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Review article

The neuroprotective effects of ferulic acid in toxin-induced models of Parkinson's disease: A review

Samira Hassani [a], Abolghasem Esmaeili [b,*]

[a] Department of Plant and Animal Biology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran
[b] Department of Cell and Molecular Biology & Microbiology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran

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ABSTRACT

Parkinson's disease is predominantly caused by dopaminergic neuron loss in the substantia nigra pars compacta and the accumulation of alpha-synuclein protein. Though the general consensus is that several factors, such as aging, environmental factors, mitochondrial dysfunction, accumulations of neurotoxic alpha-synuclein, malfunctions of the lysosomal and proteasomal protein degradation systems, oxidative stress, and neuroinflammation, are involved in the neurodegeneration process of Parkinson's disease, the precise mechanism by which all of these factors are triggered remains unknown. Typically, neurotoxic compounds such as rotenone, 6-hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl 4-phenyl pyridinium (mpp^+), paraquat, and maneb are used to Preclinical models of Parkinson's disease Ferulic acid is often referred to by its scientific name, 4-hydroxy-3-methoxycinnamic acid (C10H10O4), and is found naturally in cereals, fruits, vegetables, and bee products. This substance exhibits neuroprotective effects against Parkinson's disease because of its intriguing potential, which includes anti-inflammatory and antioxidant qualities. This review goes into additional detail about Parkinson's disease and the neuroprotective properties of ferulic acid that may help prevent the condition.

1. Introduction

Parkinson's disease (PD) as a neurodegenerative disease is the most prevalent neurological ailment following Alzheimer's disease (Nakayama et al., 2020). Pathological manifestations of PD encompass the increase of alpha-synuclein protein, forming Lewy bodies within the cytoplasm, in addition to the dopaminergic neurons in the substantia nigra pars compacta (SNpc) being destroyed (Rosman et al., 2018). The primary cause of PD motor symptoms, such as bradykinesia, tremors, and muscular stiffness, is dopamine depletion in the nigrostriatal pathway (Spillantini et al., 1998; Van Den Eeden et al., 2003). A prolonged lack of dopamine can also result in emotional, behavioral, and cognitive problems such as insomnia, sadness, anxiety, and dementia (Spillantini et al., 1998). Although the exact etiological underpinnings of PD remain incomplete, it is proposed that it arises from complex interactions between many environmental and genetic variables. Factors presumed to augment the risk of PD include genetic mutations and exposure to deleterious agents affecting nerve cells (Ganguly et al., 2018). There are currently very few highly effective treatments available for Parkinson's disease. The medications that are currently used to treat the disease primarily alleviate its symptoms. These medications include dopamine agonists (such as pramipexole and ropinirole), levodopa (L-Dopa), monoamine oxidase B inhibitors, and coenzyme Q10 (Weintraub et al., 2008). Dopaminergic neurons are preserved because aromatic L-amino acid decarboxylase (AADC) converts L-Dopa, a dopamine precursor, into dopamine. This process raises dopamine levels (Gao and Hong, 2011). Consequently, approaches that decelerate or arrest Parkinson's disease progression are a subject of profound interest (Jankovic and Poewe, 2012). The substantia nigra pars compacta contains 70–80 % dopaminergic neurons, which are lost when PD clinical indications occur. Thus, interventions capable of impeding or delaying neuronal degeneration hold considerable promise (Muñoz et al., 2020). The evolution of PD is governed by substantial factors, including oxidative stress, inflammatory processes, mitochondrial dysregulation, iron accumulation, aging, environmental factors, and hereditary predisposition. This intricate interplay of diverse variables considerably hinders the advancement of research in Parkinson's disease, as illustrated in Fig. 1. Furthermore, the heightened metabolic rate of brain

* Correspondence to: Cell and Molecular Biology & Microbiology Department, Faculty of Biological Science and Technology, University of Isfahan, P.O. Box: 8174673441, Isfahan, Iran.
E-mail addresses: aesmaeili@sci.ui.ac.ir, abesmaeili@yahoo.com (A. Esmaeili).

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tissue, coupled with the presence of oxidizable molecules such as unsaturated fatty acids and dopamine, known to produce reactive oxygen species (ROS) during metabolism, along with elevated transition metal levels and diminished antioxidant capacity, renders the brain highly susceptible to oxidative stress (Liss and Striessnig, 2019). Therefore, compounds with anti-inflammatory and antioxidant properties, such as ferulic acid, may be able to stop or slow down neurodegeneration.

2. Different mechanisms involved in Parkinson's disease

2.1. Oxidative stress and Parkinson's disease

Oxidative stress is associated with dopaminergic neurons' apoptotic death in PD. Long-chain polyunsaturated fatty acids, which are abundant in the brain, increase the formation of reactive oxygen species (ROS) and are therefore vulnerable to lipid peroxidation and oxidative stress. However, oxidative stress can cause alpha-synuclein to build up in dopaminergic neurons and other areas of the central nervous system (Vaccari et al., 2019). In addition to other detrimental effects on the development of Parkinson's disease, aggregated α-synuclein species, particularly oligomers, may increase damage to mitochondrial aerobic respiration and alter the ubiquitin-proteasome system (Masato et al., 2019). Furthermore, PD pathogenesis and development may involve metabolites from dopamine metabolism in addition to endogenous and exogenous neurotoxins (Fig. 1) (Dionísio et al., 2021). In general, dopaminergic neurons are susceptible to oxidative stress because of the different oxidants that they produce (Latif et al., 2021). As per Segura-Aguilar (Segura-Aguilar, 2021), the oxidative deamination of dopamine in dopaminergic neurons results in the generation of hydrogen peroxide (Segura-Aguilar, 2021). This compound is then reduced in the presence of iron, leading to the production of hydroxyl radicals. Moreover, the oxidation of dopamine to three ortho-quinones—dopamine ortho-quinone, aminochrome, and 5,6-indolequinone—causes the formation of neuromelanin in these neurons. Oxidative stress can be brought on by these three substances, particularly aminochrome (Segura-Aguilar et al., 1998). Although it is not specific to dopaminergic neurons, the leaking of electrons from the mitochondrial electron transport chain during ATP generation is another cause of oxidative stress (Segura-Aguilar and Mannervik, 2023).

2.2. Inflammation and Parkinson's disease

An important factor in the development of PD is neuroinflammation, which is mainly driven by immune cells in the brain, namely astrocytes and microglia. These cells are primarily responsible for the clearance of extracellular debris, with microglia playing a more predominant role compared to astrocytes and oligodendrocytes. Activation of microglia has been seen by several Parkinson's-related proteins, including alpha-synuclein, Parkin, Leucine-rich repeat kinase 2)LRRK2(, and DJ-1) Fig. 1((Wilhelmus et al., 2012). Toll-like receptor 2 (TLR2), which is agonistically activated by extracellular alpha-synuclein produced by neurons, leads to the activation of microglia (Kim et al., 2013a). Microglia are highly concentrated in the substantia nigra pars compacta and striatum, and their activation can cause neuronal death by producing inflammatory mediators, such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 beta (IL-1β), interferon gamma (IFNγ), tumor necrosis factor (TNF), CXC-chemokine ligand 8 (CXCL8), and chemokine ligand 2 (CCL2) (Tansey et al., 2022). Another

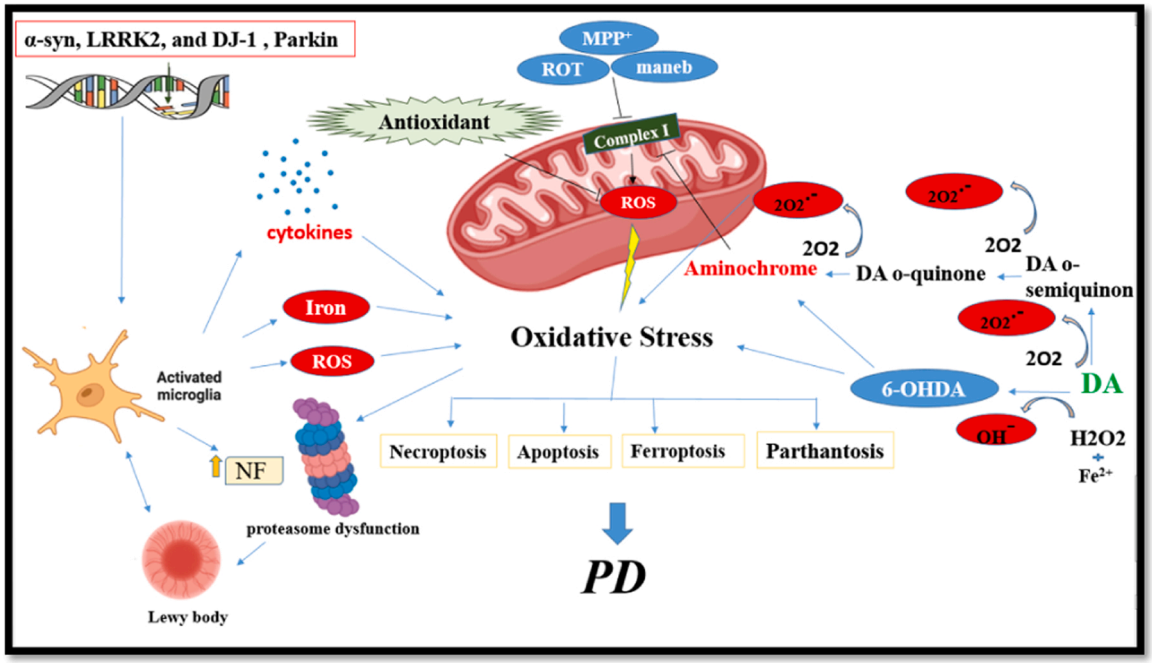

Fig. 1. Key players in the onset of PD. Oxidative stress: dopamine is stable in acidic neurotransmitter storage vesicles, at neutral cytosolic or extracellular pH, it undergoes autoxidation and forms dopamine semiquinone, especially the dopamine o-semiquinone radical. The continual O2-. Produced by the interconversion of semiquinones and quinones fuels the iron-dependent Haber-Weiss cycle, which generates very reactive OH-. When dopamine is combined with Fe2+ and H2O2, it can be converted into the neurotoxin 6-OHDA. 6-OHDA can cause oxidative stress by producing excess O2- and entering the aminochrome cycle (which is a strong inhibitor of mitochondrial complex I). Inhibition of mitochondrial complex I by endogenous and exogenous neurotoxins decreases ATP synthesis increases ROS, especially O2-, and finally, mitochondrial defects with fission and fragmentation. neuroinflammation: Several proteins related to PD, including α-syn, LRRK2, DJ-1, and Parkin activate microglia. On the other hand, activated microglia can play protective functions by producing neurotrophic factors or helping the proliferation and accumulation of α-syn. In general, oxidative stress caused by various factors including neurotoxins, increased ROS, increased iron, and activation of microglia causes cell death in dopaminergic neurons and ultimately leads to PD. Also, oxidative stress causes proteasome disorders, which in turn increases the accumulation of α-syn and the formation of Lewy bodies. ROT; rotenone, 6-OHDA; 6-hydroxydopamine, MPP+; 1-methyl-4-phenylpyridinium, DA; dopamine, NF; Neurotrophic factors, ROS; reactive oxygen species, α-syn; alpha-synuclein, LRRK2; Leucine-rich repeat kinase 2, O2-.; Superoxide radical, H2O2; hydrogen peroxide, OH-; hydroxyl radical.

mechanism leading to microgliosis and neuroinflammation in glial cells is dysfunctional phagocytosis, which results from lysosomal abnormalities linked to PD-related mutations (Tremblay et al., 2019). However, active microglia can either play protective functions by producing neurotrophic factors or contribute to the proliferation and α-synuclein aggregation)Fig. 1((Joers et al., 2017).

2.3. Cell death and Parkinson's disease

Several programmed cell death pathways may contribute to the increasing neuron death during the illness given the prolonged and complex nature of neurodegeneration in PD (Galluzzi et al., 2018). DNA fragmentation, chromatin condensation, and cell shrinkage are some of the hallmarks of apoptosis that have been found in the brains of Parkinson's disease patients after their deaths. In preclinical models of PD, neurotoxins such as rotenone (ROT), 6-hydroxydopamine (6-OHDA), and 1-methyl-4-phenylpyridinium (MPP+) induce apoptosis (Dionísio et al., 2021). Along with apoptosis, other kinds of programmed cell death associated with Parkinson's disease include necroptosis, ferroptosis, and parthanatosis (Chou et al., 2021; Shan et al., 2018; Wang et al., 2022). Numerous factors, such as TNF-α, Fas, TRAIL, interferons, and the activation of Toll-like receptors, can cause necroptosis (Grootjans et al., 2017). One sort of regulated cell death that is iron-dependent is called ferroptosis. Severe lipid peroxidation and aberrant iron metabolism are the root causes since they lead to oxidative stress and cell death (Wang et al., 2022). Ferroptosis is regulated by pathways such as iron metabolism, oxidative stress, and cytotoxic amino acid metabolism, and ferroptosis suppressor protein 1 (FSP1)- CoQ10 may influence an individual's vulnerability to it (Bersuker et al., 2019). Parthanatos, or poly (ADP-ribose) polymerase-1 (PARP1)-dependent cell death, is another kind of programmed cell death linked to PD (Park et al., 2020). An essential enzyme called PARP1 reacts to damage to DNA by encouraging DNA repair to preserve cell viability. On the other hand, excessive PARP1 activation causes nicotinamide adenine dinucleotide (NAD+) and ATP depletion in situations of excessive DNA damage, which in turn causes excessive PAR production and aggregation. This causes the apoptosis induction factor to move from the mitochondria into the nucleus, where it binds to the inhibitory factor of macrophage migration to start the death of cells. (Hu et al., 2021; Park et al., 2020).

2.4. Mitochondria and Parkinson's disease

Mitochondrial activity issues are linked to neurodegenerative illnesses such as Parkinson's disease.

This is related to the inhibition of complex I, which blocks the electron transport chain in the mitochondria and causes oxidative stress, energy depletion, and dopaminergic cell death (Xu et al., 2021). PGC1α, also known as peroxisome proliferator-activated receptor-γ coactivator 1-α, is an essential mediator of mitochondrial biogenesis. It does this by increasing the expression and function of several vital transcription factors. PGC1α specifically stimulates nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which in turn stimulates mitochondrial transcription factor A (TFAM). The synthesis of proteins and mitochondrial DNA results from this series of processes, which eventually promotes the genesis of new mitochondria (Rius-Pérez et al., 2020). Additionally, the upregulation of proteins such as uncoupling protein-2 (UCP2) is another way that the expression of PPARγ-PGC1α promotes mitochondrial uncoupling. UCP2, which is located inside the inner mitochondrial membrane, works to reduce the generation of ROS by dissipating the potential of the mitochondrial membrane and releasing the electron transport chain from ATP synthesis (Jamwal et al., 2021). Furthermore, UCP2 has been reported to suppress the generation of pro-inflammatory cytokines, prevent mitochondrial calcium excess, and prevent possible apoptosis. Reduced expression of UCP2 probably has a role in the etiology of neurodegenerative disorders and other ailments since it has been linked to mitochondrial malfunction, the accumulation of ROS, and increased cell death (Cenini et al., 2019; Jamwal et al., 2021).

3. Different neurotoxins in preclinical models for Parkinson's disease

3.1. Exogenous neurotoxins

One of the characteristics of exogenous neurotoxins is that they cause massive, very rapid, and widespread degeneration in neurons. As was previously established, any interference in the function of mitochondrial complex I might lead to an increase in ROS generation and consequent oxidative damage in brain tissue. Oxidative stress can cause the autoxidation of dopamine in dopaminergic neurons and as a result the accumulation of α-synuclein. Hence, various neurotoxins capable of inducing degeneration in dopaminergic neurons are employed in research to create a preclinical PD model (Napolitano et al., 2011). For instance, the MPTP model demonstrates motor impairments and a form of cell death that remains stable over time and does not result in the presence of α-synuclein in the cytoplasm. Although this preclinical model encompasses oxidative stress, inflammation, and the activation of glial cells, its primary utility lies in investigating cellular mechanisms due to its acute nature (Blesa et al., 2012). Because MPTP is lipophilic, it can pass across the blood-brain barrier after being administered systemically. MPTP is metabolized by MAO-B in the brain, mostly in astrocytes, to produce MPDP+. The active metabolite MPP+ is then produced when MPDP+ diffuses into the intracellular space and auto-oxidizes. MPP+ has a high affinity for dopamine transporters (DATs) on the plasma membrane, which enables it to accumulate inside dopaminergic neurons. After entering the neuron, MPP+ can inhibit complex I of the electron transport chain and block the flow of electrons. Reduced ATP synthesis and increased ROS generation, especially superoxide, result from this disturbance (Dionísio et al., 2021). A popular natural insecticide is ROT, a neurotoxin obtained from the tropical plants Lonchocarpus and Derris. It suppresses complex I of the respiratory chain of the mitochondria and causes mitochondrial malfunction similar to that seen in PD patients. Rats given ROT treatment show many of the same characteristics as those with sporadic PD, despite the drug's systemic effects: bradykinesia, decreased locomotor activity, loss of dopaminergic neurons and their striatal terminals, depletion of endogenous antioxidants, activation of microglia, inflammation, and inclusions of intra cytoplasmic α-synuclein. The rat model of ROT-induced PD is commonly used to test possible chemicals to reduce symptoms and investigate protective mechanisms since the condition is progressive and persistent (Johnson and Bobrovskaya, 2015; Litteljohn et al., 2011). Furthermore, because ROT is extremely lipophilic, it may readily cross the blood-brain barrier and impede complex I activity in the mitochondrial electron transport chain, which leads to oxidative stress, energy depletion, and the selective degeneration of nigral dopaminergic neurons (Lawana and Cannon, 2020). 6-OHDA is a dopamine metabolite and, due to its high level of structural similarity to dopamine, tends to enter through the DAT. Once inside, it causes oxidative stress and neurotoxicity in dopaminergic neurons by blocking mitochondrial respiratory chain complexes I and IV. A key characteristic of 6-OHDA is that it is unstable in the presence of oxygen. Therefore, when injected into the striatum, substantia nigra, or axon bundle in animal models, ascorbic acid must be used to prevent its oxidation before it is transported into neurons. 6-OHDA is oxidized in the cytosol of dopaminergic neurons, producing a semi-quinone radical that is highly reactive with oxygen and a cause of oxidative stress. 6-OHDA is the source of oxidative stress in these preclinical models, but this molecule is not present in the human brain (Segura-Aguilar and Kostrzewa, 2015; Vareślija et al., 2020).

Paraquat, a herbicide frequently used in the US to manage weeds in agricultural and horticultural crops, is structurally similar to MPTP and is utilized in experimental models to induce preclinical PD. Paraquat is associated with PD due to its capacity to induce dopaminergic neuron loss, reduce dopamine levels, and enhance alpha-synuclein deposition

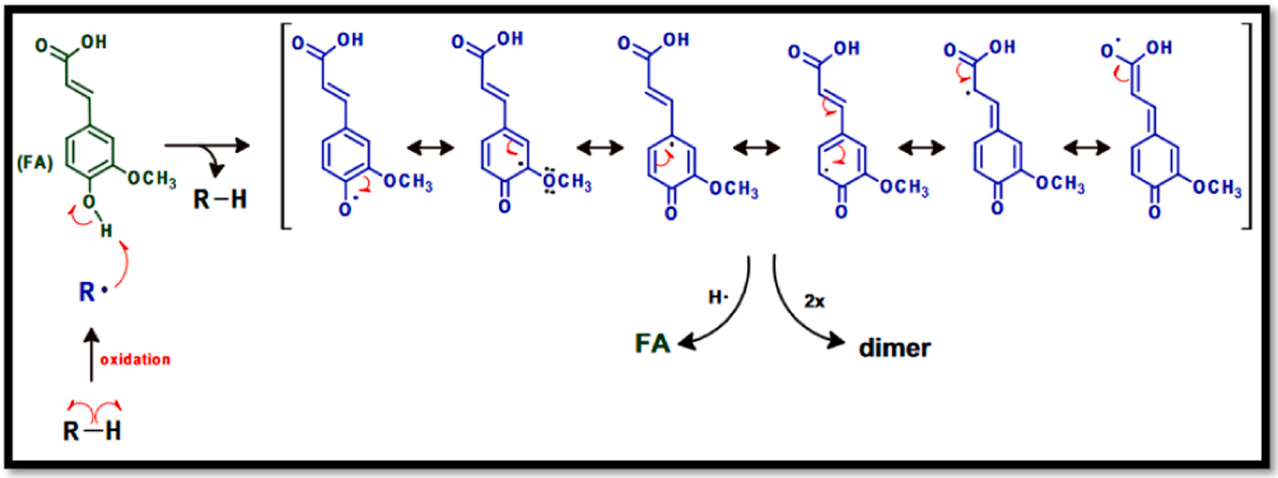

Fig. 2. FA has significant antioxidant properties due to the high level of resonance stabilization in the phenoxyl radical present in its structure and side chain conjugation which leads to the effective scavenging of free radicals (Batista, 2014a).

(Vaccari et al., 2019). Moreover, studies have illustrated that Paraquat exposure elevates ROS production and provokes movement disorders (Vaccari et al., 2019). One environmental risk factor for PD is exposure to the fungicide manganese ethylene-bisdithiocarbamate, or Maneb. Maneb changes lactate dynamics stimulates oxidative stress, and impairs mitochondrial respiration to cause Parkinson's disease. Moreover, Maneb alters the redox state of thiol peroxiredoxin 3 (Prx3) in the mitochondria and oxidizes glutathione to affect the thiol redox status of the cell (Anderson et al., 2021). However, toxin-based models do not consistently show pathological signs of Lewy bodies, often fail to replicate the complex nonmotor symptoms and extra dopaminergic involvement seen in early PD, and may not reflect the chronic and progressive nature of neurodegeneration in PD. These limitations may lead to a mismatch in the effects observed in animal models versus the comprehensive symptoms experienced by PD patients. Also, despite promising preclinical data with exogenous neurotoxins, several potential neuroprotective drugs have failed to demonstrate clinical benefit in clinical trials for PD, such as rasagiline, creatine, ubiquinone (coenzyme Q10), mitoquinone, isradipine, TCH346, neurturin, zonisamide, deferiprone (Athauda and Foltynie, 2015).

3.2. *Endogenous neurotoxins*

An ideal preclinical model for Parkinson's disease should: a) slowly mimic the degenerative process seen over many years in humans. b) Uses an endogenous neurotoxin that is formed in dopaminergic neurons containing neuromelanin in the nigrostriatal system. c) Target specific dopaminergic neurons that contain neuromelanin rather than causing extensive neuronal loss. To more closely resemble the decades-long evolution, such a model may significantly slow down the destruction process. d) Initiate every pathogenic mechanism related to breakdown, including endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, buildup of toxic alpha-synuclein oligomers, and disruption of the lysosomal and proteasomal protein degradation systems. For instance, three putative endogenous neurotoxins—neurotoxic alpha-synuclein oligomers, 3,4-dihydroxyphenylacetaldehyde (DOPAL), and aminochrome—might potentially contribute to the disease's characteristic gradual loss of dopaminergic neurons. On the other hand, microglia phagocytose dying neurons to eliminate any remnants of Lewy bodies that have developed over years of degeneration (Segura-Aguilar, 2018). Consequently, postmortem tissue only contains neurons that have withstood the years-long degeneration process (Wakabayashi et al., 2013). According to Segura-Aguilar and Mannervik (Segura-Aguilar and Mannervik, 2023), this indicates that the development of Lewy bodies is a neuroprotective process that prevents alpha-synuclein from aggregating into harmful neuronal oligomers (Segura-Aguilar and Mannervik, 2023). In reference to DOPAL, a post-mortem investigation discovered that Parkinson's patients had lower levels of aldehyde dehydrogenase-1 than controls. This enzyme is involved in the breakdown of dopamine and the conversion of DOPAL to 3,4-dihydroxyphenylacetic acid (Grünblatt et al., 2018). However, DOPAL cannot have a neurotoxic effect on these surviving neuromelanin-containing dopaminergic neurons since postmortem tissue is derived from neurons that have withstood the degeneration process during many years of Parkinson's disease, and these tissues have low levels of aldehyde dehydrogenase-1 (Segura-Aguilar and Mannervik, 2023).

3.2.1. *Aminochrome*

An endogenous neurotoxin that fits this degenerative model is aminochrome, which can provide a better research approximation of idiopathic Parkinson's than existing preclinical options by accurately reproducing key features and gradual clinical course (Huenchuguala and Segura-Aguilar, 2024; Segura-Aguilar and Mannervik, 2023). Aminochrome can create a single-neuron degeneration model where a neurotoxin produced within the damaged neuron itself initiates a degenerative process leading to just the death of that neuron. Unlike other widespread models of degeneration, this process does not impact neighboring neurons. It remains confined to a single neuron. In this single-neuron degeneration model, the death of individual neurons accumulates gradually over a long period of years rather than affecting many neurons at once (Huenchuguala and Segura-Aguilar, 2024). Aminochrome, produced during the creation of neuromelanin in dopaminergic neurons, can lead to gradual degeneration of these neurons. In the process of neuromelanin synthesis, dopamine is oxidized to three transient ortho-quinones (dopamine ortho-quinone, aminochrome, and 5,6-indolequinone), with aminochrome being the most neurotoxic and longest-lasting. The one-electron reduction of aminochrome to leukoaminochrome o-semiquinone radical generates superoxide, leading to a redox cycle that depletes cellular dioxygen and/or NAD(P)H. This cycle affects the activity of the mitochondrial respiratory chain and ultimately ATP production. The superoxide produced can be converted to hydrogen peroxide, which in the presence of reduced iron forms hydroxyl radicals, inducing oxidative stress (Huenchuguala and Segura-Aguilar, 2023). Aminochrome also forms adducts with proteins like alpha-synuclein and mitochondrial respiratory chain complex I, and other cellular components. This leads to mitochondrial dysfunction, formation of toxic alpha-synuclein oligomers, impairment of lysosomal and proteasomal degradation systems, disruption in the structure of the cellular skeleton

and microtubules, endoplasmic reticulum stress, and neuroinflammation, which causes neurotoxicity that eventually ends with the loss of a single neuron (Huenchuguala and Segura-Aguilar, 2023; Segura-Aguilar and Mannervik, 2023).

3.2.1.1. Inhibition of aminochrome neurotoxicity. The collaboration between astrocytes and neurons is crucial for maintaining neuronal health. Two enzymes, DT-Diaphorase and glutathione transferase M2–2 (GSTM2), are expressed in both dopaminergic neurons and astrocytes, and they work together to prevent the toxic effects of aminochrome. GSTM2 plays an important role in protecting dopaminergic neurons against aminochrome neurotoxicity by preventing cell death, protecting mitochondria, preventing the formation of alpha-synuclein oligomers, maintaining the lysosomal function, and preventing autophagy impairment (Segura-Aguilar et al., 2022). DT-diaphorase converts aminochrome to a less toxic form called leukoaminochrome, while, GSTM2 combines aminochrome with glutathione to create a stable compound that is resistant to oxidizing agents such as oxygen, superoxide, and hydrogen peroxide. This process prevents the neurotoxic effects of aminochrome by producing a non-toxic product, which protects dopaminergic neurons from oxidative damage. Furthermore, DT-Diaphorase inhibits the accumulation of actin and alpha/beta-tubulin caused by aminochrome, preserving the microtubule structure, function, and neuronal morphology/stability. It also plays a neuroprotective role against aminochrome neurotoxicity in neuromelanin-containing dopaminergic neurons, contributing to overall defense against oxidative stress (Segura-Aguilar et al., 2022). Segura-Aguilar et al. showed that activation of Nrf2 and the upregulation of cytoprotective enzymes can protect dopaminergic neurons from aminochrome toxicity. Therefore, phytochemical activators of KEAP1/ Nrf2 can be useful in preventing or decreasing the neurotoxic effects of aminochrome (Segura-Aguilar and Mannervik, 2023). Another noteworthy point is that mutations in the LRRK2 gene associated with familial Parkinson's disease increase the regulation of tyrosine hydroxylase and dopamine synthesis (Zhou et al., 2022). Increased expression of tyrosine hydroxylase and dopamine synthesis can lead to higher levels of free dopamine in the cytosol, contributing to increased production of neurotoxic compounds like aminochrome. Inhibition of tyrosine hydroxylase with α-methyl-l-tyrosine reduces these neurotoxic effects. Therefore, the balance between dopamine synthesis, protective enzymes, and reducing aminochrome neurotoxicity differentiates healthy aging from Parkinson's disease, where the loss of these protections or accumulation of more neurotoxins may lead to the degeneration of dopaminergic neurons and clinical symptoms (Huenchuguala and Segura-Aguilar, 2023; Zhou et al., 2022).

4. Iron and Parkinson's disease

Regulation of iron levels in the brain is essential for neuroprotection. Imbalances in iron homeostasis can lead to oxidative stress, neuroinflammation, and neuronal damage, all of which are implicated in the pathogenesis of PD. Iron's ability to change redox states enables it to participate in crucial biological processes such as oxygen transport through hemoglobin and electron transport in the mitochondrial respiratory chain, ultimately contributing to energy production and cellular function in the human body. However, iron accumulation in the brain, particularly in the substantia nigra region, is implicated in the development of Parkinson's disease. Iron bound to proteins is in its oxidized state (Fe3+), but reducing agents such as ascorbic acid, reduced flavin, or N-acetylcysteine can release it in its reduced state (Fe2+). Fe2+ catalyzes the formation of hydroxyl radicals in the presence of hydrogen peroxide, which is generated in the oxidative deamination of dopamine to 3,4-dihydroxyphenylacetaldehyde catalyzed by monoamine oxidase in dopaminergic neurons. This oxidative stress can cause neurodegeneration of neuromelanin-containing dopaminergic neurons and/or induce neuroinflammation, ultimately leading to degeneration of neuromelanin-containing dopaminergic neurons in Parkinson's disease. However, neuromelanin-containing dopaminergic neurons produce neuromelanin, which acts as an iron chelator, preventing the neurotoxic effects of Fe2+ in the presence of hydrogen peroxide. Finally, this neuromelanin containing Fe3+ is deposited in Lewy bodies (Huenchuguala and Segura-Aguilar, 2023). However as stated, when the neuron is destroyed, microglia appear and phagocytize all the remains of this neuron in the process of death. Therefore, in a patient with PD, the post-mortem tissue shows only neurons and glial cells that have survived this destructive process over the years (Segura-Aguilar and Mannervik, 2023). Therefore, the presence of iron deposits in postmortem material does not mean that iron has initiated a degenerative process of dopaminergic neurons containing neuromelanin. Consequently, if iron accumulation in postmortem material of Parkinson's patients is not evidence of neurodegeneration, this iron accumulation probably has a neuroprotective role (Huenchuguala and Segura-Aguilar, 2023). Also, a clinical study using the iron chelator deferiprone in patients with PD did not show positive effects and probably worsened clinical symptoms. This indicates that iron might not have a central role in the neurodegenerative progression of PD (Devos et al., 2022).

5. Ferulic acid

Simple phenols, phenolic acids, and polyphenols are the three main categories into which phenolic substances are systematically divided (Khoddami et al., 2013). The presence of an aromatic ring structure connected to one or more hydroxyl groups is what distinguishes these molecules. Among them, Ferulic acid (FA), a phenolic acid, is particularly common in traditional Chinese medicines and may be obtained from some foods, including fruits, bee products, cereals like rice, wheat, and barley, and a wide range of vegetables like tomatoes and sweet corn (Thapliyal et al., 2021). Typically, FA is bound to lignin and polysaccharides within plant cell walls, and it is rarely encountered in its unbound form. Chemically, its molecular composition corresponds to 4-hydroxy-3-methoxycinnamic acid (C10H10O4), featuring two isomeric forms, CIS and Trans. In its purified state, FA manifests as a yellowish powder. FA is a chemical compound of considerable significance in various biological contexts, offering a myriad of benefits, including direct and indirect anti-inflammatory, antioxidant, antiviral, anti-allergic, antimicrobial, antithrombotic, anticancer, metal chelation, improved sperm viability, and hepato-protective properties (Bandaru and Rao, 2023). This diverse range of properties renders FA a potential therapeutic candidate for addressing an array of diseases, including diabetes, cancer, cardiovascular disorders, and neurological conditions (Thapliyal et al., 2021); (Turkez et al., 2022). The antioxidant attributes of FA can be attributed to the phenolic nucleus and its conjugated C3 side chain. The phenolic hydroxyl group within FA effectively disrupts radical chain reactions by intercepting free radicals (de Oliveira Silva and Batista, 2017). When FA engages with a free radical ($R^{\bullet}$), it abstracts a radical hydrogen, regenerating a stable compound (R-H). This transformation yields the phenoxyl radical, characterized by its stability due to resonance within the aromatic ring and the unsaturated side chain. The phenoxyl radical refrains from reacting directly but rather inclines towards interaction with other radical species, such as the feruloyl radical, resulting in dimer formation (de Oliveira Silva and Batista, 2017). Furthermore, the conjugated unsaturated structure of FA endows it with potent UV absorption capabilities, affording protection against oxidative damage by limiting the amount of UV radiation that reaches the surface (de Oliveira Silva and Batista, 2017; Fenton et al., 1978). In a study dating back to 2008, a research group under the leadership of J. Zhang discovered that FA possesses cytoprotective properties, including the capacity to scavenge oxygen radicals, act as an antioxidant by reducing ferric ions, and inhibit lipid peroxidation. These properties have the potential to shield SH-SY5Y cells from cell death triggered by H2O2 (Zhang et al., 2008).

5.1. Toxicity of Ferulic acid

FA is a potentially effective medicinal substance that is easily obtained, reasonably priced, and has few adverse effects (Ghosh et al., 2017). Choi et al. demonstrated that in three cell lines—platelets, leukocytes, and erythrocytes—FA (about 300 μg/ml) did not cause appreciable toxicity (Choi et al., 2018). However, in three distinct cell lines (Caco2 (40 mg/L), L929 (10, 20 mg/L), and U937 (40 mg/L)) as well as a three-dimensional intestinal model, Truzzi et al. demonstrated that FA has toxic effects at high concentrations, indicating that excessive and uncontrolled consumption FA may have negative effects on the intestinal wall (Truzzi et al., 2020). Therefore, it can be said that FA's toxicity depends on its concentration, which can affect different cell lines differently and needs to be handled carefully (D. (Li et al., 2021).

5.2. Pharmacokinetic parameters of Ferulic acid

Reduction of curcumin produces FA and several chemical compounds. Its unsaturated beta-diketone portion is where curcumin breaks down. This part of the diketone chain can change form based on its environment, alternating between the keto and enol forms. Vanillin, ferulic aldehyde, feruloyl methane, and FA are produced as curcumin breaks down. The degradation happens by a hydrolysis reaction that goes through the diketone group. Degradation is significantly reduced when curcumin remains bound to other compounds like lipids, liposomes, cyclodextrins, and albumins (Priyadarsini, 2014). According to the typical Mediterranean diet, the majority of their consumption is food containing FA، the amount of consumed FA was calculated to be about 250–150 mg (Barone et al., 2009). The physiological importance of FA depends on its absorption and interaction with target tissues. Absorption of FA in the perfused rat intestine is proportional to the dose administered. After absorption, FA is completely recovered as conjugated forms in bile and plasma secretions. Absorption of FA is efficient, with around 50 % of an administered dose recovered in urine (Adam et al., 2002). Daily intake of FA through food can reach 150e250 mg per day. Serum albumin is the main transporter of FA in the blood. Within 30 minutes of oral administration of 521 m mol/kg bw of FA to rats, approximately 2.6 mg/g of free FA reaches the brain. 92 % of consumed free FA is excreted in urine as free FA and its glucuronide conjugates. The half-life of FA in rats is estimated to range from 10 to 30 minutes depending on dose and administration route. Free FA is detected in human plasma 10 minutes after oral administration of sodium ferulate, indicating rapid absorption. Maximum plasma concentration of free FA occurs at 24 minutes, with a half-time of 42 minutes (Zhao and Moghadasian, 2008). Also, in rats, a single dose of FA combined with Honghua (a common Chinese herb) or clopidogrel can significantly improve the bioavailability of FA (Gao and Hong, 2011). Nano formulations are another method that can cause targeted delivery and increase the bioavailability of FA (Raj and Singh, 2022).

5.3. Ferulic acid and its neuroprotective effect in reducing α-synuclein

Nrf2 activation has been connected to Parkinson's disease, and regulating this protein has been demonstrated to decrease the progression of the condition (X.-x. (Yang et al., 2022). By aiding the transport and activation of Nrf2 into the nucleus, compounds that activate Nrf2 also prevent proteasomal degradation and boost the expression of antioxidant genes (X. (Xu et al., 2016). Concerning PD, FA has exhibited neuroprotective effects through its influence on Nrf2. It is noteworthy that SIRT2, the predominant sirtuin in the brain, negatively regulates Nrf2 and contributes to the accumulation of α-synuclein via deacetylation (X. (Yang et al., 2017). Nevertheless, FA has been found to impede α-synuclein accumulation and reduce SIRT2 levels in MPP+ treated SH-SY5Y cells (Anis et al., 2020). Research conducted by Xu Li et al. has demonstrated that in SHSY5Y cells, FA reduces the oxidative damage caused by MPP+ and alleviates motor deficits induced by MPTP in Parkinsonian mice. These beneficial effects rely on FA's antioxidant properties, which orchestrate the interplay between sirtuin 2 (SIRT2) and Nrf2 pathways. Additionally, FA diminishes the levels of ROS, lipid hydroperoxides, the GSH/GSSG ratio, and the NAD+/NADH ratio while enhancing the expression of glutamate cysteine ligase and heme oxygenase-1 (Anis et al., 2020). It has also been reported that FA can inhibit α-synuclein aggregation in the substantia nigra, a prominent neuropathological hallmark of PD (Takahashi et al., 2015). Regarding in vivo studies, NL5901 nematodes genetically engineered to express both human α-synuclein and yellow fluorescent protein (YFP) exhibited a substantial reduction in YFP intensity when exposed to 25–200 μM of FA, implying FA's potential to impede α-synuclein accumulation. Moreover, FA enhanced the NL5901 worms' motor abilities as seen by an increase in the number of body bends in 20 seconds (the ideal concentration was 50 μM FA) (Long et al., 2022). Furthermore, degeneration of dopamine (DA) neurons after exposure to 6-OHDA was seen in BZ555 worms, which were transgenic for the production of green fluorescent protein (GFP) in DA neurons under the dat-1 gene promoter (Pdat-1::GFP). However, the addition of FA or L-Dopa led to a significant restoration of GFP intensity. Furthermore, these BZ555 worms, which had previously been exposed to 6-OHDA and were unable to reduce their bending frequency for food acquisition, displayed a marked reduction in their bending frequency and improved locomotion after treatment with FA or L-Dopa (Long et al., 2022). Heat Shock Proteins (HSPs) are integral in the context of protein folding and collaborate with the ubiquitin-proteasome system (UPS) to degrade aberrant proteins. They also exhibit anti-apoptotic effects and play a role in safeguarding the homeostasis of dopaminergic neurons during stressful conditions (Jia et al., 2019). In the specific context of rotenone-induced PD in rats, it has been discovered that FA possesses anti-parkinsonian properties by modulating the HSP70 levels (Fig. 3) and significantly elevating tyrosine hydroxylase levels in the striatum (Askar et al., 2019). Notably, NK Bennett and colleagues have demonstrated that scavenger receptors CD36 and SRA1 mediate the internalization of monomeric α-synuclein by microglia, subsequently leading to the formation of α-synuclein oligomers. Their research highlighted that administration of AM nanoparticles to microglia, characterized by a shell containing SR-binding amphiphiles and a poly-antioxidant FA core, reduces the monomeric α-synuclein internalization and the intracellular α-synuclein oligomers formation. This nanoparticle formulation has the additional advantage of targeted delivery of FA to microglia (Bennett et al., 2016).

5.4. Ferulic acid's antioxidative effects

The ability of a molecule or substance to lessen free radicals, attenuate the effects of ROS, and repair oxidative damage is known as antioxidant activity (de Oliveira Silva and Batista, 2017). ROS, which is implicated in various oxidative stress processes, can originate from both endogenous sources such as mitochondrial oxidative metabolism and inflammation (de Oliveira Silva and Batista, 2017) and exogenous sources like ultraviolet light (Yogeeta et al.) and environmental pollution (Y.-T. (Cheng et al., 2016). By producing a variety of oxidative mediators, oxidative stress is strongly linked to age-related disorders and plays a role in tissue degradation, early aging, cancer, and cell death (Aliev et al., 2008). α-lipoic acid, glutathione, vitamin C, and vitamin E are examples of non-enzymatic antioxidant systems; on the other hand, enzyme-based antioxidant systems comprise glutathione peroxidase (GPx), catalase, and superoxide dismutase (D. (Li et al., 2021). Antioxidants combat oxidative stress by scavenging free radicals, inhibiting oxidative enzymes, donating hydrogen radicals ($H^{\bullet}$), chelating transition metals (thus converting $O2^{-}$ and H2O2 into $HO^{\bullet}$), and repairing damaged cellular components (de Oliveira Silva and Batista, 2017). FA, in particular, prevents the generation of ROS and scavenges free radicals as part of its role as an antioxidant (Catino et al., 2016). Additionally, FA increases heme oxygenase-1 (HO-1) expression and promotes Nrf2 translocation from the cytosol to the nucleus, which increases the

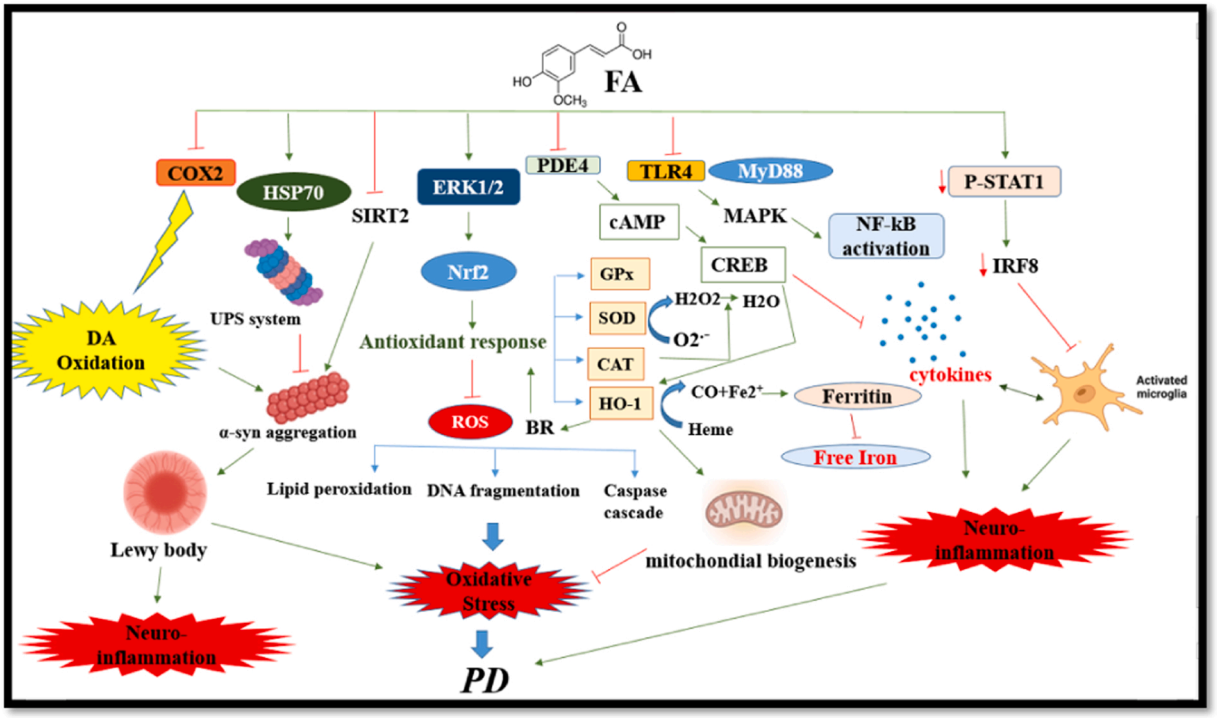

Fig. 3. An overview of FA's function in reducing oxidative stress and neuroinflammation in Parkinson's disease: By turning on Nrf2, FA triggers an increase in antioxidant enzymes and an antioxidant response. Additionally, FA can inhibit PDE4 and TLR4, which lowers the release of pro-inflammatory cytokines and stops microglia activation. It can also combat the buildup of α-synuclein through HSP70. By blocking COX-2, FA can stop dopamine from oxidizing and prevent α-synuclein from building up. On the other hand, FA reduces the levels of IRF8 and p-STAT1 and suppresses microglial activation. PDE4; phosphodiesterase 4, MAPK; mitogen-activated protein kinases, TLR4; Toll-like receptor 4, NF-Kb; nuclear factor-kappa B, ERK1/2; extracellular signal-regulated kinase 1/2, SIRT2; Sirtuin 2, HSP70; Heat shock protein 70, Nrf2; nuclear factor (erythroid-derived 2)-like 2, ROS; reactive oxygen species, cAMP; Cyclic adenosine monophosphate, CREB; cAMP response element-binding protein, SOD; Superoxide dismutase, CAT catalase, HO-1; heme oxygenase 1, p-STAT1; phosphorylated Signal transducer and activator of transcription 1, IRF8; Interferon Regulatory Factor 8, MyD88; Myeloid differentiation primary response protein 88, BR; Bilirubin, COX-2; cyclooxygenase-2.

antioxidant response (Chowdhury et al., 2016). FA additionally diminishes oxidative stress through activation of the PI3K/Akt signaling pathway and serves as an aldose reductase (AR) inhibitor (Kim et al., 2013b). In a research by Ehraz Anis et al., it was shown that FA was able to successfully reduce oxidative stress brought on by 6-OHDA, which is known to produce Parkinson's disease in rats. FA demonstrated the ability to scavenge free radicals and inhibit the caspase cascade, which decreased the overall formation of oxygen radicals and lessened the effects of oxidative stress (Anis et al., 2020).

It has been demonstrated that FA affects the heme oxygenase/biliverdin reductase (HO/BVR) pathway, which is crucial for reacting to cellular stress. S. Catino et al. showed that the treatment of SHSY5Y cells with FA increases the expression of HO-1, the transfer of the transcription factor Nrf2 from the cytoplasm to the nucleus, and ultimately the production of carbon monoxide (CO) and bilirubin (BR). Furthermore, FA treatment protects against oxidative stress triggered by the neurotoxin trimethyltin (TMT) in SHSY5Y cells by activating the HO-1/Nrf2 system and producing CO and BR (Catino et al., 2016). Studies have also indicated that FA, as an antioxidant, contributes to the recovery of decreased glutathione levels, the reduction of malondialdehyde (Ojha, Javed, Azimullah, Abul Khair, & Haque) levels, and the restoration of antioxidant enzyme activities, for example, superoxide dismutase (Nakayama et al.) and catalase (CAT) (Ojha et al., 2015). Moreover, FA has been found to enhance cell survival, reduce apoptosis, and lower levels of ROS in cell lines treated with 6-OHDA or H2O2. This effect extended to the in vivo setting, where FA was effective in reducing the overproduction of ROS in 6-OHDA-induced worms and H2O2-treated N2 C. elegans (Long et al., 2022). In a study by Kumiko Mitsui-Saitoh and Junichi Sakai, subcutaneous administration of 1-methyl-4--phenyl-1,2,3,6-tetrahydropyridine/paraquat (MPTP/p) in mice led to significantly reduced cerebral blood flow (CBF). However, mice receiving oral FA after MPTP/p exposure displayed a marked increase in CBF. The study also investigated oxygen saturation (SpO2) through the carotid artery, which did not display significant differences between the groups. This suggests that FA administration in MPTP/p-induced Parkinson's disease may increase the biological antioxidant potential (BAP) and reduce oxidative stress levels in the blood (齊藤久美子 & 酒井淳一, 2022). A study discovered that the aqueous extract of Sida cordifolia (AESC) and its different fractions, containing ephedrine and FA, have antioxidant properties. These properties were observed in a rat model of PD induced by rotenone, resulting in a decrease in catalepsy, rearing behavior, posture instability, and eosinophilic lesions in the midbrain region. Moreover, AESC was found to lower levels of thiobarbituric acid reactive substances and superoxide anion generation while increasing the levels of GSH and CAT (Khurana and Gajbhiye, 2013). Research has shown that high levels of cyclooxygenase-2 (COX-2) can cause dopamine oxidation, leading to oxidative stress and α-synuclein accumulation. However, studies have found that neural COX-2 expression is influenced by NF-κB on a genetic level. Shilpi Gupta and Kenza Benzeroual's investigation found that FA, which has antioxidative and antiapoptotic properties, can reduce the expression of α-synuclein, COX-2, NF-κB, ROS levels, and the Bax/Bcl-2 ratio compared to the increase caused by MPTP/MPP+ (Gupta and Benzeroual, 2013). Moreover, a study found that the polyphenolic fraction of bee propolis (PFP), including FA, exhibited antioxidant properties in a rat model of Parkinson's disease induced by rotenone. PFP, especially in the form of nanosheets, effectively improved the condition of damaged SH-SY5Y cells caused by rotenone. This improvement included increased cell viability, decreased lactate dehydrogenase levels, reduced ROS production, enhanced mitochondrial membrane potential, elevated activity

of antioxidant enzymes, and reduced apoptosis. In addition, nano PFP was capable of reducing lipid peroxidation, increasing GSH content, and enhancing antioxidant enzyme activity in Parkinsonian rats treated with rotenone (Mamashli et al., 2023). Rice bran extract (RBE), which contains antioxidants like tocopherols, oryzanols, and FA esters, has been shown to mitigate the neurotoxic effects of rotenone in rats. RBE improved various behavioral parameters, including body weight, motor coordination, activity, and motor stiffness. Furthermore, it reduced oxidative stress parameters, such as MDA and nitrite levels, and enhanced the levels of antioxidants such as GSH, catalase, and SOD (Kumar and Kumar, 2021). In a Drosophila model of rotenone-induced Parkinson's disease, treatment with γ-oryzanol, steryl esters of triterpenyl FA, resulted in improved locomotor performance, regeneration of acetylcholinesterase (AChE), dopamine levels, and antioxidant enzyme activities, such as MDA, CAT, and glutathione-S-transferase (Araujo et al., 2015).

5.5. Ferulic acid's anti-inflammatory properties

Treatment with γ-oryzanol, steryl esters of triterpenyl FA, in a Drosophila model of R-induced PD led to enhanced locomotor performance, regeneration of AChE, dopamine levels, and antioxidant enzyme activities, including SOD, CAT, and glutathione-S-transferas (Batista, 2014b; de Oliveira Silva and Batista, 2017). However, FA has demonstrated the capacity to modulate the inflammatory response and ameliorate various diseases by countering oxidative stress and apoptosis. It exerts a substantial influence in addressing inflammation and related conditions by preventing the release and expression of factors that cause inflammation (Liu et al., 2017). FA can effectively mitigate inflammation by preventing glial activation and inhibiting the phosphorylation of mitogen-activated protein kinases (MAPK), including p38 and c-Jun N-terminal kinase (JNK), in response to inflammatory triggers such as lipopolysaccharide (LPS). It achieves this by blocking the activation of Toll-like receptor 4 (TLR4) and nuclear factor-kappa B (NF-kB) (Fig. 3) (Liu et al., 2017; Yin et al., 2019). Additionally, FA inhibits the activation of NF-kB, cyclooxygenase (COX), iNOS, and caspase-1, which lowers the levels of chemokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) (Fig. 3) (Lampiasi and Montana, 2016). Inflammation within various brain areas, including the striatum, is regulated by the activity of phosphodiesterase 4 (PDE4) isoenzymes (Jin and Conti, 2002). When microglia are stimulated, as in the case of exposure to LPS, they produce pro-inflammatory cytokines and PDE4B (Guo et al., 2010; (Huang et al., 2016). Hao Huang and colleagues have revealed that FA, with its robust antioxidant and anti-inflammatory properties, can prevent the upregulation of PDE4 caused by LPS and stimulate the cAMP/CREB signaling pathway (Fig. 3) in PC12 cells. They observed that treatment with LPS leads to cytoskeletal changes in the F-actin structure, but pretreatment with FA (10–40 μM) or rolipram (30 μM), a PDE4B inhibitor, can counteract these effects. Furthermore, FA pretreatment can inhibit the generation of interleukin-1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) induced by LPS in these cells (Huang et al., 2016). A study by Shreesh Ojha and colleagues showed that long-term ROT administration leads to increased levels of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, along with elevated expression of inflammatory markers like Iba-1 and GFAP, as well as COX-2 and iNOS. However, pretreatment with FA before ROT administration results in reduced levels of IL-1β, IL-6, and TNF-α, and mitigates the microglia activation process by reducing Iba-1 and GFAP (Ojha et al., 2015). In cases of retinitis pigmentosa, microglia activation leads to inflammation by releasing cytokines and chemokines that hasten the death of photoreceptor cells. In BV2 cells and rd10 animals, FA has been shown to suppress microglial activation and lower the production of inflammatory factors such as TNF-α, IL-1β, and Ccl2. Additionally, FA reduces the levels of interferon regulatory factor 8 (IRF8) and phosphorylated signal transducer and activator of transcription 1 (p-STAT1), implying its capacity to regulate IRF8 expression and suppress microglial activation. Consequently, FA can effectively curb neuroinflammation and decelerate the degenerative progression of retinitis pigmentosa (Sun et al., 2021). In a research conducted by Hari Madhuri Doss and colleagues, the potential of FA to counter inflammation induced by monosodium urate crystals in rats was demonstrated (90). Pre-treatment with FA on an LPS-damaged mouse macrophage cell line resulted in the reduction of NO accumulation, inhibition of certain inflammatory mediators, such as IL-6, TNF-α, and iNOS, and modulation of Nrf2 translocation and activation of metallothioneins (MT-1, MT2), thereby exerting an antioxidant effect. Additionally, FA decreased the translocation of NF-kB by reducing the expression of phosphorylated inhibitor of nuclear factor kappa B kinase (Sarasamma et al., 2017; Lampiasi and Montana, 2016). Furthermore, FA is capable of targeting MyD88, an adaptor protein crucial in pro-inflammatory signaling initiated by the majority of toll-like receptors and interleukin-1-beta (Assanga, 2018).

5.6. Ferulic acid and cell death

Natural antioxidants like FA exhibit neuroprotective potential by mitigating cell death. FA has been found to enhance the Bcl-2/Bax ratio while reducing the protein expression of several key factors, including p53, glial fibrillary acidic protein (GFAP), phosphorylated c-Jun N-terminal kinase (p-JNK), cytochrome C, and caspase-3. Additionally, it effectively restores the expression of phosphorylated Bad (p-Bad) and the ratio of phosphorylated p38 MAPK to p38 MAPK, resulting in a reduction in apoptosis (C.-Y. (Cheng et al., 2016). FA was given orally to rats in a study using a rat model at a dosage of 100 mg/kg once daily for seven days before and following a 6-OHDA-induced lesion. The findings showed that Bcl-2 was upregulated whereas p53 and Bax were downregulated. Furthermore, in SH-SY5Y cells subjected to oxidative stress induced by cyclophosphamide treatment, FA was observed to increase Bcl-2 and decrease Bax, leading to a decrease in apoptosis (Zhang, 2008). According to research by Shreesh Ojha and colleagues, rats treated with ROT revealed a significant reduction in tyrosine hydroxylase immunoreactive (TH-ir) neurons in the striatum and dopamine neurons in the SNpc. However, pretreatment with FA offered significant protection to a substantial number of these neurons, preventing their loss (Ojha et al., 2015). Comparably, studies conducted by S. Nagarajan and associates showed that in C57BL/6 mice, MPTP caused harm to dopaminergic neurons, leading to problems with balance and coordination. The delivery of MPTP resulted in an elevation of the Bax/Bcl-2 ratio and the activation of microglial cells, signifying the induction of inflammation and apoptosis. FA pretreatment was shown to effectively mitigate the neurotoxic effects of MPTP (Nagarajan et al., 2015). In a study by FH Moghadam and colleagues, it was revealed that FA can protect neurons and promote their growth. This protection is manifested through the reduction of cell death triggered by H2O2, stabilization of p53 levels, and an increase in the presence of factors such as SIRT1, SIRT7, and MDM2. Furthermore, In PC12 cells as well as mouse brain stem cells, FA stimulates differentiation and proliferation, acting as a hormetic agent with neuroprotective and differentiation-inducing effects (Moghadam et al., 2018). Under conditions of hypoxic stress, FA mitigates ROS levels, lipid peroxidation, and cell death by activating SOD, while preventing the activation of p38 MAPK, caspase-3, and COX-2 (Lin et al., 2015). Nagaraju Bandaru and colleagues found that zebrafish treated with ROT exhibited reduced movement, increased cataleptic time, decreased cell viability, catalase levels, and dopamine levels compared to the control group. However, zebrafish treated with both ROT and FA displayed a significant increase in these factors. Furthermore, zebrafish treated with dopamine also exhibited an increase in these factors (Bandaru and Rao, 2023). FA exerts a neuroprotective effect in PC12 cells damaged by H2O2 or actinomycin D by lowering ROS levels and mitochondrial pro-apoptotic proteins, adjusting the mitogen-activated protein kinase (MAPK) pathway, and increasing brain-derived neurotrophic factor (BDNF) expression,

presumably through the regulation of microRNA expression in response to oxidative stress (D. (Li et al., 2021). In the context of PD, another characteristic feature is DNA fragmentation (Ellwanger et al., 2015). FA has been shown to ameliorate TMT-induced DNA damage in human neuroblastoma cells (Catino et al., 2016) and reduce DNA fragmentation and pyknosis in striatal neurons in Parkinsonian rats exposed to 6-OHDA, distinctive hallmarks of degenerating cells (Anis et al., 2020).

5.7. Ferulic acid and mitochondrial biogenesis

Energy homeostasis and mitochondrial dynamics are essential functions for maintaining cellular health since perturbations can lead to oxidative stress and cellular death. Two vital proteins—mitofusin 2 (Mfn2) and dynamin-related protein 1 (Drp1)—are in charge of controlling the processes of mitochondrial fission and fusion, which are important to maintaining their correct operation. Maintaining a harmonious equilibrium between these proteins is imperative for optimal mitochondrial metabolism, as any perturbations can lead to the onset of conditions including Parkinson's, Alzheimer's, and Huntington's diseases (Beal, 2005). Nonetheless, treatment with FA exhibits the capacity to modulate the expression of Drp1 and Mfn2, thereby preserving the equilibrium in mitochondrial dynamics (Fig. 4). This intervention can further ameliorate the detrimental effects induced by Parkinson's disease by scavenging free radicals, diminishing the expression of respiratory chain complexes, and mitigating oxidative stress (Anis et al., 2020). Furthermore, a critical function in adjusting mitochondrial energy metabolism is performed by PGC1α. This important mediator engages in interactions with crucial proteins associated with mitochondrial metabolism, including the cAMP response element-binding protein and nuclear respiratory factors, to orchestrate mitochondrial biogenesis. It also interacts with nuclear respiratory factors 1 and 2 (Nrf1 and Nrf2) to regulate the expression of antioxidant enzymes like SOD1. Reduced PGC1α levels are associated with increased oxidative stress vulnerability (Su et al., 2015). Nevertheless, FA exhibits the capacity to elevate PGC1α levels through an increase in NAD-dependent sirtuin deacetylase 1 (SIRT1), thereby mitigating mitochondrial dysfunction and providing protection against oxidative stress (Fig. 4) (Anis et al., 2020). Additionally, FA protects mitochondria by enhancing the recovery of the mitochondrial membrane potential, which simultaneously lowers the generation of ROS and cytochrome c

Table 1
Anti-Parkinson effect of Ferulic acid.

Author/year	References	Administration	Experimental models	Treatment of inducer-PD	Treatment of Ferulic acid
H Nakayama et al., (Nakayama et al., 2020)	(Nakayama et al., 2020)	H2O2/ Actinomycin D	PC12 cell	↑ROS, ↑oxidative stress	↓ROS, ↓SMAC/Diablo, ↓Bad, ↓ERK, ↑BDNF, ↓Apoptosis, ↓oxidative Stress, ↓pro-apoptotic proteins
Tosin A. Olasehinde et al.,(Olasehinde et al., 2019)	(Olasehinde et al., 2019)	Seaweeds(contain FA) Zinc sulfate and/or aqueous-ethanol extracts	HT-22 cells	↓ GSH, ↓superoxide dismutase, ↓ catalase ↑acetylcholinesterase activity	↑antioxidant enzyme ↑GSH, ↑MDA, ↑NO, improved cholinergic transmission disrupted by Zn
FH Moghadam et al., (Moghadam et al., 2018)	(Moghadam et al., 2018)	FA(50 μg for 12 h) H2O2	PC12 cells	↑P53, ↑Usp7	↓P53, ↓Usp7, ↑SIRT1, ↑SIRT7, ↑MDM2, ↓Usp7
S Catino et al., (Catino et al., 2016)	(Catino et al., 2016)	TMT (10 μM for 24 h) FA (1–10 μM for 6 h)	SH-SY5Y cell line	↑lipid peroxidation, ↑4-HNE, ↑ROS/RNS	↓lipid peroxidation, ↓DNA fragmentation, ↓ROS/RNS, ↑ HO-1/ Nrf2, ↑HO-1/BVR
Gupta S, Benzeroual K, 2013	(Gupta and Benzeroual, 2013)	FA MPTP/MPP+	PC12 cells	↑α-synuclein, ↑COX-2, ↑ NF-κB, ↑Bax/Bcl-2 ratio	↓α-synuclein, ↓COX-2, ↓NF-κB, ↓ Bax/ Bcl-2 ratio
H Huang et al., (Huang et al., 2016)	(Huang et al., 2016)	LPS (1 μg/ml) for 8 h FA((0, 2.5, 5.0, 10, 20, or 40 μM)	PC12 cells	↑PDE4, Changes in F-actin, ↑TNF-α, ↑IL-1β	↑cAMP/CREB signaling, ↓ PDE4, ↓ IL-1β, ↓ TNF-α, ↓inflammation
Shreesh Ojha et al.,(Ojha et al., 2015)	(Ojha et al., 2015)	ROT (2.5 mg/kg) FA(50 mg/kg, 30 min prior to ROT) for 4 weeks	male Wistar rats	↓ endogenous antioxidants ↑ lipid peroxidation ↑pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) ↑Iba-1, ↑GFAP, ↑COX-2, ↑iNOS ↑activated microglia and astrocytes	restored antioxidant enzymes prevented depletion of glutathione inhibited lipid peroxidation ↓pro-inflammatory cytokines
Kumar S, Kumar P, 2021	(Kumar and Kumar, 2021)	hexane extract of Rice bran (250 & 500 mg/kg) (contains FA) ROT (2 mg/kg(for 28 days	Rat	↓GSH, ↓CAT, ↓SOD, ↑MDA	GSH, ↑CAT, ↑SOD, ↑MDA
SM Araujo et al., (Araujo et al., 2015)	(Araujo et al., 2015)	γ-oryzanol (steryl triterpenyl esters of FA) ROT (7 days)	Drosophila melanogaster	mitochondrial dysfunction, ↓motor function, ↓AChE activity, ↓dopamine, ↓SOD, ↓CAT, ↓glutathione-S-transferase	↑motor function, ↑AChE activity, ↑dopamine, ↑SOD, ↑CAT, ↑glutathione-S-transferase
Lampiasi N, Montana G, 2016	(Lampiasi and Montana, 2016)	FA(100 μM)) 1 hour pretreatment (LPS (100 ng/ml) for 18 hours	RAW 264.7	↑ROS, ↑NO, ↑ IL-6, ↑TNF-α, ↑IL-10.	↑MT-1, ↑ MT2, ↑Nrf2, ↓NF-kB
E Anis et al., (Anis et al., 2020)	(Anis et al., 2020)	6-OHDA(4 mg/ml FA(100 mg/kg doses peroral (p. o.) once daily for 7 days pre-lesion and 7 days post-lesion	Left striatum of the rat	↑ROS, ↑Apoptosis, ↓mitochondrial membrane potential, ↑oxidized lipids, ↓GSH,	↓Drp1, ↑Mfn2, ↑TH, ↑Sirt1,↑PGC1α, ↓Bax, ↑Bcl2, ↓ROS, ↓DNA fragmentation, ↓pyknosis, ↓oxidative stress
Enrique de Font-Réaulx,(de Font-Réaulx, 2016)	(de Font-Réaulx, 2016)	oral Multi-Target Treatment) contains FA 50 mg, apigenin 100 mg, gamma oryzanol (Ellwanger et al.) 50 mg, and sylimarin 150 mg for 38 months(	40 patients −32–90 years(23 female and 17 male)	-	synergistic effect in control of apoptosis, oxidative damage, mitochondrial degeneration, caspase activation, syncytin-mediated neuro-inflammation, and MAPK activation

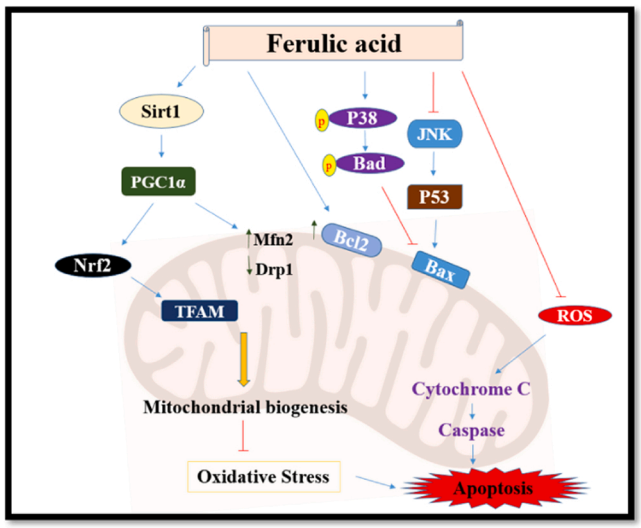

Fig. 4. FA's role in maintaining mitochondrial dynamics and preventing apoptosis: FA can raise the production of p-Bad, phosphorylate p38 MAPK, and inhibit JNK. Therefore, it increases Bcl2 decreases Bax and, ultimately decreases apoptosis. Additionally, FA can increase mitochondrial biogenesis by modulating Drp1 and Mfn2 and increasing the expression of Sirt1 and PGC1α. Sirt1; NAD-dependent sirtuin deacetylase 1, PGC1α; Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, Mfn2; mitofusin 2, Drp1; dynamin-related protein 1, Bad; Bcl-2-associated death promoter, Bax; Bcl-2 associated X, Bcl-2; B-cell lymphoma 2, JNK; c-Jun N-terminal kinases, P53; protein 53, TFAM;Mitochondrial transcription factor A.

release. In conclusion, the maintenance of cellular health depends critically on the control of mitochondrial dynamics and energy metabolism. FA therapy helps to maintain this equilibrium, protecting against oxidative stress and the ensuing cellular death (Yogeeta et al., 2006).

5.8. *The role of Ferulic acid in autophagy and DNA fragmentation*

Autophagy, an evolutionarily conserved process, entails the sequestration of damaged or superfluous cellular constituents within autophagosomes, subsequently delivering them to lysosomes for degradation and recycling into the cytosol (Mizushima, 2007). Recent studies highlight the protective function of autophagy in neurodegenerative disorders, mainly via promoting the prompt breakdown of accumulated or toxic proteins and damaged organelles (F. (Guo et al., 2018). A deficit or obstruction in the autophagic flow has been noted concerning Parkinson's disease, which results in the build-up of α-synuclein and/or compromised mitochondria. This emphasizes how important autophagy is to the pathophysiology of PD (Ondaro et al., 2022). Investigations directed by Tao Long and colleagues have demonstrated that FA, by stimulating autophagy, can elicit several advantageous outcomes. Among them are the improvement of food-sensing behavior, the decrease of ROS levels, the mitigation of DA neuron degeneration, and the prevention of α-synuclein aggregation and locomotor performance in Caenorhabditis worms. Furthermore, FA has the potential to augment cell viability, lower ROS levels, and prevent apoptosis in PC-12 cells subjected to 6-OHDA or H2O2 treatment. Thus, FA holds promise for mitigating oxidative damage to neurons through the activation of autophagy (Long et al., 2022).

6. Conclusion and future directions

Highly valued in traditional Chinese medicine, FA is a phenolic acid with a diversity of bioactive qualities, including antioxidant, anti-inflammatory, free radical scavenging, mitochondrial protection, and iron-chelating capacities. Its notable antioxidant attributes stem from the considerable resonance stabilization present in the phenoxyl radical within its chemical structure, combined with side chain conjugation, rendering it proficient at scavenging free radicals. The etiology of Parkinson's disease is closely related to neuroinflammation, oxidative stress, and mitochondrial dysfunction, which lead to cellular disturbances and neurodegeneration. Activation of Nrf2, stimulation of PGC1α, attenuation of α-synuclein accumulation, prevention of glial activation, induction of mitochondrial biogenesis, prevention of dopamine oxidation, inhibition of lipid peroxidation, induction of antioxidant enzymes, mitigation of pro-inflammatory cytokines, suppression of the caspase cascade, elevation of Bcl2 levels, and reduction of Bax levels are some of the mechanisms by which FA exerts its powerful effects. These multifaceted actions can effectively counteract neuroinflammation and the demise of dopaminergic neurons in the context of Parkinson's disease. Consequently, it is proposed that the inclusion of FA-containing foods in the diet may offer a strategic approach to managing and potentially preventing Parkinson's disease, thus delaying the onset of progressive neurological disorders. Despite the abundant preclinical evidence of FA against PD models, very limited clinical trials have been conducted in this field. Therefore, according to the many properties of FA to deal with Parkinson's disease, the development of clinical trials is suggested. Also, since exogenous neurotoxins such as rotenone, 6-hydroxydopamine, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) trigger widespread and rapid cell death in dopaminergic neurons, an experimental model that mimics the slow cell death observed in PD over many years, and focusing on the death of dopaminergic neurons, is proposed.

Declaration of Competing Interest

None.

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