Chemosphere 377 (2025) 144348

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

The neurotoxicity of pesticides: Implications for Parkinson's disease

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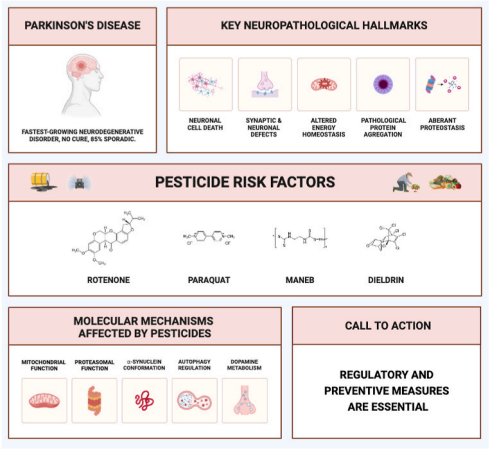
HIGHLIGHTS

- Key molecular pathways contribute to parkinsonism induced by rotenone, paraquat, maneb, and dieldrin.
- Pesticides disrupt mitochondrial and proteasomal functions, impair autophagy, and interfere with dopamine transport and metabolism, contributing to neurodegeneration.
- Pesticides share common neurotoxic mechanisms but also exhibit distinct pathways of toxicity.
- New regulatory and preventive measures to mitigate the neurotoxic effects of pesticides are needed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Handling editor: Giulia GUERRIERO

Keywords:
Parkinson's disease
Pesticides
Neurotoxicity
Rotenone
Paraquat

ABSTRACT

Parkinson's disease (PD) is the fastest-growing neurodegenerative disorder worldwide, and no effective cure is currently available. Neuropathologically, PD is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra and by the accumulation of alpha-synuclein (aSyn)-rich proteinaceous inclusions within surviving neurons. As a multifactorial disorder, approximately 85 % of PD cases are sporadic with unknown etiology. Among the many risk factors implicated in PD, exposure to neurotoxic pesticides stands out as a significant contributor. While the effects of many are still uncharacterized, it has already been shown that rotenone, paraquat, maneb, and dieldrin affect critical cellular pathways, including mitochondrial and proteasomal dysfunction, aSyn aggregation, autophagy dysregulation, and disruption of dopamine metabolism. With

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https://doi.org/10.1016/j.chemosphere.2025.144348
Received 2 September 2024; Received in revised form 4 March 2025; Accepted 19 March 2025
Available online 9 April 2025

Maneb
Dieldrin

the constant rise in pesticide usage to meet the demands of a growing human population, the risk of environmental contamination and subsequent PD development is also increasing. This review explores the molecular mechanisms by which pesticide exposure influences PD development, shedding light on their role in the pathogenesis of PD and highlighting the need for preventative measures and regulatory oversight to mitigate these risks.

1. Introduction

Parkinson's disease (PD) is part of a heterogeneous group of disorders known as synucleinopathies, comprising over 15 % of all neurodegeneration cases (Calabresi et al., 2023). The World Health Organization (WHO) reports a doubling in the prevalence of PD over the last 25 years, with global estimates in 2019 exceeding 8.5 million affected individuals. Projections from the US Census Bureau indicate that over 1.000.000 people may suffer from PD by 2030 (Marras et al., 2018). Pathologically, PD manifests as a selective and progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), accompanied by depletion of the neurotransmitter dopamine (DA) and accumulation of insoluble protein aggregates known as Lewy Bodies (LB) in the soma of neuronal cells and Lewy neurites (LN) in the axons (Fig. 1) (Volpicelli-Daley et al., 2014; Miraglia et al., 2018). These aggregates are mainly comprised of misfolded alpha-synuclein (aSyn) but also phosphorylated tau (p-tau) and amyloid beta protein (Aβ) (Sengupta and Kayed, 2022). Post-mortem analyses reveal that LB initially appear in regions such as the olfactory bulb (OB), the enteric nervous system (ENS), and the dorsal motor nucleus of the vagus, progressing to areas including the locus coeruleus, pons-midbrain, and SNpc with disease advancement. Ultimately, LB are found in the temporal cortex and limbic regions (Koeglsperger et al., 2023; Borghammer et al., 2022). A significant decline (60 %–80 %) in DA levels in the striatum underlies the severe clinical motor symptoms of PD, including bradykinesia, resting tremor, rigidity, facial palsy, shuffling gait, and postural instability (V Kalia and Lang, 2015). Non-motor symptoms, such as autonomic dysfunction, olfactory impairment, depression, anxiety, and sleep disorders, often emerge early in the disease course (Fig. 1) and likely arise from disruptions not only in the dopaminergic system but also in other crucial non-dopaminergic systems (Schapira et al., 2017), including noradrenergic, serotonergic, and cholinergic (Qamar et al., 2017).

Until the late 90s, PD was considered a sporadic disorder, unrelated to genetic factors. Observations of acute parkinsonism induced by the lipophilic chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al., 1983) reinforced this understanding, revealing selective damage to dopaminergic neurons in the SNpc (Langston and Ballard, 1983; Langston et al., 1984). Further studies revealed that MPTP effectively crosses the blood-brain barrier (BBB), where it is metabolized into the active toxic metabolite 1-methyl-4-phenylpyridinium (MPP^+) (Javitch et al., 1985). MPP^+ enters neurons through dopamine transporters (DAT), leading to the selective damage of dopaminergic neurons by inhibiting mitochondria complex I, depleting adenosine triphosphate (ATP), and inducing oxidative stress (dot et al., 1985; Singer and Ramsay, 1990). Due to the high affinity of MPP^+, even low concentrations of MPP^+ administered over extended periods induced several PD hallmarks in rats, including the accumulation of aSyn inclusions, loss of dopaminergic neurons, reduced DA levels, activated microglia, loss of serotonin (5-HT) and altered DA metabolite ratios [3,4-dihydroxyphenylacetic acid (DOPAC):DA] (Yazdani et al., 2006). The expression of aSyn is upregulated both at transcriptional and translational levels through MPP^+-induced iron signalling, significantly contributing to oxidative stress and apoptosis (Kalivendi et al., 2004). Indeed, knockdown of aSyn protected neurons from MPP^+-induced toxicity, which displayed intact nuclei and mitochondrial membrane potential (MMP), along with reduced cytochrome *c* release (Wu et al., 2009). The protection conferred by aSyn knockdown

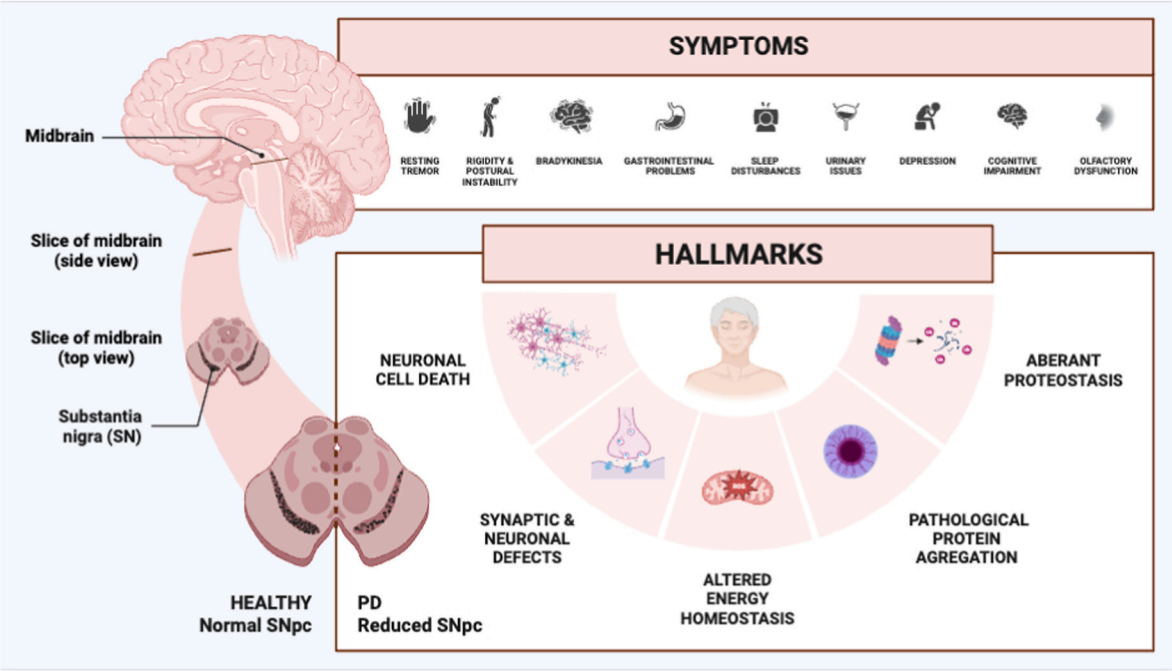

Fig. 1. Symptoms and pathological hallmarks of PD. Comparative representation of the SNpc in healthy individuals, characterized by a dense population of pigmented dopaminergic neurons, and in patients diagnosed with PD, marked by a significant loss of these neurons. The figure also highlights the key pathological hallmarks of PD and the major motor and non-motor symptoms experienced by patients. Created with BioRender.com.

was attributed not only to alterations in DAT function but also to a reduction in DAT expression on the cell surface, a decrease in the total number of intracellular vesicles, and an increase in the density of vesicular monoamine transporter 2 (VMAT2) molecules per vesicle. These changes diminished MPP^+ uptake into the cells and storage pathways and prevented MPP^+-induced activation of nitric oxide synthase (NOS) (Fountaine et al., 2008).

Sporadic PD is understood to result from a combination of genetic and environmental risk factors, while familial PD cases are directly linked to specific genetic mutations inherited either in an autosomal dominant or recessive manner (Inamdar et al., 2007; Blauwendraat et al., 2020). Currently, it is recognized that 5–10 % of PD cases follow a classical Mendelian inheritance pattern, and around 15 % of PD patients have a family history of the disease (Lesage and Brice, 2009), with at least 24 chromosomal regions implicated in the disorder (Funayama et al., 2023). Well-established PD genes include autosomal dominant forms (SNCA, LRRK2, and VPS35) and autosomal recessive forms (PRKN, PINK1, and DJ-1) (Funayama et al., 2023). Although genetic factors play a crucial role, the rising global prevalence of PD (Dorsey and Bloem, 2018) is not solely attributable to aging populations or genetic predisposition but also to environmental factors, such as pesticides, heavy metals, and solvents (Dorsey et al., 2018; Ascherio and Schwarzschild, 2016). Among these, pesticides are of particular concern due to their widespread use in agriculture and their persistent presence in food chains and the environment (Carvalho, 2017). Before gaining approval for use in the European Union (EU), pesticides are subjected to rigorous toxicological evaluation that assesses their acute and chronic toxicity, carcinogenic potential, and impacts on reproduction and development. However, these regulatory protocols fall short in assessing the full range of their effects on the nervous system. Current guidelines mandate neurotoxicity assessments only if the active ingredient exhibits known neurotoxic properties or shares structural similarities with known neurotoxicants (Carvalho, 2017; Handford et al., 2015). This reactive approach leaves significant gaps in our understanding of how many pesticides might subtly but profoundly affect neural health.

Given the pervasive nature of pesticide residues in everyday food consumption and inadequate monitoring of their long-term toxicological impacts, the role of pesticide exposure as a modifiable risk factor for neurological disorders, including PD, warrants urgent attention (Cannon and Greenamyre, 2010; Meerman et al., 2023). Strengthening the regulatory framework to incorporate comprehensive neurotoxicity testing for all pesticide formulations, both active ingredients and commercial mixture, along with increased monitoring of chronic low-dose exposure, is essential to mitigate these risks associated with pesticide-related neurodegeneration. Current regulatory approaches often prioritize acute toxicity endpoints such as carcinogenicity and reproductive toxicity, while developmental and adult neurotoxicity assessments remain underutilized or absent in standard pesticide approval processes. This regulatory gap is particularly concerning given the growing body of evidence linking chronic pesticide exposure to PD and other neurodegenerative disorders.

The inadequacy of existing regulatory frameworks is exemplified by the case of chlorpyrifos, an organophosphate pesticide widely used in agriculture since 1965 in the USA. Although chlorpyrifos received regulatory approval in the EU in 2005, it was subsequently banned by the European Food Safety Authority (EFSA) in 2020 (Statement on the available outcomes, 2019) and by the U.S. Environmental Protection Agency (EPA) in 2021, following mounting evidence of its genotoxicity and developmental neurotoxicity. However, the EPA's 2021 decision to revoke all chlorpyrifos tolerances was later challenged in court, leading to a reversal that required the agency to reinstate the previously stablished residue limits (US Environmental Protection Agency, 2025). Despite these bans, chlorpyrifos continues to be used in several countries, including India, Canada, and Australia, demonstrating the fragmented and inconsistent nature of global pesticide regulation (Wołejko et al., 2022). A similar concerning case is glyphosate, the world's most widely used herbicide. Despite substantial scientific evidence linking glyphosate exposure with neuroinflammation, mitochondrial dysfunction, and cognitive deficits, the EU renewed glyphosate's approval until 2033 (Álvarez et al., 2023), raising serious concerns about the robustness of current risk assessment frameworks. The European Chemicals Agency (ECHA)'s hazard classification system has also been criticized for failing to adequately account for glyphosate's potential neurotoxicity, reflecting broader regulatory blind spots in assessing long-term neurological effects. Even more troubling is the continued approval of paraquat in the USA, despite decades of compelling scientific evidence linking paraquat exposure to increased PD risk. Rather than banning the pesticide, the EPA has opted to impose risk mitigation measures, such as restricting aerial application and requiring specialized training for applicators. However, these measures fall short of adequately protecting farmworkers, rural communities, and the general population from chronic paraquat exposure and its well-documented neurotoxic effects. These examples illustrate the systemic failure of current regulatory systems, which often underestimate neurotoxicity risks, particularly from chronic low-dose exposures or pesticide mixtures used in real-world agricultural settings. Regulatory frameworks, such as those of EFSA and EPA, continue to prioritize data from short-term, high-dose toxicity studies, which are poorly suited to detect subtle, cumulative damage to dopaminergic neurons that can evolve over years or decades.

The current understanding of PD largely stems from both *in vitro* and *in vivo* PD models (Cannon and Greenamyre, 2010; Salari and Bagheri, 2019). Genetic models arise from the manipulation of known familial PD genes, but do not fully represent the majority of PD cases. Conversely, neurotoxin models, widely used in PD research, use toxic chemical compounds to specifically damage the nigrostriatal pathway, which allows for the modelling and assessment of disease progression (Tieu, 2011). Utilizing neurotoxicants has also been instrumental in elucidating the influence of environmental factors on PD development and progression. This review aims to provide an overview of the molecular pathways impacted by known neurotoxic pesticides and their involvement in the development of PD/parkinsonism. This understanding can guide future efforts to identify and mitigate the effects of neurotoxic pesticides, as the current regulations set by the EFSA and other international agencies are inadequate for evaluating pesticides neurotoxicity (Meerman et al., 2023; Bloem and Boonstra, 2023; Shan et al., 2023).

2. Pathological hallmarks of PD

The etiology of PD is thought to involve intricate cellular and molecular changes that ultimately give rise to the neuropathologic and physical manifestations of the disease. Rather than attributed to a single alteration, the pathology of PD arises from a complex interplay of various factors, resulting in the depletion of DA and the death of dopaminergic neurons. Among the identified alterations, aSyn aggregation, dysfunctional mitochondria, oxidative stress, impaired clearance pathways, and synaptic dysfunction are considered hallmarks of PD (Kouli et al., 2018) (Fig. 1), involved in the cellular phase of the disease (Chopra et al., 2024).

2.1. Alpha-synuclein

aSyn, a small 140-amino acid protein that naturally exists either as an unfolded monomer or a folded tetramer, is central to the cellular and molecular alteration associated with the pathological processes of PD (Bartels et al., 2011). It contains three distinct regions: an amino-terminal lipid-binding region, a central hydrophobic region which contributes to its oligomerization, and an acidic carboxy-terminal (Goedert et al., 2024). aSyn is constitutively expressed in various cellular compartments, including synaptic terminals, nucleus, mitochondria, endoplasmic reticulum (ER), Golgi apparatus, and endolysosomal system (Maroteaux et al., 1988; Li et al., 2007; Hoozemans et al., 2007; Gosavi et al., 2002; Lee et al., 2004), but its physiological function

in each cellular compartment remains poorly understood (Bernal-Conde et al., 2020). Nonetheless, it is widely accepted that aSyn plays a role in membrane curvature and in converting large vesicles into highly curved membrane tubules and vesicles (Varkey et al., 2010), synaptic vesicle trafficking, including vesicle clustering and docking, N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) complex formation, and DA release (Burré et al., 1979). Its conformational flexibility enables interaction with multiple molecules and proteins, transitioning between monomers, tetramers, oligomers (soluble conformations), and fibrils (insoluble conformations characterized by β-sheet conformation) (Wong and Krainc, 2017a), with properties that influence its stability, seeding and propagation (Burré et al., 1979; Longhena et al., 2017; Wong and Krainc, 2017b). There is still debate within the scientific community regarding the toxic, protective, or consequential nature of aSyn aggregates, as well as the triggers causing its abnormal aggregation (Riederer et al., 2019). Some researchers believe these aggregates are harmful to neurons and contribute to neurodegenerative diseases, while others suggest they may be a defence mechanism to sequester misfolded proteins. Another perspective is that the aggregates are simply a byproduct of underlying disease processes. Ongoing research aims to determine whether genetic factors, environmental influences, or a combination of both contribute to the abnormal aggregation of aSyn. Potential explanations include SNCA missense mutations and increased gene copy number, abnormal expression levels, truncation, dysfunction in clearance pathways, and post-translational modifications. Exposure to environmental factors such as heavy metals, solvents, and pesticides has also been implicated in aSyn oligomerization through oxidative stress, ubiquitin-proteasome inhibition, mitochondria impairment, reactive oxygen species (ROS) accumulation, and altered lipid metabolism (Antony et al., 2013; Shvachiy et al., 2023; Yuan et al., 2022; Olufunmilayo et al., 2023).

Oligomeric forms of aSyn have been shown to disrupt SNARE complex formation, impair DA release, and reduce synaptic vesicle motility (Choi et al., 2013). These disruptions may contribute to elevate intracellular Ca^{2+} levels, initiating a toxic cascade of events that ultimately lead to neuronal dysfunction and degeneration (Ronzitti et al., 2014; Danzer et al., 2007). This mechanism aligns with the Adverse Outcome Pathway (AOP) entitled *Calcium overload in dopaminergic neurons of the substantia nigra leading to parkinsonian motor deficits* (AOP: 464 https://aopwiki.org/aops/464). In this AOP 464, calcium overload in dopaminergic neurons is identified as a critical key event (KE) in the progression toward Parkinsonian motor deficits, the adverse outcome (AO). This pathway highlights how dysregulated calcium homeostasis in the SNpc, exacerbated by factors like aSyn oligomers, drives neurodegeneration. Elevated intracellular Ca^{2+} levels can impair mitochondrial function, enhance oxidative stress, and activate proteolytic enzymes, accelerating the loss of dopaminergic neurons essential for motor control.

2.2. Altered energy homeostasis and mitochondrial dysfunction

Altered energy homeostasis, driven by mitochondrial dysfunction, is increasingly recognized as a pivotal pathological hallmark of PD (Henrich et al., 2023). Mitochondria are essential to maintain neuronal energy balance, especially in DA neurons of the SN. These neurons are particularly vulnerable due to their high metabolic demands (Chan, 2020), relatively low mitochondrial density, and unique structural features (Liang et al., 2007; Carly et al., 2024). Relying heavily on oxidative phosphorylation for ATP generation, DA neurons require this energy for neurotransmitter release, maintaining ionic gradients, and overall cellular homeostasis. Disruptions in mitochondrial function prejudice these processes, profoundly compromising neuronal viability and synaptic activity, key contributors to PD pathology (Duarte et al., 2023).

Under normal conditions, ROS generated during oxidative phosphorylation are neutralized by antioxidant defences. However, mitochondrial dysfunction disrupts this balance, resulting in excessive ROS accumulation, oxidative damage to lipids, proteins, and mitochondrial DNA, as well as glutathione (GSH) depletion. This cascade impairs mitochondrial efficiency, creating a vicious cycle of worsening energy deficits and oxidative stress (Olufunmilayo et al., 2023). A hallmark of PD is mitochondrial complex I dysfunction, which reduces ATP production and increases ROS generation. This dual impact affects energy-intensive processes like axonal transport, vesicle trafficking, and synaptic function (González-Rodríguez et al., 2021a). Recent findings in complex I-deficient mouse models suggest that DA neurons initially compensate for energy deficits by shifting to a Warburg-like metabolism with increased reliance on glycolysis. While this adaptation may offer short-term survival benefits, it ultimately leads to axonal degeneration and progressive neuronal loss (González-Rodríguez et al., 2021b). These disruptions are further intensified by the pathological effects of aSyn, which permeabilizes mitochondrial membranes, impairs the electron transport chain (ETC), and exacerbates oxidative stress. Heightened oxidative stress accelerates the aggregation of soluble aSyn into toxic oligomers and fibrils, creating a deleterious feedback loop that further damages mitochondria and neurons (Cascella et al., 2022). Mitochondrial dysfunction associated with pathogenic aSyn also plays a significant role in both idiopathic and monogenic forms of PD. Evidence includes mitochondrial complex I deficiencies and mutations in mitochondrial quality-control proteins, such as PINK1 and Parkin, in post-mortem PD brains (Karimi-Moghadam et al., 2018; Haque et al., 2022). These findings align with an AOP entitled *Inhibition of the mitochondrial complex I of nigrostriatal neurons leads to parkinsonian motor deficits* (AOP: 3 https://aopwiki.org/aops/3), which describes the mechanistic sequence connecting complex I inhibition to motor deficits characteristic of PD. The inhibition of mitochondrial complex I serves as the molecular initiating event (MIE) in this AOP. This disruption triggers mitochondrial dysfunction and impaired proteostasis, resulting in the accumulation of misfolded proteins such as aSyn and the degeneration of DA neurons in the nigrostriatal pathway. The degeneration of these neurons, critical for dopamine release in the striatum, underpins the motor control impairments that manifest as the AO.

Disruptions in mitochondrial dynamics, particularly imbalances in the fission and fusion processes, further exacerbate synaptic dysfunction in PD. Proper mitochondrial dynamics ensure the distribution of functional mitochondria to synaptic terminals, which is vital for maintaining synaptic integrity (Yang and Lu, 2009; Su et al., 2010). In PD, loss of functional mitochondria at synapses contributes to early synaptic failure, a pivotal event in neurodegeneration. Elevated ROS levels also compromise membrane integrity, and promote the release of cytochrome *c*, activating apoptotic pathways and leading to neuronal death (Bose and Beal, 2016). Impaired mitophagy, the process of clearing damaged mitochondria, has emerged as another critical factor in PD pathology. Dysfunctional mitophagy results in the accumulation of defective mitochondria, amplifying ROS production and disrupting energy homeostasis (Xiao et al., 2022). This imbalance triggers widespread cellular damage, including inflammatory responses that heighten neuronal vulnerability and accelerate disease progression (Scorziello et al., 2020).

2.3. Proteostasis

The continuous state of oxidative stress resulting from mitochondrial dysfunction also adversely affects the proteostasis network, changing the morphology and folding properties of the ER and disturbing cellular proteolysis pathways. Indeed, impaired proteolysis significantly contributes to the onset and progression of PD, leading to the accumulation of aberrant proteins such as aSyn (Bao et al., 2016; Jagtap et al., 2023). In physiological conditions, proteolysis is primarily accomplished via two main pathways: the ubiquitin-proteasome system and the autophagy-lysosomal pathway (Hipp et al., 2019). The proteasome, a multi-subunit complex, degrades transient, misfolded, or damaged proteins, while autophagy eliminates long-lived proteins, cytosolic fractions, and organelles, through various mechanisms including

macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Klaips et al., 2018). In PD, there is a decrease in the proteolytic activity of the proteasome, attributed to factors such as oxidative stress, and accumulation of aSyn aggregates. Studies have shown that impaired 26S proteasome activity precedes the onset of motor symptoms and dopaminergic degeneration (McKinnon et al., 2020). Moreover, post-mortem PD brains exhibit signs of dysfunctional macroautophagy, CMA and mitophagy. Elevated levels of microtubule-associated protein 1A/1B-light chain 3 (LC3) in LB within the SN suggest alterations in basal autophagy (Tanji et al., 2011), while reduced levels of cathepsin D, heat shock cognate 70 (HSPA8/HSC70) (Chu et al., 2009) and lysosomal-associated membrane protein 2A (LAMP2A) indicate impaired lysosomal function (Alvarez-Erviti et al., 2010). Overexpression of aSyn inhibits autophagy by interfering with various processes, including inhibition of Ras-related protein (RAB1A), mislocalization of autophagy-related protein 9 (ATG9), and reduced formation of autophagic structures associated with the ER (Winslow et al., 2010), and disruption of the autophagolysosome maturation process (Sarkar et al., 2021). It also affects autophagy by increasing lysosomal Ca^{2+} release, leading to alkalization, reduced expression of lysosomal associated membrane protein 1 (LAMP1), and overall disruption of lysosomal morphology and distribution (Nascimento et al., 2020). These findings underscore the intricate interplay between mitochondrial dysfunction, proteostasis impairment, and aSyn pathology in the pathogenesis of PD.

2.4. Synaptic and neuronal homeostasis

While PD neuropathology is characterized by the loss of dopaminergic neurons, it is important to note that approximately 80 % of synaptic terminals and axons are already lost by the time clinical symptoms manifest, and a diagnosis is made. Post-mortem examinations have shown that the loss of dopaminergic terminals and axons occurs before the degeneration of dopaminergic neurons (Kordower et al., 2013). Under physiological conditions, aSyn plays a crucial role in DA and DAT homeostasis, as well as in DA catabolism and synthesis. aSyn modulates the phosphorylation levels of tyrosine hydroxylase (TH), the rate-limiting enzyme for DA synthesis, keeping it in its inactive state (Butler et al., 2015). In DA neurons, DA is synthesized through the action of TH and aromatic amino acid decarboxylase (AADC) and can be taken up from the extracellular space. The newly synthesized or imported DA is subsequently stored in vesicles with the assistance of VMAT2. However, increased levels of aSyn dysregulate DA synthesis, leading to disturbances in TH and VMAT2 activity, resulting in cytosolic accumulation of DA and oxidative damage (Roede et al., 2011; Alter et al., 2013). This dysregulation promotes interactions between oxidized DA and aSyn, further contributing to aSyn accumulation. Additionally, the loss of DA reuptake results in axonal swelling and dystrophic axons (Lundblad et al., 2012). On the other hand, a lack of aSyn in DA neurons decreases striatal DA levels and impairs DAT function, negatively impacting DA metabolism.

Furthermore, the accumulation of aSyn in pre-synaptic terminals significantly contributes to dying-back neurodegeneration and synaptic dysfunction. Synaptic function relies on the precise release of neurotransmitters and calcium, along with cytoskeletal adaptations, presynaptic vesicle formation and postsynaptic signalling. Failures within this network are observed as an early event preceding neuronal loss (Südhof, 2012). As mentioned previously, aSyn is enriched in presynaptic terminals and several studies suggest that dysregulation of aSyn adversely affects synaptic function. Elevated aSyn levels have been linked with alterations in synaptic vesicle size and impaired vesicle trafficking. Additionally, aSyn disrupts the formation and distribution of SNARE complex proteins, leading to disturbances in synaptic vesicle fusion at the active zone and reducing vesicle recycling efficiency (Lashuel et al., 2013).

Microglia, the resident immune cells of the central nervous system (CNS), are responsible for monitoring brain health, degrading misfolded proteins and cellular waste, and maintaining homeostasis (Arcuri et al., 2017). In response to disturbances in brain homeostasis, microglia transition to an active state known as microgliosis, which enables them to phagocytose debris and release cytokines and chemokines. In PD, inflammation is a key component of neurodegeneration. The release of proinflammatory cytokines contributes to the neurodegeneration of DA neurons (Alter et al., 2013; Isik et al., 2023), with PD patients exhibiting elevated levels of cyclo-oxygenase 2 (COX-2) and NOS. Furthermore, aSyn has been implicated as a trigger of neuroinflammation, as misfolded aSyn increases the expression of inflammatory markers such as TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin-1 beta), IL-6 (interleukin 6), iNOS (inducible nitric oxide synthase), and COX-2 (Knott et al., 2000).

3. Pesticides as risk factors for PD

Pesticides are chemical substances used to control or eliminate pests and are categorized based on their target organisms (e.g., herbicides, insecticides and fungicides) and origin (natural or synthetic). Additionally, they play a vital role in controlling vector-borne diseases and improving public health (Oerke, 2006; Parra-Arroyo et al., 2022). However, out of the annual 3 billion kilograms of pesticides used globally, only a mere 1 % proves effective (Carvalho, 2017). This inefficiency has resulted in the widespread, indiscriminate, and often random use of pesticides, leading to environmental contamination and adverse health effects (Hernández et al., 2013). The dispersal of pesticides has contributed to the mass mortality of various species such as bees, birds, amphibians, fish, and small mammals (Köhler and Triebskorn, 2013), as their molecular targets are not limited to intended pests but also affect non-target organisms (Judson et al., 2009). Occupational activity, including farming, industry, and household activities, represents the primary source of human pesticide exposure and poisoning. However, indirect exposure through contaminated water, soil, and food puts the entire population at risk (Fig. 2). Notably, the EFSA has consistently reported high levels of multiple pesticides exceeding legal limits in various food products like bananas, table grapes, sweet peppers, broccoli, and wheat (Richardson et al., 2019).

Chronic exposure to pesticides has been linked to the development of several disorders, including cancer, male sterility, immune system dysfunction, respiratory issues, endocrine disorders, and neurological disorders such as PD. The association between pesticide exposure and PD development gained significant credibility, especially considering events like the MPTP incident and the structural similarities between certain pesticides and neurotoxins (Lai et al., 2002; Freire and Koifman, 2012; Engel, 2001; Tanner et al., 2011). Several epidemiological studies further support this association. For example, surveys conducted in Canada, France, and California revealed higher PD prevalence rates in regions with extensive pesticide use, particularly among agricultural workers (Moisan et al., 2011a; Ritz and Yu, 2000; Barbeau et al., 1987; Tüchsen and Astrup Jensen, 2000). Similarly, a large cohort study in Denmark found a significantly elevated risk of PD development among agriculture and horticulture workers. Specifically, agriculture workers exposed to pesticides like rotenone (Pouchieu et al., 2018), organochlorine, and arsenic insecticides (Elbaz et al., 2009) over prolonged periods have shown an increased PD risk. Similarly, case-control studies in regions like northern India have shown a clear correlation between pesticide exposure and PD incidence, with specific pesticides like dieldrin associated with a significant proportion of PD cases (Chhillar et al., 2013). In addition to epidemiologic evidence, research conducted on animals and cellular models has further validated and deepened the understanding of the association between pesticide exposure and PD risk. As the global population continues to grow and climate change exacerbates pest-related challenges, the reliance on pesticides is expected to increase, leading to continued and increased exposure to hazardous contaminants. Understanding the toxic effects of chronic

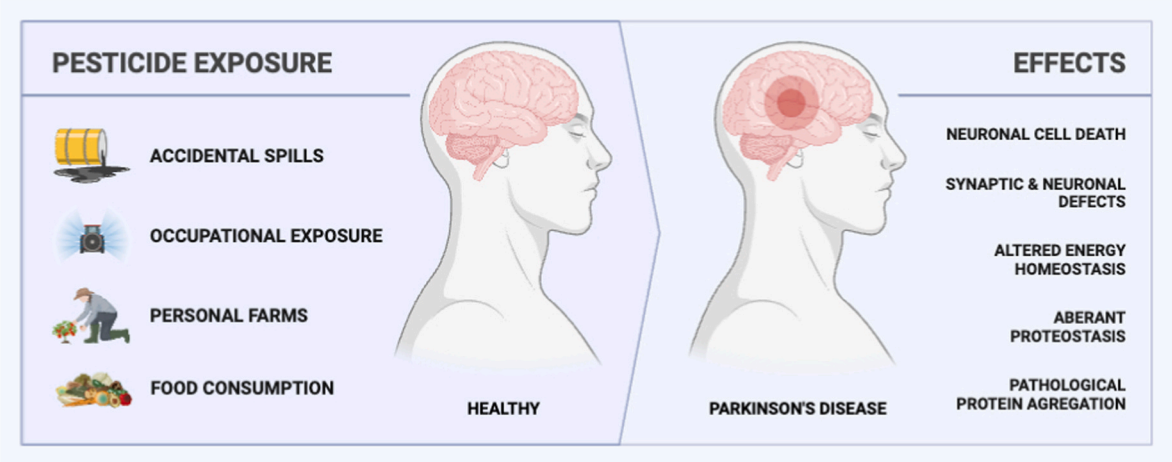

Fig. 2. Pathways of pesticide exposure and their impact on brain health. The figure illustrates the main routes through which pesticides can contaminate the human body and their subsequent effects on brain health. The primary pathways of exposure and the key pathological hallmarks associated with pesticide-induced PD are highlighted. Created with BioRender.com.

pesticide exposure on the CNS remains alarmingly limited, and the current neurotoxicity assessment protocols are outdated and insufficient to address these concerns. Present evaluations rely heavily on functional observational battery (FOB), a screening tool that is inherently subjective and often lacks the depth required for a thorough investigation. Notably, FOB assessments rarely include detailed histopathological examinations of critical neural regions, such as the SN, which are pivotal in disorders like PD (Gauvin et al., 2016). Additionally, most neurotoxicity studies are constrained by their short duration and limited scope. They often fail to consider the cumulative and synergistic effects of prolonged exposure to multiple pesticides, a scenario that reflects real-world agricultural practices.

This oversight is particularly troubling given that the evaluation of pesticide neurotoxicity typically hinges on the observation of overt clinical neurological symptoms. Such an approach is profoundly inefficient, as clinical signs of parkinsonism only manifest after approximately 60 % of dopaminergic neurons have already been lost (Bloem and Boonstra, 2023; Gauvin et al., 2016; Krewski et al., 2020). To bridge these critical gaps, regulatory frameworks must be modernized to incorporate more sensitive and comprehensive methodologies. Long-term studies with advanced histopathological, biochemical, and molecular analyses should become standard practice. Additionally, the development of biomarkers for early detection of pesticide-induced neurodegeneration could transform our ability to identify risks before irreversible damage occurs. Addressing these shortcomings is essential to safeguard public health and mitigate the potential neurological risks associated with chronic pesticide exposure.

In the following section, pesticides that have been identified as risk factors for PD development will be discussed in more detail. To gather relevant literature, we conducted a PubMed search using the keywords “alpha-synuclein” AND “Parkinson’s disease” AND “Pesticides”. From the retrieved publications, we excluded reviews and studies that only used pesticides to induce toxicity to test compounds that might reverse the effect. Our focus will be on the molecular and cellular targets of these pesticides, as revealed by *in vivo* and *in vitro* models, as well as the subsequent neuropathological effects associated with exposure to these chemicals. Table S1 lists published studies for each pesticide, including vital information such as the specific model organisms used in each study, the concentrations of pesticides applied, and pesticide-induced effects on cellular and molecular mechanisms. This compilation aims to provide a thorough overview of the current research landscape, facilitating a deeper understanding of the relationship between pesticide exposure and PD development.

3.1. Rotenone

Rotenone, a natural occurring lipophilic insecticide derived from the roots of plants in the Leguminosa family (Soloway, 1976), has a complex history of use and regulation. Although banned from agricultural use in the USA, Canada, and the EU, due to its potential health and environmental risks, rotenone remains in use worldwide as a piscicide and as an ingredient in certain broad-spectrum insecticides (EPA 7508C, 2005; Canada, 2008). The EPA classifies rotenone’s toxicity based on its formulation, ranging from slightly to highly toxic. One of its notable characteristics is its non-persistence and non-accumulation in the environment and animals, respectively, as it quickly degrades under the influence of light and heat (Ling and New Zealand, 2003). Due to its lipophilicity, rotenone can easily penetrate biological membranes, including BBB (Jr et al., 1996), exerting its effects primarily within the CNS (Zhou et al., 2016). Epidemiologic studies have linked rotenone exposure, either alone or in combination with other pesticides, to an increased risk of developing PD (Ott, 2006; Moisan et al., 2011b). Hence, efforts have been made to replicate rotenone-induced PD pathology in both *in vivo* and *in vitro* models, to gain a deeper understanding of its impact on human health and elucidate the molecular mechanisms involved in disease progression (Fig. 3).

Rotenone was first demonstrated by electron paramagnetic resonance spectroscopy to inhibit mitochondrial complex I, specifically hindering the transfer of electrons from iron-sulphur centres to ubiquinone, thereby blocking oxidative phosphorylation (Palmer et al., 1968) (Fig. 3a). This inhibition leads to ATP depletion and the generation of ROS, causing damage to proteins, lipids, and nucleic acids, ultimately culminating in apoptosis (Li et al., 2003). Rotenone exposure also resulted in severe mitochondrial morphology changes, including swelling, crest fracture, and degeneration (Wu et al., 2015). Later research demonstrated that rotenone specifically targets the mitochondrial complex I *in vivo*, inducing behavioural and neuropathological changes in rats that closely resemble the features of PD (Betarbet et al., 2000). The acute intoxication with rotenone also led to a significantly reduced activity of mitochondrial complex II, caused by an increase in superoxide radicals and peroxynitrite (Panov et al., 2005) (Fig. 3b). Rotenone-induced oxidative stress further resulted in the oxidation of protein deglycase DJ-1, also known as Parkinson disease protein 7 (PARK7) (Fig. 3c) and its redistribution and accumulation in mitochondria (Betarbet et al., 2006). The group also demonstrated that, beside DJ-1 oxidation, mitochondrial complex I inhibition had a direct impact on proteasomal activity, accompanied by an increase in ubiquitinated proteins and elevated levels of aSyn expression (Betarbet et al.,

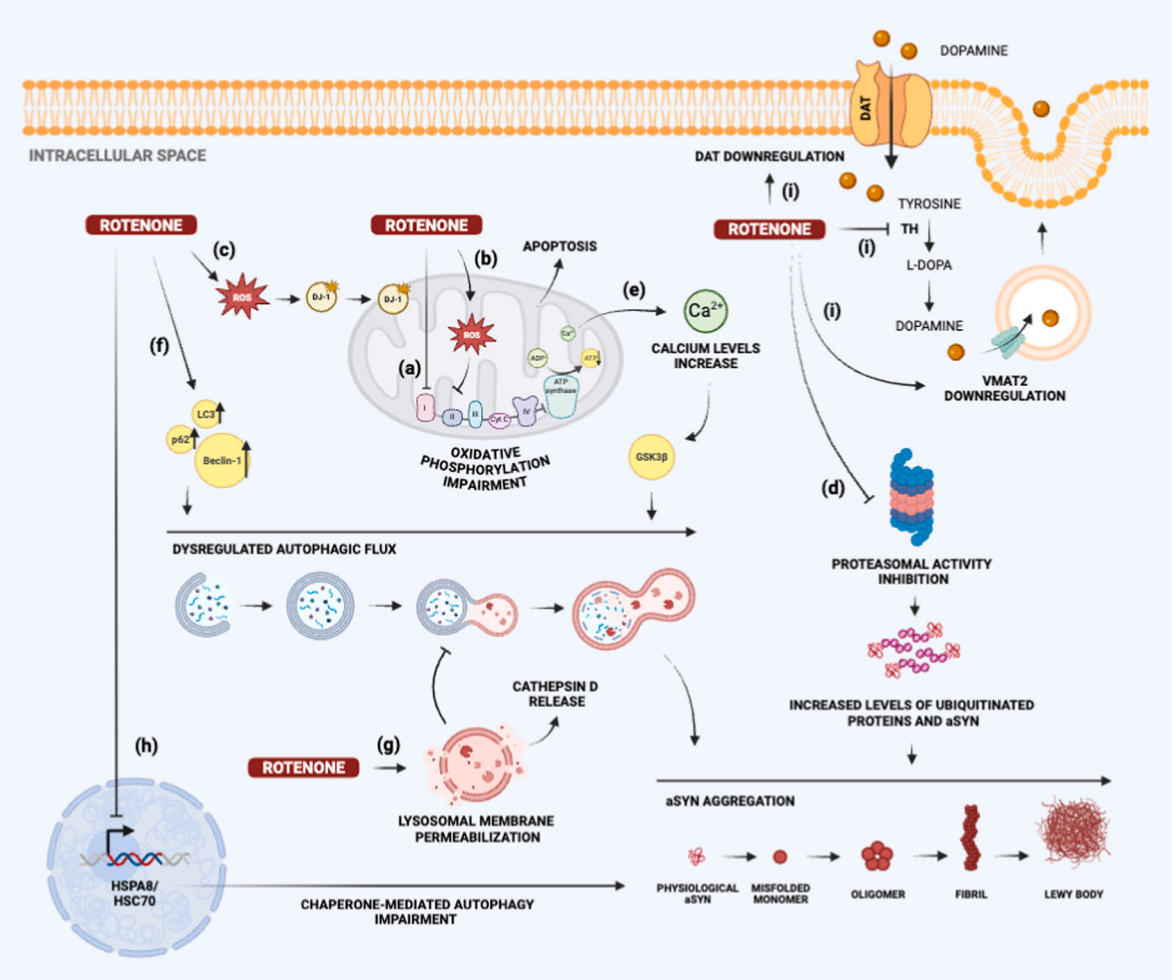

Fig. 3. Intracellular effects of rotenone on cellular functions. The figure illustrates the various intracellular effects of rotenone, a pesticide known to induce PD-like symptoms, highlighting its impact on mitochondria (a, b and c), proteasomal activity (d), autophagy (e, f, g and h), DA metabolism (i), and aSyn aggregation. This figure does not discriminate between the different cellular models reviewed. Created with BioRender.com.

2006) (Fig. 3d). On the other hand, sirtuin-3 (SIRT3), a deacetylase located in the mitochondria, was shown to act as a neuroprotective agent in rotenone-induced Parkinson cell model. Downregulation of SIRT3 exacerbated rotenone-induced aSyn accumulation, along with decreases in superoxide dismutase (SOD) and GSH levels, and loss of MMP (Zhang et al., 2016a).

Over the years, rotenone was shown to affect other cellular processes, related or not to inhibition of mitochondrial complex I. For instance, several data demonstrate the involvement of autophagy in rotenone-induced parkinsonian models both *in vitro* and *in vivo*. Rotenone was found to decrease the phosphorylation of protein kinase B (PKB), also known as AKT, and glycogen synthase kinase 3 beta (GSK3b) via a calcium-dependent pathway in PC12 cells leading to impairment of autophagy, and increased aggregation of aSyn, further exacerbating the pathological process associated with PD (Yuan et al., 2015) (Fig. 3e). On the other hand, rotenone-induced ROS upregulated LC3 expression and accumulation of autophagic vacuoles in SH-SY5Y cells (Wu et al., 2015; Xiong et al., 2013). Autophagic vacuoles and lysosomes were also observed in the lesioned SN of the parkinsonian animal (Xiong et al., 2013), indicating widespread cellular alterations induced by rotenone exposure. Along with LC3 up-regulation, increased Beclin 1 and ubiquitin-binding protein p62 levels in rats and PC12 cells have also been observed (Fig. 3f), suggestive of autophagy dysfunction (Wu et al., 2015; Yuan et al., 2015; Chen et al., 2018). Other data indicate that rotenone affects the lysosome, as rotenone-induced dopaminergic cell death coincided with an irregular distribution of cathepsin D (Fig. 3g). In control conditions, cathepsin D co-localized with LAMP2, indicating proper lysosomal function. However, *in vitro* treatment with rotenone disrupted this co-localization due to the loss of lysosomal membrane integrity, resulting in the leakage of cathepsin D from the lysosomal lumen into the cytosol (Wu et al., 2015). This impairment of lysosomal function led to dysregulated autophagic flux and compromised lysosomal activity, resulting in increased accumulation of aSyn in DA neurons. Interestingly, aSyn protein levels (but not mRNA levels) were elevated in PC12 cells, showing impaired protein degradation (Wu et al., 2015). Sala et al. (2016) further showed that the toxic effect of rotenone on aSyn levels is amplified when macroautophagy is inhibited. These authors also shown that rotenone-induced alterations in HSPA8/HSC70 chaperone expression may contribute to aSyn aggregation, particularly through impairment of the CMA pathway and propagation of soluble and fibrillar forms of aSyn (Fig. 3h). This study revealed a decrease in the HSPA8/HSC70 mRNA levels following rotenone exposure in both cortical neurons and SH-SY5Y, possibly associated with decreased mitochondrial bioenergetics, a primary outcome of mitochondrial complex I inhibition, leading to decreased ATP levels and induction of macroautophagy. This was later evidenced by the concurrent increase in LC3-phosphatidylethanolamine conjugate (LC3-II) levels and autophagosome accumulation, indicative of autophagic flux dysregulation in SH-SY5Y cells.

Rotenone selectively targets DA neurons, which exhibit heightened

vulnerability to its toxic effects. This susceptibility has been attributed to the unique structural and metabolic features of dopaminergic neurons. They possess long, extensively branched, and poorly myelinated axons, which not only increase their exposure to environmental toxins but also impair their ability to efficiently carry out repair and maintenance processes (Gcwensa et al., 2021; Wong et al., 2019). Moreover, their high energy demand makes them particularly reliant on optimal mitochondrial function, rendering them highly susceptible to oxidative stress and mitochondrial dysfunction (Pissadaki and Bolam, 2013). In addition, growing evidence highlights the critical role of endogenous DA in the selective vulnerability of dopaminergic neurons in PD pathophysiology (Zhou et al., 2023). Chronic low-dose exposure of rotenone has been shown to induce significant nigrostriatal degeneration in animal models (Betarbet et al., 2000; Panov et al., 2005; Sherer et al., 2003a, 2003b, 2003c), partly through disruption of key proteins involved in DA homeostasis, including TH, DAT, and VMAT2 (Moisan et al., 2011b) (Fig. 3i). While rotenone decreased the expression of both TH and VMAT2 in PC12 cells, DAT expression was paradoxically increased (Sai et al., 2008). These changes collectively impair DA metabolism and storage, amplifying cytosolic DA accumulation. Specifically, reduced TH expression lowers DA synthesis, but this effect is offset by increased DAT expression, which enhances DA reuptake from the synaptic cleft into the cytoplasm. Simultaneously, the reduction in VMAT2 expression impairs the sequestration of DA into synaptic vesicles, leaving more DA in the cytosol. Cytosolic DA is inherently unstable and prone to auto-oxidation, producing ROS and highly reactive DA quinones (DAQs) (Zhou and Lim, 2009; Laurent et al., 2025), which can modify proteins, including aSyn, and contribute to cellular toxicity. Also, cytosolic DA is metabolized by monoamine oxidase (MAO), generating not only ROS but also 3,4-dihydroxyphenylacetaldehyde (DOPAL), a highly toxic DA metabolite that can further damage cellular components (Masato et al., 2019). Indeed, rotenone has been shown to increase MAO activity, further exacerbating oxidative stress and DA-related toxicity (Sai et al., 2008). This interplay between impaired DA handling and oxidative stress forms a toxic cycle that is particularly devastating to dopaminergic neurons. The accumulation of toxic DA metabolites and DAQs contributes to aSyn aggregation, with cytoplasmic inclusions of aSyn observed in dopaminergic neurons following prolonged rotenone exposure (Betarbet et al., 2000; Sherer et al., 2003a).

Furthermore, rotenone exposure is associated with the activation of microglia and astrocytes, key indicators of neuroinflammatory response (Sherer et al., 2003c). Interestingly, microglial activation occurs prior to detectable neuronal degeneration, as demonstrated by Wang and colleagues (Zhang et al., 2021; Wang et al., 2023), suggesting that neuroinflammation acts as both a trigger and amplifier of dopaminergic neurotoxicity in the context of rotenone exposure. Indeed, mice treated with rotenone exhibited cognitive decline and the classical hallmarks of PD, including neuronal damage, synaptic loss, and increased levels of phosphorylated aSyn at Ser129. However, prior to the onset of neuronal damage and aSyn pathology, the authors observed elevated levels of ionized calcium-binding adapter molecule 1 (Iba-1), a marker of microglial activation, in the hippocampus and cortex of rotenone-treated animals (Zhang et al., 2021), which suggests that microglial activation occurs early in the disease process. Remarkably, when microglial activation was inhibited, the toxicity and cognitive impairment induced by rotenone were alleviated (Zhang et al., 2021). In another study, the same group showed that rotenone specifically upregulated the expression levels of complement receptor 3 (CR3) and its ligand iC3b, proteins expressed in microglia cells. This upregulation was associated with neurodegeneration, increased levels of aSyn phosphorylated at Ser129, hypertrophic microglia and astrocytes, and elevated mRNA levels of inflammatory markers such as iNOS and IL-1β. These effects were mediated via activation of nuclear factor-κB (NFκB) and signal transducer and activator of transcription (STAT)-dependent pathways. In contrast, mice deficient in CR3 showed ameliorated phenotypes when exposed to the same rotenone concentrations (Wang et al., 2023), which suggests that CR3 may play a critical role in mediating the neurotoxic effects of rotenone.

Non-motor symptoms of PD often precede the classical neuropathology in the brain, where LB and LN are typically encountered in the ENS (Braak et al., 2006). Recognizing this, several research groups have explored the deleterious effects of rotenone on gastrointestinal tract function and PD-related ENS pathology. Following 6 months of the last rotenone treatment, a significant increase in aSyn aggregates was observed in the ENS, accompanied by a slight but persistent loss of myenteric ganglion and delayed gastrointestinal tract transit time (Drolet et al., 2009). Another study replicated the appearance of aSyn aggregates in the ENS. However, authors also noted accumulation and aggregation of aSyn in other areas of the nervous system, including the dorsal motor nucleus of the vagus, intermediolateral nucleus and SN, with concentrations that did not induce mitochondrial complex I inhibition in the brain (Pan-Montojo et al., 2010). Moreover, aSyn aggregates in the ENS exhibited characteristics such as β-sheet conformation, phosphorylation at Ser129, and gliosis. Following 3 months of intragastric rotenone administration, aSyn accumulation was also observed in the SNpc, which was associated with neurodegeneration and impaired motor coordination (Pan-Montojo et al., 2010). This underscores the widespread impact of rotenone exposure on aSyn pathology and its implications for motor dysfunction in PD.

Finally, an important feature of PD is a slight gender-imbalance, since men are more prone to developing PD (Zirra et al., 2023). Many studies focus predominantly on male animals, overlooking potential discrepancies in primary symptoms and onset timing between males and females (Tamas et al., 2005; Bourque, 2011). Male rats exposed to 2.8 mg/kg of rotenone daily for 2 weeks exhibited severe motor symptoms and experienced dopaminergic neuron loss in the SNpc and their terminal projections. In contrast, female rats treated with the same dosage showed almost no motor symptoms and did not experience dopaminergic neuron loss by the end of the second week. Moreover, male rats displayed strong microglial activation, whereas females showed no evidence of neuroinflammation even with the equivalent dose. Both male and female animal models exhibited aSyn pathology, although female rats required higher doses of rotenone to manifest it. Nevertheless, male rats exhibited increased p62 and loss of LAMP1 in dopaminergic neurons, indications of potential defects in autophagic flux, protein degradation, and increased aSyn levels before neurodegeneration. Curiously, female rats only demonstrated a dose-dependent increase in p62, indicating a differential response to rotenone-induced toxicity between genders (De Miranda et al., 2019).

3.2. Paraquat

Paraquat is a broad-spectrum herbicide within the bipyridylium chemical family, notable for its structure, comprising two covalently bonded methylpyridine rings. Initially synthesized in 1882, its application as an herbicidal agent was recognized only later, finding utility in agriculture practices aimed at weed and grass control in cotton, soybean, sugar cane, and corn crops (Cao et al., 2018). Despite its historical use, the acute toxicity associated with paraquat has driven regulatory action in approximately 30 countries, leading to its prohibition in those regions. However, it remains prevalent in agricultural contexts, particularly in nations such Japan, Australia, the US, and New Zealand. The EPA classifies paraquat as a restricted-use pesticide due to its considerable potency, with an LD_{50} (median lethal dose) for adults estimated to be around 3–5 mg/kg, roughly equivalent to 1–2 teaspoons (Fortenberry et al., 2016). The observed parallels between the neurotoxic effects of paraquat and those induced by MPTP has drawn significant interest, as paraquat shares a structural resemblance to MPP^+, the active metabolite MPTP (Zhang et al., 2016b). This similarity underscores its potential to negatively impact the dopaminergic nigrostriatal system, contributing to the manifestations of PD-like symptoms. Indeed, investigations involving individuals exposed to pesticides revealed the significant risk

that paraquat poses for the development of PD (Tanner et al., 2009). This potential risk factor finds additional support from both *in vitro* and *in vivo* studies, providing invaluable insights into the intricate molecular mechanisms that underlie its neurotoxic effects (Fig. 4).

An intriguing aspect of the mechanism of action of paraquat is its ability to cross the BBB through the same neutral amino acid transporter used by L-valine and L-dopa, allowing its access to neuronal environments in a Na^+- dependent manner (Shimizu et al., 2001). Once inside neurons, paraquat exerts its toxic effects at the cytosolic level through cyclic redox reactions. PQ toxicity is primarily driven by its reduction through oxidoreductase enzymes, such as NADPH oxidase, forming the paraquat monocation radical ($PQ^{\bullet+}$). This reactive intermediate interacts with molecular oxygen, regenerating the paraquat dication (PQ^{2+}) and perpetuating a redox cycle. This cyclical process allows PQ to persist in tissues for extended periods, continuously generating ROS and contributing to prolonged oxidative stress. Additionally, paraquat depletes reduced NADPH, a critical cofactor in cellular antioxidant defence, and promotes lipid peroxidation, further compromising cell membrane integrity and function (Bus et al., 1976; Blanco-Ayala et al., 2014) (Fig. 4a). This compound also significantly affects mitochondrial function by altering oxygen consumption rates and disrupting the activities of several key respiratory complexes (Fig. 4b). Notably, complex I was identified as the primary site of superoxide production, as it facilitates the reduction of PQ^{2+} to $PQ^{\bullet+}$ using electrons from NADH oxidation (Cochemé and Murphy, 2008). The formation of $PQ^{+\cdot}$ within the mitochondrial matrix triggers a cascade of deleterious events, including increased ROS production, inhibition of aconitase activity, and disruption of mitochondrial bioenergetics, all of which contribute to cellular dysfunction and neuronal damage. PQ was also shown to inhibit the activity of complex I *in vivo* (Tawara et al., 1996), along with complexes III and IV (Palmeira et al., 1995) in isolated rat liver mitochondria. In addition to compromising oxidative phosphorylation, PQ alters the MMP and partially inhibits ATPase activity, reducing ATP production and lowering the adenosine diphosphate/oxygen (ADP/O) ratio (Yamamoto et al., 1987). The short-lived nature of the $PQ^{\bullet+}$ under physiological oxygen concentrations adds another layer of complexity to paraquat's mitochondrial toxicity. Although $PQ^{\bullet+}$ generated in the cytosol can diffuse into mitochondria, its rapid reoxidation to PQ^{2+} minimizes this pathway's contribution. Instead, most $PQ^{\bullet+}$ is generated within the mitochondrial matrix itself, amplifying local oxidative stress. This localized production set off a vicious cycle of ROS accumulation, lipid peroxidation, and mitochondrial dysfunction (Cochemé and Murphy, 2008).

Paraquat induces neurotoxicity by disrupting DA metabolism through multiple pathways. It can reduce the levels of key dopamine metabolites, such as DOPAC, homovanillic acid (HVA), and 3-methoxytyramine (3-MT), and decrease their ratios relative to DA, specifically DOPAC:DA, HVA:DA, and 3-MT:DA (Kuter et al., 2007). This disruption is closely tied to $PQ^{\bullet+}$, which acts as a substrate for DAT. In the brain, PQ^{2+} undergoes an initial extracellular reduction to $PQ^{\bullet+}$, mediated by

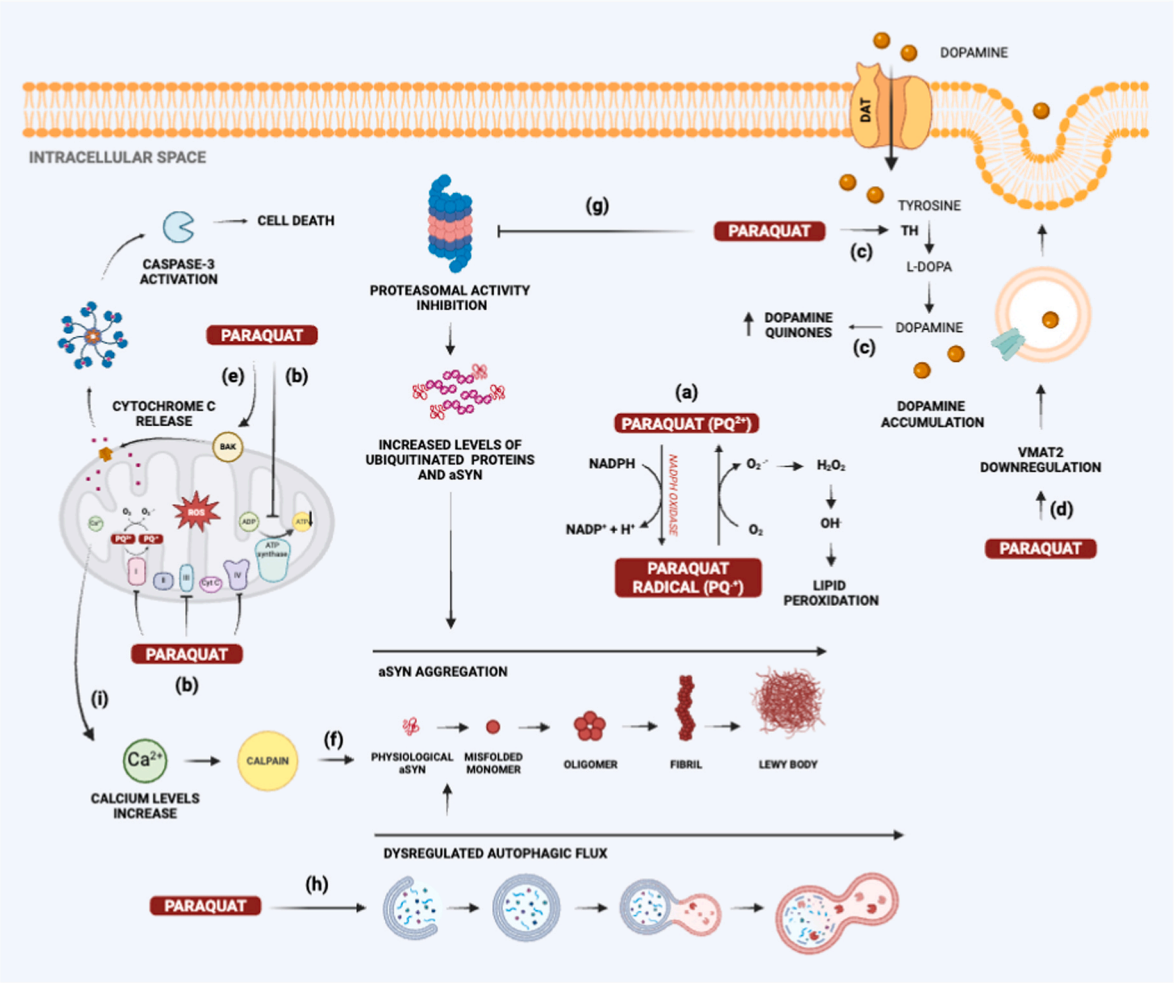

Fig. 4. Intracellular effects of paraquat on cellular functions. The figure illustrates the various intracellular effects of paraquat, a pesticide known to induce PD-like symptoms, highlighting its impact on oxidative stress and lipid peroxidation (a), mitochondria (b and d), calpain activation (c and h), proteasomal activity (f), autophagy (g) and aSyn aggregation. This figure does not discriminate between the different cellular models reviewed. Created with BioRender.com.

enzymes like NADPH-oxidase found on microglial cells. Subsequently, $PQ^{\bullet+}$ accumulates in dopaminergic neurons, where it induces oxidative stress, cytotoxicity, and further disturbances in DA metabolism. Notably, impaired DAT function has been shown to reduce $PQ^{\bullet+}$-induced neurotoxicity, underscoring DAT's critical role in mediating PQ's effects. In addition to DAT, $PQ^{\bullet+}$ is also a substrate for the organic cation transporter 3 (Oct3), which is highly expressed in non-dopaminergic cells within the nigrostriatal regions (Rappold et al., 2011). PQ also increases cytosolic DA levels by activating TH and inhibiting MAO. This leads to an accumulation of DA and the formation of toxic quinoproteins. Moreover, PQ reduces VMAT2 expression, which impairs DA sequestration into vesicles and heightens cytosolic DA concentration (Fig. 4c). Although TH activity increases, catechol-*O*-methyltransferase (COMT) levels remain unaffected (Lou et al., 2012). The disruption of DA metabolism caused by elevated cytosolic DA levels amplifies the risk of DA oxidation and ROS production. While PQ alone generates ROS, its interaction with DA significantly increases ROS levels (Rappold et al., 2011). Specifically, the oxidized form PQ^{2+} induces the production of hydrogen peroxide (H_2O_2) in rat brain mitochondria, with complex III and MMP playing significant roles in the process (Castello et al., 2007).

Neuroinflammation, a complex immune response mediated primarily by microglia and astrocytes, serves as a crucial defence mechanism in the brain. However, under chronic stimulation, whether triggered by genetic predispositions or environmental exposures such as pesticides, this protective response becomes maladaptive, fostering a pro-inflammatory environment that promotes neurotoxicity and progressive neuronal loss (Kempuraj et al., 2016). Paraquat-induced neurotoxicity provides a clear example of how chronic pesticide exposure triggers pathological neuroinflammation. In rodent models, paraquat exposure induced pronounced neuroinflammatory responses within the SN, frontal cortex, and hippocampus, characterized by increased expression of pro-inflammatory cytokines, including IL-1β and TNF-α, which are strongly implicated in PD pathogenesis. The SNpc is particularly vulnerable, where extensive microglia activation coincides with the progressive loss of dopaminergic neurons, reinforcing the link between chronic glial activation and neurodegeneration in PD (Mitra et al., 2011). *In vivo* studies further illustrated paraquat's indirect impact on microglial activation. In BV2 microglial cells, PQ exposure induces morphological changes associated with an activated phenotype, upregulates TNF-α and IL-1β mRNA, and increases protein expression of chaperonin (HSP60) and toll-like receptor 4 (TLR4), suggesting activation of innate immune signalling pathways central to inflammation and glial-mediated neurotoxicity (Sun et al., 2018). Additionally, a two-dose PQ treatment in mice resulted in a time-dependent increase in activated microglia within the SNpc, culminating in dopaminergic cell death. Similarly, NADPH-oxidase activation, a hallmark of microglial oxidative stress, contributes to ROS production, further amplifying dopaminergic vulnerability to paraquat-induced damage (Purisai et al., 2007). Astrocytes also play a key role in PQ-triggered neuroinflammation. In 3D whole rat brain cell cultures undergoing early neuronal differentiation, low-dose paraquat initially triggers astrogliosis, followed by delayed microglial activation. This biphasic glial response is accompanied by early upregulation of pro-inflammatory cytokines (IL-6 and IL-1β), coupled with downregulation of the anti-inflammatory IL-4 (interleukin 4), reflecting a shift toward a pro-inflammatory state. Notably, astrocytic activation persists even after PQ withdrawal, with proteomic analyses revealing prolonged changes in the astrocyte secretome. At 20 days post-exposure, microglial activation becomes prominent, marked by the upregulation of CD86 (cluster of differenciation 86), ITGAM (integrin alpha M), and IB4 (isolectin I-B4), while TNF-α levels remain elevated, highlighting the potential for sustained microglial dysfunction to perpetuate neuroinflammation long after pesticide clearance. Such chronic glial activation represents a critical mechanism through which pesticide exposure contributes to progressive neurodegeneration, ultimately compromising neuronal survival and accelerating PD onset (Sandström von Tobel et al., 2014).

As aSyn is central to PD pathology, great efforts have been made to understand the impact of this protein on the progression of the disease. Paraquat up-regulates aSyn levels in mice, prompting its conformational shift towards amyloid fibril species (Manning-Bog et al., 2002). The same authors demonstrated that paraquat initiates a shift in aSyn species, transitioning from tetramers to monomers, and that aSyn truncation was mediated by the cytosolic protease calpain (Fig. 4e) (Nuber and Selkoe, 2023). Contrary to expectations, the authors later reported that overexpression of aSyn in mice appeared to offer protection against paraquat-induced dopaminergic degeneration (Manning-Boğ et al., 2003), consistent with a potential role of aSyn in neuronal plasticity and recovery (Kholodilov et al., 1999). Therefore, the contribution of aSyn to neurodegenerative diseases may involve not only the gain of toxic functions but also the loss of normal protective functions. When aSyn loses its ability to defend against toxic insults, neurons become more vulnerable, potentially accelerating the progression of neurodegenerative diseases. In the end, paraquat induces cell death, through the Bcl-2 homologous antagonist/killer (Bak)-dependent intrinsic pathway, with the release of cytochrome *c*, activation of caspase-3, and cleavage of poly (ADP-ribose) polymerase (PARP) (Fei et al., 2008)(Fig. 4d).

Several studies have highlighted the significance of dysfunctional proteostasis in the accumulation of aberrant aSyn (McKinnon et al., 2020). Paraquat was found to reduce proteasomal activity, in SH-SY5Y cells, preceding a significant decrease in mitochondrial complex V activity and a depletion of ATP levels. Specifically, paraquat led to a decrease in the protein levels of the 19S proteasome subunit and an increase in the levels of aSyn and overall ubiquitinated proteins (Yang and Tiffany-Castiglioni, 2007) (Fig. 4f). Furthermore, paraquat exposure led to an increase in the autolysosomal membrane proteins ATG12 (autophagy related 12) and LAMP2A, highlighting the perturbation of autolysosome clearance (Fig. 4g) (Nuber et al., 2014). Beside dysfunctional clearance pathways paraquat-induced increased levels of ROS in the SN, hippocampus, and frontal cortex resulted in intriguing patterns of aSyn protein expression: decreased levels were detected in the SN, remained normal in the frontal cortex, and significantly increased in the hippocampus (Mitra et al., 2011).

Another crucial aspect of PD is the early onset of neuropsychiatric symptoms, including constipation, depression, anxiety, and olfactory deficits. The OB holds particular interest in PD research, as it represents the first brain region to exhibit aSyn aggregates, a hallmark of the disease. Notably, approximately 90 % of PD patients experience olfactory dysfunction, highlighting its potential as an early indicator of the condition (Braak et al., 2003). In addition, the OB serves as a potential entry for environmental toxins, including pesticides, into the brain through sensory neurons, contributing to the development of PD. To further study the pathogenic role of aSyn accumulation in the OB during the early stages of PD, transgenic mice expressing the familial PD-linked A30P mutant aSyn in OB neurons were exposed to low doses of paraquat (Nuber et al., 2014). The study revealed that olfactory dopaminergic neurons exhibit heightened sensitivity to paraquat in the presence of aSyn. Specifically, paraquat-induced degeneration of olfactory dopaminergic cells was observed exclusively in mice expressing aSyn. Similarly, to observations with rotenone, paraquat exposure disrupts calcium homeostasis through mitochondrial damage leading to calpain over-activity (Fig. 4h). This inhibits autophagy, resulting in the accumulation of truncated and insoluble forms of aSyn (Nuber et al., 2014). Additionally, aSyn phosphorylated at Ser129 was detected in the ENS of transgenic A53T mice chronically exposed to paraquat, alongside increased glial fibrillary acidic protein (GFAP) expression, indicative of reactive gliosis (Naudet et al., 2017). However, phosphorylated aSyn was not observed in the brain, probably due to paraquat's neurotoxic effects manifesting first in the ENS before progressing to the CNS. It is worth noting that the 8-week duration of this study may have been insufficient to detect significant phosphorylation and accumulation of aSyn in the CNS, processes that typically require longer periods to manifest (Naudet et al., 2017).

To date, extensive research has elucidated the multifaceted impact of paraquat exposure, revealing its role in inducing oxidative stress, depleting ATP levels, disrupting proteasomal function (Yang and Tiffany-Castiglioni, 2007), impairing autophagy (Nuber et al., 2014), and triggering neurodegeneration characterized by increased expression of aSyn, microglia activation, and gliosis (Nuber et al., 2014; Naudet et al., 2017). However, significant gaps remain in the understanding of the influence of environmental pollutants on neuronal lipid metabolism and neuroinflammation. The CNS has the second highest lipid content and diversity (Bozek et al., 2015), crucial for cell signalling and energy supply (Tracey et al., 2018). Yet, lipid damage, whether direct or indirect due to exposure to neurotoxicants, emerges as a prominent feature in neurodegenerative disorders (Reed, 2011). Recently, Tong et al. (2022) unveiled a novel aspect of PD toxicity, demonstrating its disruptive effect on lipid metabolism and composition, particularly in the midbrain. Their study documented PD-exposed mice exhibiting hallmark Parkinsonian features, including motor deficits to dopaminergic degeneration in the SN, alongside elevated aSyn protein levels in the midbrain. Authors further found that paraquat downregulates the expression of key PD-related genes such SNCA, PARKIN, PINK1, DJ-1, and VPS35, potentially perturbing their neuroprotective functions. Most notably, the authors established a correlation between motor dysfunction and increased levels of pro-inflammatory lipids, including ceramide, lysophosphatidylcholines, lysophosphatidylinositols and lipopolysaccharides. Increased cytokines induced neuroinflammation in the midbrain, further linking these pro-inflammatory lipids to motor impairments (Tong et al., 2022).

3.3. Maneb

Maneb, belongs to the family of manganese ethylene-bis-dithiocarbamate (Mn-EBDC) surface-acting fungicides (Stadler et al., 2022). Initially registered in 1962, maneb finds extensive application in safeguarding food and ornamental plants against bacterial and fungal threats, both in the field and during storage. Unfortunately, the need for frequent maneb application coupled with its non-specific mode of action is detrimental not only to target organisms but also to non-target species within the ecosystem (Gullino et al., 2010). In 2017, several countries implemented bans on the use of maneb; however, it continues to be applied in some of the world's biggest food-producing countries, including Brazil, India, and China (Lemes et al., 2014). Both acute and chronic exposure to maneb have been associated with adverse effects in the CNS among agricultural workers. These effects manifest as Parkinsonism-like motor symptoms, encompassing postural tremor and bradykinesia, alongside complaints of fatigue, memory issues, and drowsiness (Ferraz et al., 1988). Animal studies have corroborated these findings, demonstrating that maneb can cross the BBB and induce neurological deficits akin to PD, such as motor impairments and anxiety, coupled with nigrostriatal degeneration and a decrease in DA levels (Fig. 5).

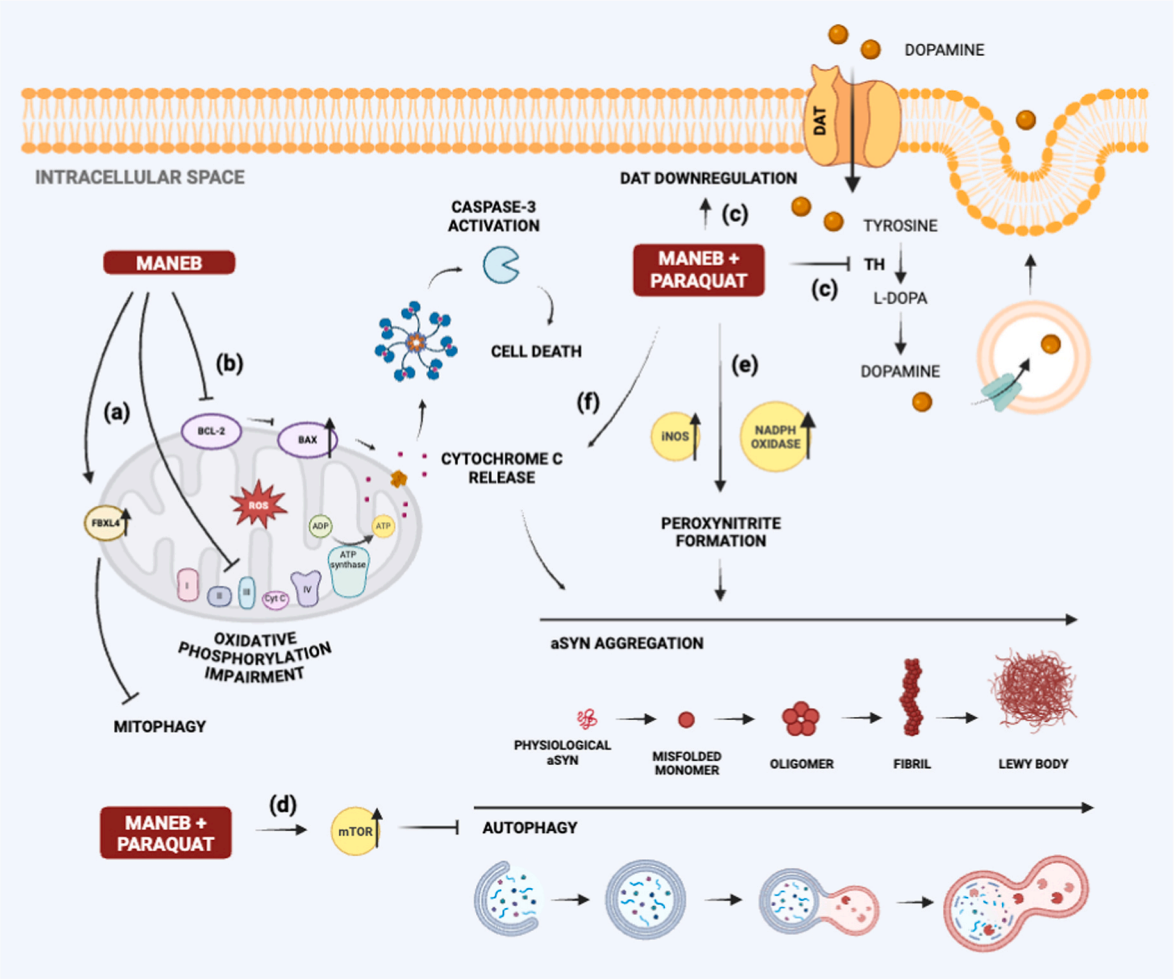

Fig. 5. Intracellular effects of maneb alone or in combination with paraquat on cellular functions. The figure illustrates the various intracellular effects of maneb, a pesticide known to induce Parkinson-like symptoms, highlighting its impact on mitochondria (a and b). It also illustrates the intracellular effects of simultaneous exposure of maneb and paraquat in DA metabolism (c), autophagy (d) and aSyn aggregation (f and e). This figure does not discriminate between the different cellular models reviewed. Created with BioRender.com.

Mechanistically, maneb exerts its neurotoxic effects through mitochondrial dysfunction and oxidative stress. Maneb was reported to preferentially bind and inhibit mitochondrial complex III, resulting in mitochondrial respiratory chain impairment (Zhang et al., 2003) and to increase the levels of F-box/LRR-repeat protein 4 (FBXL4), a mitochondrial protein that controls bioenergetic homeostasis by inhibiting mitophagy (Fig. 5a). In SH-SY5Y cells, exposure to maneb induced toxicity by increasing ROS production, reducing the mitochondrial count, and decreasing MMP, indicative of mitochondrial dysfunction (Liu et al., 2023). Maneb is also known to disrupt the GSH antioxidant and neurotransmitter system, disturbing the phenylalanine and tryptophan metabolism pathways, dopaminergic synapse and synaptic vesicle cycle (Liu et al., 2022). Maneb triggers dopaminergic neuronal death via the mitochondria apoptotic pathway, with mice exhibiting decreased Bcl-2 expression alongside increased levels of Bax (Bcl-2-associated X protein) and cytochrome *c* release, as well as activated caspase-3 (Liu et al., 2023) (Fig. 5b).

Finally, maneb was also found to increase levels of total and phosphorylated aSyn in IMR-32 cells. This group also pointed to a protective role of aSyn, showing that IMR-32 cells overexpressing aSyn and treated with maneb were less vulnerable to ROS, lipid peroxidation and cell death. Mechanistically, aSyn diminished maneb toxicity via the antioxidant system, through increased expression of SIRT1 (sirtuin 1) and FoXO3a (Forkhead box O3a) (Conde et al., 2023).

3.4. Combined effects of paraquat and maneb

While studying the effects of individual pesticides has provided invaluable insights into PD pathology and molecular mechanisms, there is a growing recognition of the importance of studying the combined impact of pesticides commonly used in the same agricultural regions and crops. Given the prevalence of multiple pesticide residues in food items, there is a compelling need to establish models that reflect this reality, thereby allowing for a more comprehensive understanding of PD etiology. Among the most frequently combined pesticides in crop cultivation are paraquat and maneb (Fig. 5).

Mice exposed to low doses of paraquat + maneb exhibited locomotor deficits attributable to reduced levels of TH and DAT proteins in striatum (Fig. 5c), alongside a decrease in dopaminergic neurons and the onset of reactive gliosis. Furthermore, a single administration of MPTP (15 mg/kg) which had no discernible effect on control mice, exacerbated the vulnerability in the nigrostriatal system of mice already exposed to paraquat, maneb, or both (Thiruchelvam et al., 2000). When double mutant mice (A30P + A53T) were exposed to paraquat + maneb, the accentuated decrease in DA levels were closely followed by the loss of dopaminergic neurons. However, while the DA levels of aSyn-expressing mice exposed to both pesticides also decreased, the decline was not as pronounced as in the double mutant group. This trend was similarly observed regarding the levels of DOPAC, HVA and DA turnover (Thiruchelvam et al., 2004; Coughlan et al., 2015).

While some studies on PD models do not find the accumulation and aggregation of aSyn, it is important to understand the factors that trigger its aggregation. In fact, Willis et al. (Wills et al., 2012) observed that, despite the extreme toxicity of the combined paraquat + maneb treatment in mice, it was not accompanied by increased levels of aSyn or enhanced 26S proteolytic activity. Nevertheless, paraquat + maneb--treated mice exhibited increased levels of the mammalian target of rapamycin, mTOR (Fig. 5b), decreased autophagic flux, and increased levels of HSC70, HSP70 (heat shock protein 70) and HSP90 (heat shock protein 90) proteins, indicating impaired autophagy but not CMA, despite elevated levels of autophagic proteins such as Beclin-1 and ATG12 (Wills et al., 2012). Nevertheless, aSyn pathology lies at the core of PD, shown by the numerous mutations in the SNCA gene, post-translational modifications, oxidative stress, and exposure to agrochemicals. However, the detailed mechanism by which these factors cause aSyn to aggregate is still not fully understood (Lashuel et al., 2013). For example, a study conducted by Kumar et al., 2016a, 2016b demonstrated that the initial step leading to aSyn aggregation in dopaminergic neurons of mice treated with paraquat + maneb may be the formation of aSyn radicals. These authors uncovered two distinct processes through which aSyn radical formation could occur. In the first proposed mechanism (Fig. 5e), paraquat + maneb-induced oxidative stress triggers microgliosis, resulting in increased levels of p67 phox, NAD(P)H oxidase subunit, indicative of NADPH oxidase activation, and increased iNOS activity, leading to the production of high amounts of nitric oxide. Consequently, NADPH oxidase and iNOS facilitate the formation of peroxynitrite-aSyn radical (Kumar et al., 2016a). In the second process (Fig. 5f) mitochondrial dysfunction caused by exposure to both paraquat and maneb results in the leakage of cytochrome *c* into the cytosol. Upon interaction with aSyn, cytochrome *c* promotes radical formation and induces a conformational change, leading to the formation of oligomers (Kumar et al., 2016b). Both pathways, while distinct in their mechanism, could contribute to radical formation and aSyn aggregation. The first involves peroxynitrite diffusion from microglia cells, while the second is mediated by cytochrome *c* leakage from mitochondria of dopaminergic neurons (Kumar et al., 2016a, 2016b).

3.5. Dieldrin

Dieldrin, a synthetic organochloride cyclodiene insecticide, was first synthesized in 1946 and subsequently commercialized. Its versatility was remarkable, from controlling soil pests such as termites, grasshoppers, and beetles in perennial crops, to combating tropical vector-borne diseases like malaria, yellow fever, and river blindness. Curiously, at one point, dieldrin was even utilized to protect electrical and telephone cables (de Jong, 1991). However, its lipophilic nature enables it to cross the BBB, leading to its accumulation in lipid-rich tissue, particularly the brain. There, the insecticide blocks the gamma-amino-butyric-acid (GABA) receptors, resulting in hyperexcitation and massive influx of calcium ions via the glutamate receptor channel, impairing synaptic transmission in the CNS (Martyniuk et al., 2010). Recognizing its mode of action, bioaccumulative nature, and environmental persistence, the EPA prohibited dieldrin production and restricted its usage in the USA in 1974. This action was followed by other developed countries, discontinuing the agriculture application of dieldrin (Suwalsky et al., 2002). Despite the ban on dieldrin many years ago, this insecticide continues to pose a significant threat to the environmental diversity and human health, persisting in soil, rivers, and food samples. Alarmingly, studies examining post-mortem PD brains have revealed dieldrin accumulation in the tissue of 6 out 20 cases (Fleming et al., 1994; Corrigan et al., 1996).

The neurotoxicity of dieldrin was also demonstrated *in vivo*, where chronic exposure to the pesticide induced dopaminergic cell death (Chun et al., 2001) and inhibition of mitochondrial respiration (Fig. 6a) (Bergen, 1971). Furthermore, dieldrin was responsible for the decrease in the DA metabolites DOPAC and HVA, while increasing cysteinyl-catechol levels (cys-DA and cys-DOPAC), the oxidative byproduct of DA, indicative of DA accumulation into the cytosol (Fig. 6b). The disruption of DA compartmentalization was accompanied by increased oxidative stress, as evidenced by elevated carbonyl levels, and decreased levels of the antioxidant GSH in the striatum. In this study, increased oxidative stress following exposure to dieldrin was also correlated with decreased DAT levels (Fig. 6c), demonstrating dieldrin's preferential neurotoxic effects on dopaminergic terminals (Hatcher et al., 2007). Subsequent investigations unveiled that dieldrin reduces proteasomal activity in cells overexpressing aSyn, resulting in the accumulation of aSyn-ubiquitin aggregates (Sun et al., 2005) (Fig. 6d). This triggered apoptotic cell death, evidenced by DNA laddering and cleavage of caspase-3, along with an increase in oxidative stress (Sun et al., 2005) (Fig. 6e).

Developmental exposure to dieldrin leads to changes in the dopaminergic system and increases susceptibility to subsequent toxic insults

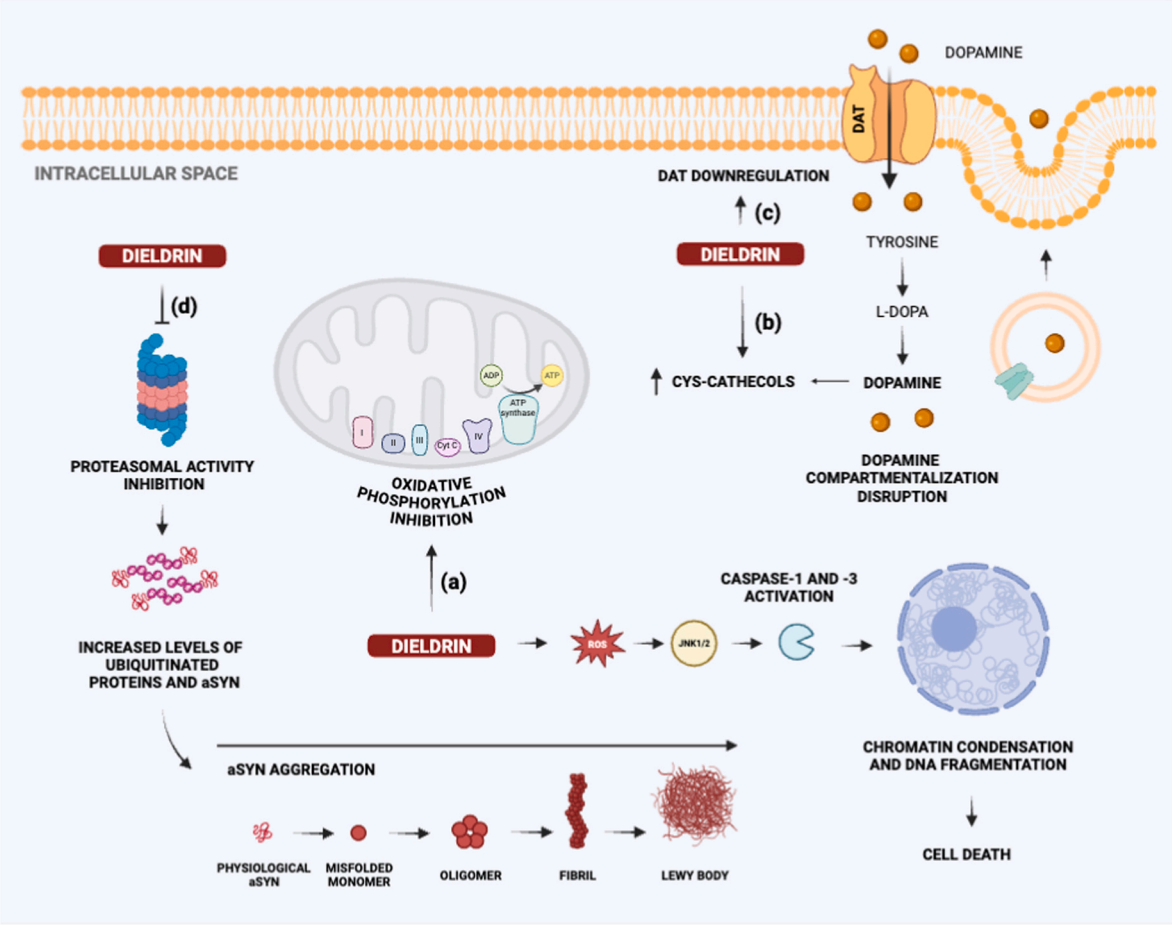

Fig. 6. Intracellular effects of dieldrin on cellular functions. The figure illustrates the various intracellular effects of dieldrin, a pesticide known to induce Parkinson-like symptoms, highlighting its impact on mitochondria (a), DA metabolism (b and c), proteasomal activity (d), caspase activation (e) and aSyn aggregation. This figure does not discriminate between the different cellular models reviewed. Created with BioRender.com.

(Richardson et al., 2006). Offspring of female mice exposed to dieldrin during breeding and lactation exhibited increased mRNA and protein levels of DAT, VMAT2, nuclear receptor-related 1 (NURR1) and paired like homeodomain 3 (PITX3), indicating specific alterations in dopaminergic neurochemistry. Interestingly, only male offspring displayed an increased DOPAC:DA ratio, suggesting persistent dysfunction of VMAT2. Following exposure to the neurotoxin MPTP, male offspring exhibited a marked vulnerability, characterized by a significant striatal DA loss and increased levels of aSyn and GFAP levels. This indicates that developmental exposure to dieldrin induces a latent state of DA dysfunction, rendering neurons more vulnerable later in life (Richardson et al., 2006). Similarly, developmental exposure to dieldrin followed by injection of preformed fibrils in male offspring resulted in increased DA release, although no changes in VMAT2 uptake activity were observed by the authors (Boyd et al., 2023). Nevertheless, both studies support the concept of silent neurotoxicity, where the deleterious effects of early-life exposure to environmental toxins manifest years after a triggering event (Kraft et al., 2016).

3.6. Other pesticides

While much of the research conducted with rotenone, paraquat, maneb and dieldrin aimed to establish a PD model and understand the molecular mechanisms underlying the disorder, in reality, all paved the way for investigating other pesticides that could induce neurotoxicity and Parkinsonism-like symptoms.

Following the association of paraquat with PD (Manning-Bog et al., 2002), diquat, another bipyridyl herbicide, emerged as a seemingly safer alternative for use in agriculture, aquatic areas and households, due its lower toxicity to humans compared to paraquat. However, due to its structural similarity to MPTP, concerns about its neurotoxicity persist. Diquat was shown to promote oxidative stress, which can trigger the formation of H_2O_2, leading to lipid peroxidation and cell death in hepatocytes. Later, Nisar et al. (2015) revealed that diquat is neurotoxic, although not specific to dopaminergic neurons. Indeed, diquat was found to induce cell death in both dopaminergic and GABAergic neurons, independently of aSyn. The group demonstrated that the toxicity exerted by diquat was not mitigated by DAT inhibition, suggesting a different mode of cell entry. Upon closer examination, involvement of the caspase-dependent pathway in cell death induced by diquat was ruled out, with only p53 and PARP activation observed at a later stage. Diquat was then found to induce necroptosis, as evidenced by the reduction of diquat toxicity with necrostatin-1 treatment (Nisar et al., 2015). However, another study reported that diquat toxicity is primarily due to aggregated aSyn and that CMA was found to rescue diquat toxicity by effectively eliminating monomeric and dimeric aSyn species (Kim and Koh, 2021).

Dithiocarbamate (DTC) fungicides constitute another class of pesticides with a significant association with neurotoxicity. Apart from their agricultural applications, they have been exploited in the rubber industry and to treat industrial effluents (Kanchi et al., 2014). While maneb is the most well-known DTC, this fungicide class also includes zineb, ziram and a more soluble salt, NaDMDC. Unfortunately, there is a scarcity of studies exploring the impact of other DTCs on PD

development. Ziram functions by inhibiting the enzyme aldehyde dehydrogenase (ALDH), crucial for clearance of oxidative species (Fitzmaurice et al., 2014). However, the exact mechanism underlying its neurotoxic effect remains elusive. Ziram has been reported to induce a conformational change in the zebrafish aSyn isoform γ1 into β-sheet-rich fibrils, exhibiting selective neurotoxicity toward dopaminergic neurons (Lulla et al., 2016a). Ziram's neurotoxicity was associated with inhibition of E1 ligase, responsible for the ubiquitination process and crucial for protein degradation. This inhibition led to an increase in aSyn levels and subsequent death of dopaminergic neurons (Chou et al., 2008; Lulla et al., 2016b). On the other hand, another study reported no discernible effects of ziram on the proteasome, which could be due to differences in experimental models used in both studies (Martin et al., 2016). However, both studies find that ziram differentially affects the presynaptic functions of aminergic and glutamatergic nerve terminals at the Drosophila neuromuscular junction.

A less hazardous class of insecticides, increasingly replacing organophosphate and carbamate pesticides, is pyrethroids. Originally derived from the flower *Tanacetum cinerariifolium*, pyrethroids are chemically synthetized to enhance their resistance (Matsuo, 2019). Their widespread application spans from agriculture, forestry, textile industries, to even personal protection against malaria and Zika virus. Moreover, pyrethroids feature prominently in household insecticides and animal parasite remedies (Ranson et al., 2011). While pyrethroids exhibit low toxicity to mammals, their lipophilic nature enables them to cross the BBB, where they induce permanent opening of voltage-gated sodium channels, leading to depolarization. They have also been shown to reduce the activity of cholinesterase and cytochrome p450 (Bradberry et al., 2005). Other investigations have implicated pyrethroids in PD incidence, with fenpropathrin recapitulating key PD features in SH-SY5Y cells, including aSyn aggregation, diminished MMP, and oxidative stress, ultimately culminating in cell death. Moreover, chronic exposure of rats to fenpropathrin resulted in increased DAT expression, decreased VMAT2 levels, and dopaminergic neurons loss (Xiong et al., 2016). Similarly, permethrin has been demonstrated to decrease DA levels and induce dopaminergic neuronal loss (Nasuti et al., 2017). A study by Romero et al. (2017) showed that alpha-cypermethrin-treated cells exhibited increased expression of several pro-apoptotic genes, alongside key autophagy-related genes, as well as increased oxidative stress, characterized by increased nitric oxide levels, lipid peroxidation, and DNA damage.

Organophosphate pesticides are a broad class of persistent insecticides widely applied in agriculture and even in chemical warfare, exemplified by sarin. Epidemiologic studies have established a strong association between organophosphate exposure and increased PD incidence (Firestone et al., 2005; Hancock et al., 2008). Renowned for their hydrophobicity, organophosphates readily cross the BBB, and, once inside the brain, inhibit the enzyme acetylcholinesterase, resulting in the accumulation of the neurotransmitter acetylcholine at cholinergic synapses. This accumulation causes cellular dysfunction by increasing its ATP consumption and disrupting oxidative phosphorylation, which leads to the production of ROS (Jokanović, 2018).

Dichlorvos, a pesticide predominantly used domestically in developing countries, has been shown to selectively induced degeneration of dopaminergic neurons, perturb DA synthesis and increase aSyn levels (BK et al., 2010). Indeed, dichlorvos inhibits mitochondrial complex I (Kaur et al., 2007) and leads to altered mitochondria morphology, characterized by swelling and disintegration (BK et al., 2010). In addition to its impact on complex I inhibition, dichlorvos inhibits mitochondrial complex IV, alongside with increased ROS production, decreased manganese superoxide dismutase (MnSOD) activity, and increased lipid peroxidation (BK et al., 2010).

In contrast, chlorpyrifos, extensively used in the USA until 2021 for corn and soy production, induced cell death in primary cortical neurons through the pro-apoptotic protein BBC3/PUMA (Bcl-2-binding component 3/p53 upregulated modulator of apoptosis). Preceding apoptosis, chlorpyrifos induced aSyn protein aggregation, ER stress and autophagy (Anderson et al., 2021).

4. Conclusion

The extensive and indiscriminate use of pesticides, while essential for enhancing food production and controlling vector-borne diseases, presents significant risks to environmental and public health. The alarming inefficiency in pesticide application results in widespread environmental contamination and exposure, affecting numerous non-target species. In the last decades, chronic pesticide exposure has been strongly linked to numerous health disorders, including neurological diseases such as PD. Indeed, epidemiological studies consistently demonstrate a higher prevalence of PD among populations with significant pesticide exposure, particularly agricultural workers. These findings have been consistently supported by animal and cellular studies, highlighting the neurotoxic effects of specific pesticides. Widely used pesticides such as rotenone, paraquat, maneb, and dieldrin have been shown to penetrate the BBB, exerting profound neurotoxic effects, particularly in the context of PD. These pesticides target multiple molecular pathways, impacting several cellular processes (Table 1). A

Table 1
Shared and pesticide-specific molecular targets, cellular alterations, and distinctive neurotoxic effects of selected pesticides associated with PD. This table summarizes the overlapping and pesticide-specific molecular and cellular targets, highlighting key processes such as mitochondrial dysfunction, oxidative stress, proteasomal impairment, disruptions in dopamine metabolism, and promotion of aSyn aggregation. The neurotoxic effects column highlights the characteristic features that define each pesticide's neurotoxic profile, providing insight into their individual contributions to PD pathogenesis.

Pesticide	Cellular and Molecular Effects	Neurotoxic Effects
Rotenone	• Inhibits mitochondrial complex I • Excessive ROS generation • Impairs proteasomal function and autophagy • Disrupts dopamine metabolism and vesicular storage • Activates microglia • Promotes aSyn aggregation	Strong mitochondrial complex I inhibitor; directly disrupts dopamine handling and promotes aSyn pathology with prominent neuroinflammatory response.
Paraquat	• Inhibits mitochondrial complexes I, III, IV, and V • Excessive ROS generation • Reduces proteasomal activity • Disrupts dopamine metabolism and vesicular storage • Causes lipid dyshomeostasis • Increases aSyn expression and aggregation	Broad mitochondrial inhibitor affecting multiple complexes; disrupts lipid homeostasis alongside dopamine metabolism and aSyn aggregation.
Maneb	• Inhibits mitochondrial complex III • Increases ROS production • Depletes GSH antioxidant defenses • Upregulates aSyn expression	Primarily impacts oxidative stress and antioxidant responses, contributing to increased aSyn expression.
Dieldrin	• Inhibits oxidative phosphorylation • Impairs proteasomal degradation • Disrupts dopamine metabolism and vesicular storage • Increases aSyn aggregation	Combines mitochondrial dysfunction with direct disruption of dopamine storage and aSyn aggregation.

unifying feature among these pesticides is their disruption of mitochondrial function, albeit through different mitochondrial complexes. This disruption leads to decreased ATP production and elevated levels of oxidative stress, which are hallmarks of neurodegeneration. Rotenone is particularly associated with impaired autophagy, a critical cellular process for clearing damaged organelles and proteins. In contrast, paraquat and dieldrin inhibit proteasome activity, further hindering the degradation of damaged or misfolded proteins and contributing to their accumulation within neurons. Additionally, paraquat and maneb have been demonstrated to upregulate the expression of aSyn, a protein implicated in the formation of toxic aggregates and LB in PD pathology. Both rotenone and dieldrin significantly impair DA metabolism, a key factor in the degeneration of dopaminergic neurons. Furthermore, rotenone induces microgliosis, promoting a heightened state of neuroinflammation that exacerbates neuronal damage. Paraquat, on the other hand, exerts its neurotoxic effects primarily by disrupting lipid homeostasis, a vital component for maintaining neuronal membrane integrity and function.

Understanding the molecular pathways disrupted by pesticides provides valuable insights into potential therapeutic strategies for PD. As referred above the pesticide's rotenone, paraquat, maneb, and dieldrin affect key cellular functions such as mitochondrial integrity, autophagy, protein degradation pathways, and dopamine metabolism, processes that are central to PD pathogenesis. By targeting these disrupted pathways, novel therapeutic interventions could be developed. For instance, enhancing mitochondrial protection or promoting mitochondrial biogenesis may help prevent energy deficits and oxidative stress that drive neurodegeneration. Similarly, strategies aimed at boosting autophagic clearance or restoring proteasomal function could reduce the accumulation of toxic proteins, such as aSyn, which is a hallmark of PD. Furthermore, targeting aSyn aggregation through molecular chaperones or inhibitors could prevent its accumulation in dopaminergic neurons, mitigating the toxic effects associated with pesticide exposure. These insights also open new avenues for precision medicine, where interventions could be tailored to patients based on their specific molecular alterations.

In addition to highlighting the harmful effects of rotenone, paraquat, maneb, and dieldrin on human health and their established associations with neurodegeneration, our review emphasizes the urgent need for further research into underexplored pesticides, many of which are still widely used despite neurotoxicity data. Our review reveals that these lesser-studied pesticides may pose significant risks, disrupting key cellular processes such as protein clearance pathways, oxidative phosphorylation, and aSyn homeostasis, hallmarks of PD pathology. Expanding research to encompass a broader spectrum of commonly used pesticides, including those not yet linked to neurodegeneration, is also essential to fully understand the environmental contribution to PD risk. Additionally, advancing the development of biomarkers for early detection of pesticide-induced neurotoxicity is of paramount importance. Identifying reliable biomarkers, whether from blood, urine, or other accessible matrices, could allow for earlier identification of at-risk populations, enabling timely intervention before the onset of clinical symptoms. Beyond individual-level monitoring, longitudinal cohort studies tracking pesticide-exposed populations over time could offer invaluable insights into exposure-response relationships, cumulative toxicity, and gene-environment interactions contributing to PD development. Such studies would help clarify how chronic low-dose exposures, mixtures of multiple pesticides, and occupational or residential proximity to treated areas influence neurodegenerative risk over decades.

From a public health perspective, this review also underscored the critical importance of strengthening preventive measures. As PD is the fastest-growing neurological disorder worldwide, with cases projected to reach 12.9 million by 2040, preventive strategies must evolve to incorporate stricter pesticide regulations, comprehensive post-market surveillance, and well-designed human biomonitoring programs. However, developing effective biomonitoring faces numerous challenges, including identifying pesticide-specific exposure biomarkers, selecting the most informative biological matrices, and developing highly sensitive analytical methods capable of detecting low-level pesticide residues. Nevertheless, robust biomonitoring programs, particularly in agricultural regions and high-risk occupational settings, could enable early detection of pesticide exposure long before PD symptoms manifest. Such early detection opens a crucial window for preventive interventions, whether through environmental controls, regulatory reforms, or the development of therapeutic strategies aimed at counteracting early-stage neurotoxicity. Finally, integrating exposure data from longitudinal biomonitoring with clinical and molecular assessments could significantly enhance our understanding of how pesticide exposure contributes to PD progression and comorbidities. This integrative approach could not only guide regulatory policy changes but also inform personalized prevention strategies, ultimately helping to reduce the global burden of pesticide-associated PD and related neurodegenerative diseases. A fundamental shift towards proactive prevention, combining scientific discovery with public health action, is imperative to confront the rising tide of PD and ensure healthier environments for future generations.

CRediT authorship contribution statement

Leslie Amaral: Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Márcia Martins:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Manuela Côrte-Real:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Tiago F. Outeiro:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Susana R. Chaves:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **António Rego:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

Funding

This work was funded by national funds (Portuguese Science Foundation, FCT) via the institutional programs supporting CBMA (UIDB/04050/2020, DOI: 10.54499/UIDB/04050/2020) and ARNET (LA/P/0069/2020, DOI: 10.54499/LA/P/0069/2020), and funding to Susana Chaves (DOI:10.54499/DL57/2016/CP1377/CT0026). Leslie Amaral was supported by an individual doctoral grant (2020.05944.BD).

Declaration of competing 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.

Acknowledgments

We thank the many researchers who have worked in this field over the years and apologize in advance for any work we may not reference. We tried our best to list all works, but it is nonetheless possible that not all publications were listed using the keywords chosen for the literature search.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2025.144348.

Data availability

No data was used for the research described in the article.

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