





Review

# Soil to Synapse: Molecular Insights into the Neurotoxicity of Common Gardening Chemicals in Alzheimer's and Parkinson's Disease

Niti Sharma  and Seong Soo A. An \* 

Department of Bionano Technology, Gachon Bionano Research Institute, Gachon University, 1342 Seongnam-daero, Sujung-gu, Seongnam-si 461-701, Gyeonggi-do, Republic of Korea; nitisharma@gachon.ac.kr

\* Correspondence: seongan@gachon.ac.kr; Tel.: +82-31-750-8755

## Abstract

The common gardening herbicides and fertilizers are crucial for weed control and plant growth, yet they may have potentially harmful impacts on neurological health. This review explored the possible effects of these chemicals on neurodegenerative disorders, especially Alzheimer's disease (AD) and Parkinson's disease (PD). The mode of action of several frequently used gardening chemicals (paraquat, glyphosate, 2,4-dichlorophenoxyacetic acid: 2,4-D, and ammonium chloride) in AD and PD has been highlighted. The mechanisms involved are glutamate excitotoxicity, dopaminergic pathway disruption, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic dysfunction, and gut–brain-axis dysregulation, crucial in the pathophysiology of AD and PD. Although the links between these substances and neurodegenerative conditions remained to be seen, growing evidence indicated their detrimental effects on brain health. This highlights the need for further research to understand their long-term consequences and develop effective interventions to mitigate the adverse effects of commonly used chemicals on human health and the environment.

**Keywords:** gardening chemicals; herbicides; mode of action; neurodegeneration; Alzheimer's disease; Parkinson's disease; gut–brain axis



Academic Editor: Kiminobu Sugaya

Received: 27 May 2025

Revised: 26 June 2025

Accepted: 2 July 2025

Published: 4 July 2025

**Citation:** Sharma, N.; An, S.S.A. Soil to Synapse: Molecular Insights into the Neurotoxicity of Common Gardening Chemicals in Alzheimer's and Parkinson's Disease. *Int. J. Mol. Sci.* **2025**, *26*, 6468. <https://doi.org/10.3390/ijms26136468>

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## 1. Introduction

Neurodegenerative diseases (NDs) are characterized by progressive synaptic failure, neural network disruptions, and the accumulation of physicochemically modified protein variants within the brain. NDs impact millions of individuals across the globe. Alzheimer's disease (AD) is one of the most prevalent ND, and according to estimates, there are 32 million people with AD dementia, 69 million with prodromal AD, and 315 million with preclinical AD worldwide [1]. Parkinson's disease (PD) is the second most common ND worldwide, with a prevalence of approximately 10 million affected people globally [2]. While age and genetics remained the primary risk factors for the onset of all NDs, environmental stimuli (pollutants, toxins, and heavy metals) would significantly raise the risk for NDs.

Fertilizers, pesticides, and herbicides are regularly employed in residential gardens to improve soil nutrients and manage pests and undesirable vegetation. Typical examples consisted of paraquat (PQ), glyphosate, 2,4-dichlorophenoxyacetic acid (2,4-D) (a component of Agent Orange), and ammonium chloride. China is the largest manufacturer of PQ, producing over 100,000 tons per year [3]. Glyphosate is the most commonly used herbicide, with 740,000 to 920,000 tons of use predicted for the year 2025 [4]. It is used frequently as it is

less toxic than the others, displaying a lethal dose (LD<sub>50</sub>) of 4230 mg/kg/body weight (BW) than ammonium chloride (LD<sub>50</sub>: 1650 mg/kg/BW), 2,4,5-T (LD<sub>50</sub>: 390 mg/kg/BW), 2,4-D (LD<sub>50</sub>: 375 mg/kg/BW, debarred in 3 countries), and PQ (LD<sub>50</sub>: 150 mg/kg/BW, debarred in 46 countries) [5,6]. The dioxin contaminant in Agent Orange (herbicide and defoliant used in the Vietnam War) is most toxic with an LD<sub>50</sub> of 107 µg/kg when administered subcutaneously in humans [7]. Despite a ban on its use in 1971, an analogous blend is still being used by US forest departments across the country [8]. If not managed appropriately, these chemicals can be harmful to humans and may pollute soil and water resources.

The human body can be exposed to common herbicides like PQ, glyphosate, 2,4-D, and similar substances through ingestion, inhalation, or skin absorption [9]. They enter the body and may reach the brain either through the bloodstream by crossing the blood–brain barrier (BBB) or indirectly by triggering systemic inflammation and oxidative stress [10]. Research indicated that exposure to pesticides had detrimental impacts, linked to reproductive and developmental toxicity [11,12], besides raising the likelihood of developing respiratory disorders, cancer, and NDs [13–16]. Mostly, these chemicals manifested their detrimental effects through oxidative stress, bringing DNA damage, lipid peroxidation, inflammation, and immune evasion, which could subsequently lead to various ailments [17,18]. Notably, there is mounting evidence that early pathological alterations in NDs like AD and PD may have their origins outside of the brain, specifically in the olfactory or gastrointestinal systems. According to the widely discussed “dual-hit” hypothesis, harmful substances may first affect the gastrointestinal tract or the olfactory system, and then spread to the brain through the vagus nerve or olfactory pathways [19,20]. Early accumulation of α-synuclein in the gut and olfactory bulb in PD, and amyloid-β in the olfactory system in AD, supports this concept [21]. However, evidence from neuropathological studies suggests that not all PD align with the dual-hit hypothesis [22]. Notably, a subset of individuals does not exhibit α-synuclein pathology in the dorsal motor nucleus of the vagus (DMV), a key region implicated in the gut-to-brain transmission route, indicating that alternative initiation sites may exist in PD pathogenesis [23]. While the exact entry route may vary depending on the chemical and individual factors, these peripheral pathways likely play a key role in how environmental exposures contribute to neurodegeneration.

The gut microbiota is now recognized to have a crucial and increasingly better-defined role in the pathogenesis of AD and PD through what’s termed the gut–brain axis—a two-way bidirectional communication network between the gut and CNS. This communication is mediated by various factors, including chemicals produced by the gut microbiome and environmental contaminants [24–26]. Pesticide exposure can alter the balance and diversity of the gut microbiota, leading to dysbiosis. Recently, Chen et al. [27] studied the metabolic alterations in the gut microbiota caused by several pesticides (organochlorides, organophosphates, and pyrethroids). The study showed that even minute amounts (0.05–1 µg/mL) of these chemicals can either boost or block the growth of gut bacteria. The bioaccumulation of pesticides in the gut potentially increases health risks by disrupting hundreds of key metabolic processes, including those related to amino acids, sugars, and fats [27].

In this work, the molecular mechanisms involved in the neurotoxic actions of some commonly used gardening chemicals were reviewed with a particular emphasis on the mechanisms associated with neurodegenerations in AD and PD.

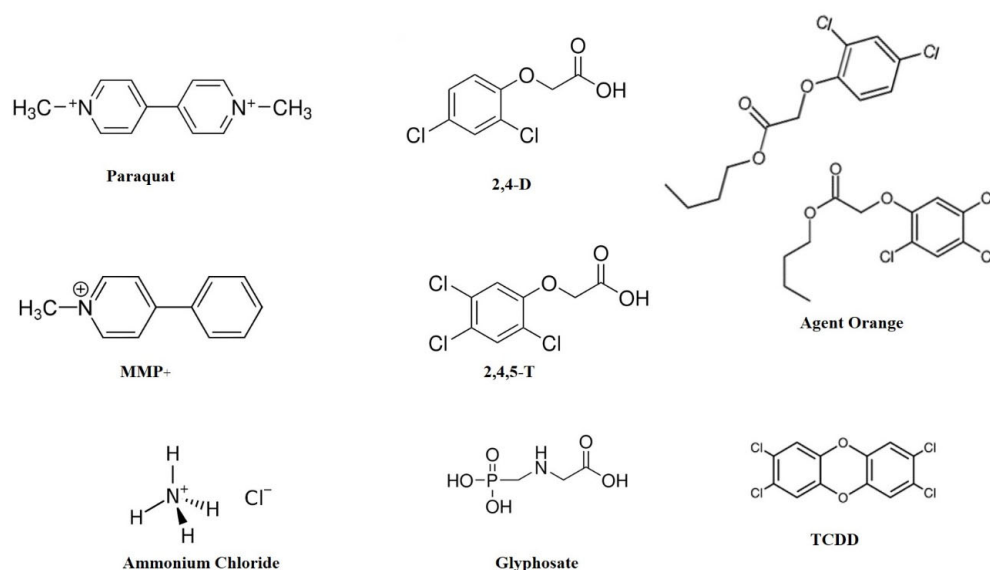
## 2. Materials and Methods

This review aimed to comprehensively analyze existing research articles related to common gardening chemicals in neurodegeneration. The literature search was carried out in the specialized databases PubMed, Google Scholar, and Web of Science for relevant and important information until May 2025. The search terms used were “paraquat”,

“glyphosate”, “ammonium chloride”, “Agent Orange”, “2,4-dichloro phenoxy acetic acid”, “2,4,5-Trichlorophenoxyacetic acid”, with the filters “Alzheimer’s disease”, “Parkinson’s disease”, “neurodegeneration”, and “gut–brain-axis”. Exclusion criteria: articles not specifying neurodegeneration were excluded. Non-English literature was excluded.

### 3. Mode of Action of Some Common Gardening Chemicals in Neurodegeneration

Herbicides are commonly used in farming and gardening to control weeds, but increasing evidence points to their possible neurotoxic effects; hence, their contribution to neurodegenerative conditions has come under scrutiny. The most prevalent herbicides, including PQ, glyphosate, 2,4-D, and ammonium chloride (Figure 1), have been linked with neurotoxicity by different mechanisms.



**Figure 1.** Chemical structures of some common gardening chemicals. MMP<sup>+</sup> is a neurotoxin with a structural resemblance to paraquat. Agent Orange is a 1:1 cocktail of 2,4-D and 2,4,5-T. TCDD is a contaminant present in Agent Orange. Abbreviations: 2,4-D: 2,4-dichloro phenoxy acetic acid; 2,4,5-T: 2,4,5 trichloro phenoxy acetic acid; MMP<sup>+</sup>: 1-methyl-4-phenyl pyridinium; TCDD: 2,3,7,8-Tetrachlorodibenzodioxin.

PQ is an extremely toxic bipyridinium herbicide with a structural resemblance to 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>), an infamous neurotoxin (Figure 1). Both PQ and MPP<sup>+</sup> have been implicated in inducing PD, albeit through distinct mechanisms [28]. MPP<sup>+</sup>, a toxic metabolite of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is transported into the dopaminergic neurons through dopamine transporter (DAT), where it inhibits mitochondrial complex I, leading to neurotoxicity. In contrast, PQ is largely transported via organic cation transporter-3 (OCT3) and does not inhibit mitochondrial complex I. Instead, it induces oxidative damage by generating free radicals and lipid peroxidation in the brain [28]. Glyphosate, the active ingredient in most commercial herbicides, is also associated with neuroinflammation and disruption of the gut–brain axis, the factors contributing to the pathogenesis of both AD and PD [29]. Equivalently, 2,4-D, an active ingredient of the infamous Agent Orange, was found to induce oxidative stress, neuroinflammation, and dopaminergic neurodegeneration [30]. Ammonium chloride ( $\text{NH}_4\text{Cl}$ ), though less studied, is speculated to impact neuronal homeostasis by acid-base balance disturbances and cellular metabolic mechanisms. In addition, it disrupts the homeostasis of chloride ions ( $\text{Cl}^-$ ) within and outside neurons essential factor for proper GABAergic inhibitory signaling. Disturbance of chloride ion balance may hinder GABAergic inhibi-

tion, potentially leading to excessive neuronal excitation. Nonetheless, overexcitation can also arise from various factors, including increased glutamatergic signaling, modified ion channel activity, and neuroinflammatory reactions [31]. As these chemicals were employed extensively and internationally, investigating their possible connections with neurodegenerations is important for public health, policy-making, and identifying safer alternatives. The detailed mode of action of these chemicals has been discussed in the following sections.

### 3.1. Paraquat (PQ)

PQ (1,1'-dimethyl-4,4'-bipyridylium dichloride or methyl viologen;  $[(C_6H_7N)_2] Cl_2$ ) is a widely used contact herbicide. It is a quick-acting and non-selective chemical that kills leaves and stems, but not the roots, as it does not travel through the plant's vascular system. It targets the electron transfer chain (ETC) in the photosystem I (PS-I) to generate the toxic reactive oxygen species (ROS), eventually killing the plant [32]. While PQ is strongly attached to the soil particles, it can quickly depreciate upon light exposure and can stay active and transportable in water. PQ is toxic to humans and can be absorbed through the skin, digestive tract [33], and placental barrier [34], causing multiple organ failure. It is not metabolically transformed in the body and is excreted unchanged through the kidneys [35]. Approximately 20% of the ingested PQ is absorbed in the stomach, after which it primarily distributes to the lungs, kidneys, liver, and muscles. PQ is metabolized by redox cycling catalyzed by several enzymes: NADPH-cytochrome P<sub>450</sub> reductase (CPR), xanthine oxidase (XO), and nitric oxide synthase (NOS), producing ROS and reactive nitrogen species (RNS). This cycle oxidizes lipids and proteins and damages DNA, especially in neurons, astrocytes, and endothelial cells [36].

#### 3.1.1. BBB Permeability

The capacity of PQ to penetrate the BBB is moderately intricate. The response hinged on the manner and location of its crossing. It could cross through limited passive diffusion, as observed in a study where only 0.05% of injected PQ reached the brain within the first hour and remained in the cerebro-circulatory system after 24 h [37]. The results suggested that PQ does not easily penetrate the BBB, but could accumulate in areas of the brain, lacking a BBB, including the pineal gland, cerebral ventricular linings, olfactory bulb, and hypothalamus [37]. PQ's transport across the BBB is possible in conditions when the brain is damaged due to any reason (NDs, aging, inflammation) [10,38]. Research indicated that after multiple low-dose exposures, PQ can penetrate the BBB by increasing ROS generation in the brain [39]. Microglia play a significant role in PQ transport through their connections with the BBB. PQ exposure triggers microglia by activating NADPH oxidase (NOX2), elevating ROS, leading to increased BBB permeability by damaging the epithelial cells [38]. In addition, unwarranted activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway may augment interleukin 6 (IL-6) production, oxidative stress, and inflammation. Thus, persistent exposure to PQ affects BBB functionality and injures the brain tissue.

The other routes of PQ transport mainly include OCT3, which is present in the endothelial cells of the BBB, astrocytes, and neurons. OCT3 plays a major role in mediating PQ uptake in glial and neuronal cells and is considered the most significant transporter for its neurotoxicity [40]. In contrast, L-type amino acid transporter 1 (LAT1), which is highly expressed at the BBB, has the potential to facilitate PQ's entry into the brain, but it is not the primary route. Additionally, the DAT ( $Na^+/Cl^-$ -dependent symporter) expressed on dopaminergic neurons, selectively transports monovalent cationic substrates like  $PQ^+$  (closer physicochemical resemblance to MPP<sup>+</sup>) rather than the usual divalent cation ( $PQ^{2+}$ ), which is not a suitable substrate for it. In biological systems, the occurrence and stability

of PQ<sup>+</sup> are minimal, which is why its involvement in PQ neurotoxicity through DAT is uncertain [41].

### 3.1.2. Mechanism of Demyelination

Myelin is a lipid-rich sheath covering the nerve cell axons to insulate them and enhance the speed at which electrical signals (action potentials) travel along the axon. Insulation is crucial for effective motor, sensory, and cognitive functions. Demyelination leads to reduced nerve conduction and degeneration of neurons, all of which contribute to cognitive decline and motor impairments, the key characteristics of neurodegenerative conditions [42,43]. PQ leads to demyelination mainly by inducing oxidative stress and neuroinflammation [44]. PQ also downregulates the expression of genes involved in myelin integrity (Claudin 5:Cldn5), myelin maintenance (UDP galactosyltransferase 8A: Ugt8a and SRY-box-containing gene: Sox10), oligodendroglia proliferation and differentiation (Sox2); Schwann cell migration and myelination (human epidermal growth factor receptor 3: HER3) [45].

The oxidative stress generated by PQ results in lipid peroxidation of the myelin sheath, causing structural and functional damage [46]. Microglial activation by increased ROS releases pro-inflammatory cytokines that damage oligodendrocytes, the cells responsible for myelin production and maintenance. The resulting BBB disruption allows peripheral immune cells to infiltrate the central nervous system (CNS), which enhances immune-mediated demyelination [44]. In addition, PQ hinders the removal of glutamate by astrocytes, resulting in an excessive buildup of glutamate and excessive activation of N-methyl-d-aspartate receptors (NMDAR), which raises intracellular calcium levels, resulting in oligodendrocyte apoptosis [43].

### 3.1.3. Mechanism of Neurodegeneration in AD

PQ has been shown to induce oxidative stress, particularly within the mitochondria of neurons, which increases A $\beta$  levels in the brain [47] and activates NLR family pyrin domain containing 3 (NLRP3) inflammasome [48]. PQ-induced oxidative stress inhibited neural progenitor cells (NPCs) and affected the wingless-type protein (Wnt) pathway in mice [49]. In particular, PQ modulates Wnt via microRNA (miRNA) in human neural progenitor cells (hNPCs) with direct relevance to AD [50]. Wnt signaling is recognized to be dysfunctional in AD, and stimulation of the Wnt/ $\beta$ -catenin signaling pathway inhibits  $\beta$ -secretase (BACE-1) expression, inhibits A $\beta$  production, and tau hyperphosphorylation in the brain [51].

PQ has also been known to inhibit hippocampal neurogenesis, interfere with hippocampus-dependent learning and memory, and reduce AKT phosphorylation [52]. AKT normally activates the mammalian target of rapamycin (mTOR), which is essential for cell growth and neurogenesis. Studies indicate that the activation of AKT could safeguard against neuronal cell loss in AD by inhibiting glycogen synthase kinase-3 beta (GSK-3 $\beta$ ), a protein suppressing neurogenesis [53].

### 3.1.4. Mechanism of Neurodegeneration in PD

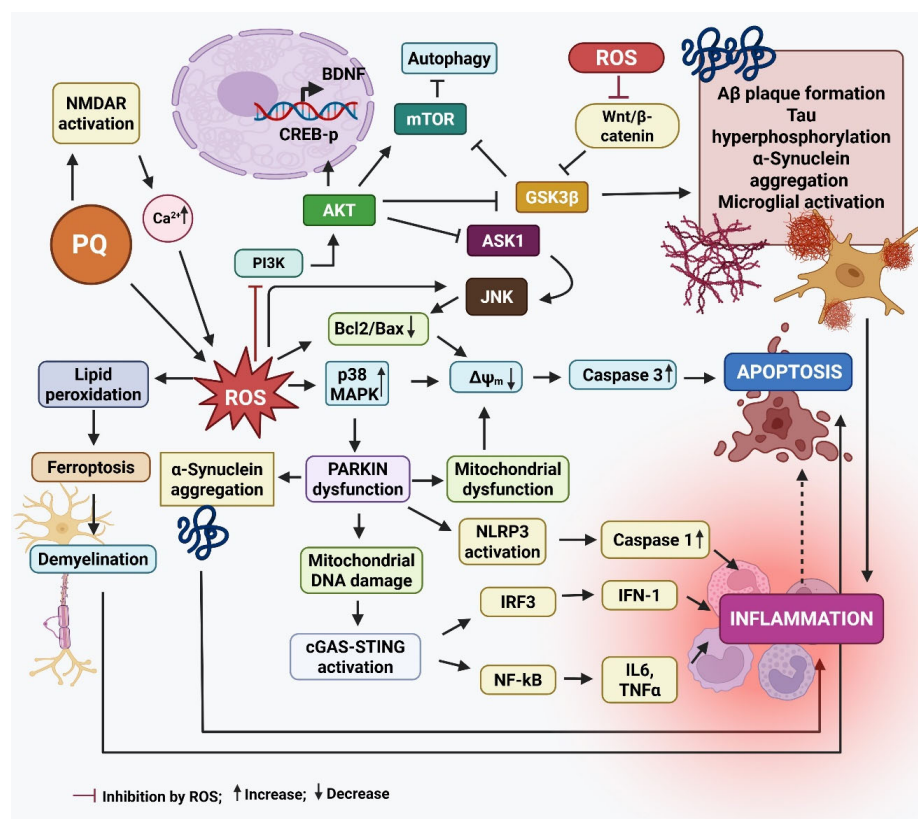
Long-term repeated exposure to PQ can selectively impair the nigrostriatal dopaminergic (DA) system, affecting locomotion and cognitive abilities [54]. Prolonged PQ exposure induces oxidative stress, which eventually impairs the BBB and damages the brain tissue. This may be due to the overactivation of the PI3K/AKT signaling pathway, which leads to increased IL-6 production and oxidative stress, contributing to inflammation-related brain injuries [55]. PQ induced PD-like lesions in certain rodent models, but there was no evidence of causing human brain lesions directly [56]. PQ oxidizes the cytosolic thioredoxin 1 (TRX1) and activates c-Jun N-terminal kinase (JNK) and caspase-3, resulting in



the apoptotic death of DA neurons. PQ might activate autophagy in neurons through apoptotic signal-regulating kinase 1 (ASK1) [57], a member of the mitogen-activated protein kinase family. In substantia nigra (SNr), PQ increased  $\alpha$ -synuclein production and aggregation in a dose-dependent manner [58]. By activating NMDAR, PQ contributes to excitotoxicity and increased ROS. In turn, increased ROS worsens the situation by inhibiting glutamine synthase in astrocytes, reducing glutamate uptake, and finally causing neuronal cell death [59]. PQ increased the level of NADPH oxidase 1 (NOX1), which has been implicated in producing toxic chemicals called superoxide ( $O_2^{\bullet-}$ ), in rat brain cells (N27 cells). It also activated Ras-related C3 botulinum toxin substrate 1 (Rac1), a protein that is essential for NOX1 to produce these reactive species and trigger cellular damage [60]. PQ harms the brain by over-activating microglia through a specific pathway involving macrophage antigen complex-1 (Mac1), which triggers inflammation via NOX and NLRP3 inflammasome. This excessive inflammation leads to brain cell damage and memory problems [61]. Chronic exposure to PQ increased the levels of GSK-3 $\beta$ , a protein involved in several cellular functions and signaling, in the midbrain and pons but reduced those in the striatum [62]. PQ also damages key brain areas that control movement and reward, reducing the number of DA neurons in the brain [63]. In addition, the PQ-exposed rats also had decreased dopamine breakdown products (DOPAC) and noradrenaline in the striatum important for brain function, resulting in movement problems in the rats [64]. Thus, in short, besides promoting  $\alpha$ -synuclein expression and aggregation, PQ influences several other pathogenic pathways, including oxidative stress, mitochondrial dysfunction, excitotoxicity via NMDA receptor activation, neuroinflammation (NOX1, Mac-1/NLRP3 activation), and apoptotic signaling (JNK/caspase-3 and ASK1 pathways).

Several epidemiological studies, such as the Agricultural Health Study (AHS), have indicated a higher risk of PD in people with job-related exposure to PQ. Tanner et al. (2011) found that individuals who used PQ faced about a 2.5-fold increased risk of developing PD (Odds ratio (OR): 2.5, 95% CI: 1.4–4.7) in contrast to non-users [65]. Likewise, a meta-analysis of data from cohort and case-control studies demonstrated that exposure to PQ was linked to a 2-fold increased risk for PD (strata odds ratio interval (sOR): 2.19; 95% CI: 1.48–3.26) [66]. A subsequent meta-analysis showed an association between PD and PQ exposure (OR 1.64; 95% CI: 1.27–2.13;  $I^2$  24.8%) [67]. There is a statistically significant association between paraquat exposure and PD. Vaccari et al. (2019), on the other hand, note that the odds of PD given PQ exposure from the only cohort study were a non-significant 1.08 (95% CI: 0.57–2.04) and 1.25 (95% CI: 1.01–1.51) from case-control studies [68]. A critical review of reviews was undertaken, focusing on reviews published between 2006 and 2021, concluded that the relation between PD and PQ exposure is not confirmed [69]. Recently, Paul et al. showed that people who lived or worked near areas where PQ was regularly applied had a higher risk of developing PD (OR: 2.08, 95% 1.31, 3.38). Similar increased risks were also seen for people living near PQ-treated areas (OR: 1.91, 95% CI: 1.30–2.83). The strongest associations were found in individuals diagnosed with PD before age 60 [70].

Figure 2 summarizes the main events leading to neurodegeneration by PQ exposure.



**Figure 2.** The mode of action of paraquat that results in neurodegeneration. Paraquat (PQ) plays a significant role in the development of Parkinson's disease (PD) by increasing the production of  $\alpha$ -synuclein, a protein that tends to clump together and form Lewy bodies, a key feature of PD. These protein aggregates contribute to the death of dopamine-producing neurons in the substantia nigra. PQ also activates stress-related signaling pathways, like Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (p38 MAPKs), which push neurons toward programmed cell death (apoptosis). At the same time, it triggers the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) pathway, leading to the release of inflammatory molecules like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 beta (IL-1 $\beta$ ), which worsens inflammation in the brain. Another damaging effect of PQ is its interference with the cell's ability to clear damaged mitochondria—a process known as mitophagy—by disrupting the PINK1/Parkin pathway. This leads to dysfunctional mitochondria building up in neurons. Additionally, PQ induces ferroptosis, a type of cell death linked to iron buildup and oxidative damage to cell membranes, particularly in dopamine neurons. When Parkin, a protein critical for cellular cleanup systems, is deficient or dysfunctional, it causes misfolded proteins like  $\alpha$ -synuclein to accumulate. Parkin dysfunction also increases DNA damage and may worsen inflammation through several pathways, including the NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, and the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, all of which drive the production of inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ , IL-1 $\beta$ , IFN-I). This chain of events sets off a vicious cycle: mitochondrial damage leads to inflammation, which in turn damages more neurons and mitochondria, amplifying the disease process in PD. In AD, PQ promotes the clumping of amyloid-beta (A $\beta$ ) proteins by increasing oxidative stress (ROS), making it harder for the brain to clear A $\beta$  and damaging neuron membranes. It activates enzymes like Glycogen synthase kinase-3 beta (GSK-3 $\beta$ ), which increase the abnormal phosphorylation of tau proteins, leading to the formation of neurofibrillary tangles—another major hallmark of AD. It also reduces the activity of cAMP-response element binding protein (CREB) and levels of brain-derived growth factor (BDNF), both of which are essential for memory and the ability of neurons to adapt and form new connections (synaptic plasticity). Furthermore, it impairs the Wnt/ $\beta$ -catenin pathway, a key signaling route in brain development and repair. When this pathway is disrupted, it can lead to cell death and prevent neural progenitor cells (NPCs) from multiplying and forming new neurons. Created by [Biorender.com](#).

### 3.2. Glyphosate

Glyphosate (N-(phosphonomethyl)glycine) is an organophosphorus compound with the trade name of Roundup. It is a common, non-selective, and broad-spectrum herbicide. It stops the plants from producing specific proteins essential for their growth by interfering with the shikimic acid pathway via competitively inhibiting enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) [71]. The resulting inhibition of EPSP decreases the production of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) that are essential for protein synthesis and plant development. Although glyphosate is degraded by soil microorganisms, resulting in its low levels, frequent use can increase its accumulation in the soil, potentially intensifying the likelihood of groundwater contamination [72]. Humans can be exposed to glyphosate primarily through ingestion or inhalation, the cutaneous uptake is minor. Glyphosate does not undergo significant metabolism in mammals and only a small amount (<1%) is metabolized to aminomethyl phosphonic acid (AMPA). Glyphosate and AMPA do not exhibit any tendency of bioaccumulation [73] and are eliminated from the body within 24–48 h [74].

#### 3.2.1. BBB Permeability

In vitro studies on brain microvascular endothelial cells (BMECs) have shown that glyphosate and AMPA can enhance BBB permeability. Glyphosate crosses the BBB through passive transcellular diffusion [75] and active transport mediated by LAT1 and LAT2 [76]. Mechanistically, glyphosate downregulates key tight junction proteins, disrupting endothelial barrier integrity. This facilitates the infiltration of peripheral immune cells into the brain parenchyma, initiating neuroinflammatory processes [75]. Once inside the CNS, glyphosate and AMPA further exacerbate BBB dysfunction and stimulate inflammatory responses, including upregulation of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [77]. Though current evidence suggests a sound mechanistic connection between glyphosate exposure and disruption of the BBB, additional in vivo research is required to measure BBB penetration and evaluate subsequent neurological effects.

#### 3.2.2. Mechanism of Neurodegeneration in AD

Glutamate excitotoxicity is a key pathological mechanism in AD, contributing to synaptic dysfunction, neuronal loss, and cognitive decline. Glyphosate has been reported to inhibit glutamate transporters, leading to glutamate activity in the synapse, increasing NMDAR overstimulation, mitochondrial dysfunction, and  $\text{Ca}^{2+}$ -mediated neuronal damage [78–80]. The activation of extracellular signal-regulated kinases (ERK) and  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII) signaling pathways by glyphosate was also shown to enhance glyphosate-induced neurotoxicity [81]. In a related study, glyphosate-based herbicides (GBH) exposure increased the CSF levels of excitatory amino acids, suggesting that GBH may cause an imbalance in the downstream metabolism of arginine and excitatory amino acids, which may worsen GBH-induced neurotoxicity [82]. Glyphosate elevated TNF $\alpha$  expression and soluble A $\beta$  and disrupted the brain's transcriptome in a dose-dependent manner [77]. Even after a 6-month recovery period after exposure, the byproduct of glyphosate (AMPA) remained detectable in the brain. This persistent presence of AMPA, along with neuroinflammation and AD-like pathology (elevated insoluble A $\beta_{42}$  and hyperphosphorylated tau), suggested a detrimental impact of glyphosate on brain health [83].

A recent epidemiological study evaluated human exposure to glyphosate and used an AD memory test to explore a possible relationship between glyphosate exposure and cognitive function. The findings showed a substantial inverse association between urine glyphosate levels and CERAD-WLT (Consortium to establish a registry for Alzheimer's



disease word list memory test) scores, pointing to a link between increased long-term glyphosate exposure and cognitive loss [84]. Also, glyphosate exposure in older adults was positively associated with impaired performance on the CERAD Delayed Recall (DR) test, with an odds ratio (OR) of 1.52 (95% CI: 1.01–2.30;  $p$ : 0.049) [85], providing new epidemiological evidence of the harmful effect of glyphosate on cognitive functions. A more recent study has reported a significant inverse relationship between urinary glyphosate levels and performance on memory recall tasks, including the CERAD Delayed Recall test, with OR of 1.52 (95% CI: 1.01–2.30;  $p$ : 0.049) [85], frailty prevalence (adjusted OR: 1.14, 95% CI: 1.04–1.25; quartiles  $p$ : 0.002), and all-cause mortality (adjusted hazard ratio HR: 1.19, 95% CI: 1.07–1.31;  $p$ : 0.005) [86] indicating a possible link between glyphosate exposure and cognitive impairment, frailty, and all-cause mortality in older adults.

### 3.2.3. Mechanism of Neurodegeneration in PD

Given that glyphosate is used extensively worldwide, exposure to it is probably a potential environmental risk factor for PD. Glyphosate exposure during gestation and lactation caused glutamate excitotoxicity and oxidative stress in the rat model through NMDAR activation, cholinergic transmission impairment, astrocyte dysfunction, ERK1/2 overactivation, and reduced phosphorylation of nuclear factor kappa light-chain enhancer of activated B cells (NF- $\kappa$ B) [80]. Glyphosate worsened MPTP-induced dopaminergic neurotoxicity in adult mice's striatum and SNr [87]. Several research findings linked glyphosate exposure to neurodegeneration in PD through inhibition of acetylcholinesterase (AChE) activity, mitochondrial dysfunction, neuroinflammation, apoptosis, and oxidative stress [88,89]. Glyphosate caused cell death in neuronal-differentiated pheochromocytoma (PC12) cells in addition to activating apoptotic pathways. The deactivation of Beclin-1 reduced both apoptosis and autophagy in glyphosate-treated cells, suggesting its involvement in the cell death mechanisms induced by glyphosate [90].

In some epidemiological cases, glyphosate-induced parkinsonism has been reported several years after acute and chronic exposure [91,92]. The glyphosate neurotoxicity resulted in loss of dopaminergic neurons, resulting in rigidity, slowness, and resting tremor with no impairment of short-term memory [92]. It is speculated that acute GBH poisoning or long-term exposure could result in the early onset of PD [93].

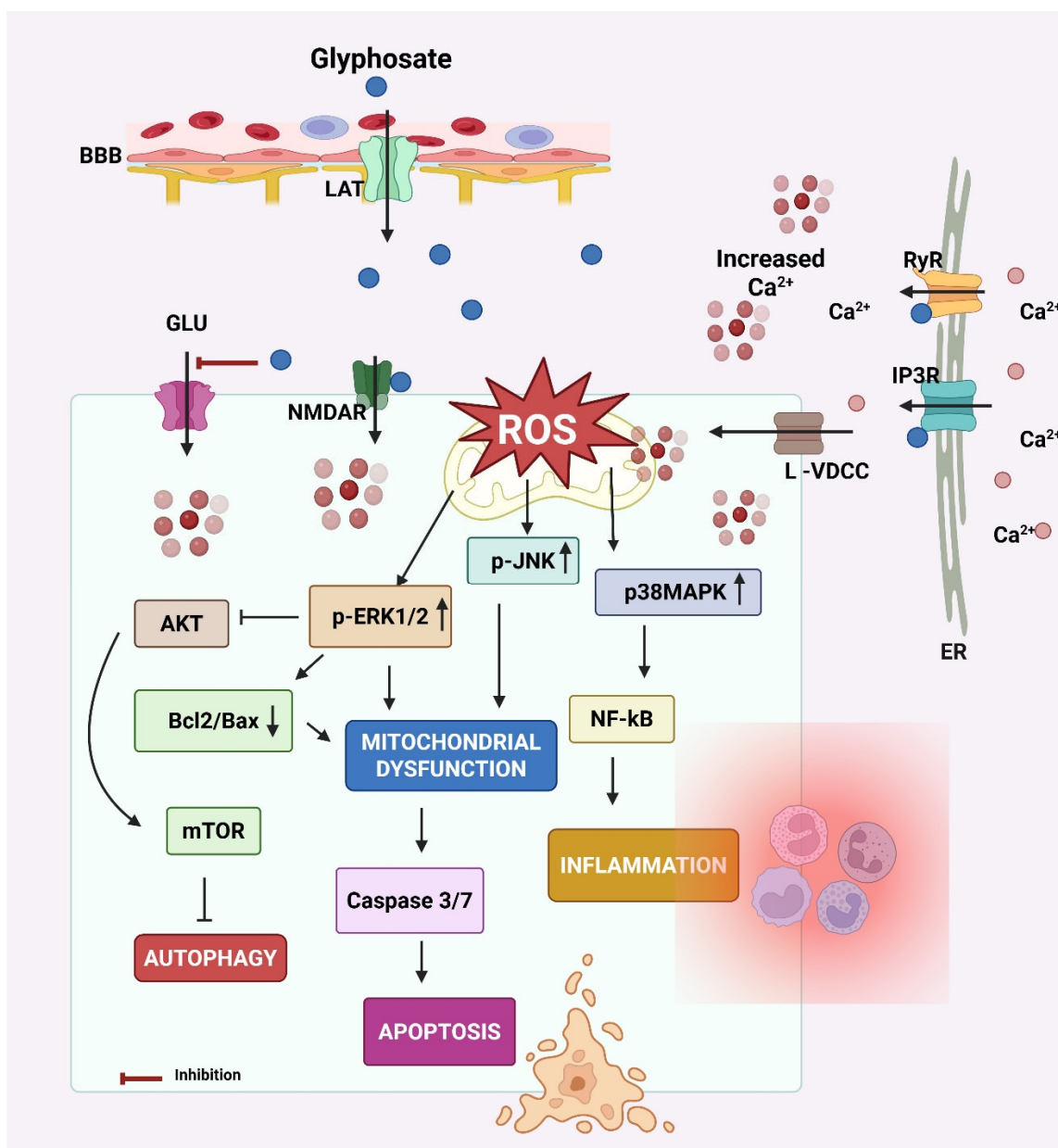
### 3.2.4. Effect on Hippocampal Long-Term Potentiation (LTP) and Learning

Poor hippocampus long-term potentiation (LTP) and learning are associated with both AD and PD through distinct mechanisms. A $\beta$  oligomers and tau disrupt synapses and LTP, which causes AD to directly target the hippocampus, resulting in severe learning and memory difficulties [94]. Although oxidative stress and neuroinflammation are present in both disorders that further disrupt synaptic function, AD causes direct hippocampal injury from the start, while PD-related LTP impairments arise after dopamine dysfunction, and alpha-synuclein ( $\alpha$ -synuclein) accumulation further deteriorates the hippocampal function [95].

Recently, the effect of glyphosate on synaptic transmission and LTP induction was studied in vivo and ex vivo rat hippocampal slices. The herbicide reduced synaptic transmission in the hippocampal Cornu Ammonis 1 (CA1) area and had adverse effects on memory and learning. Nevertheless, the effect was reversed by pretreatment with TLR4 antagonist (TAK-242) and microglia inhibitor, minocycline [96], suggesting the involvement of neuroinflammation in this process. Astrocytic dysfunction, which is often initiated by microglia, can influence not only neuronal survival but also stimulate further microglial activation. Glyphosate stimulated mitochondrial respiratory chain enzymes in a rat astrogloma cell line [97] and elevated the expression of astrocyte marker, glial fibrillary

acidic protein (GFAP) [98]. Therefore, alterations in astrocytic function brought on by this herbicide may be a factor in neuroinflammation and LTP [99].

The key events leading to neurodegeneration by glyphosate have been summarized in Figure 3.



**Figure 3.** Mechanism of neurodegeneration by glyphosate. Glyphosate crosses the blood–brain barrier (BBB) via the L-type amino acid transporter (LAT). Glyphosate increases intracellular calcium ( $\text{Ca}^{2+}$ ) levels by activating N-methyl-D-aspartate receptors (NMDAR) and L-type-voltage-dependent calcium channels (L-VDCC) at the cell membrane and inositol 1,4,5-trisphosphate (IP3R) receptors and ryanodine (RyR) at the endoplasmic reticulum (ER) membrane. The elevated intracellular  $\text{Ca}^{2+}$  results in oxidative stress by increasing reactive oxygen species (ROS) generation. ROS accumulation creates oxidative stress, a key trigger for activating MAPK signaling cascades, including extracellular signal-regulated kinases 1 and 2 (ERK 1/2) and p38 mitogen-activated protein kinase (p38MAPK). Both kinases are known to regulate cellular responses to stress, inflammation, and survival/death signals. These effects increase calcium influx from extracellular sources. Calcium signaling can activate the ERK1/2 pathway. Calcium can also modulate the protein–protein interactions of ERK1/2, influencing its subcellular localization and the repertoire of its substrates. ERK signaling pathways

can influence the balance between Bcl-2 and Bax, both of which play crucial roles in cell death. Elevated intracellular  $\text{Ca}^{2+}$  and sustained ERK/p38 signaling activate NF- $\kappa$ B and caspases that promote inflammation and apoptosis, respectively. p38 MAPK can directly phosphorylate calcium channels, altering their structure and function, and thus affecting their ability to allow calcium ions to pass through. Additionally, ERK1/2 can influence other calcium channel subtypes, including L-type channels, which are important for neurotransmitter release in neurons. In glial cells, this cascade also contributes to neuroinflammation and release of cytokines (e.g., IL-1 $\beta$ , TNF- $\alpha$ ), further harming neurons. Glyphosate also decreases glutamate (GLU) uptake by astrocytes, resulting in GLU excitotoxicity due to increased GLU in the synaptic cleft. Created by [Biorender.com](https://www.biorender.com).

### 3.3. Agent Orange

Agent Orange (AO), a chemical herbicide, is a mixture of equal parts of two synthetic auxins, 2,4,5-T and 2,4-D. Additionally, AO contained traces of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), often known as “dioxin”, a byproduct formed during 2,4,5-T synthesis. TCDD is hazardous even in trace levels, causing immediate and long-term effects. AO’s immunosuppressive, carcinogenic, and teratogenic effects are most likely brought on by TCDD toxicity [100,101]. Human exposure occurs through ingestion, inhalation, skin, or eyes. Owing to its chemical stability, AO degrades slowly in the soil. The primary constituents, 2,4-D and 2,4,5-T, are susceptible to degradation over time, particularly in specific circumstances (e.g., moisture, temperature, and the presence of microbes). However, the harmful dioxins are far more enduring and can linger in the environment for decades [102].

AO damages the plants by oversaturating them with artificial auxins, which results in unregulated cell growth that impairs the vascular system, depriving the plants of nutrients, and eventually killing them. It was used by the U.S. military as part of its herbicidal warfare program, ‘Operation Ranch Hand’, during the Vietnam War from 1961 to 1971 to clear millions of acres of forests [103]. The “orange” name comes from the color of the containers used for its storage. The chemicals are absorbed into the body when people are exposed to AO, particularly through direct skin contact, vapor inhalation, or consumption of polluted food or water. Following absorption, the substances are transported to different tissues via the bloodstream [104]. The 2,4-D and 2,4,5-T are metabolized by the liver and are subsequently eliminated in the urine. Contrarily, dioxins can build up in the adipose tissues, impacting many different biological systems, including the nervous system [105]. Several epidemiology studies have linked these components of AO to cancer, respiratory, endocrine, and neurological diseases [106]. Epidemiological studies on AO exposure and its association with AD and PD have shown mixed results. The report published by the US Health and Medicine Division indicated suggestive but limited evidence that exposure to AO utilized during the Vietnam War correlates with a higher likelihood of developing PD [107]. AO has been known to exert toxic and degenerative effects on the human nervous system, as observed in a Korean Vietnam veterans study group. The adjusted ORs were significantly highest for AD (OR 1.64), followed by systemic atrophies affecting the nervous system, including spinal muscular atrophy (OR 1.27), and peripheral polyneuropathies (OR 1.09) [106], besides increased risk for all types of dementia [108]. Martinez et al. [109] found that veterans exposed to AO had nearly double the prevalence of dementia. While aging may be a confounding factor, the exposed group showed accelerated brain atrophy in the bilateral frontal (especially, the ventrolateral prefrontal area) and temporal lobes, compared with the age-matched control group [110], implying an effect beyond physiological aging. One retrospective study showed significant differences in the hemispheric Unified Parkinson’s Disease Rating Scale (UPDRS) between patients with and without AO exposure [111].

### 3.3.1. BBB Permeability

It has been shown that both 2,4-D and 2,4,5-T can enter the brain by crossing the BBB and blood-CSF barrier (BCSFB) via specific organic anion transporters (OATs) [112]. The transport requires energy and is blocked by ouabain (which blocks  $\text{Na}^+/\text{K}^+$  ATPase) and phlorizin (a glucose transport inhibitor) [113,114]. 2,4-D is a substrate of OAT3 in the choroid plexus. However, high concentrations of 2,4-D can inhibit this clearance mechanism, leading to its accumulation in the brain and CSF [115].

### 3.3.2. Mechanism of Neurodegeneration in AD

Earlier research demonstrated that 2,4-D exhibited lipotoxic effects on Schwann cells, myelin, and gangliosides [116], which are essential for effective brain function and conductivity. Researchers investigated the effect of short-term exposure to 2,4-D or 2,4,5-T (constituents of AO) in human CNS-derived neuroepithelial cells (PNET2) [117]. The exposure significantly impaired mitochondrial function, induced degenerative morphological changes, and reduced cell viability. Correspondingly, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression was significantly inhibited while 4-hydroxy-2-nonenal (HNE), a marker of lipid peroxidation, was increased. Exposure to 2,4,5-T progressively increased tau phosphorylation. A similar, though less pronounced, effect was seen with 2,4-D. Both herbicides significantly elevated amyloid precursor protein (APP) and  $\text{A}\beta$  levels. Finally, increased choline acetyltransferase (ChAT) and decreased AChE expression by the herbicides altered cholinergic function significantly [117]. In TCDD-treated human neuroblastoma cells, transcriptional (binding to xenobiotic response elements, crosstalk with other transcription factors) and post-transcriptional (microRNA, mRNA stability, alternate splicing) regulatory mechanisms participate in AhR-mediated dysregulation of AChE [118].

In a recent study, the effect of 2,4-D, 2,4,5-T, or both (D+T) was evaluated on AD biomarker expression using rat brain slices [119]. Histopathological changes included degeneration of neurons, white matter, and endothelial cells, as well as molecular/biochemical abnormalities that indicated cytotoxic injury, lipid peroxidation, DNA damage, and increased immunoreactivity to GFAP, activated Caspase 3, phosphorylated tau,  $\text{A}\beta$ , and ChAT. The combined effect (D+T) was more pronounced than the single component [119]. This study suggested that AO exposures cause molecular and metabolic alterations in frontal lobe brain tissue that resemble diseases linked to early-stage AD-type neurodegeneration. Also, AD patients exposed to AO had significantly greater levels of plasma  $\text{A}\beta$  oligomer than the control and AD patients without AO exposure, suggesting that AO might affect the AD pathology via a different mechanism [120].

Dioxin exposure disrupts granule cell neurogenesis [121] and might lead to dementia and AD through interconnected pathways. It strongly activates the aryl hydrocarbon receptor (AhR), which leads to widespread changes in gene expression [122]. This activation results in the induction of oxidative stress and neuroinflammation, demyelination [123], increased production of neurofilaments, decreased AChE [124], and several other genetic/epigenetic changes [125]. Studies have shown white matter changes in the brain after dioxin exposure as seen by reduced fractional anisotropy (FA) in the cingulum hippocampal region (CGH) and the right uncinate fasciculus (UNC) [126]. These regions are crucial for memory, cognition, and emotional processing; hence, dioxin exposure largely results in mild cognitive impairment (MCI) and AD.

Aging itself poses a significant risk for AD, marked by increased oxidative stress, dysfunctional mitochondria, weak detoxification mechanisms, and reduced neuroplasticity. These age-related vulnerabilities can act synergistically with environmental toxins such as dioxin and AO components, enhancing tau hyperphosphorylation, amyloid build-up, and

synaptic dysfunction, accelerating the AD-like pathology. Thus, aging is a key modifier of chemical-induced AD phenotypes and should be considered an interacting risk factor in environmental neurotoxicity models [127].

### 3.3.3. Mechanism of Neurodegeneration in PD

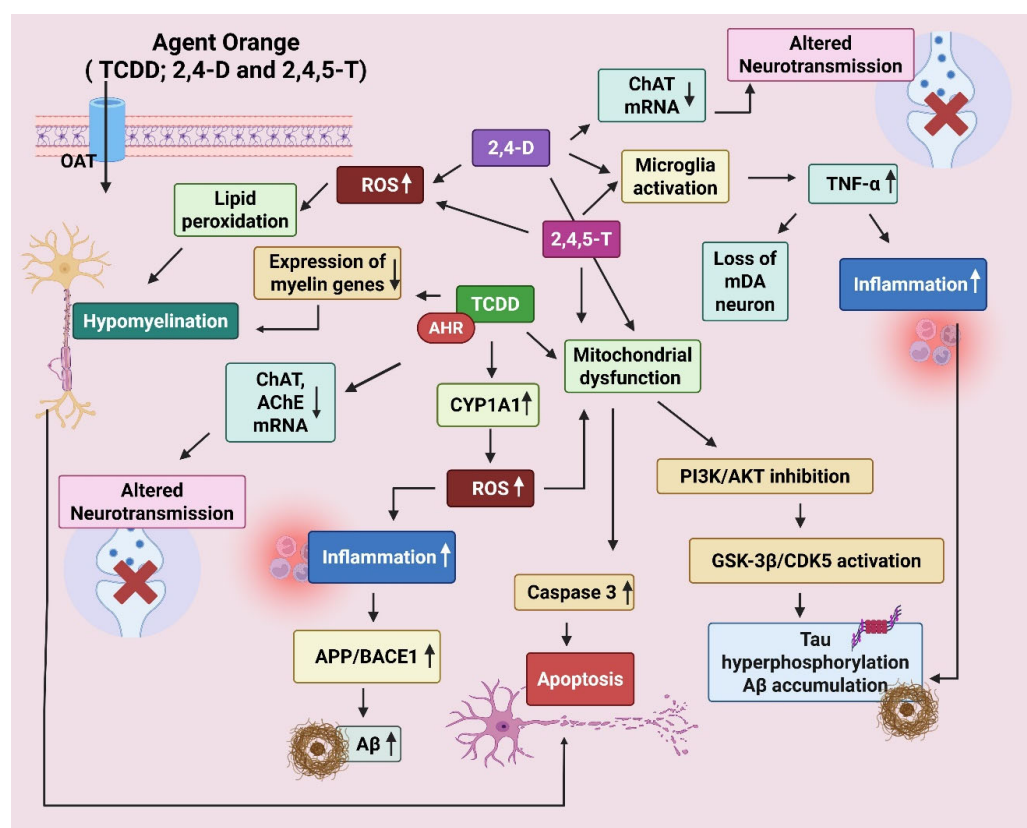
To elucidate the effects of AO exposure on PD, the clinical characteristics and 18F-N-(3-fluoropropyl)-2 $\beta$ -carboxymethoxy-3 $\beta$ -(4-iodophenyl) nortropane (FP-CIT) positron emission tomography (PET) uptake between patients with AO exposure and patients with no exposure were investigated [111] though it did not account for lifestyle factors. The AO-exposure significantly increased stiffness and tremors and decreased facial expression scores in the patients than the control. All basal ganglia areas displayed reduced 18F-FP-CIT uptake and a higher asymmetry index of anterior and posterior putamen in patients exposed to AO [111]. This finding suggests the possibility of a different pathophysiology of PD in patients exposed to AO from idiopathic PD. The PD incidence was 1.68 times greater when AO exposure and drug-induced parkinsonism (DIP)-risk drug usage were combined, and 1.31 times higher when AO exposure was used alone. The findings imply that individuals with AO exposure should be closely monitored, especially when on DIP-risk medications [128].

Previously, Bortolozzi et al. [129] studied the effect of 2,4-D in rats and observed a reduction in serotonin, dopamine, and their metabolites in the brain. Such disruptions can worsen PD pathology by contributing to both motor (bradykinesia and rigidity) and non-motor (depression and fatigue) features [130]. The 2,4-D's neurotoxic effects can be related to the dopaminergic system via microglial activation [131]. It also influenced monoamine (MAO) activity in adult rats' basal ganglia [132] and caused reversible changes in dopamine (D2-type) receptors [129,133]. Moreover, chronic exposure to 2,4-D affected object recognition memory in rats [134,135]. Of special interest is that 2,4-D reduces levels of white matter sulfatides that are linked to cognitive-motor dysfunction [136]. Additionally, ceramide conversion to glucosyl- or galactosylceramide is the intermediate process in sphingomyelin biosynthesis, which is inhibited by 2,4-D. Sphingomyelin has a critical role in the maintenance of the plasma membrane and myelin [136]. Higher doses and longer exposure durations disrupted brain lipid expression by lowering gangliosides, needed for inter-neuronal communication and connectivity [137]. Alterations in lipid expression, particularly of sulfatides and gangliosides, compromise myelin stability and neuronal signaling, both crucial for motor regulation. In aged rats, 2,4-D reduced locomotion and rearing and enhanced immobility in the open-field test, effects that corresponded with reduced striatal content of serotonin. These effects were reversed by treatment with 5-hydroxytryptophan (5-HTP), a precursor to serotonin, improving locomotion and rearing frequencies and diminishing immobility period [135], suggesting serotonergic restoration alleviated some motor impairments.

In the Agricultural Health Study (AHS) cohort, incident PD and the use of various pesticides, including 2,4,5-T, were studied. The results indicated that 2,4,5-T increased PD risk (Hazard ratio [HR]: 1.57, 95% confidence interval [CI]: 1.21–2.04) [138]. These findings were consistent with the earlier AHS-wide analysis based on 78 self-reported incident PD cases [139]. A case–control study reported that PD risk was tripled in a person exposed to the 2,4-D (OR: 2.59; 1.03–6.48), compared to no exposure [140].

The mechanism of neurodegeneration by AO and its components has been illustrated below (Figure 4).





**Figure 4.** Mechanism of neurodegeneration shown by Agent Orange (AO). AO is a cocktail of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), 2,4-Dichlorophenoxyacetic acid (2,4-D), and 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T). The chemicals enter the brain through organic anion transporters (OATs). TCDD disrupts oligodendrocyte development via aryl hydrocarbon receptor (AhR) activation. It decreases the expression of myelin-producing genes, resulting in hypomyelination. It also reduces choline acetyltransferase (ChAT) and Acetylcholinesterase (AChE) expression via AhR and cytokine-mediated signaling. TCDD forms DNA adducts via AhR-CYP1A1, resulting in oxidative damage (ROS). 2,4-D/2,4,5-T leads to mitochondrial dysfunction, caspase-3 activation, and apoptosis. Increase APP (amyloid precursor protein) and  $\beta$ -secretase (BACE1), enhance amyloid beta ( $A\beta$ ) production. Tau phosphorylation is promoted by activation of GSK-3 $\beta$  (glycogen synthase kinase 3 $\beta$ ) and CDK5 (cyclin-dependent kinase 5). TCDD-induced oxidative stress and cytokines can activate GSK-3 $\beta$  via inhibition of the PI3K/Akt pathway. Created by [BioRender.com](#).

### 3.4. Ammonium Chloride

Ammonium chloride ( $\text{NH}_4\text{Cl}$ ) is commercially used as a fertilizer to improve soil structure and provide nitrogen to plants. It can also be used to make the soil more acidic, which is beneficial for plants thriving in acidic soil. When used selectively, it can serve as a weed-control tool. Excess ammonium ions cause chlorosis, leaf burn, and stunted growth, thereby killing the weed [141]. Sometimes it is mixed with glyphosate or other herbicides for a better effect. Nearly 90% of  $\text{NH}_4\text{Cl}$  is used in the production of various compound fertilizers. Its overuse affects soil health by increasing acidity and also contributes to water pollution. It can enter the human body through inhalation, ingestion, and skin contact [142]. Once inside the body, it dissociates into ammonium ( $\text{NH}_4^+$ ) and chloride ( $\text{Cl}^-$ ) ions. The ammonium ion is converted into urea in the liver and excreted through the kidneys in urine. When taken in large amounts, it can lead to a variety of health issues like asthma, gastritis, stomach ulcers, dermatitis, and renal toxicity [143].

### 3.4.1. BBB Permeability

The systemic administration of  $\text{NH}_4\text{Cl}$  leads to the formation of ammonia ( $\text{NH}_3$ ), which can readily cross the BBB. At physiological pH ( $\sim 7.4$ ), the major fraction of ammonia (99%) appears as  $\text{NH}_4^+$ , and the rest appears as  $\text{NH}_3$ . Early tracer studies suggested that from plasma, over 20% of ammonia is transported as  $\text{NH}_4^+$  to the brain [144], while in other locations (astrocytes) protein-mediated transport of  $\text{NH}_4^+$  was noticed. To a certain extent,  $\text{NH}_4^+$  can compete with  $\text{K}^+$  and use  $\text{K}^+$  transporting proteins for the movement [144]. Other findings indicated the importance of the blood pH gradient for the forward flux of ammonia from the blood into the brain [145]. It can also influence ion channels, glutamine transporters, vacuolar-type  $\text{H}^+$ -ATPase (V-ATPase), and aquaporins (AQP-4), contributing to neurotoxicity, excitotoxicity, and cerebral edema [146–148]. These alterations lead to excitotoxicity by hindering astrocytic glutamate absorption and enhancing NMDA receptor overactivation, resulting in calcium overload, oxidative stress, and neuronal injury [149,150]. The main signs of this toxicity involve elevated intracellular  $\text{Ca}^{2+}$ , mitochondrial impairment, and increased ROS [150]. Severe BBB dysfunction is characterized by the loss of tight junction proteins (e.g., claudin-5), enhanced permeability due to MMP-9 activation, and astrocyte swelling [151]. Astrocyte swelling leads to severe inflammation due to the release of several pro-inflammatory cytokines, including  $\text{TNF-}\alpha$ ,  $\text{IL-1}\beta$ , and  $\text{IL-6}$  [152]. Thus, high levels of ammonia are neurotoxic and can cause severe BBB dysfunction, mitochondrial damage, neuroinflammation, and cognitive decline [153,154].

### 3.4.2. Mechanism of Synaptic Dysfunction

Synaptic dysfunction is a common hallmark of both AD and PD, and  $\text{NH}_4\text{Cl}$  has been widely used to model certain aspects of this pathology. Acute exposure to  $\text{NH}_4\text{Cl}$  (5 mM) has been shown to reversibly decrease excitatory synaptic transmission at the CA3–CA1 synapses in the mouse organotypic hippocampal coinciding with depolarization of astrocytes and altered astrocytic passive membrane properties, but without affecting CA1 neuronal membranes. Crucially, the inhibition of astrocytic glutamine synthetase prevents this synaptic suppression, highlighting the key role of astrocyte metabolism in maintaining neurotransmission [146]. These acute effects, largely attributed to  $\text{NH}_4\text{Cl}$ -induced intracellular alkalization, disrupt ion gradients and promote transient synaptic vesicle (SV) release [155,156]. While such changes may not directly drive Parkinsonian degeneration, prolonged dysregulation of vesicle trafficking and  $\alpha$ -synuclein homeostasis has been implicated in dopaminergic neuron vulnerability in PD [157,158]. A study documented that  $\text{NH}_4\text{Cl}$  changed the passive membrane properties of astrocytes, suggesting that the altered astrocytic function affects synaptic transmission [146]. In parallel, earlier studies using CA1 pyramidal neurons in acute rat hippocampal slices have demonstrated that low concentrations of  $\text{NH}_4\text{Cl}$  (1–4 mM) depolarized the neurons by  $\sim 15$  mV and severely impaired synaptic potentials, with recovery times of 10–15 min after  $\text{NH}_4\text{Cl}$  washout [159].

As discussed above, these acute effects are largely attributed to  $\text{NH}_4\text{Cl}$ -mediated intracellular alkalization, which disrupts ion gradients, leads to membrane depolarization, and triggers intracellular calcium overload, ultimately interfering with synaptic vesicle release and pH-sensitive signaling [155]. Elevated ammonia levels can activate astrocytes and microglia, leading to the release of inflammatory cytokines and promoting neuroinflammation, which may contribute to chronic neuropathology [160]. While these findings outline early astrocyte- and neuron-driven dysfunction, the long-term or chronic effects of  $\text{NH}_4\text{Cl}$  remain poorly characterized.

### 3.4.3. Mechanism of Neurodegeneration in AD

Earlier research has shown that  $\text{NH}_4\text{Cl}$  exposure induced mitochondrial permeability transition (MPT), a mechanism related to mitochondrial dysfunction and often brought on by oxidative stress [161]. Increased ammonia levels raised mature APP in astrocytes, elevating  $\text{A}\beta$  production. This resulted from the increased endocytosis of APP into the endoplasmic reticulum, where BACE1 and  $\gamma$ -secretase enzymes produce  $\text{A}\beta_{42}$  [162].  $\text{A}\beta$  aggregates interact with glutamatergic neurotransmission, which weakens excitatory synaptic plasticity, resulting in cognitive decline [163]. Significant microglial activation, neuroinflammation, and cell loss were observed in the astrocyte-microglia co-culture model after  $\text{NH}_4\text{Cl}$  incubation [164]. Autophagy and lysosomal pathology are inextricably linked in AD as the autophagy-lysosomal pathway (ALP) helps in eliminating misfolded proteins and other cellular waste.  $\text{NH}_4\text{Cl}$  is a lysosome inhibitor that reduces autophagic flux by increasing the level of misfolded proteins, mitochondrial stress, and neuronal loss [165]. Disruption of autophagic flux leads to toxic protein accumulation and neuronal damage, which accelerates AD progression.

### 3.4.4. Mechanism of Neurodegeneration in PD

$\text{NH}_4\text{Cl}$  inhibited lysosome-mediated degradation, resulting in the cytosolic buildup of  $\alpha$ -synuclein and myocyte enhancer factor 2D (MEF2D) proteins in a human dopaminergic neuroblastoma SH-SY5Y cell line. It lowered MEF2D expression in the nucleus, consequently diminishing its protective role against mitochondrial dysfunction and oxidative stress [166]. In an earlier study,  $\text{NH}_4\text{Cl}$  (16 mM) excessively stimulated acid-sensitive ion channels (ASICs) in dopamine neurons of the midbrain. The depolarization and continuous firing of action potentials may lead to neuronal dysfunction or injury, as in PD [167]. Cultured astrocytes exposed to ammonium exhibited impaired function of the 5-hydroxytryptamine receptor 2B (5-HT<sub>2B</sub>) as evidenced by a loss of 5-HT-induced  $\text{Ca}^{2+}$  signaling and ERK1/2 phosphorylation. Elevated ammonium also increases the activity of the RNA-editing enzyme, adenosine deaminase acting on RNA 2 (ADAR2), resulting in aberrant RNA editing of 5-HT<sub>2B</sub> mRNA contributing to astrocytic dysfunction [168]. Given the interaction of 5-HT<sub>2B</sub> with dopaminergic neurons, such dysregulation might influence motor control, as seen in PD.

The main events in the neurodegeneration caused by  $\text{NH}_4\text{Cl}$  have been presented in Figure 5.

While ammonium chloride triggers molecular and neuronal changes resembling AD and PD in lab studies, there is no epidemiological evidence in human populations to support it as a risk factor. Therefore, more studies on human populations are needed in this direction.

Below is a comparative table (Table 1) summarizing key characteristics of common gardening chemicals concerning their chemical nature, molecular weight, routes of human exposure, transport across the BBB, mitochondrial entry mechanisms, and their modes of action in AD and PD pathogenesis.

**Table 1.** Mode of action of some common gardening chemicals in AD and PD.

Chemical	Disease	Study	Dose/Treatment	Effect	Mechanism	Refs.
Paraquat	AD	APP/PS1 mice	10 mg/kg; i.p./3 weeks	Cognition impairment, elevated A $\beta$ levels, NLRP3 inflammasome activation	Oxidative stress, Inflammation	[48]
		APP transgenic mice	10 mg/kg; i.p./4 weeks	Impaired associative learning and memory, and increased A $\beta$ levels	Oxidative stress	[47]
		C57BL/6J mice; isolated NPCs	40 to 120 $\mu$ M	Wnt/ $\beta$ -catenin signaling pathway inhibition; Reduced cellular $\beta$ -catenin, p-GSK-3 $\beta$ , and cyclin-D1 and increased Bax/Bcl2	Oxidative stress	[49]
		C57BL/6J Mice	1.25 mg/kg; i.p./3 weeks	Negatively affected adult hippocampal neurogenesis and cognitive function; Reduced AKT phosphorylation	Oxidative stress, Inflammation	[52]
		hNPCs	100 $\mu$ M	Downregulated Wnt signaling pathway via miRNA in hNPCs	Oxidative stress, decreased activity of glutamate receptors	[50]
	PD	C57BL/6 Mice	10 mg/mL/oral/4 months	Decreased SOD, GSH-PX; Increased MDA and GSSG; Decreased number of TH positive neurons and expression of DAT	Oxidative stress	[54,169]
		Human neuroblastoma SK-N-MC cell line	100–500 $\mu$ M	Trx1 oxidation; Activation of JNK and caspase 3; Death of the dopaminergic neurons	Oxidative stress, Apoptosis	[170]
		C57BL/6 Mice	10 mg/kg/i.p./once a week/3 consecutive weeks	Increased $\alpha$ -synuclein production and aggregation	Oxidative stress, Inflammation	[58]
		C57BL/6 Mice; Rat dopaminergic neural cell line N27	10 mg/kg/i.p./once/every 3 days	Increased Nox1	Oxidative stress	[60]
	AD/PD	Wistar rats	10 mg/kg/2 mL/i.p./once a week/37 weeks	Altered levels of GSK-3 $\beta$ in the midbrain and striatum	Defective signaling pathway	[64]
		Sprague Dawley rats; PHBME cells	30 mg/kg/i.p./twice per 3 weeks; 80 $\mu$ M	Over-activated PI3K/AKT signaling; Increased IL-6 production; BBB dysfunction	Oxidative stress, Inflammation	[55]
		C57BL/6J mice; MSC80 cell line	10–30 mg/kg/i.p./1 week; 100 $\mu$ M	Demyelination	Oxidative stress, Inflammation	[44,46]

Table 1. Cont.

Chemical	Disease	Study	Dose/Treatment	Effect	Mechanism	Refs.
Glyphosate	AD	C57BL/6J mice; APP/PS1 primary cortical neurons	125–500 mg/kg/oral gavage/14 days	Elevated TNF $\alpha$ and soluble A $\beta$ <sub>40–42</sub> ; Cytotoxicity; Disrupted transcriptome	Inflammation	[77]
		3xTg-AD mice	50 or 500 mg/kg daily/13 weeks, followed by a 6-month recovery period	Elevated A $\beta$ and tau pathology and worsening spatial cognition after recovery; Increased inflammatory cytokines	Inflammation	[83]
		Wistar rats	0.38% orally during pregnancy and lactation (till 15-day-old); Hippocampal slices	NMDA receptor overstimulation; Mitochondrial dysfunction, Ca <sup>2+</sup> -mediated neuronal damage; Activation of ERK and CaMKII	Glutamatergic excitotoxicity and oxidative damage	[81]
		Wistar rats	400 mg/kg/oral/single dose	Increased excitatory amino acids	Excitotoxicity	[82]
	PD	C57BL/6 mice	10 mg/kg/14 days	Dopaminergic neurotoxicity in the striatum and SNr	Oxidative damage	[87]
		Wistar rats	0.36% at gestational day 5 (GD5) and continually up to postnatal day 15 (PND15) or up to postnatal day 60 (PND60)	NMDA receptor activation, impairment of cholinergic transmission; Astrocyte dysfunction; ERK1/2 overactivation; Decreased NF- $\kappa$ B phosphorylation	Glutamatergic excitotoxicity and oxidative damage	[80]
		Neuronal-differentiated PC12 cells	10–40 mM	Activated autophagy and apoptotic pathways	Apoptotic and autophagic cell death	[90]
	AD/PD	Sprague Dawley albino rats; Hippocampal slices	16.9 mg/kg/i.p.; 1 $\mu$ M and 100 $\mu$ M	Inhibited LTP and learning	Inflammation	[96]



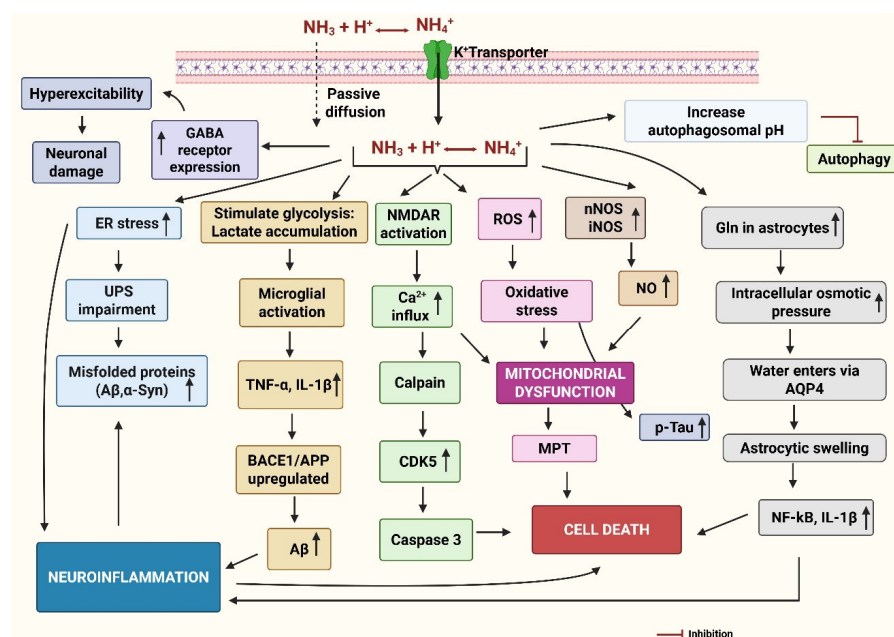
Table 1. Cont.

Chemical	Disease	Study	Dose/Treatment	Effect	Mechanism	Refs.
Agent Orange/ Components	AD	Human CNS-derived neuroepithelial cells	250 µg/mL (2,4-D and 2,4,5-T)	Increased Aβ, tau phosphorylation, and lipid peroxidation; Increased ChAT; Decreased AChE	Oxidative damage, Cytotoxicity	[117]
		Long-Evans rat frontal lobe slice cultures	250 µg/mL (2,4-D;2,4,5-T, or both)	Cytotoxic injury; Lipid peroxidation, DNA damage; Increased immunoreactivity to activated Caspase 3, GFAP, phosphorylated tau, Aβ, and ChAT	Oxidative damage, Cytotoxicity	[119]
		Wistar Rat	9.28 × 10 <sup>−3</sup> g per hectare (g.a.i/ha)/oral and nebulize (2,4-D)	Impairment of exploration and recognition memory	Oxidative stress	[134]
		Human neuroblastoma SK-N-SH cell line	0.1–10 nM (Dioxin)	Suppressed neuronal AChE via AhR-mediated transcriptional down-regulation	Cholinergic neurotransmission	[124]
	PD	Plasma		Higher plasma Aβ oligomer	Amyloidosis	[120]
		Patients with Agent Orange exposure	Clinical profile and FP-CIT PET findings	Lower facial expressions, tremors, and rigidity; Significantly lower caudate/putamen ratios		[111]
		C57BL/6 mice	30 µg TCDD/Kg/i.p.	AhR-mediated induction of CYP1A1; Activation of NF-κB; Selective dopaminergic neuronal damage	Oxidative stress, Inflammation	[121]
		Wistar rats	70 mg/kg/day of 2,4-D from gestation day (GD) 16 to postpartum day 23	Adverse neuronal changes (in D2 receptors, tyrosine hydroxylase, and dopamine beta-hydroxylase) and behavioral changes	Decreased DA neurotransmission	[129,133]
		Wistar rats	100 and 200 mg/kg/oral of 2,4-D	Behavioral changes and neurochemical parameters	Dopamine dysfunction	[135]
		Retrospective cohort study		1.31 times higher PD risk		[128]
		AHS		2,4,5-T positively associated with increased PD risk (HR: 1.57, 95%CI: 1.21–2.04)		[138]

Table 1. Cont.

Chemical	Disease	Study	Dose/Treatment	Effect	Mechanism	Refs.
Ammonium Chloride	AD	Cortical astrocytes from a rat	10 mM	Elevated APP expression; Increased A $\beta$ production	Amyloidogenesis	[162]
		Cultured astrocytes	5 mM	Mitochondrial permeability transition	Oxidative stress	[161]
		Primary rat glial co-cultures of astrocytes	20 mM	Microglial activation; Cell death	Inflammation	[164]
		Rat hippocampal cultures	5–50 mM	Increased [Ca <sup>2+</sup> ] <sub>i</sub>	Membrane depolarization	[155]
	PD	Human dopaminergic neuroblastoma SH-SY5Y cell line	10 mM	Increased accumulation of $\alpha$ -synuclein and MEF2D protein	Dysfunctional lysosome-mediated degradation	[166]
		Mouse midbrain dopamine neurons	16 mM	ASICs' gating and desensitization	Neuronal dysfunction	[167]
		Male CD-1 mice; Cultured mouse astrocytes	33 units/kg/i.p./3 days; 3 mM ammonia for 3 days	Increased ADAR2; Loss of 5-HT induced Ca <sup>2+</sup> signaling and ERK1/2 phosphorylation		[168]
	AD/PD	Entorhino-hippocampal tissue cultures of mice	5 mM	Decreased spontaneous excitatory synaptic activity	Synaptic transmission dysregulation	[146]

Abbreviations. A $\beta$ : Amyloid-beta; AChE: Acetylcholinesterase; AD: Alzheimer's disease; ADAR2: Adenosine Deaminase Acting on RNA 2; AHC: Agricultural Health Study; AhR: Aryl hydrocarbon receptor; AKT: Protein kinase B; APP: Amyloid precursor protein; ASIC: Acid-sensitive ion channels; Bax/Bcl2: BCL2-associated X/B-cell lymphoma 2; Ca<sup>2+</sup>: Calcium ion; CaMKII: Ca<sup>2+</sup>/calmodulin-dependent protein kinase II; ChAT: Choline acetyltransferase; CI: Confidence interval; 2,4-D: 2,4-Dichlorophenoxyacetic acid; DAT: Dopamine transporter; ERK1/2: Extracellular signal-regulated kinases; FP-CIT PET: FN-(3-fluoropropyl)-2 $\beta$ -carbon ethoxy-3 $\beta$ -(4-iodophenyl) nortropane positron emission tomography; FAP: Glial fibrillary acidic protein; GSH-PX: Glutathione peroxidase; GSSG: Oxidized glutathione; GSK-3 $\beta$ : Glycogen synthase kinase-3 beta; hNPCs: Human Neural Progenitor Cells; HR: Hazard ratio; 5-HT: 5-Hydroxytryptamine receptor 2B; [Ca<sup>2+</sup>]<sub>i</sub>: Intracellular calcium concentration; i.p.: Intraperitoneal; JNK: c-Jun N-terminal kinases; MDA: Malondialdehyde; MEF2D: Myocyte enhancer factor 2D; MSC80: Mouse Schwann cell line; NF- $\kappa$ B: Nuclear factor kappa light-chain enhancer of activated B cells; NMDA: N-methyl-D-aspartate; NLRP3: NOD-like receptor family pyrin domain containing 3; NOX1: NADPH oxidase 1; NPCs: Neuronal progenitor cells; PD: Parkinson's Disease; PHBME: Primary human brain microvascular endothelial cells; SNr: Substantia nigra; SOD: Superoxide dismutase; 2,4,5-T: 2,4,5-Trichlorophenoxyacetic acid; TH: Tyrosine hydroxylase; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; Trx1: Thioredoxin; Wnt: Wingless-type Family Member.



**Figure 5.** The mechanism of neurodegeneration by ammonia. Ammonia is present as  $\text{NH}_3$  at physiological pH, which readily diffuses in the brain and extracellular space.  $\text{NH}_4^+$  is transported via potassium ( $\text{K}^+$ ) transporters. The oxidative stress activates the microglia, resulting in the release of pro-inflammatory cytokines, increased amyloid precursor protein (APP) processing and beta-secretase (BACE1) activity to generate amyloid-beta ( $\text{A}\beta$ ), increased phosphorylation of tau, and aggregation of alpha-synuclein ( $\alpha\text{-Syn}$ ). Elevated ammonia generates oxidative stress by producing reactive oxygen species (ROS) and generating nitric oxide (NO) by neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS). ROS and excessive NO are the key sources of mitochondrial dysfunction, induction of mitochondrial permeability transition (MPT), and impaired energy metabolism both in neurons and astrocytes. Activation of NMDA receptors leads to the opening of the ion channel, allowing increased  $\text{Ca}^{2+}$  ions into the post-synaptic neuron, causing mitochondrial ROS, and activating calpain, which can induce neuronal death directly. Activated calpain also activates cyclin-dependent kinase (CDK5) and caspase3, causing neuronal death. Ammonia can increase the rate of cerebral glucose utilization and oxygen consumption, leading to increased lactate release from the brain, particularly in the astrocytes. Elevated lactate can activate microglia and release inflammatory cytokines like tumor necrosis factor-alpha ( $\text{TNF-}\alpha$ ) and Interleukin-1 beta ( $\text{IL-1}\beta$ ). ER stress can impair the unfolded protein response (UPR), causing protein misfolding and accumulation, contributing to inflammation. Excess ammonia increases levels of glutamine (Gln) in the astrocytes, which eventually leads to astrocytic swelling due to influx of water through aquaporin (AQP4) channels and osmotic lysis. Ammonia can increase the expression of gamma-aminobutyric acid (GABA) receptors, further contributing to enhanced GABAergic transmission. This can contribute to neurodegeneration by increasing inhibitory neurotransmission, disrupting energy metabolism, and promoting inflammation. Ammonia also increases the autophagosome pH and inhibits autophagy. Created by [Biorender.com](#).

#### 4. Effect of Common Gardening Chemicals on Gut–Brain-Axis

The gut–brain axis represents a complex network of communication systems between the gut and the brain, comprising the enteric nervous system, autonomic nervous system, and the immune system. Disruptions in the gut–brain axis can impact brain health and contribute to neurodegenerative processes. Gut dysbiosis can disrupt the production of neurotransmitters like serotonin, which plays a role in mood and cognitive function. In addition, gut dysbiosis can trigger inflammation in the gut, which can then spread to the brain via this axis, contributing to neuroinflammation [171].

Exposure to PQ and glyphosate has been linked to disruptions in the gut microbiota, which may contribute to the development of neurodegenerative diseases such as AD and

PD. Glyphosate exerts an inhibitory effect on microbial EPSP synthase, mainly affecting beneficial bacteria. On the contrary, *Clostridium* and *Salmonella* are resistant to it, suggesting the role of glyphosate in causing dysbiosis [148]. The overgrowth of bacteria such as *Clostridia* generates high levels of toxic metabolites in the brain, contributing to the development of neurological deviations. Glyphosate's disruption of manganese homeostasis selectively affects *Lactobacillus* and can lead to several disorders, such as PD [149]. Although the mechanism remains uncertain, it could be correlated to dysbiosis. Intestinal dysbiosis in PD patients causes an immunological stimulation and may contribute to  $\alpha$ -synuclein misfolding [150]. If dysbiosis results in endotoxemia (leaky gut), infiltrated bacterial by-products such as lipopolysaccharides (LPS) could initiate inflammatory pathways [99]. Human gut dysbiosis is also linked to AD etiology in animals exposed to Gly, where there is an imbalance in the intestinal bacterial composition. AD patients showed a reduced level of both Firmicutes and Bifidobacteria and an increase in Bacteroidetes [172,173]. *Pseudomonas* break down glyphosate to phosphate and carbon (for amino acid synthesis) and formaldehyde (toxic by-product) [174], and low levels of formaldehyde can induce amyloid-like misfolding of tau protein in neurons, forming protein aggregates similar to those observed in association with AD [175]. Moreover, a correlation was noted between an abundance of *Escherichia* and *Shigella* in the guts of AD individuals and brain amyloidosis and behavioral impairment [152]. Additionally, elevated levels of LPS have been found in the brain and plasma of patients with AD [153]. Lower levels of sulfate in the brain have been associated with neurological diseases, especially AD and PD [176]. Glyphosate might block the movement of sulfate from the gut to the liver and also interfere with the body's ability to make sulfate in blood vessels and blood cells. Over time, this could cause a serious lack of sulfate in many parts of the body [177,178]. Similarly, PQ exposure in a mouse model resulted in gut dysfunction by disrupting the gut microbiota, damaging the intestinal epithelial barrier, and activating the inflammatory cascade. Additionally, the presence of  $\alpha$ -synuclein aggregates in the colon and midbrain, and the altered metabolism of short-chain fatty acids (SCFAs), was reported [179]. This suggests that pathological  $\alpha$ -syn and SCFAs from the gut may be significant components of the gut-brain axis. Exposure to 2,4-D and dioxin-like compounds shifted the Firmicutes-to-Bacteroidetes ratio to a dysbiosis one and affected the metabolism of urea, amino acids, and carbohydrates [180,181] and caused a systematic deficiency of essential vitamins [182]. However, there are not any research studies evaluating their impact on gut microbiota and resultant effects on the gut-brain axis in the context of AD and PD. While direct evidence linking ammonium chloride to AD or PD via the gut-brain axis is limited, the neurotoxic effects of its metabolite, ammonia, suggest a potential indirect role [183]. Further research is needed to fully understand these connections and their implications for neurodegenerative diseases.

## 5. Regulatory Overview of the Selected Gardening Chemicals

According to the present legal status and international regulatory frameworks concerning the compounds, PQ has been banned in over 70 countries due to health risks, yet it remains in use in the United States (US) [184]. A critical review based on the studies published between 2006 and 2021 found no conclusive evidence between PQ exposure and PD [69]. In its 2021 interim decision, the Environmental Protection Agency (EPA) announced "insufficient evidence to link PQ exposure to PD", and as of February 2025, the US EPA has not banned the herbicide PQ [185]. Nonetheless, recent studies have suggested an association between PQ exposure and an increased risk of PD, promoting renewed scrutiny and calls for regulatory action. The forthcoming EPA report is expected to offer a revised assessment of the potential health risks linked to PQ [186].

Based on early toxicological evaluations, the US EPA classified glyphosate in the lowest toxicity category (category IV), considering it essentially non-toxic and non-irritating [187]. However, growing evidence indicates that glyphosate exhibits cytotoxic and genotoxic properties, promotes oxidative stress, and may be carcinogenic. In light of these concerns, the International Agency for Research on Cancer (IARC) classified glyphosate as “probably carcinogenic to humans” [188]. In 2020, the EPA recommended updating product labels to reduce harm, including clearer spray drift warnings and consistent labeling. However, after a court challenge in 2022, the EPA withdrew these recommendations [189]. Meanwhile, Bayer announced it would stop selling glyphosate-based herbicides for home use in the U.S. by 2023 due to mounting lawsuits [190]. Despite this, glyphosate products remain on the market with no label changes. In 2024, the EPA rejected a petition to ban glyphosate, stating there was no new evidence of increased toxicity [191]. The European Chemicals Agency (ECHA) determined that glyphosate is not a carcinogen, yet it can result in significant eye injury and is harmful to aquatic organisms. Also, the European Food Safety Authority (EFSA) found “no critical areas of concern” for human, animal, and environmental health from the use of glyphosate in agriculture [192]. As a result, in 2023, the European Commission (EC) approved the renewal of glyphosate’s authorization for an additional ten years [193].

While the original AO mixture has been banned, its components, especially 2,4-D, are still used. Global health and safety agencies, including the World Health Organization (WHO), EC, U.S. EPA, Health Canada, and New Zealand authorities, have reviewed 2,4-D and have found it noncarcinogenic in animal studies [194]. Regulatory oversight of 2,4-D varies globally, as it is banned in some countries due to potential health and environmental effects [194], but the U.S. EPA allows its continued use with certain restrictions [195]. Lastly, the use of ammonium chloride is regulated under general chemical safety and environmental protection laws [196]. It is not presently categorized as a neurotoxic chemical, but it is regulated by occupational exposure limits and assessments of environmental hazards [197].

## 6. Conclusions

In conclusion, there is growing evidence linking common gardening chemicals to the development of neurodegenerative disorders like AD and PD. Despite being useful for removing weeds and encouraging plant growth, chemicals such as PQ, glyphosate, AO, and  $\text{NH}_4\text{Cl}$  can be extremely neurotoxic if overused or improperly handled. These chemicals can remain in soil, water, and plant matter, resulting in pollution across various trophic levels. When they enter the food chain, they can cause the buildup of toxic substances in higher organisms, impacting the health of wildlife as well as human populations that eat contaminated crops or livestock products. For instance, PQ and  $\text{NH}_4\text{Cl}$  infiltrate groundwater, affecting surrounding aquatic ecosystems. Traces of glyphosate were reported in several foods (cereals, honey, meat, and milk) in quantities that could lead to long-term health hazards, especially with prolonged exposure. Likewise, dioxins are very stable and often accumulate within the food chain, mainly in fatty tissues. These chemicals are associated with a higher risk of neurodegenerative diseases, despite some controversial findings. The mechanism of action involves glutamate excitotoxicity, dopaminergic pathway disruption, oxidative stress, mitochondrial dysfunction, neuroinflammation, and synaptic dysfunction, crucial in the pathophysiology of AD and PD. Even with increasing evidence connecting these herbicides to neurodegenerative disorders, regulatory bodies like the U.S. EPA have not consistently prohibited them. Ongoing discussion surrounds their safety, underscoring the necessity for more definitive epidemiological and mechanistic research. These incidents highlight the need for stricter laws and environmentally friendly agricultural practices to



lessen the effects of these toxins on the environment and food supply. In addition, regulatory and policy recommendations should be strengthened and include (i) reclassification of neurotoxic herbicides under stricter hazard categories, (ii) mandatory neurotoxicity testing as part of pesticide registration, (iii) labeling requirements highlighting risks to neurological health, and (iv) phase-out plans for high-risk substances, especially in residential or gardening contexts. Also, environmental/human monitoring should be expanded to track chronic low-dose exposure and its links to neurodegeneration. Long-term research and an improved comprehension of exposure trends are crucial for guiding public health policies and minimizing the risk of neurotoxic environmental exposure. Additional research is essential to clarify the specific mechanisms of action and create preventive measures to reduce these risks.

While numerous studies highlight the acute neurotoxic effects of gardening chemicals, far less is known about their long-term impact, especially from chronic low-dose exposure. Moreover, long-term exposure may not only increase the risk of neurodegeneration but also affect reproductive health, hormone regulation, and immune function. Environmentally persistent residues of these chemicals can alter soil microbiota and reduce biodiversity, with downstream effects on human health. Notably, there are no reported epidemiological studies evaluating the association between  $\text{NH}_4\text{Cl}$  exposure and increased risk of neurodegenerative diseases, despite substantial experimental evidence. Lifestyle factors (such as physical activity, diet, smoking, and occupational exposures) and aging can significantly influence the development and progression of AD and PD. Therefore, future studies (longitudinal, case-control, and biomarker-based) that include such cofounders are strongly recommended to investigate the potential neurotoxic effects of this chemical in human populations, especially in vulnerable populations such as farmers, gardeners, and children living near treated areas.

**Author Contributions:** Conceptualization, N.S. and S.S.A.A.; writing—original draft preparation, N.S.; writing—review and editing, N.S. and S.S.A.A.; funding acquisition, S.S.A.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (Grant number RS-2023-00251396) and by the Korea Institute of Marine Science & Technology Promotion (KIMST) funded by the Ministry of Oceans and Fisheries (Grant number RS-2025-02292973).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The original contributions presented in this study are included in the article.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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