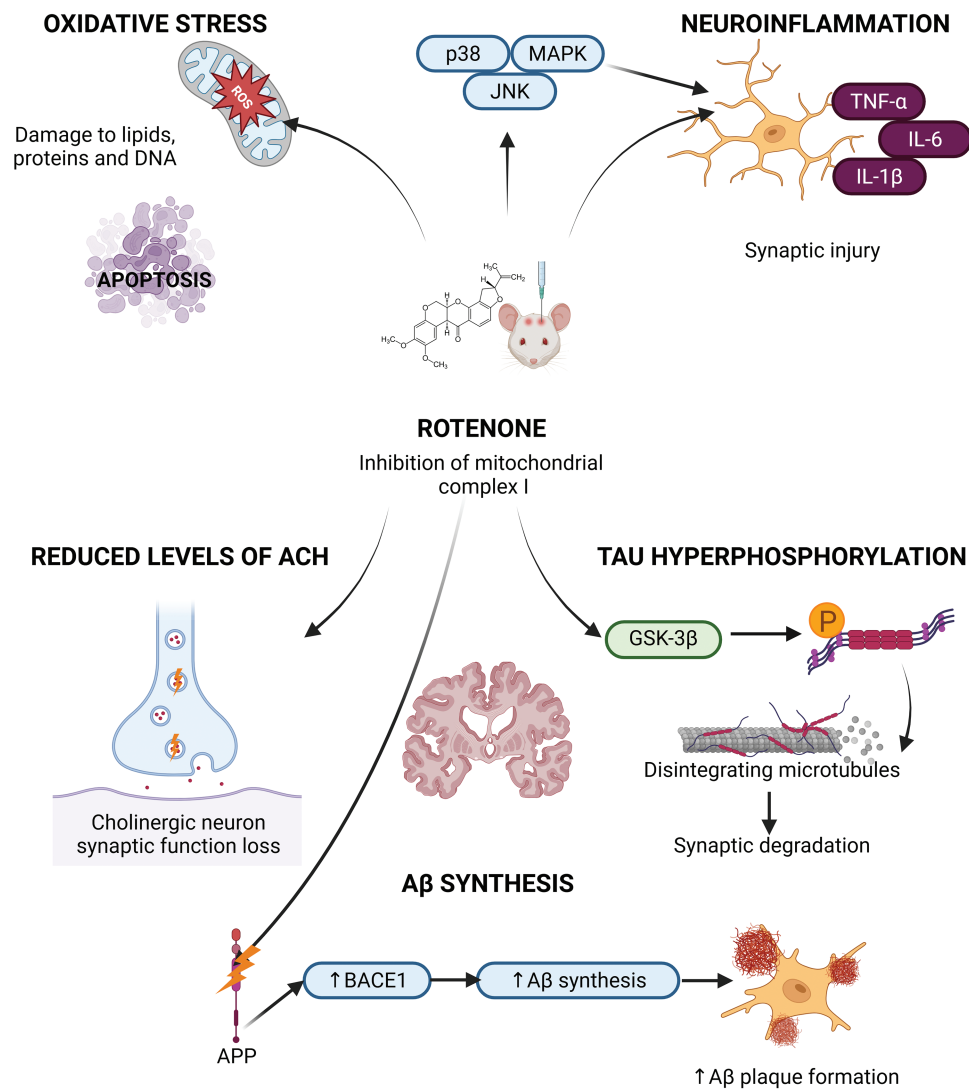


Figure 2: Schematic representation of the molecular mechanisms by which rotenone contributes to Alzheimer's disease (AD) pathogenesis. Rotenone, a mitochondrial complex I inhibitor, induces mitochondrial dysfunction and excessive production of reactive oxygen species (ROS), leading to oxidative stress. This cascade promotes tau hyperphosphorylation, amyloid- β (A β) accumulation, neuroinflammation, and activation of apoptotic pathways, including caspase-3. These combined effects contribute to neuronal degeneration characteristic of AD (Created with [BioRender.com](https://www.biorender.com))

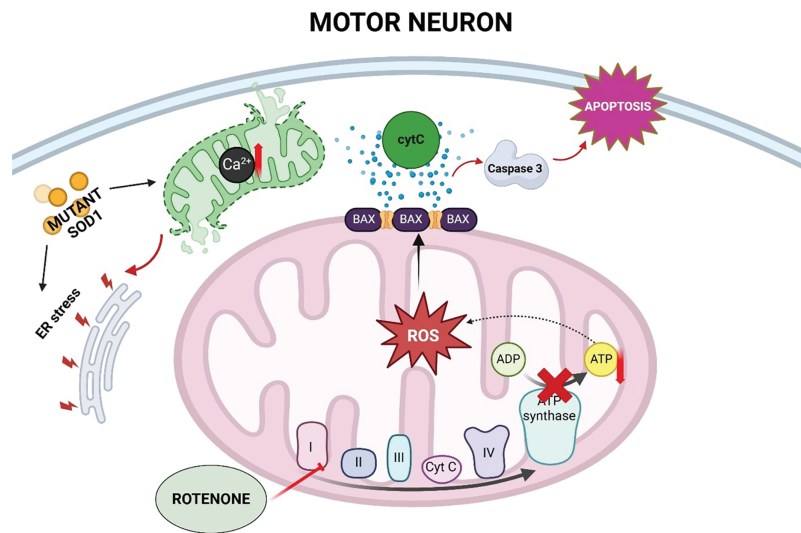


Figure 3: Schematic representation of the proposed mechanisms by which rotenone exposure may contribute to amyotrophic lateral sclerosis (ALS) pathogenesis. Rotenone inhibits mitochondrial complex I, leading to excessive reactive oxygen species (ROS) production and ATP (adenosine triphosphate) depletion in motor neurons. These changes, together with calcium (Ca^{2+}) dysregulation and endoplasmic reticulum (ER) stress, activate pro-apoptotic pathways involving cytochrome c (cytC), BAX, and caspase 3. Mutations in superoxide dismutase 1 (SOD1) can exacerbate these processes, further promoting neuronal cell death (Created using [BioRender.com](#))

6 Impact of Rotenone on Mitochondrial Function and Oxidative Stress

Rotenone markedly disrupts mitochondrial function by obstructing electron transport from NADH to ubiquinone (CoQ10), hence disturbing the proton gradient across the inner mitochondrial membrane [72]. This limitation diminishes ATP synthase (complex V) activity, hence, decreasing ATP generation is vital for cellular functions [11,73]. Electron buildup at complex I facilitates their transfer to molecular oxygen, resulting in the production of ROS, such as superoxide anion (O_2^-) [5,17,42]. Oxidative stress destroys membrane lipids, structural proteins, and mitochondrial DNA (mtDNA), which further disrupts mitochondrial function by destabilizing membrane potential and initiating cytochrome c release and caspase-9-mediated death [9,74–77]. Rotenone-induced oxidative stress stimulates proinflammatory responses, notably via NF- κ B signaling, which enhances proinflammatory cytokine production in glial cells and worsens neuronal dysfunction [22,78,79]. These effects are frequently observed in Parkinson's disease models, where rotenone produces dopaminergic neuronal death in the substantia nigra and locus coeruleus regions particularly susceptible to oxidative stress and mitochondrial dysfunction leading to motor symptoms such as hypokinesia and stiffness [80,81]. The buildup of ROS resulting from mitochondrial respiratory chain inhibition has catastrophic biological effects [78,82,83]. Although rotenone does not exhibit cell-type selectivity like the MPTP model, its prolonged suppression of mitochondrial complex I results in irreversible degeneration of the nigrostriatal pathway, rendering it a commonly utilized yet systematically lethal model [33,47,75]. The suppression of complex I and subsequent ROS generation has extensive biological implications [73,77,78]. Lipid peroxidation produces hazardous byproducts such as 4-hydroxynonenal (4-HNE), which compromise membrane integrity and mitochondrial function [84–86]. Protein oxidation, especially of cysteine, methionine, and tyrosine, results in diminished enzymatic activity and facilitates aggregation, which contributes to the cytoplasmic and mitochondrial inclusions observed in PD and AD [87,88]. mtDNA is particularly susceptible owing to its restricted repair capabilities; oxidative base alterations can result in mutations,

mitochondrial impairment, and bioenergetic collapse [89–91], thereby triggering DNA damage responses such as p53 signaling and apoptosis, which contribute to progressive neuronal degeneration [92] (Fig. 4).

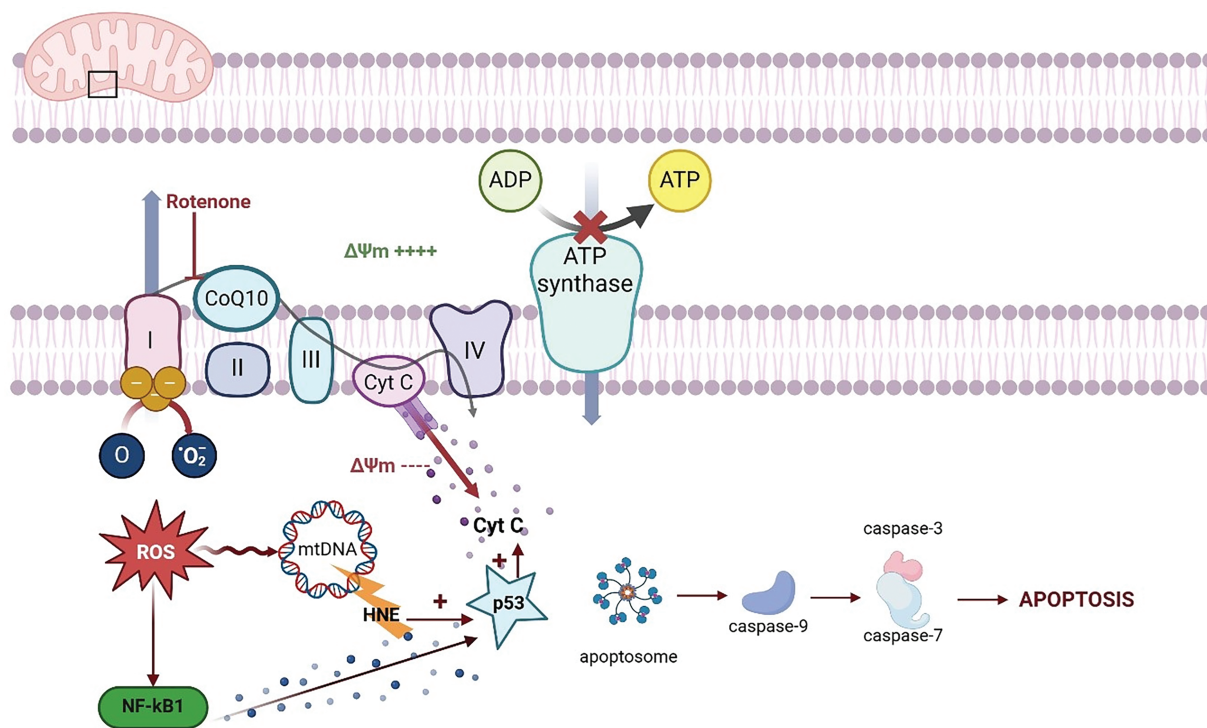


Figure 4: Schematic representation of the mechanisms underlying rotenone-induced mitochondrial dysfunction and oxidative stress. Rotenone selectively inhibits complex I (NADH: ubiquinone oxidoreductase) of the electron transport chain (etc), impairing electron flow and promoting the premature leakage of electrons. This results in an overproduction of reactive oxygen species (ROS), which in turn leads to oxidative damage of mitochondrial proteins, lipids, and mitochondrial DNA (mtDNA). The ensuing oxidative stress disrupts the mitochondrial membrane potential ($\Delta\Psi_m$) and compromises ATP synthesis, ultimately triggering the release of pro-apoptotic factors such as cytochrome c (Cyt C). This release activates caspase-dependent apoptotic pathways, further contributing to cellular degeneration. Additionally, the accumulation of lipid peroxidation products, such as 4-hydroxynonenal (HNE), exacerbates cellular injury by modifying key biomolecules involved in cellular homeostasis. The figure also highlights the activation of stress signaling pathways (e.g., NF- κ B and p53), which modulate the cellular response to mitochondrial damage and oxidative stress (Created using [biorender.com](https://www.biorender.com))

7 Mechanism of Neural Apoptosis and Synaptic Dysfunction

Rotenone-induced oxidative stress triggers apoptotic signaling and synaptic damage through the inhibition of mitochondrial complex I and the elevation of ROS production [5,42]. The increase of ROS causes damage to lipids, proteins, and DNA, hence activating the intrinsic apoptotic pathway via the alteration of mitochondrial membrane potential [84]. The release of cytochrome c stimulates apoptotic protease activating factor-1 (APAF-1) and procaspase-9, resulting in the activation of caspase-3 and subsequent DNA fragmentation [93–95]. Rotenone disturbs intracellular calcium equilibrium, resulting in the activation of calpain, a protease that degrades essential synaptic proteins including spectrin and synaptophysin thereby hindering synaptic plasticity [96,97]. The decrease of anti-apoptotic proteins, such as Bcl-2, and the increase of pro-apoptotic proteins, such Bax, further heighten neuronal susceptibility [98]. These processes

cumulatively lead to synaptic deterioration, impairments in dopaminergic transmission, and malfunction of the cortical-striatal network, which are indicative of Parkinson's disease progression [5,99] (Fig. 5).

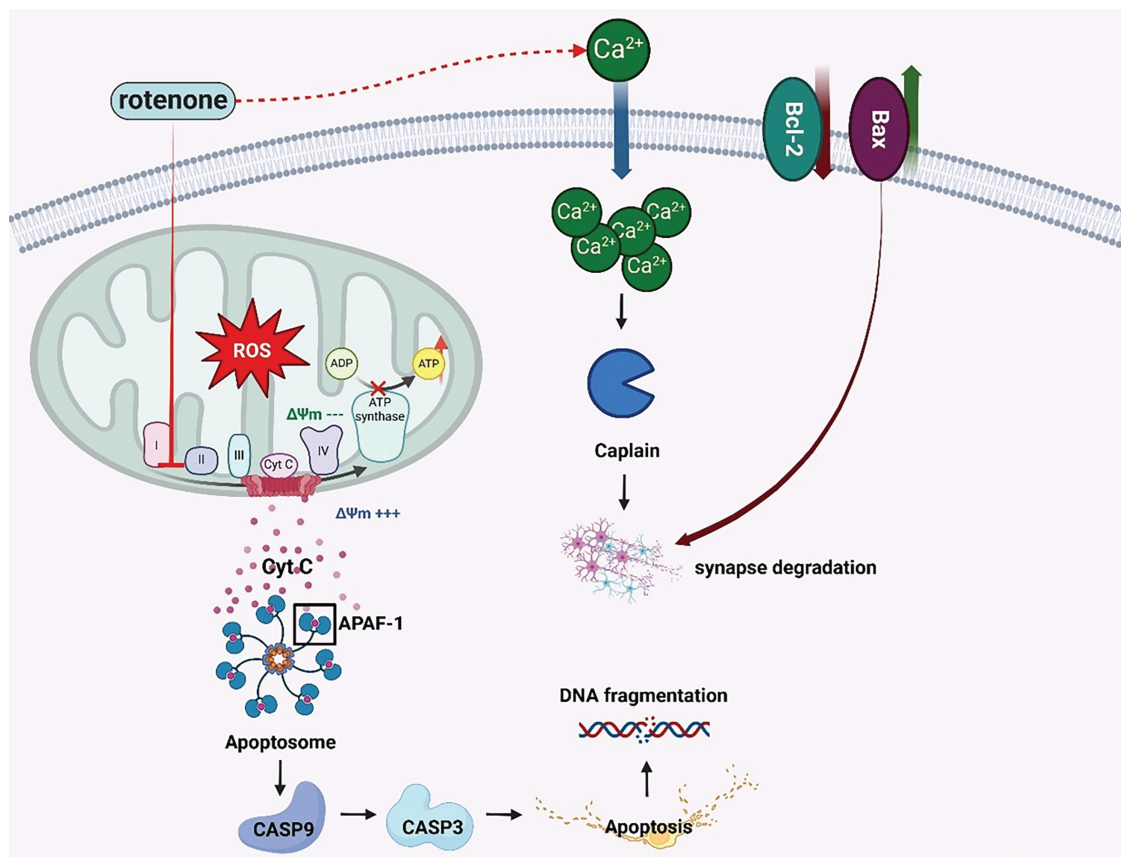


Figure 5: Schematic representation of rotenone-induced neural apoptosis and synaptic dysfunction. Rotenone-mediated inhibition of mitochondrial complex I increases reactive oxygen species (ROS) production and disrupts the mitochondrial membrane potential ($\Delta\Psi_m$). This promotes the release of cytochrome c (Cyt C) into the cytosol, where it binds apoptotic protease-activating factor 1 (APAF-1) to form the apoptosome, leading to caspase-9 and caspase-3 activation and, ultimately, apoptosis. Concurrently, pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) members of the Bcl-2 family regulate mitochondrial outer membrane permeability, further modulating cell death pathways. Elevated intracellular calcium (Ca^{2+}) levels activate calpain, a protease that contributes to synaptic degradation by cleaving key synaptic proteins. These combined events underline the neuronal loss and impaired synaptic integrity characteristic of rotenone-induced neurotoxicity (Created using [BioRender.com](https://www.biorender.com))

8 Modification of Calcium Metabolism and Excitotoxicity Induced by Rotenone

Rotenone-induced mitochondrial dysfunction disrupts intracellular calcium homeostasis, essential for neuronal signaling and survival [23]. Mitochondria modulate calcium by buffering cytosolic concentrations, a mechanism reliant on mitochondrial membrane potential ($\Delta\Psi_m$) [76,77]. Rotenone impairs $\Delta\Psi_m$, reducing calcium sequestration and resulting in cytosolic calcium accumulation, which activates pro-apoptotic pathways and intensifies excitotoxicity [24,100]. Excitotoxicity results from the excessive release of glutamate and the overactivation of NMDA receptors, allowing calcium to enter neurons [101]. Increased intracellular calcium initiates harmful cascades, such as calpain activation and the destruction of vital neuronal proteins [102]. Simultaneously, the activation of phospholipase A2 facilitates the release of fatty acids and the generation of pro-inflammatory eicosanoids, exacerbating neuronal dysfunction [103–105].

Supplementary processes encompass the activation of Protein Kinase C (PKC) and neuronal nitric oxide synthase (nNOS), resulting in the generation of nitric oxide (NO) [106,107]. Nitric oxide (NO) interacts with the superoxide anion to produce peroxynitrite (ONOO^-), a highly reactive entity that inflicts damage on cellular constituents [108–111]. Calcium imbalance triggers the opening of the mitochondrial permeability transition pore (mPTP), leading to cytochrome c release and death through caspases 3 and 9 [112–114]. Liu et al. (2016) showed that rotenone exposure elevates intracellular calcium levels in dopaminergic neurons, impairing neurogenesis and exacerbating excitotoxicity, which accelerates neurodegeneration [23,26]. Addressing calcium metabolism and excitotoxicity may provide therapeutic opportunities to counteract rotenone-induced harm (Fig. 6).

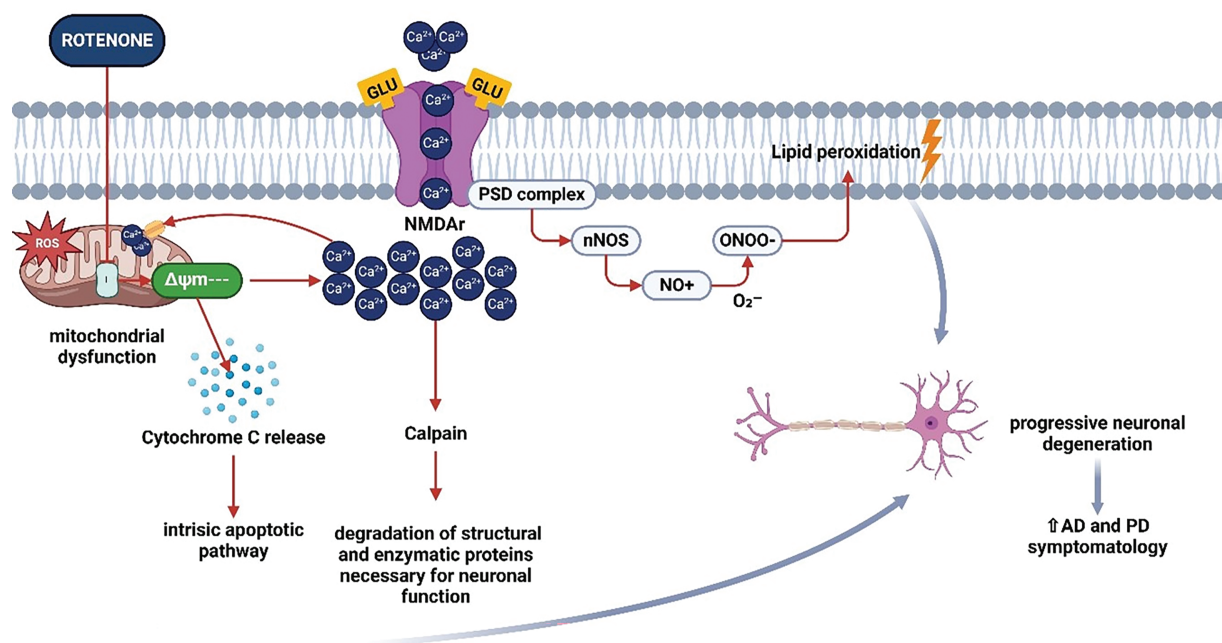


Figure 6: Schematic representation of rotenone-induced alteration of calcium metabolism and excitotoxicity. Rotenone-mediated inhibition of mitochondrial complex I leads to elevated reactive oxygen species (ROS) production, causing mitochondrial dysfunction and the release of cytochrome c (Cyt C). This event initiates the intrinsic apoptotic pathway, ultimately contributing to neuronal cell death. Concurrently, oxidative stress and impaired energy metabolism disrupt Ca^{2+} homeostasis, promoting excessive glutamate (Glu) receptor (NMDAr) activation and increased Ca^{2+} influx. This Ca^{2+} overload activates calpain, a protease responsible for the degradation of essential synaptic and structural proteins. Additionally, heightened intracellular Ca^{2+} stimulates neuronal nitric oxide synthase (nNOS), resulting in nitric oxide (NO) production, which combines with superoxide (O_2^-) to form peroxynitrite (ONOO^-). This potent oxidant drives lipid peroxidation, damages postsynaptic density (PSD) proteins, and exacerbates neuronal degeneration. Together, these processes accelerate excitotoxic injury and are implicated in the progression of Alzheimer's disease (AD) and Parkinson's disease (PD) (Created using BioRender.com)

9 Induction of Glial Cell Activation by Rotenone

Neuroinflammation in rotenone models entails the activation of glial cells, particularly microglia and astrocytes, as a reaction to neuronal damage and oxidative stress [115–118]. Microglia, the immune cells of the central nervous system, transition from a quiescent state to a pro-inflammatory (M1) phenotype, secreting cytokines (e.g., $\text{TNF-}\alpha$, $\text{IL-1}\beta$, IL-6), nitric oxide (NO), and reactive oxygen species (ROS), all of which contribute to neuronal injury [60,117,119]. Their persistent stimulation increases immune cell infiltration and sustains inflammation [120]. Astrocytes facilitate neuronal metabolism and repair but

have a reactive behavior following neurotoxic insults such as rotenone exposure [121,122]. They secrete cytokines, chemokines, and prostaglandins, which may exacerbate inflammation and neurodegeneration if prolonged. While astrocytic activation may initially confer protection, prolonged stimulation amid oxidative stress and mitochondrial malfunction fosters a pro-inflammatory condition [123–125]. Communication between astrocytes and microglia is compromised in rotenone models [126]. Activated microglia generate reactive oxygen species and cytokines that affect astrocytes, which then release further inflammatory mediators [116,119], exacerbating neuronal injury [127]. The persistent stimulation of glial cells perpetuates neuroinflammation, hinders synaptic plasticity, and leads to cognitive and motor deterioration in models of PD, AD, and amyotrophic lateral sclerosis [117,128]. Recent research have observed sex-based differences in the effects of rotenone, but most models predominantly employ male mice [129,130]. Additional investigation into sexual dimorphism may improve the reliability and translational significance of these models. Comprehending these relationships is essential for formulating therapeutics aimed at modulating glial responses and inflammation in neurodegenerative disorders (Fig. 7).

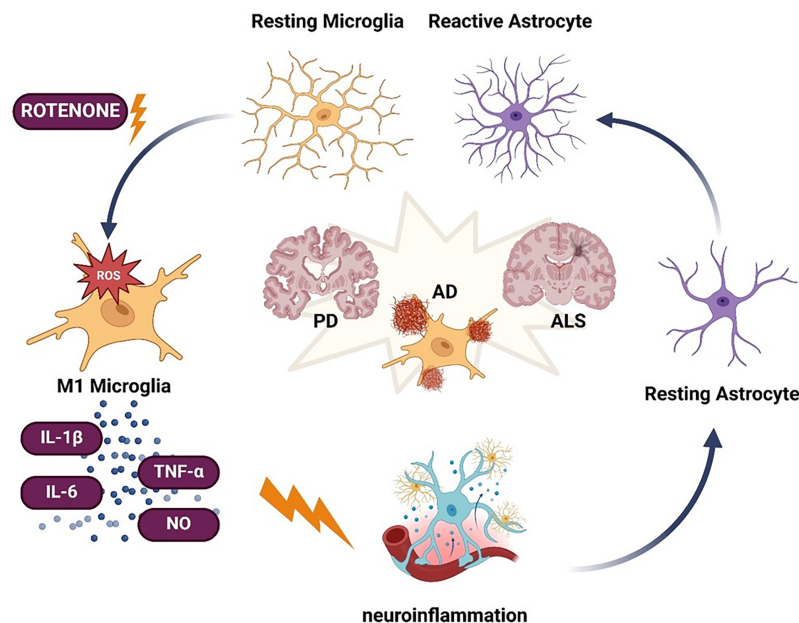


Figure 7: Schematic representation of rotenone-induced glial cell activation and its contribution to neurodegenerative diseases. Rotenone-triggered oxidative stress (ROS) drives microglia toward a pro-inflammatory (M1) phenotype, characterized by the release of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and nitric oxide (NO). Concurrently, astrocytes transition from resting to a reactive state, further amplifying the neuroinflammatory response. Prolonged glial activation and inflammation are implicated in the pathogenesis and progression of Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS) (Created using BioRender.com)

10 Signaling Pathways Associated with Rotenone-Induced Neuroinflammation

Rotenone stimulates multiple critical intracellular pathways that govern cytokine synthesis and glial activation, both of which are vital in neuroinflammation [131]. The NF-κB pathway is essential for regulating inflammatory responses; ROS generated by rotenone exposure activate NF-κB, leading to the transcription of pro-inflammatory genes such as TNF-α, IL-1β, IL-6, and iNOS [132–135]. The PI3K/AKT/mTOR pathway, essential for cell survival and metabolism, is affected by rotenone-induced oxidative stress, leading to glial activation and chronic inflammation. Notably, mTOR activation may impede autophagy and enhance

neuronal vulnerability and damage [136,137]. The Wnt/ β -catenin signaling system, which governs brain development and inflammatory responses, is disrupted by rotenone, exacerbating neuroinflammatory processes and glial activation. Recent investigations suggest that modifying this pathway may diminish neuroinflammation and neurodegeneration [138–140]. Despite these insights, it is essential to recognize that the effects of rotenone on these pathways may vary according to dosage, method of administration, and duration of exposure, hence limiting the translational relevance of the findings. These pathways promote sustained glial activation and inflammation, which are critical contributors to neurodegeneration (Fig. 8) [40]. A thorough comprehension of their functions may enhance the development of therapeutic strategies for neurodegenerative disorders, such as Parkinson's, Alzheimer's, and ALS [60,131]. A variety of pharmaceuticals, including antioxidants such as resveratrol, N-acetylcysteine, NF- κ B inhibitors, mitochondrial modulators like mitochondrial-targeted antioxidant mitoquinone (MitoQ), and glial contact regulators, have shown promise in preclinical studies for mitigating chronic inflammation and neuronal injury [141] (Fig. 8).

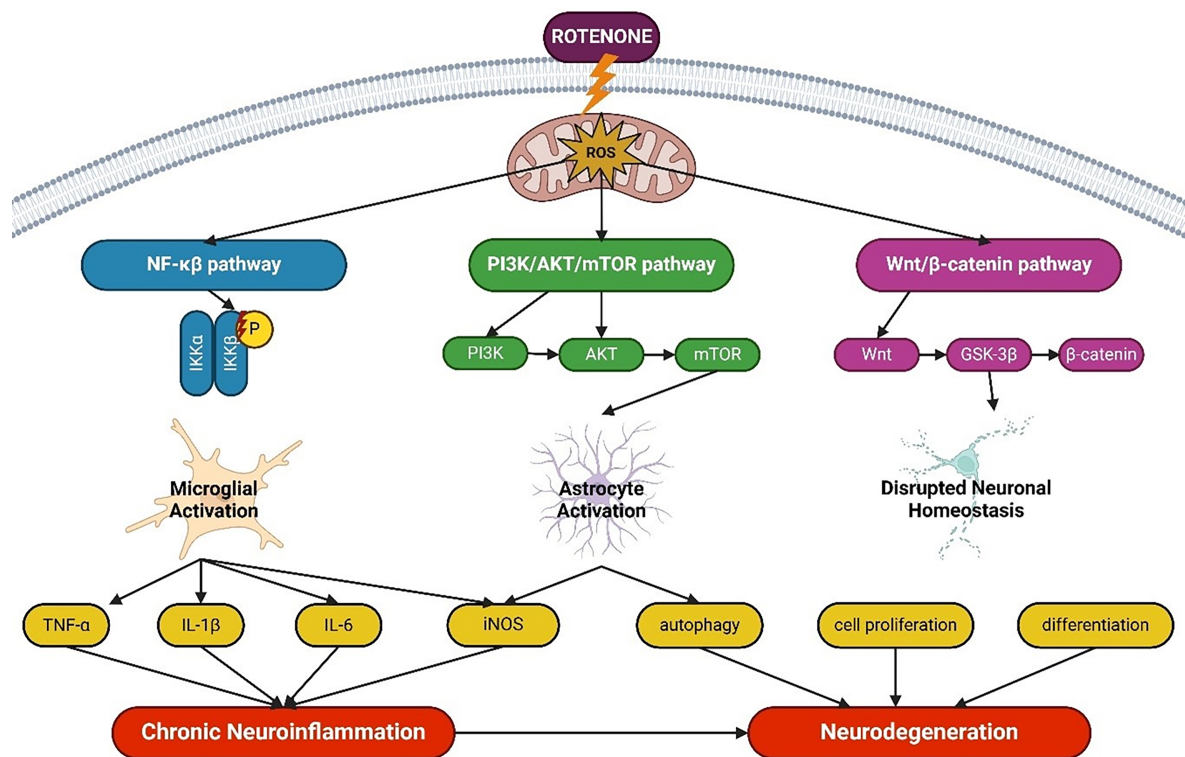


Figure 8: Schematic representation of the key signaling pathways implicated in rotenone-induced neuroinflammation. Rotenone-generated reactive oxygen species (ROS) activate the NF- κ B pathway, driving microglial activation and the production of pro-inflammatory mediators (e.g., TNF- α , IL-1 β , IL-6, and iNOS). Simultaneously, the PI3K/AKT/mTOR pathway in astrocytes modulates autophagy and cell survival, whereas the Wnt/ β -catenin pathway influences neuronal homeostasis through effects on cell proliferation and differentiation. Together, these pathways promote chronic neuroinflammation and neuronal dysfunction, ultimately contributing to neurodegeneration. Abbreviations: NF- κ B, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; GSK-3 β , glycogen synthase kinase-3 β (Created using [BioRender.com](https://www.biorender.com))

11 Limitations and Future Directions

Notwithstanding progress in employing rotenone-based models for the investigation of neurodegenerative disorders, numerous significant limitations persist and warrant attention in forthcoming research. The compound's limited selectivity and systemic toxicity may impact non-neuronal tissues, confounding the assignment of reported effects solely to neurodegenerative pathways. Furthermore, diversity in delivery routes, dosing schedules, and exposure durations frequently leads to contradictory results among studies, so undermining reproducibility and constraining translational applicability. These models inadequately reproduce the progressive and multifaceted characteristics of human neurodegenerative illnesses like Parkinson's and Alzheimer's, as they typically lack the genetic and environmental complexity inherent to these ailments. Moreover, variations in rotenone sensitivity among different species and strains further limit the applicability of experimental results.

Future research must prioritize the standardization of experimental protocols including dose, duration, and administration modalities to enhance reproducibility and address these constraints. The incorporation of female animals and the implementation of sex-based studies are crucial for revealing differential susceptibilities and informing the creation of more inclusive therapeutic techniques [142,143]. A notably interesting avenue is the development of combinatory models that amalgamate genetic predispositions with environmental exposures, providing a more precise depiction of the intricate etiologies of neurodegenerative disorders. Increased focus should be directed towards the identification of translational biomarkers and therapeutic outcomes to enhance clinical applicability. A thorough examination of glial signaling dynamics, particularly the functional interaction between astrocytes and microglia, may yield essential mechanistic insights and broaden treatment possibilities in rotenone-based preclinical models. A comprehensive analysis of glial signaling dynamics, including the functional interaction between astrocytes and microglia, is crucial due to the established disparities in mitochondrial function among these glial cells and neurons. Such findings may provide essential molecular insights and broaden therapeutic options within rotenone-based preclinical models.

12 Conclusion

Mitochondrial dysfunction, particularly when triggered by rotenone, significantly contributes to the pathogenesis of neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. This chemical inhibits complex I of the mitochondrial electron transport chain, impeding ATP synthesis and fostering a pro-oxidative environment that elevates the formation of ROS and disturbs intracellular calcium homeostasis. Moreover, rotenone exposure induces a sustained inflammatory response mediated by microglia, activating pro-inflammatory pathways such as TLR4 and NF- κ B, hence exacerbating neurodegeneration. Glial cells, especially microglia and astrocytes, play a crucial role in disease progression, since their overactivation and malfunction result in neuronal excitotoxicity and disrupt energy metabolism, heightening neuronal vulnerability to oxidative damage. The activation of additional intracellular signaling pathways, including PI3K/AKT/mTOR and Wnt/ β -catenin, regulates the inflammatory response and impacts glial function, hence aggravating chronic inflammation and leading to neurodegeneration. These processes underscore the significance of mitochondrial malfunction, glial inflammation, and the disturbance of calcium homeostasis in rotenone-induced neurotoxicity. Focusing on the restoration of mitochondrial function and the modulation of glial inflammation may offer a potential strategy for creating therapies for diseases such as Parkinson's, Alzheimer's, and other neurodegenerative disorders.

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Abbreviations

PD	Parkinson's disease
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
TNF- α	Tumor necrosis factor alpha
IL	Interleukin
NF- κ B	Nuclear factor-kappa B
PI3K	Phosphoinositide 3-Kinase
AKT	Protein kinase B
mTOR	Mammalian Target of Rapamycin
ATP	Adenosine triphosphate
NADH	Nicotinamide adenine dinucleotide
ROS	Reactive oxygen species
TLR4	Toll-like receptor 4
NMDA	N-methyl-D-aspartate
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MAPK	Mitogen-activated protein kinase
JNK	Jun N-terminal kinase
GSK-3 β	Glycogen synthase kinase-3 beta
A β	Amyloid-beta
APP	Amyloid precursor protein
BACE1	β -secretase
iNOS	Inducible nitric oxide synthase
NO	Nitric oxide
SOD1	Superoxide dismutase 1
CoQ10	Ubiquinone
mtDNA	Mitochondrial DNA
4-HNE	4-hydroxynonenal
APAF-1	Apoptotic protease activating factor-1
$\Delta\Psi_m$	Mitochondrial membrane potential
MitoQ	Mitochondrial-targeted antioxidant mitoquinone

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