Journal of Biosciences and Medicines, 2025, 13(5), 75-99
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Interactions between Oxidative Stress and Mitochondrial Dysfunction in Parkinson's Disease: Potential of Natural Antioxidants

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How to cite this paper: Yue, Y.Q., Jiang, W.B., Wang, X.M., Tian, Z.H., Cui, Y.X. and Zhou, X. (2025) Interactions between Oxidative Stress and Mitochondrial Dysfunction in Parkinson's Disease: Potential of Natural Antioxidants. *Journal of Biosciences and Medicines*, **13**, 75-99.
https://doi.org/10.4236/jbm.2025.135007

Received: April 8, 2025
Accepted: May 16, 2025
Published: May 19, 2025

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in a spectrum of motor and non-motor symptoms. Among the critical pathological mechanisms in PD, oxidative stress and mitochondrial dysfunction have emerged as significant contributors to neuronal death. Reactive oxygen species (ROS), produced during dopamine metabolism and mitochondrial respiration, lead to oxidative damage, while mitochondrial dysfunction exacerbates energy deficits and disrupts cellular homeostasis. The interplay between these processes engenders a detrimental cycle of neurodegeneration. Recent investigations have concentrated on the potential of antioxidants, including polyphenols, flavonoids, and certain vitamins, for their potential to mitigate both oxidative stress and mitochondrial dysfunction. These compounds exhibit neuroprotective properties by scavenging ROS, preserving mitochondrial integrity, and promoting mitophagy. Notably, antioxidants such as curcumin, resveratrol, and quercetin have demonstrated efficacy in experimental models of PD, reducing ROS levels, restoring mitochondrial function, and preventing neuronal loss. Furthermore, advancements in delivery systems have enhanced the bioavailability of these antioxidants, amplifying their therapeutic potential. This review delves into the dual pathological roles of oxidative stress and mitochondrial dysfunction in PD, elucidating the multifaceted protective effects of natural antioxidants. In this review, we sum-

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marize the current literature on natural antioxidants' role in oxidative stress and mitochondrial dysfunction in PD and discuss possible therapeutic approaches targeting this interaction

Keywords

Parkinson's Disease, Oxidative Stress, Mitochondrial Dysfunction, Antioxidants, Antioxidant

1. Introduction

Parkinson's disease (PD) is the second most common and progressive neurodegenerative disorder characterized by degeneration and death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) early in the disease [1]. World Health Statistics 2023 reported that according to global estimates in 2019, approximately 8.5 million people worldwide have PD, an 81% increase from 2000. PD may be difficult to recognize in the early stages of the disease, with early stages extending over 10 years [2]. The clinical presentation of PD encompasses a spectrum of motor symptoms, including bradykinesia, muscular rigidity, resting tremors, and disturbances in postural gait. Moreover, the disease manifests through a range of non-motor symptoms, such as olfactory impairments, cognitive decline, psychiatric disorders, sleep disruptions, autonomic dysfunction, pain, and fatigue. These symptoms profoundly deteriorate the quality of life of affected individuals [3]. As the duration of PD disease increases in patients, both motor and non-motor symptoms worsen. Respiratory complications and side effects of long-term medication also become more prominent, adding to the challenges faced by individuals with PD and placing a greater burden on their families and society. Postgraduate students have found that oxidative stress and mitochondrial dysfunction play a key role in the pathological progression process, and there is a close interaction between the two, forming a vicious cycle. Mitochondrial dysfunction leads to an increase in ROS production and triggers oxidative stress. Oxidative stress, in turn, can further damage mitochondria and aggravate mitochondrial dysfunction, jointly promoting the occurrence and development of Parkinson's disease. At present, the treatment for Parkinson's disease mainly involves controlling symptoms, improving the quality of life and slowing down the progression of the disease through drug intervention, surgical operations and various other treatment methods [4]. However, as the etiology and pathogenesis of Parkinson's disease have not been fully clarified, the existing treatment methods still cannot prevent the progression of the disease and have many limitations. Further in-depth research is needed to explore more effective treatment methods.

Oxidative stress represents a key pathological hallmark of PD, primarily driven by reactive oxygen species (ROS) produced during dopamine metabolism. This

excessive ROS generation induces dopaminergic neuron degeneration, leading to neurotoxicity [5]. Lim *et al.* emphasize that oxidative stress is a key driver of neuronal death in PD, though the underlying cellular pathways remain incompletely elucidated [6]. Likewise, Li *et al.* provide evidence that oxidative stress markers—such as elevated protein carbonyl levels and lipid peroxidation—are significantly increased in the dopaminergic neurons of PD patients, implying a direct link between oxidative damage and neuronal degeneration [7]. Asemi-Rad *et al.* further supports this by demonstrating that oxidative stress inflicts widespread damage to lipids, proteins, and DNA, ultimately culminating in dopaminergic neuron loss [8].

Importantly, oxidative stress is closely intertwined with mitochondrial dysfunction, another critical pathological feature of PD. Mitochondria, as the central hubs of cellular energy production and signaling, serve as both key generators of ROS and are particularly vulnerable to oxidative damage. Mitochondrial dysfunction contributes to neuronal energy deficits, exacerbates oxidative stress, impairs mitophagy, and disrupts calcium homeostasis, further accelerating dopaminergic neuron degeneration [9] [10] Mitochondrial anomalies have been consistently documented across genetic, laboratory, epidemiological, and clinical studies, highlighting their systemic and pathogenic role in PD [11]. Given the dual roles of oxidative stress and mitochondrial dysfunction in driving PD pathology, multi-targeted mitochondrial therapies hold significant promise in modifying the course of the disease.

In recent studies, natural antioxidants, including polyphenols, flavonoids, and select vitamins, have garnered significant interest for their prospective roles in preventing and managing PD. These compounds confer neuroprotection by effectively mitigating oxidative stress and ameliorating mitochondrial dysfunction. Natural antioxidants exhibit neuroprotective effects by scavenging ROS, reducing oxidative damage to lipids, proteins, and DNA, and enhancing the overall resilience of dopaminergic neurons [12]. Moreover, natural antioxidants have been shown to influence mitochondrial health by promoting mitophagy, stabilizing mitochondrial membrane potential, and maintaining calcium homeostasis, which are crucial in preventing further mitochondrial dysfunction [13]. These findings suggest that natural antioxidants could serve as multi-targeted therapeutic agents, potentially slowing the progression of PD by addressing both oxidative stress and mitochondrial dysfunction. Literature indicates that natural antioxidants, including curcumin, resveratrol, and quercetin, have demonstrated efficacy in reducing ROS levels, restoring mitochondrial function, and preventing neuronal loss in experimental models of PD [14].

This review aims to elucidate in detail how oxidative stress and mitochondrial dysfunction interact and aggravate neuronal damage, and to evaluate natural antioxidants as potential options for the treatment of PD by summarizing their applications in PD and how they play a protective role by reducing oxidative stress and improving mitochondrial function.

2. Mechanisms of Oxidative Stress and Mitochondrial Dysfunction in PD

2.1. Oxidative Stress

Oxidative stress is a biological condition characterized by an imbalance between the production of ROS and the body's antioxidant defenses. This imbalance can lead to significant cellular damage, influencing various diseases and physiological processes [15]. Dopamine itself is a significant contributor to ROS generation in PD. The oxidation of dopamine, particularly in the presence of metal ions like iron, leads to the formation of highly reactive hydroxyl radicals [16]. This process is particularly relevant in the basal ganglia, which is rich in iron and susceptible to oxidative damage. The auto-oxidation of free cytosolic dopamine can also produce toxic quinones, further amplifying oxidative stress and neuronal injury. Neuroinflammation is another pathway through which ROS are generated in PD. Activated microglia release ROS as part of the inflammatory response, which can contribute to neuronal damage [17]. Concurrently, Oxidative stress is closely linked to the pathogenic aggregation of α-synuclein (α-Syn), a hallmark of PD. This oxidative stress accelerates cellular senescence and fosters α-Syn aggregation, further disrupting cellular homeostasis and compromising neuronal integrity. Such disruptions impair both proteasomal and mitochondrial function, perpetuating a vicious cycle of neurodegeneration (**Figure 1**) [18].

Several studies have provided evidence for the presence of oxidative stress in PD. Yoritaka *et. al.* conducted immunochemical studies and found that oxidative stress was present within nigral neurons in PD patients, suggesting a potential contribution to nigral cell death [19]. Kruman *et al.* further supported this by providing evidence that 4-hydroxynonenal, a product of membrane lipid peroxidation, mediates oxidative stress-induced neuronal apoptosis in PD [20]. Additionally, Hunot *et al.* observed increased nuclear translocation of NF-κB, a transcription factor associated with oxidative stress-induced apoptosis, in dopaminergic neurons of PD patients [21]. Ischiropoulos *et al.* discussed the controversies surrounding the role of oxidants in neurodegeneration, highlighting the difficulty in determining whether oxidative stress is a primary cause or a secondary epiphenomenon in PD [22]. Furthermore, Lau *et al.* found that higher serum levels of uric acid, a natural antioxidant and free radical scavenger, were associated with a decreased risk of PD, supporting the hypothesis that oxidative stress contributes to the development of the disease [23]. Henchcliffe *et al.* discussed the roles of mitochondrial dysfunction and increased oxidative stress in neuronal loss in PD, emphasizing the potential for mitochondrial therapy in patient management [24]. Overall, these pieces of evidence suggest that oxidative stress plays an important role in the development of PD.

In healthy cells, the production of ROS is tightly controlled, and antioxidant systems efficiently neutralize excess ROS [25]. The mitochondria continuously generate low levels of ROS as part of normal metabolic activity, but SOD, glutathione, and catalase work in tandem to prevent oxidative stress. When this balance

is disturbed, as seen in PD due to mitochondrial dysfunction, dopamine oxidation, or α-Syn pathology, the excessive ROS overwhelms these antioxidant defenses, leading to oxidative damage of proteins, lipids, and DNA [26]. In PD, the decline in these antioxidant defenses, especially in neurons of the substantia nigra, contributes to cell death and the progression of the disease [27].

2.2. Mitochondrial Dysfunction

Mitochondria are essential organelles in eukaryotic cells, primarily known for their role in energy production. However, their functions extend far beyond this, encompassing various aspects of cellular metabolism, signaling, and homeostasis. Mitochondria are often referred to as the "powerhouses" of the cell due to their role in aerobic oxidative phosphorylation, a process that generates ATP, the primary energy currency of the cell [28]. The respiratory chain and ATP synthase complexes, located in the inner mitochondrial membrane, are central to this energy conversion process. This multifaceted role makes mitochondria crucial for both normal cellular function and the response to stress or disease. Mitochondrial dysfunction refers to the impaired function of mitochondria, the organelles responsible for energy production through oxidative phosphorylation. Mitochondrial dysfunction can be classified into the following categories: impaired ATP production, mitochondrial respiratory chain disorders, mitochondrial DNA mutations and damage, mitochondrial autophagy disorders, calcium homeostasis disorders, and defects in mitochondrial quality control [29] These dysfunctions contribute to mitochondrial damage through mechanisms such as increased oxidative stress, impaired energy metabolism, and the accumulation of damaged mitochondrial components. This dysfunction is characterized by a decrease in ATP production, increased production of ROS, and disturbances in mitochondrial dynamics, including fission and fusion processes.

Mitochondrial dysfunction serves as a primary source of ROS in PD. The inhibition of the electron transport chain, particularly at complex I, results in the accumulation of electrons that react with molecular oxygen to produce superoxide anions, subsequently generating ROS [30]. This heightened generation of ROS further intensifies neuronal damage [31]. Additionally, postmortem studies have demonstrated significant mitochondrial DNA damage in the substantia nigra of PD patients, indicating that oxidative stress is a critical factor in the degeneration of dopaminergic neurons [32].

2.2.1. ATP

Adenosine triphosphate (ATP) is a critical molecule in cellular biology, serving as the primary energy currency of the cell. It is synthesized through various metabolic pathways, primarily within mitochondria, and is vital in numerous cellular processes. ATP is produced via oxidative phosphorylation in mitochondria, where the electron transport chain (ETC) generates a proton gradient that drives ATP synthesis through ATP synthase [33].

ATP is essential for maintaining cellular homeostasis and viability. It is involved in various metabolic pathways, including protein synthesis, providing the energy required for tRNA charging and forming peptide bonds [34]. The balance of ATP levels is critical; excessive ATP can disrupt normal cellular functions, while insufficient ATP can lead to cell death through mechanisms such as necroptosis, particularly in response to oxidative stress. Impaired ATP production is a significant feature of PD, with various studies highlighting the role of mitochondrial dysfunction and metabolic disturbances in this neurodegenerative disorder. Oxidative stress exacerbates ATP depletion, and ROS are also generated during ATP abnormalities, which in turn damage cellular components and lead to cell death [35].

Research has demonstrated that genetic mutations, such as those in the leucine-rich repeat kinase 2 (LRRK2) gene, can lead to mitochondrial depolarization and impaired ATP synthesis in fibroblasts derived from PD patients [36]. ATP production is reduced, thereby exacerbating the neurodegenerative processes observed in PD. Additionally, environmental toxins that inhibit mitochondrial function, such as rotenone, have been shown to cause significant ATP depletion, further implicating mitochondrial dysfunction in the disease's etiology [37]. The interplay between oxidative stress and mitochondrial dysfunction exacerbates ATP depletion, as ROS generated during mitochondrial impairment can damage cellular components, leading to cell death.

Moreover, studies have indicated that glucose metabolism is altered in PD, with increased reliance on glycolysis rather than oxidative phosphorylation for ATP production in peripheral blood cells from PD patients [38]. This metabolic shift may reflect an adaptive response to mitochondrial dysfunction but ultimately contributes to insufficient ATP levels, which are critical for neuronal health and function [38]. The relationship between ATP levels and neuronal activity is further underscored by findings that ATP-sensitive potassium channels are upregulated in PD, suggesting a compensatory mechanism in response to energy deficits. As such, targeting mitochondrial ATP synthesis and its associated pathways may represent a promising therapeutic strategy for PD.

Nicotinamide adenine dinucleotide (NAD^+) is a critical coenzyme in ATP synthesis, facilitating the transfer of electrons during glycolysis and the tricarboxylic acid cycle to the ETC, where ATP is generated. A decline in NAD^+ levels has been associated with mitochondrial dysfunction, reduced ATP production, and increased oxidative stress, all of which are implicated in PD pathogenesis [39]. Enhancing NAD^+ levels has been shown to restore mitochondrial function and improve neuronal survival in preclinical models of PD [40]. Recent findings emphasize that Sirtuin-3 (SIRT3), a mitochondrial protein, functions as an oxidized NAD^+-dependent deacetylase. SIRT3 plays a crucial role in maintaining mitochondrial integrity and function and is involved in mitochondrial ATP production, energy metabolism, antioxidant defenses, and the regulation of cell death and proliferation. The down-regulation of NAD^+ levels and reduced SIRT3 activity are associated with aging and are pathologically linked to the pathogenesis of PD. Further-

more, SIRT3 negatively correlates with α-Syn aggregation and dopaminergic neuronal degeneration in PD. In PD models, SIRT3 chemical activators and NAD^+ precursors upregulate SIRT3 activity, thereby preventing dopaminergic neuronal degeneration. Activation of SIRT3 enhances the mitochondrial antioxidant defense system, which is crucial for counteracting oxidative stress—a key factor in neurodegenerative diseases such as PD [41]. Therefore, SIRT3 represents a promising therapeutic target for PD. Functional modulators of SIRT3 with neuroprotective capabilities hold significant research potential for treating PD (**Figure 1**).

2.2.2. Mitochondrial Respiratory Chain

The mitochondrial respiratory chain (MRC), or the ETC, is a critical component of cellular respiration, primarily located in the inner mitochondrial membrane. It consists of four main enzymatic complexes (I-IV). It is integral to the process of oxidative phosphorylation, where it facilitates the production of ATP through the transfer of electrons derived from metabolic substrates. The chain transfers electrons from reduced cofactors, such as NADH and FADH2, through a series of redox reactions, ultimately reducing molecular oxygen to water at Complex IV, known as cytochrome c oxidase (**Figure 1**) [42].

Complex I (NADH: ubiquinone oxidoreductase) initiates the electron transport process by oxidizing NADH, transferring electrons to ubiquinone (CoQ), while concurrently contributing to the establishment of a proton gradient across the mitochondrial membrane—an essential prerequisite for ATP synthesis via ATP synthase. Complex II (succinate dehydrogenase) also feeds electrons into the chain; however, it does not participate in proton pumping. The electrons then flow through Complex III (ubiquinol-cytochrome c oxidoreductase) and conclude at Complex IV, where molecular oxygen is reduced (**Figure 1**).

In the context of PD, MRC dysfunctions in PD manifest as both quantitative and functional aberrations, with a pronounced impact on complex I. Studies reveal that individuals with sporadic PD often exhibit significant deficiencies in MRC complex I, correlating mitochondrial impairment with genes implicated in the disease, such as PRKN, PINK1, DJ-1, and HTRA2 [43]. A critical aspect of mitochondrial pathology in sporadic PD is the impairment of mitochondrial complex I. This is evident in PD patients as reduced protein levels or activity of mitochondrial complex I in the substantia nigra, diminishing the proton gradient across the inner mitochondrial membrane and thus impeding ATP synthesis. Additionally, a complex I deficiency leads to elevated production of superoxide radicals, precipitating oxidative stress and consequent damage to cellular DNA and proteins, contributing to neurodegeneration [44]. This highlights the potential for therapeutic strategies that target mitochondrial respiration to protect against neuronal damage.

While the focus has predominantly been on complex I, dysfunction in other MRC components has also been implicated in PD. Alterations in complexes III and IV have been reported, though less frequently, contributing to mitochondrial dysfunction and neuronal degeneration. In murine models of PD, administration

of brain-derived neurotrophic factors has been shown to enhance the activity of respiratory chain Complex I and II + III, mitigate mitochondrial damage, and consequently reduce the loss of tyrosine hydroxylase-positive dopaminergic neurons induced by MPTP [45]. Moreover, mice expressing a mutated form of α-synuclein demonstrate an accumulation of α-synuclein within mitochondria. This accumulation is associated with mitochondrial degeneration, damage to mitochondrial DNA (mtDNA), and a decline in the function of the respiratory chain Complex IV, culminating in neurodegeneration [44].

2.2.3. Mitochondrial DNA

MtDNA is a distinct type of DNA located within the mitochondria, the energy-producing organelles in eukaryotic cells. Unlike nuclear DNA, mtDNA is circular and is inherited maternally, meaning it is passed down from mothers to their offspring without recombination. mtDNA mutations are intricately linked to the pathogenesis of PD. Research has elucidated that such mutations precipitate mitochondrial dysfunction, thus exacerbating the onset and progression of PD. Research indicates that oxidative stress is a critical factor in inducing mtDNA damage. For instance, chronic exposure to ROS has been shown to lead to increased mitochondrial-generated ROS, reduced mitochondrial function, and continuous mtDNA damage, which can result in mutations. Conversely, mtDNA mutations can also enhance the production of ROS, creating a feedback loop that perpetuates oxidative stress. This phenomenon is particularly evident in the context of aging, where the accumulation of mtDNA mutations is thought to contribute to the aging process through increased ROS generation and subsequent cellular damage (**Figure 1**) [46].

Notably, the Twinkle protein, essential for maintaining mtDNA replication and integrity, when compromised, may trigger mutations and alterations in mtDNA copy numbers. This impairment disrupts mitochondrial functionality and accelerates neuronal degeneration, highlighting a critical pathway in PD's neurodegenerative process. Moreover, mutations in genes such as CHCHD2 have been shown to cause early-onset PD through mechanisms involving mitochondrial dysfunction. Quantitative measurement of mtDNA damage has been proposed as a potential blood biomarker for detecting PD [47]. Casa-Fages and colleagues undertook a detailed investigation of spastic paraplegia type 7, correlating it with mitochondrial dysfunctions akin to those observed in PD. Their genetic scrutiny within a Spanish patient cohort revealed mutations in mitochondrial DNA and variations in its blood levels. These findings underscore the significant role that mitochondrial anomalies play in the onset and progression of PD.

MtDNA is linked to various severe disorders, where traditional treatments mainly provide symptomatic relief and rarely curb disease progression. Recent breakthroughs in gene therapy, however, herald new possibilities for rectifying these mutations. Techniques employing mitochondrially targeted TALENs and Zinc finger nucleases have shown promise in adjusting mitochondrial heteroplasmy levels, crucial for balancing healthy and mutant mtDNA to diminish disease mani-

festations [48]. Advances in DNA-editing enzymes have demonstrated the feasibility of manipulating heteroplasmy ratios to below symptomatic thresholds in both cellular and animal models, hinting at future gene therapy applications in humans. These emerging therapeutic strategies signify a shift towards more targeted and potentially curative treatments for mitochondrial DNA mutations.

2.2.4. Mitochondrial Mitophagy

Mitophagy refers to the selective sequestration and degradation of damaged mitochondria by cells through the autophagy process, thereby maintaining mitochondrial and cellular homeostasis. As an evolutionary mechanism, this selective autophagy eliminates excess protein aggregates and damaged cellular components, particularly in response to pathogenic protein oligomers, genetic mutations, oxidative stress, or physical injury. By preventing the buildup of defective mitochondria, mitochondrial autophagy plays a crucial role in neuroprotection against neurodegenerative disorders such as PD, Alzheimer's disease, and others [49].

Mitochondria are particularly susceptible to oxidative damage due to their role in energy production and their exposure to high levels of ROS generated during cellular respiration [50]. In the context of PD, impaired mitophagy has been linked to the accumulation of damaged mitochondria, which exacerbates oxidative stress and contributes to neuronal cell death. For instance, mutations in genes such as PINK1 and Parkin, which are essential for the initiation of mitophagy, have been shown to disrupt this process, leading to increased oxidative stress and neuronal vulnerability [51]. The failure of mitophagy to clear damaged mitochondria can create a vicious cycle where oxidative stress further impairs mitophagy, resulting in a detrimental feedback loop that accelerates neurodegeneration (**Figure 1**).

Recent studies have highlighted the signaling pathways that connect oxidative stress to mitophagy regulation. For example, the activation of c-Abl, a nonreceptor tyrosine kinase, has been implicated in aggravating mitophagy disorders under oxidative stress conditions [52]. Additionally, the Mst1/2-BNIP3 axis has been identified as crucial for mitophagy induction in response to mitochondrial stress, underscoring the importance of these pathways in neuronal survival. Furthermore, the interaction between ROS and mitophagy has been shown to involve various mediators, including AMBRA1, which can restore mitophagy in the context of oxidative stress.

2.2.5. Calcium Homeostasis

Calcium homeostasis is a critical cellular process that maintains the balance of calcium ions (Ca^{2+}) within cells, playing a pivotal role in mitochondrial function [53]. Mitochondria serve as dynamic buffers in calcium homeostasis, capable of both uptaking and releasing calcium ions, thereby modulating intracellular calcium levels. This modulation impacts various cellular processes, including energy production and apoptosis. The accumulation of calcium within mitochondria serves as a signaling mechanism that regulates metabolic pathways and can determine cell fate by either promoting survival or triggering programmed cell death.

In dopaminergic neurons, particularly vulnerable in PD, the influx of cytosolic calcium is primarily mediated through calcium channels. Effective mitochondrial buffering of this influx is essential to prevent cellular toxicity [54]. However, the accumulation of ROS within mitochondria can disrupt calcium homeostasis, leading to mitochondrial permeability transition pore (mPTP) opening, which is a key event in the initiation of cell death pathways (**Figure 1**) [55].

The interplay between ROS and calcium is complex. Elevated ROS levels can enhance mitochondrial calcium uptake, which, when coupled with the already high calcium influx characteristic of dopaminergic neurons, results in calcium overload [56]. This overload can impair mitochondrial bioenergetics, as seen in studies where mitochondrial dysfunction was linked to reduced ATP production and impaired calcium handling. Furthermore, the dysregulation of calcium signaling is exacerbated by misfolded proteins such as alpha-synuclein, which can form pore-like structures on cellular membranes, further disrupting calcium homeostasis and promoting oxidative stress [56].

Mitochondrial calcium overload not only leads to energy deficits but also triggers apoptotic pathways. Excessive calcium can activate various calcium-dependent enzymes, including those involved in apoptosis, thereby promoting neuronal death [56]. Moreover, the relationship between ROS and calcium is bidirectional; while ROS can induce calcium overload, elevated calcium levels can also enhance ROS production, creating a vicious cycle that accelerates mitochondrial damage and neuronal loss. This cycle is particularly detrimental in the context of PD, where mitochondrial dysfunction is an early and pivotal event in the disease process [56].

2.2.6. Loss of Mitochondrial Membrane Potential

Loss of mitochondrial membrane potential (MMP) is a critical event in cellular apoptosis and mitochondrial dysfunction, playing a vital role in various cellular processes, including ATP synthesis, mitochondrial biogenesis, and metabolite transport. The MMP is primarily maintained by the ETC, which creates an electrochemical gradient across the inner mitochondrial membrane [57]. When this potential is compromised, it triggers a cascade of events that can ultimately lead to cell death. The loss of MMP is closely associated with the initiation of apoptosis, facilitating the release of pro-apoptotic factors such as cytochrome c from the mitochondrial intermembrane space into the cytosol. This release activates caspases, crucial enzymes for executing apoptosis [57]. For instance, studies have shown that stimuli like oxidative stress and chemotherapeutic agents can induce loss of MMP, resulting in cell death (**Figure 1**).

A prominent mechanism involved in this process is the PINK1/Parkin pathway, crucial for mitophagy—the selective degradation of damaged mitochondria. In healthy cells, PINK1 is rapidly degraded; however, upon loss of MMP, it accumulates on the outer mitochondrial membrane and recruits Parkin, initiating the degradation of dysfunctional mitochondria [58]. This recruitment is vital for maintaining mitochondrial quality control, and its impairment is observed in PD models,

leading to the accumulation of damaged mitochondria and subsequent neuronal death [59]. Specifically, fibroblasts derived from PD patients exhibit decreased PINK1 levels following mitochondrial depolarization, indicating a failure in the mitophagy process [60].

The maintenance of MMP is governed primarily by the electrochemical gradient established by the ETC during oxidative phosphorylation. This gradient is created through the sequential transfer of electrons across the mitochondrial inner membrane, resulting in the active transport of protons into the intermembrane space, which subsequently drives ATP synthesis via ATP synthase [61]. The integrity of the ETC is essential for sustaining MMP; any disruption can lead to a decrease in MMP, often associated with increased mitochondrial ROS production and subsequent cellular stress.

To conclude, maintaining mitochondrial membrane potential is a multifaceted process that includes the electron transport chain, mitochondrial dynamics, calcium signaling, and specific ion channels. Disruptions in any of these systems can lead to significant cellular dysfunction, highlighting the critical role of mitochondrial membrane potential in cellular metabolism and survival.

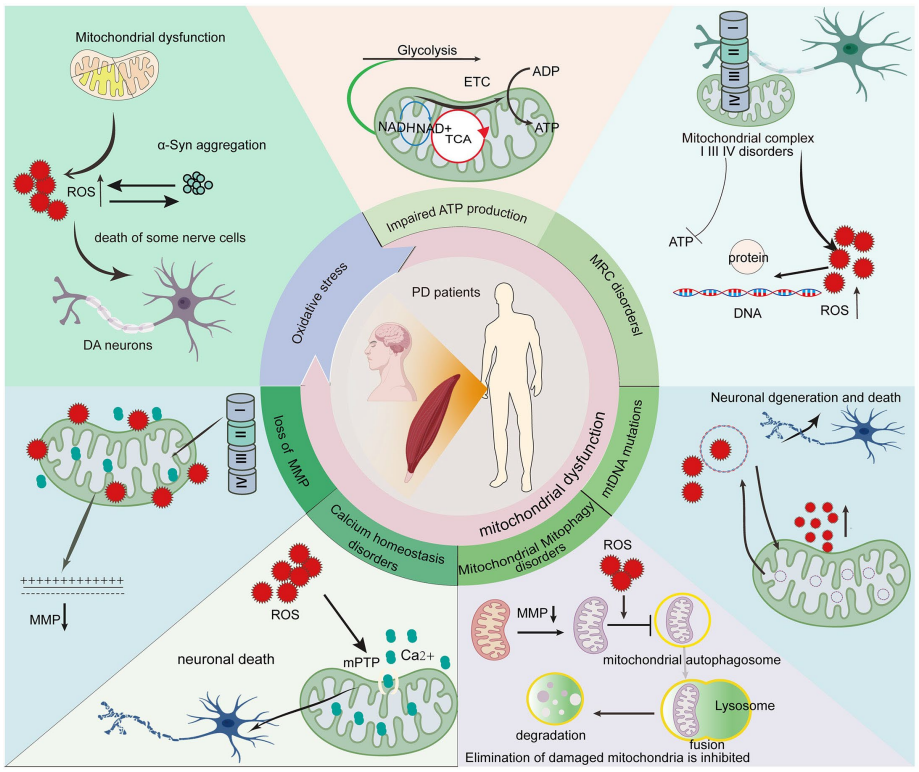

Figure 1. Mechanisms of oxidative stress and mitochondrial dysfunction in Parkinson's disease. (Created with BioGDP.com)

3. Current Status of Research on Natural Antioxidants in Parkinson's Disease

Antioxidants can be classified into enzymatic and non-enzymatic categories. En-

zymatic antioxidants include key enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, which actively neutralize ROS [62]. Non-enzymatic antioxidants, on the other hand, are primarily phytochemicals found in plant foods, such as flavonoids, phenolic acids, and vitamins [63]. These compounds can donate electrons to free radicals, effectively neutralizing them and preventing cellular damage [64].

Natural antioxidants are abundant in fruits, vegetables, seeds, and other plant-based foods. Common examples include Vitamin C and E, carotenoids, and polyphenols like flavonoids and phenolic acids. Additionally, many medicinal plants are also rich in antioxidants, contributing to their therapeutic properties. Noteworthy compounds include thymol, eugenol, and sesamol, which have been utilized in traditional medicine for their health-promoting effects [65].

Understanding the diverse sources and mechanisms of natural antioxidants enhances our ability to develop innovative strategies for their repurposing and combination in therapeutic contexts, maximizing their potential health benefits.

3.1. Polyphenols and Flavonoids

Polyphenols, particularly flavonoids, are significant natural antioxidants recognized for their neuroprotective properties. Grape seed extract, rich in polyphenols such as proanthocyanidins and resveratrol, has shown potential in preventing and alleviating symptoms of PD due to its robust antioxidant capacity [66]. Flavonoids like isoquercitrin and quercetin have demonstrated protective effects against oxidative stress in dopaminergic neurons, emphasizing their promise as neuroprotective agents in PD [67]. Furthermore, studies indicate that flavonoids can enhance neuroplasticity and improve cognitive functions often impaired in neurodegenerative diseases.

Curcumin pre-treatment has been effective in mitigating mitochondrial damage in both LRRK2 mutant PD models and healthy control fibroblasts by targeting oxidative stress pathways [68]. In mouse models of PD induced by paraquat and manganese exposure, the NADPH oxidase inhibitor apocynin significantly reduced M1-type inflammatory responses, leading to improvements in cognitive deficits, decreased neurodegeneration in the hippocampus, and reduced α-synuclein aggregation [69].

Green tea polyphenols have also been shown to protect neurons from apoptosis in both cellular and animal models of PD by scavenging ROS and regulating cell survival signaling pathways [69]. Resveratrol, a plant-derived polyphenol, provides neuroprotective effects by modulating genes involved in antioxidative enzyme regulation and mitochondrial dynamics, while also enhancing mitophagy through SIRT-1 and AMPK/ERK pathways, thereby protecting against mitochondrial dysfunction [16]. Rutin, another flavonoid, has demonstrated improved bioavailability and effectiveness in reducing oxidative stress in PD models when used in self-nanoemulsifying drug delivery systems [70].

Moreover, mangiferin has proven effective in alleviating motor impairments

induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and in enhancing tyrosine hydroxylase expression in the substantia nigra of PD mice, thereby improving mitochondrial structure and ATP synthesis [71]. Research by Zhang *et al.* indicated that polydatin significantly mitigates Parkinsonism in murine models by enhancing glycolytic processes in dopaminergic neurons, emphasizing the critical role of ATP synthesis in preventing neuronal degeneration in PD [72].

Lycopene nanodots, designed to cross the blood-brain barrier, have shown promise in enhancing mitochondrial function and promoting mitophagy. These antioxidative nanodots protect neuronal mitochondrial function in vitro and in vivo by facilitating PINK1/Parkin-mediated mitophagy in MPTP-affected neurons, aiding in the elimination of harmful α-synuclein and improving the viability of dopaminergic neurons [73].

Furthermore, Urolithin A has been observed to prevent dopaminergic neuronal degeneration and neuroinflammation by promoting microglial mitochondrial autophagy and inhibiting NLRP3 inflammasome activation in models of lipopolysaccharide-induced BV2 cellular inflammation and MPTP-induced PD [74]. Similarly, Hyperoside may exert neuroprotective effects by modulating mitochondrial autophagy in both a rotenone-induced rat model of PD and an SH-SY5Y cell model [75].

Table 1. Representative substances among polyphenols and flavonoids with antioxidant and mitochondrial protective functions.

Substance	Study subjective	Targeting mechanism	Study reference
Curcumin	Fibroblasts	Reduce mitochondrial damage	[68]
apocynin	Mice and cell	Inhibits oxidative stress and neuroinflammation	[69]
Green tea polyphenols	Rat	Inhibits oxidative stress	[69]
Resveratrol	Mice	Inhibits oxidative stress and neuroinflammation	[16]
Rutin	Rat	Inhibits oxidative stress	[70]
mangiferin	Mice	Promotes mitophagy	[71]
poly dating	Mice	promotion of glucose metabolism in neurons	[72]
Lycopene	Mice	Promotes mitophagy and promotes the secretion and outflow of α-Syn	[73]
Urolithin A	Cell and mice	promoting microglial mitochondrial autophagy and inhibiting NLRP3 inflammasome activation	[74]
Hyperoside	Cell and rat	Promotes mitophagy	[75]
baicalein	Cell	enhanced mitobiogenesis to restore mitochondrial function	[76]
catechol	Cell	the inhibition of α-syn cytotoxic fibrillization and mitochondrial dysfunction	[77]

Exploratory studies in a rotenone-induced PD model revealed that baicalein alleviates behavioral impairments and depletes dopaminergic neurons while en-

hancing mitochondrial functionality through cAMP-responsive element-binding protein (CREB) and glycogen synthase kinase-3β (GSK-3β) signaling pathways [76]. Additionally, in vitro analyses have shown that catechol inhibits the cytotoxic assembly of α-synuclein, preserving mitochondrial integrity during critical stages of PD progression [77]. Here, we have summarized some representative substances among polyphenols and flavonoids with antioxidant and mitochondrial protective functions in (**Table 1**).

3.2. Vitamis and Coenzymes

Vitamins A, C, and E have demonstrated protective effects against oxidative-induced neuronal death in PD. These vitamins function by scavenging nitrogen and oxygen-reactive species and inhibiting protein aggregation, thereby mitigating oxidative stress [78]. Coenzyme Q10 (CoQ10) has been studied for its potential to alter PD pathogenesis by addressing mitochondrial complex-1 deficiency and free radical generation. Clinical studies suggest that CoQ10 may slow disease progression in PD patients.

Similarly, α-lipoic acid has demonstrated significant benefits in PD models, particularly in improving behavioral impairments induced by 6-hydroxydopamine. It reinstates ATP levels within the midbrain and ameliorates mitochondrial morphology by curtailing fragmentation and vacuolization. Western blot analyses have further shown that α-lipoic acid significantly preserves midbrain dopaminergic neurons and reestablishes the equilibrium of mitochondrial dynamics, encompassing fission, fusion, and transport processes. These findings collectively suggest that α-lipoic acid may exert substantial neuroprotective effects in animal models of PD through its modulation of mitochondrial dynamics [79]. We have summarized some vitamins and coenzyme substances used for the treatment of Parkinson's disease, and their therapeutic mechanisms are shown in (**Table 2**).

Table 2. Vitamins and coenzymes are representative substances used to treat Parkinson's disease.

Substance	Mechanism of action	Study reference
Vitamins A	Involved in neurotransmitter metabolism	[78]
Vitamins B	Affect the metabolism of nerve cells	[78]
Vitamins C	Strengthen the antioxidant defense system	[78]
Vitamins E	Clear free radicals	[78]
Coenzyme Q10	Promote the generation of ATP	[80]
α-lipoic acid	Improve behavioral disorders	[79]
Nicotinamide adenine dinucleotide	Participate in REDOX reactions	[39]

3.3. Saponins

Gypenosides is derived from the plant Gynostemma pentaphyllum, gypenosides exhibit antioxidative effects by increasing glutathione content and enhancing superoxide dismutase activity. These effects help protect dopaminergic neurons in

PD models [80].

3.4. Phenolic Compounds

Piceatannol, Thymoquinone, and Esculetin: These phenolic compounds have been identified as strong kinase inhibitors that reduce oxidative dysfunction and neuronal loss in PD models. They offer dual antioxidant and kinase inhibitor properties, making them useful for PD treatment [81].

3.5. Carotenoids

Several other natural antioxidants have been identified for their neuroprotective effects. For instance, crocin, a compound derived from saffron, has been shown to exert antioxidant effects and improve cognitive functions in animal models of PD [82]. Additionally, compounds like N-acetylcysteine have been studied for their ability to enhance endogenous antioxidant defenses and mitigate oxidative stress in neuronal cells.

3.6. Other Phytochemicals

Minerals such as zinc and selenium are crucial in antioxidant defense mechanisms. For example, zinc has been shown to enhance the activity of various antioxidant enzymes, providing neuroprotective effects in PD models [83]. The antioxidant urate, a naturally occurring compound, is associated with a lower risk of PD and may offer neuroprotective benefits through its free radical scavenging properties.

Additionally, artemisinin has also demonstrated neuroprotective effects against 6-OHDA and MPP+ induced neuronal injuries in both in vitro and in vivo studies. This compound activates the ERK1/2 signaling pathway, which helps to reduce oxidative stress, improve mitochondrial dysfunction, and inhibit apoptosis, suggesting artemisinin has potential therapeutic value in maintaining mitochondrial function [84].

Moreover, anacardic acids effectively prevent behavioral changes and oxidative stress in a rat model of PD, likely linked to their modulatory effects on mitochondrial functionality and SOD gene expression. Geraniol exhibits strong neuroprotective effects in rotenone-induced Parkinson's models by reducing oxidative stress and preserving mitochondrial function, attributed to its enhanced antioxidant defense system and modulation of autophagic flux [85]. Similarly, rosmarinic acid shows dose-dependent neuroprotective properties in a rotenone-induced SH-SY5Y cell model by inhibiting Abl tyrosine kinase, reducing α-synuclein and Tau phosphorylation, restoring mitochondrial membrane potential and ATP levels, and inhibiting rotenone-induced ROS overproduction [86].

Cistanoside A notably enhances motor functions and increases the density of tyrosine hydroxylase-positive cells in the SNpc of mice. In vitro studies highlight its role in alleviating MPP^+-induced reductions in neuronal and mitochondrial membrane potentials through stimulating autophagosome activity and recruiting

key proteins like PINK1 and Parkin to damaged mitochondrial membranes, facilitating robust mitochondrial autophagy [87].

Andrographolide, a diterpenoid lactone, has shown significant neuroprotective effects in Parkinson's models by targeting mitochondrial dynamics. This compound directly binds to DRP1, inhibiting its GTPase activity, which prevents DRP1 oligomerization and subsequent mitochondrial fragmentation. This intervention mitigates motor impairment, enhances neuronal survival, and improves mitochondrial function in rat models [88]. Lastly, astragalus polysaccharide reverses MPTP-induced mitochondrial structural impairments, decreases ROS levels, and elevates mitochondrial membrane potential in murine models of PD. The other phytochemical substances used for treating Parkinson's disease and their therapeutic mechanisms are shown in (**Table 3**).

Table 3. Other phytochemicals used for treating Parkinson's disease.

Substance	Mechanism of action	Study reference
Zinc	Enhance the activity of various antiox-idant enzymes	[83]
Selenium	Affect the metabolism of nerve cells	[83]
Artemisinin	Strengthen the antioxidant defense system	[84]
Geraniol	Enhance the antioxidant defense system and regulate autophagic flux	[85]
Rosmarinic acid	Inhibit the excessive production of ROS	[86]
Cistanoside A	Stimulate the activity of autophagosomes	[87]
Andrographolide	Improved mitochondrial function	[88]

4. Challenges and Outlook

4.1. Challenges in Using Natural Antioxidants in PD

Complexity of PD pathogenesis: PD involves multiple pathological processes, including oxidative stress, mitochondrial dysfunction, and protein aggregation. Natural antioxidants, while beneficial, may not address all these aspects comprehensively. The multifactorial nature of PD requires a multi-targeted therapeutic approach, which is challenging to achieve with single antioxidant compounds [89].

Bioavailability issues: Many natural antioxidants, such as rutin, suffer from low bioavailability, limiting their therapeutic efficacy. Innovative delivery systems, like self-nanoemulsifying drug delivery systems, have been developed to enhance the bioavailability of such compounds, but these solutions add complexity to treatment protocols.

Lack of clinical evidence: Despite promising preclinical results, there is a lack of robust clinical trials demonstrating the efficacy of natural antioxidants in PD. This gap in evidence makes it difficult to establish standardized treatment protocols and gain regulatory approval [89].

Variability in natural compounds: The composition of natural antioxidants can

vary significantly depending on their source and preparation methods. This variability can lead to inconsistent therapeutic outcomes and poses a challenge for standardization and quality control in clinical settings.

4.2. Prospects for Natural Antioxidants

Clinical Trials and Bioavailability: While preclinical studies are promising, translating these findings into effective therapies requires rigorous clinical trials. Challenges such as bioavailability, pharmacokinetics, and potential drug interactions need to be addressed to optimize the therapeutic use of natural antioxidants [90].

Nanotechnology and Delivery Systems: Advances in nanotechnology could enhance the delivery and efficacy of natural antioxidants by improving their stability and targeting capabilities. Encapsulation in nanocarriers is being explored to overcome issues related to rapid degradation and excretion.

Combination therapy: The integration of antioxidants in combination therapies is also gaining traction. For instance, combining antioxidants with other neuroprotective agents may enhance their effectiveness by targeting multiple pathways involved in PD pathology. This multifaceted approach could lead to more comprehensive treatment strategies that address both oxidative stress and neuroinflammation, which are critical in PD progression [91]. Resveratrol, when combined with L-dopa, enhances the neuroprotective effects of levodopa on dopamine neurons, helping to slow PD progression. Its potent antioxidant and anti-inflammatory properties protect nerve cells from damage caused by free radicals and inflammation. Additionally, resveratrol improves mitochondrial function, boosting ATP production and providing essential energy for nerve cells. This combination therapy showcases the advantages of using resveratrol alongside L-dopa in managing PD [91].

5. Conclusions

The interaction between oxidative stress and mitochondrial dysfunction is a critical aspect of the pathophysiology of PD. Mitochondrial dysfunction is characterized by impaired energy production, particularly in dopaminergic neurons, which are particularly vulnerable to oxidative damage due to their high metabolic demands and the presence of dopamine, a neurotransmitter that can generate ROS upon oxidation [92]. This dysfunction is often linked to a deficiency in mitochondrial complex I, which has been observed in the substantia nigra of PD patients. The impairment of this complex leads to decreased ATP production and increased oxidative stress, creating a vicious cycle that exacerbates neuronal damage [93].

The potential of natural antioxidants in the treatment of PD is increasingly recognized due to their ability to mitigate oxidative stress, a key factor in the pathogenesis of this neurodegenerative disorder. Oxidative stress results from an imbalance between ROS and the body's antioxidant defenses, leading to neuronal damage, particularly in dopaminergic neurons of the substantia nigra, which are critically affected in PD [12]. Natural antioxidants, including polyphenols, flavo-

noids, and vitamins, have shown promise in preclinical and clinical studies for their neuroprotective effects.

While natural antioxidants present a promising avenue for the treatment of PD, it is essential to consider the complexity of their mechanisms and the challenges in translating preclinical findings into clinical success. Further research is needed to optimize their delivery and efficacy in human subjects. Additionally, while antioxidants can mitigate oxidative stress, they are not a standalone cure and should be considered as part of a comprehensive treatment strategy for PD. At the same time, we should also increase research on natural antioxidants in the treatment of PD, especially their clinical feasibility.

Acknowledgements

Author Contributions: Conceptualization, Y.Y., W.J., and X.Z.; writing—review and editing, Y.Y., and X.W.; writing—review and editing, Y.Y., W.J., Z.T., Y.C., and X.Z.; supervision, Y.C., and X.Z. All authors have read and agreed to the published version of the manuscript.

Funding

This study was funded by the Graduate Innovation Project of Chongqing University of Technology, grant number gzlcx20243222.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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