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A decade of MPTP-based zebrafish research in Parkinson's disease: toward translational understanding

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Abstract

An innovative study focused on using adult zebrafish, Danio rerio, to model human neurological diseases has demonstrated their use in pharmaceutical development and genetic disease research. Zebrafish, owing to their significant genetic similarity to humans, cost-effective maintenance, rapid reproductive cycles, and efficient embryo generation, provide a suitable model for evaluating pharmacological efficacy in a high-throughput, in vivo context. Presently, most of the research using zebrafish models for Parkinson's disease (PD) generates the condition in larval or embryonic creatures owing to the simplicity of administration, with progression through developmental stages occurring within a few days. The use of early-stage organisms constrains the applicability of zebrafish as models for adult diseases, particularly age-related neurodegenerative disorders. Recently, researchers have endeavoured to enhance the applicability of zebrafish as models for Parkinson's disease. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been identified as a prodrug that, upon injection, effectively encapsulates the biochemical pathways and symptomatology linked to Parkinson's disease. Utilising MPTP in an adult zebrafish model may facilitate breakthroughs in Parkinson's disease research. This article emphasises new research on this model, juxtaposing it with the human variant of Parkinson's disease.

Keywords: *zebrafish, Parkinsonism, animal models, neurodegeneration, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Dopamine*

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1. Introduction

Preclinical research serves as an initial phase prior to the more complex and rigorous clinical or human research [1]. Translational research functions as a conduit between preclinical and clinical research, enabling the interpretation of preclinical findings and their implementation in clinical studies [2, 3]. In preclinical research, animal models are essential for the evaluation of safety and efficacy prior to human application, particularly in the areas of drug discovery and treatment efficacy [4–6]. Throughout the years, researchers have identified a variety of animal species that are appropriate for use as models in scientific research. Chia et al. [7] provides a variety of animal examples, such as fruit flies (*Drosophila melanogaster),* zebrafish (*Danio rerio*), roundworms (*Caenorhabditis elegans*), rats (*Mus musculus* and *Rattus norvegicus*), and non-human primates. In an optimal world, animal species should be manageable, exhibit sufficient information accessibility, and possess comparative and translational potential [8]. The need to conduct most brain investigations in vitro, which is only feasible through postmortem analysis, presents significant challenges and constraints in human-based neuroscience research [9–11]. Consequently, zebrafish, fruit flies, and rodents, which exhibit substantial functional similarities to humans, offer valuable alternatives for researchers who are undertaking in-depth investigations of the nervous system. The zebrafish, also known as Danio rerio, has been employed as a model organism in a variety of brain-related investigations for the past three to four decades [12]. This species belongs to the Cyprinidae family and is a freshwater teleost. Researchers have rapidly developed methodologies for the most effective utilisation of zebrafish in neurological research [13]. The zebrafish has emerged as a prominent model for research in the disciplines of neurodegenerative, neurodevelopmental, and neuropharmacological research because of its significant neurofunctional and behavioural similarities to humans [14, 15]. Additionally, the zebrafish's neural system is well-defined, rendering it an appropriate model for the investigation of Parkinson's disease, the second most prevalent neurodegenerative disorder after Alzheimer's. This means that the zebrafish could potentially replace rodent models. The complexity of Parkinson's disease and the obstacles associated with its treatment present significant challenges for researchers, despite their extensive knowledge of its epidemiology and potential therapies [16, 17]. This review investigates the utilisation of zebrafish in neuroscience research, with particular emphasis on Parkinson's disease-related investigations.

2. Parkinson's disease

The gradual destruction of dopaminergic neurones in the substantia nigra pars compacta causes Parkinson's disease, a neurological condition characterised by movement impairment. According to the 2015 Global Burden of Disease Study, the prevalence and death rates of Parkinson's disease (PD) have significantly increased during the past 25 years, and predictions indicate that this trend may continue [18]. According to Ray Dorsey et al. [19], the overall number of people who died from PD in Malaysia and Southeast Asia in 2016 was 514 and 11,900, respectively. The

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number of PD patients worldwide has risen from 6.1 million in 2016 to over 10 million in the present day [19]. Due to the rising number of PD cases, specialists from all around the world have joined forces to carry out in-depth research on the condition.

2.1. Pathogenesis and aetiology

PD impacts the population of dopaminergic neurones in the substantia nigra pars compacta as shown in **Figure 1**. The gradual degeneration of dopamine neurones in the substantia nigra pars compacta, which is the origin of the nigrostriatal dopaminergic system, diminishes the supply of dopamine to the striatum, the brain region that is primarily responsible for facilitating voluntary movements [20, 21]. Lewy bodies (LBs), which are defined as the intracellular accumulation of α-synuclein protein, are an additional pathological characteristic of PD. This process is believed to initiate in the olfactory bulb and medulla oblongata, and it subsequently spreads to other brain regions as the disease advances [21]. Additionally, mitochondrial abnormalities within the brain have been identified in scientific investigations of PD. Individuals with PD exhibited a reduced level of mitochondrial complex I, an enzyme that is essential for the mitochondrial electron transport chain [22]. Impaired energy production is the consequence of a deficiency in this enzyme, which ultimately leads to the demise of DA neurones [23] (**Figure 1**).

The prevalence of the condition is substantially influenced by a variety of environmental and genetic factors, as evidenced by comprehensive clinical and non-clinical PD studies. The most recognised aetiology and primary contributing factor associated with the development of PD is an extended lifespan [24, 25]. Approximately 96% of people with PD diagnoses are over the age of 60 [26]. Researchers have identified numerous anthropogenic substances that increase the probability of a person developing symptoms of PD. These substances comprise the synthetic opioid 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [27] and the herbicides paraquat and rotenone [28]. Environmental variables and genetic factors both contribute to the prevalence of PD. Autosomal dominant or recessive variants of PD can result from mutations in specific genes. Mutations in the *SNCA* or *LRRK2* genes result in autosomal-dominant PD, while mutations in the *PRKN* or *PINK1* genes are associated with autosomal-recessive PD [29, 30]. The search for effective therapies is further complicated by the fact that PD is classified as a multifactorial condition, as its aetiology is a combination of genetic and environmental factors.

2.2. Clinical symptoms and available treatments

PD symptoms are generally divided into two categories: motor symptoms and non-motor symptoms. Most PD symptoms are the consequence of the progressive degeneration of dopaminergic neurones; however, specific symptoms are induced by the dopaminergic medications that patients are prescribed [31, 32]. PD affects the cerebral region responsible for regulating movement. Resting tremor, bradykinesia, dyskinesia, postural instability, and muscular rigidity are the primary symptoms of Parkinson's disease [33, 34]. Non-motor symptoms are manifestations that are not associated with motor functions and affect individuals with PD. Symptoms include cognitive impairments, somnipathy, autonomic dysfunctions, and mental abnormalities, all of which significantly reduce quality of life [35, 36].

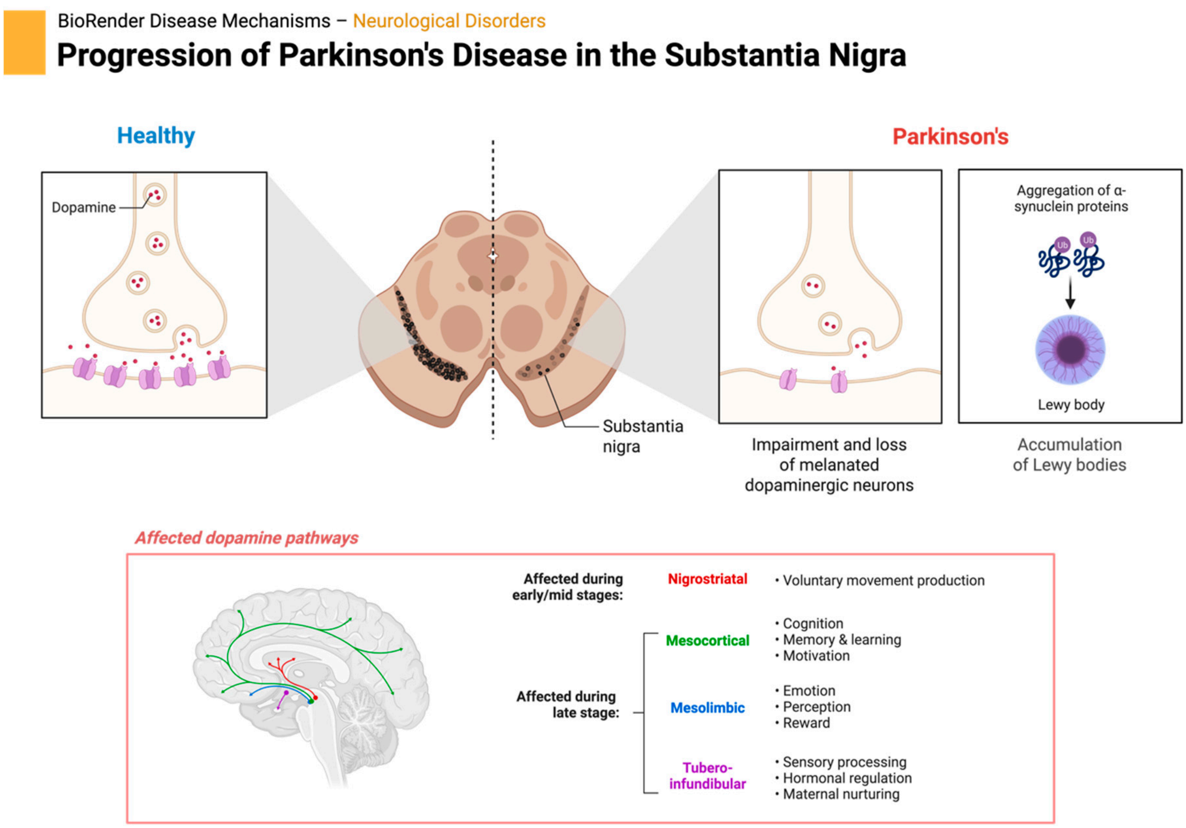

Figure 1 • Progression of PD in the substantia nigra. Created in BioRender. Younes, N. (2025) https://BioRender.com/jtibbf5.

At present, there is no medication that can completely cure PD (**Figure 2**). For more than six decades, beginning in the 1960s, symptomatic patients have received medications including levodopa, dopamine agonists, and monoamine oxidase (MAO) inhibitors to restore dopamine levels and neurotransmission in the brain, thereby improving motor functions [37, 38]. These medications slow the progression of PD while concurrently causing certain unavoidable side effects. Patients in the advanced stage of PD require higher doses of levodopa per administration; these higher doses reduce tremors but increase the likelihood of visual hallucinations and delusions [39]. Patients exhibiting insufficient responses to pharmacological treatments may opt for deep brain stimulation, a technique that utilises electrical impulses to interfere with abnormal motor functions [40]. However, like levodopa, this method may only alleviate uncontrollable tremors without targeting the fundamental issue of dopamine neurotoxicity.

2.3. Animal models of Parkinson's disease throughout decades

Researchers have developed novel approaches to gather substantial data on PD through animal investigations. The quantity of published works on animal-based PD research has increased consistently from the early 2000s to the present [41]. The classification of animal models of PD typically involves three groups: non-human primates, rodents, and non-mammalian species [7]. According to Konnova and Swanberg [42], non-human primates, including macaques, marmosets, and monkeys, provide valuable insights into PD due to their genetic and physiological similarities to humans, which differentiate them from other models. Moreover, neuroimaging studies that involve macaques provide advantages by reducing the complications and obstacles associated with human postmortem research [43]. The application of this species as a PD model is restricted by its high cost, significant time demands, substantial labour requirements, and complex ethical considerations [7, 44, 45]. Conversely, rodents have been the primary focus of investigations into PD for the past few decades [46]. In the 1960s, Flinn et al. [47] conducted the first documented investigations to employ rodent models in PD research. The rat neural system is well-characterised, and its functions are readily comparable to those of humans [48]. Rats and rodents are more cost-effective and manageable than non-human primates. Extensive research has resulted in the optimisation and standardisation of methodologies for PD evaluations in this species, utilising rodent models [49]. In addition to rodents, PD diagnostic models frequently involve non-mammalian species. In comparison to non-human primates and rodents, nematodes, fruit flies, and zebrafish provide advantages such as brief life cycles, simplicity of genetic manipulation, and reduced costs [50, 51]. Although the volume of published research utilising non-mammalian species is less extensive than those involving rodents, these studies have made substantial contributions to PD research, particularly in the exploration of molecular pathways and the screening of potential pharmaceuticals. The incorporation of data from a variety of animal species has allowed researchers to acquire significant insights into PD at the genomic, proteomic, and metabolomic levels, despite the challenges they have had to overcome as shown in **Figure 3** which illustrates the Gut-Brain axis for PD.

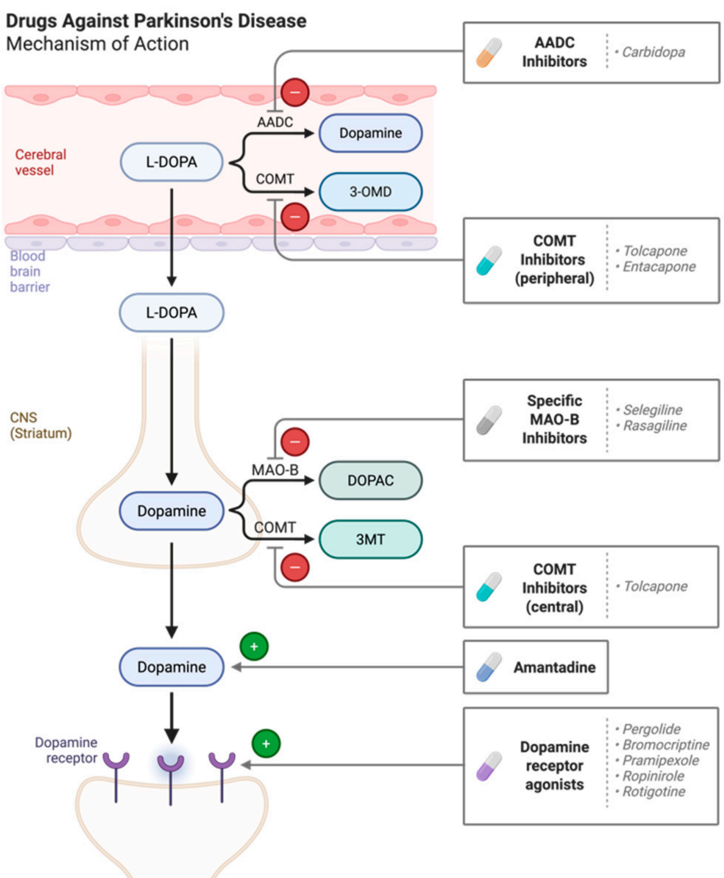

Figure 2 • Available anti-PD drugs and their mechanism of action. Created in BioRender. Younes, N. (2025) https://BioRender.com/0x0upee.

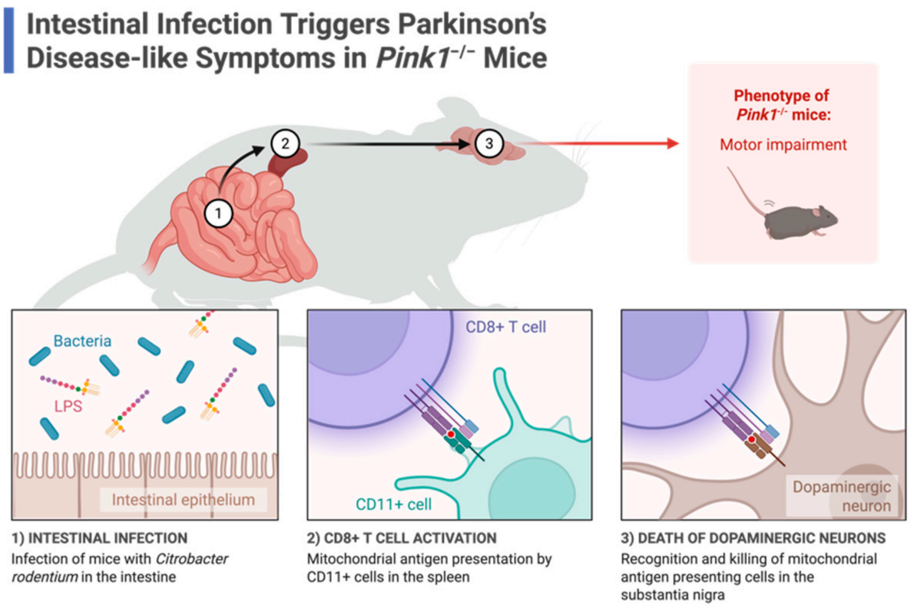

Figure 3 • This figure illustrates the mechanisms by which an intestinal infection induces Parkinson's disease-like symptoms in *Pink1* −/− mice. The absence of Pink1 leads to the activation of CD8+ T cells both peripherally and in the brain after intestinal infection, culminating in the destruction of dopaminergic neurones in the substantia nigra. Created in BioRender. Younes, N. (2025) https://BioRender.com/whvluaz.

3. Zebrafish as a model organism

3.1. Historical background

George Streisinger, a molecular scientist at the University of Oregon, initiated the use of zebrafish in research in the 1950s. Streisinger suggested that the transparent characteristics of zebrafish larvae facilitate the investigation of vertebrate neurodevelopment, a field that was previously restricted by inadequate methodologies and unsuitable animal models [52, 53]. The substantial discoveries made by Streisinger and his associates regarding neurological development have inspired other researchers to integrate zebrafish into their research. Researchers have conducted numerous studies on zebrafish since the species' introduction a decade ago, resulting in a more comprehensive comprehension of the development of the neurological system [53].

By the 1900s, standardised methodologies for their upbringing had been established, and research on zebrafish had made significant progress [54]. At the same time, genetic information became accessible through online repositories and databases [55]. The National Institutes of Health (NIH) launched the Trans-NIH Zebrafish initiative in 1998, recognising the zebrafish as a valid animal model for scientific research [56]. A variety of research disciplines, including neurodegeneration, neurodevelopment, neurobehavior, toxicity, and pharmacological discoveries, have employed zebrafish as a model organism [57]. Zebrafish are an appropriate model for the investigation of neurodegenerative diseases due to their extensive involvement in the study of the neurological system. Through gene suppression or transgenic expression of mutant genes, zebrafish models frequently replicate diseases such as Huntington's, Alzheimer's, and Parkinson's. As a result, neurodegenerative research that employs zebrafish not only provides insights into phenotypic variables but also offers insights into genotypic and molecular pathways.

PD disrupts the formation of dopaminergic neurones in the striatum and the substantia nigra pars compacta (SNpc). The posterior tuberculum of the ventral diencephalon and the ventral telencephalon are the pertinent regions in zebrafish [58, 59]. Parkinson's disease has been associated with the expression of numerous genes, such as *SNCA, PRKN, PINK1, PARK7,* and *LRRK2* (see **Table 1** for more details). According to Xi et al. [60], there are two primary categories of zebrafish models for Parkinson's disease: neurotoxin-induced models and genetic models. In zebrafish models, MPTP is the primary neurotoxin responsible for the development of Parkinson's disease. It results in the degeneration of dopaminergic neurones and a decrease in the levels of dopamine, norepinephrine, and serotonin in the brain, particularly in the posterior tuberculum of the ventral diencephalon. The motor dysfunctions detected in the MPTP-induced zebrafish model are comparable to those observed in Parkinson's disease patients [61]. 6-Hydroxydopamine (6-OHDA) is a prevalent neurotoxin that functions as an oxidative analogue of dopamine. It induces mitochondrial dysfunction, which results in the demise of dopaminergic and noradrenergic neurones [62]. The genetic model simulates autosomal-dominant or -recessive PD in humans by employing transgenic zebrafish that express specific defective genes [60]. Since its introduction as a model organism, the zebrafish has provided valuable insights into the development and degeneration of the nervous system. Neurological research was labour-intensive and lacking in flexibility prior to the establishment of this species. This was primarily due to the limitations associated with rodents and non-human primates, such as prolonged life cycles and complex ethical considerations. Zebrafish offer unique research benefits that are not feasible with other animal models. In research investigations, researchers have identified a variety of challenges and limitations that are associated with the use of this species.

Table 1 • Summary of five PD-associated genes and its encoded protein, normal functions, and observed effects of its mutations.

PD-associated gene	Encoded protein	Normal function(s)	Observed effects of mutations
SNCA	Synuclein	Regulates synaptic transmission	Lewy bodies formation Motor impairment Reduced dopamine level Reduced mitochondrial activity Increased ROS production
PRKN	Parkin	Protein degradation (autophagy)	Lewy bodies formation Mitochondrial dysfunction (mitochondrial complex I inhibition) Increased susceptibility to MPP+
PINK1	PINK1	Mitochondrial quality control Oxidative stress response mechanism	Mitochondrial dysfunction Developmental retardation Increased ROS production Increased susceptibility to MPTP
PARK7	DJ-1	Oxidative stress response mechanism	Muscle rigidity and tremors Motor impairment Increased ROS production Impaired mitophagy
LRRK2	LRRK2	Protein degradation (autophagy) Immune response mechanism	Abnormal protein degradation Increased ROS production Motor impairment Weakened immunity

SNCA: Alpha-synuclein; *PRKN*: Parkin RBR E3 ubiquitin protein ligase; *PINK*1: PTEN-induced kinase 1; *PARK*7: Protein deglycase DJ-1; *LRRK*2: Leucine-rich repeat kinase 2; ROS: Reactive oxygen species; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPP^+: 1-methyl-4-phenylpyridinium.

3.2. Advantages of zebrafish model

Zebrafish, as a vertebrate, exhibits greater physical similarity to humans compared to non-mammalian models like *C. elegans* and *D. melanogaster*. Moreover, the behaviours and characteristics exhibited by zebrafish are comparable to those of humans. Zebrafish exposed to MPTP exhibit movement deficits, characterised by decreased swimming speed and abnormal swimming behaviour, resembling bradykinesia-like symptoms that are observed in Parkinson's disease patients [61, 63]. Genome sequencing analysis reveals that the zebrafish genome shares 70% similarity with the human genome [64, 65]. Furthermore, 80% of the genes are located on the same chromosomes and in the same order, indicating conserved synteny between the two species [64, 66]. The distinctive characteristics of zebrafish as a model organism arise from their transparent embryos, which develop externally, facilitating real-time observation of developmental processes [67]. Furthermore, these embryos exhibit a high capacity for the absorption of administered compounds or neurotoxins [57].

Zebrafish offer advantages over other animal models, such as enhanced fertility and a brief life cycle. Zebrafish can generate approximately 200 to 300 eggs per week [68]. This gives the species a significant advantage, as a larger sample size can be utilised in each experiment, resulting in more significant findings. Zebrafish reach sexual maturity in three to four months [69] and have a typical lifespan of three to four years [70]. The abbreviated life cycle can substantially reduce both the duration and cost of an experiment, especially when the experimental design requires a comprehensive analysis of the entire developmental process. The care and maintenance techniques for zebrafish are simpler and less complex compared to those for rodents and non-human primates [71].

3.3. Challenges of zebrafish model

Zebrafish provide numerous advantages that have led to important observations and new discoveries. However, several limitations must be recognised when utilising this species as a research model. The external development of zebrafish embryos enables real-time observation; however, the uptake of chemicals by individual embryos may vary, especially with oral administration [72]. Additionally, the metabolic pathways and absorption rates of specific substances or chemicals in embryos grown externally may differ from those in human embryos [13, 67]. A comprehensive assessment is essential to determine the effective dosage and avoid misinterpretation of the results. Zebrafish possess an intrinsic capacity for regeneration and neurogenesis, enabling the replacement of cellular damage or loss [73, 74]. Dopaminergic neurodegeneration caused by 6-OHDA was repopulated thirty days post neurotoxin administration [75]. This phenomenon presents challenges to investigations of degenerative diseases, as it directly contradicts the concept of degeneration. This understanding provides a new and promising basis for research in neural regeneration [73, 76].

4. Zebrafish as a model of Parkinson's disease

In comparison to their invertebrate counterparts, *C. elegans* and *D. melanogaster*, zebrafish demonstrate a significantly closer physical relationship to humans. The measurable characteristics and pathologies of zebrafish and humans are very similar. The mapping of the dopaminergic nervous system in zebrafish has been the result of extensive research since its initial designation as a model organism in 1998 [77]. At 19 h post-fertilisation (hpf), dopaminergic neurones were initially characterised in the posterior tuberculum of the ventral diencephalon of zebrafish embryos. This region is analogous to the human substantia nigra (SN). The ventral telencephalon, which corresponds to the human striatum, was demonstrated to be the destination of this group of neurones. This process is a prime example of the nigrostriatal dopaminergic neural system, which is of paramount importance in the pathogenesis of Parkinson's disease [47]. The zebrafish brain's exhaustive data on dopaminergic neural projections, in conjunction with its susceptibility to experimental manipulations, renders this species an advantageous specimen for the investigation of molecular pathways associated with PD.

Zebrafish are a critical model for the investigation of a variety of neurological disorders due to their rapid maturation, substantial brood sizes, and economical husbandry. The human brain and zebrafish brain exhibit numerous homologous and highly conserved structures, despite their differences in configuration [51]. Experiments that utilise zebrafish to generate PD models frequently involve the regions associated with the disease in humans. The olfactory bulb and telencephalon are among these regions. The olfactory bulb is a brain region that is abundant in dopaminergic neurones and is closely associated with memory and learning. It plays a crucial role in the sense of smell [51, 78]. In humans, the telencephalon, or cerebrum, is a significant component of the brain that is responsible for the preponderance of sensory processing and all voluntary motor control. Comparable to the substantia nigra in humans, the diencephalon is a neuron-rich region of the brain that is responsible for the regulation of virtually all coordinated movements in fish. *Danio rerio* are vertebrate teleosts that contain orthologs for over 78% of human genes, in contrast to commonly used invertebrate models such as Drosophila melanogaster and Caenorhabditis elegans [79].

The process in this model is nearly identical to that in humans due to the highly conserved catecholamine production cascade and the observed high genetic homology. Vesicular monoamine transporter 2 (VMAT2) facilitates the transmission of dopamine as a signal between neurones. The synaptic cleft of signalling neurones is where the dopamine transporter (DAT) is located, which facilitates the release of dopamine into the synapse. Dopamine is bound to the dopamine receptor (D1 Receptor) on the dendritic end of a receiving neurone, which results in the activation of cyclic adenosine monophosphate (cAMP). cAMP functions as a secondary mediator that enables signal transduction between neurones in the central nervous system [80]. The neurotransmitter pathways for noradrenergic, serotonergic, histaminergic, and dopaminergic systems in zebrafish exhibit substantial conservation and are pertinent to discussions regarding PD [77, 81]. The meticulous investigation of dopamine's synthesis is necessary for the study of PD. Tyrosine, an indispensable amino acid, serves as the precursor to dopamine. The enzyme tyrosine hydroxylase (TH) catalyses the hydroxylation of L-tyrosine, a rate-limiting step that results in the production of the dopamine precursor, L-DOPA [82, 83]. In microglia and TH-positive neurones, aromatic amino acid decarboxylase converts L-DOPA to dopamine.

4.1. Parkinson's disease -associated genes expressed in zebrafish

Decades of comprehensive research have resulted in the discovery of many genes linked to the development of Parkinson's disease in zebrafish. These genes include *SNCA, PRKN, PINK1, PARK7, and LRRK2*, which encode the proteins synuclein, *PARKIN*, *PINK*1, *DJ-1*, and *LRRK2*, respectively, all exhibiting considerable similarity and analogous roles to those seen in humans. Zebrafish do not naturally produce alpha-synuclein aggregates due to the absence of the *SNCA* gene [84]. Both humans and zebrafish possess the protein-coding gene for beta-synuclein (*SNCB*). Beta-synuclein is a protein closely related to alpha-synuclein, exhibiting distinct properties [85]. In contrast to alpha-synuclein, beta-synuclein is not typically linked to PD pathology or the formation of Lewy bodies; however, it seems to play a protective role against the aggregation and toxicity of alpha-synuclein [86]. Zebrafish do not possess alpha-synuclein; however, they express the analogous proteins beta-synuclein and gamma-synuclein [87]. In zebrafish knockdown models, beta-synuclein has been directly associated with Parkinson's disease-like motor and behavioural deficits, establishing its significance as a marker in PD modelling [88]. Beta-synuclein has been examined in zebrafish models to explore its functions and potential protective effects against alpha-synuclein-induced toxicity [84].

4.2. Toxin-induced zebrafish model of Parkinson's disease

The study of PD in zebrafish requires the use of several chemical-based models to induce and examine the pathophysiology of the illness. Because of its genetic similarity to humans and the ease of genetic modification, the zebrafish has become a popular model organism in neurobiology research. Some of the most used chemical models for zebrafish PD are listed in **Table 2**.

For years, zebrafish studies have employed a variety of neurotoxins, including MPTP, 6-OHDA, paraquat, and rotenone, to elicit symptoms that are like those of Parkinson's disease. Nevertheless, research suggests that a variety of small-molecule medications can effectively replicate Parkinsonian symptoms in zebrafish, despite the challenges associated with recapitulating the complexity of human diseases in animal models. The numerous substances that have been used to induce Parkinson's disease in zebrafish have been the subjects of previous research [89]. This review examines MPTP as a potential model for Parkinson's disease, emphasising its relatively straightforward administration in zebrafish. The MPTP induction of Parkinson's disease has been utilised since 2004 and has gained increasing recognition, despite the ongoing debate regarding its limitations. An exhaustive search from 2001 to 2023 identified 20 papers that explicitly addressed MPTP in adult zebrafish [90].

Table 2 • Summary of the advantages and limitations of toxic animal model in Parkinson's disease research.

Model name	Species	Pros	Cons	References
MPTP	*Mice*	- Mimics motor/non-motor symptoms - Clinically relevant - Easy to administer - Cost-effective	- No consistent Lewy body formation - Limited progressive neurodegeneration - Strain-specific susceptibility	[7]
MPTP	*Cynomolgus monkeys*	- Closest to human PD - Mimics motor symptoms well - Supports long-term therapy studies	- Ethical concerns - Expensive and time-consuming - Variable sensitivity among primates	[78, 91]
6-OHDA	*Rats*	- Targets nigrostriatal dopaminergic neurons - Reproducible motor deficits - Useful in drug testing	- Does not cross BBB naturally - No Lewy body formation - Rapid degeneration unlike human PD	[92, 93]
Rotenone	*Rats/Mice*	- Induces both motor and GI symptoms - Mimics α-synuclein aggregation - Relevant to environmental exposure	- High mortality rates - Variable responses - Affects multiple systems beyond the dopaminergic pathway	[94, 95]
Paraquat	*Rats*	- Mimics oxidative stress - Induces dopaminergic neuron loss - Useful in studying gene–environment interaction	- Inconsistent dopaminergic damage - Poor reproducibility - Conflicting epidemiological data	[96, 97]
Reserpine	*Rats*	- Simple model - Mimics akinesia and rigidity - Good for screening reversal treatments	- Not suitable for studying chronic drug effects - Depletes all monoamines, not dopamine-specific	[98]
Haloperidol	*Rats/Mice/C. elegans*	- Models motor symptoms - Useful for testing rigidity-reducing agents - Simple administration	- Indirect dopaminergic action - May not replicate dopaminergic neuron degeneration - Test conditions not standardised	[99, 100]
Rotenone	*Drosophila, Snails, C. elegans*	- Fast, economical, and genetically tractable - Allows for high-throughput screening - Useful for mitochondrial and oxidative stress studies	- No α-synuclein homologue in *C. elegans* - Limited neural complexity - Translational relevance is limited	[101]

4.2.1. 6-hydroxydopamine

Animal models often use 6-hydroxydopamine (6-OHDA) as a neurotoxin to induce symptoms like PD. The major neuronal population impacted in PD is dopaminergic neurones, which are the focus of the selective damage brought on by 6-OHDA. Zebrafish are a useful model for studying the degeneration of these neurones because their dopaminergic systems are comparable to those of humans. Assessing the behaviour of adult zebrafish with lesions caused by 6-OHDA revealed significant reductions in both speed and distance travelled [59, 102]. Dopaminergic neurones, the main neurones impacted in PD, are the precise target of 6-OHDA. Zebrafish are a useful model for researching the function of certain peptides in neurodegenerative illnesses because they have a dopaminergic system that is comparable to that of humans. It was noted that 9 of the 118 peptides examined in a case study exhibited significant alterations when 6-hydroxydopamine was introduced to the zebrafish brain to induce Parkinsonian symptoms. More specifically, just one peptide showed an increase in expression, whereas eight peptides displayed a decrease. The most notable changes were seen in the dynamic cytoskeleton and the intracellular and extracellular proteins involved in lipid metabolism [103]. 6-OHDA is a neurotoxin that is often injected directly into the targeted area of the brain due to its inability to pass across the blood–brain barrier. Administering 6-hydroxydopamine (6-OHDA) to zebrafish results in the death of dopamine (DA) neurones, which reduces the amount of dopamine in the affected region. The administration of varying dosages of 6-OHDA caused damage to DPN, leading to over 85% elimination in different parts of the brain. Notably, researchers found that 30 days after the creation of the lesion, the lesioned zebrafish's DPN completely recovered. As a result, the study successfully created a stable PD zebrafish model by 6-OHDA, a simple and repeatable method [59].

6-OHDA has proven its capacity to obstruct Complex I of the electron transport chain and respiration. Additionally, it has been noted that 6-OHDA may endure autoxidation, which leads to the formation of a quinone that can interact with macromolecules through redox cycling [104]. The presence of iron may facilitate the oxidation of 6-OHDA [105]. The mitochondrial electron transport chain (ETC) disruption is the predominant mechanism among these Parkinsonian toxicants, which implies that the toxicants associated with sporadic Parkinson's disease may also function as ETC inhibitors. Rotenone, MPP+, and potentially 6-OHDA are ETC inhibitors that obstruct electron flow in the electron transport chain. The production of reactive oxygen species (ROS) that induce oxidative damage to DNA, lipids, and proteins is a consequence of the diversion of electrons by the inhibition of ETC Complex I or III [106]. They are believed to facilitate the release of iron from complexes within the electron transport chain. Rotenone, 6-OHDA, and MPP+ promote this process. Hydrogen peroxide and free iron interact to generate hydroxyl radicals, which are highly reactive in the oxidation of macromolecules [107].

4.2.2. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MPTP was identified in the early 1980s as a result of the injection of heroin contaminated with MPTP, which resulted in the development of Parkinsonism [108, 109]. Parkinsonism has been observed to be induced by MPTP in a variety of animal species, such as primates, rodents, and zebrafish, as well as in humans [15] Since its discovery, MPTP has been the primary neurotoxin employed in Parkinson's disease research, and thus has been established as a critical model of the disorder [108]. MPTP is applicable to all developmental stages (embryonic, larval, adult) in zebrafish model studies.

In laboratory animals, particularly zebrafish, the chemical substance 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is often used as a model for PD and has been used to induce the degeneration of dopaminergic neurones [110]. There has been evidence of hypolocomotion and motor incoordination in adult zebrafish administered MPTP [111]. Furthermore, it has been shown that when large dosages of MPTP are applied, zebrafish swimming behaviour exhibits unique computational patterns. According to the study's overall conclusions, giving MPTP to adult zebrafish operates as a late-stage PD experimental model. This model has unique cognitive traits [110]. It is important to keep in mind that MPTP may harm zebrafish eggs as well as adult fish. By damaging dopaminergic neurones, MPTP reduces the quantity of dopaminergic cells in the zebrafish embryonic diencephalon, according to earlier research. This results in decreased expression of *BDNF*, *DJ1*, *LRRK*, and *PINK1*, as well as decreased locomotor activity, AChE levels, antioxidant enzyme activities, and mortality and hatching rates [112]. CVMIs of MPTP in adult transgenic zebrafish reveal a significant reduction in dopaminergic neurones in the telencephalon and olfactory bulbs (OBs) of Tg (dat:eGFP) fish. An examination of mCherry and mitochondrial gene expression in zebrafish showed that MPTP may result in mitochondrial fragmentation in dopaminergic neurones. The *PINK1/PARKIN* pathway is also known to be involved in mitophagy. Researchers found that the telencephalon and olfactory sections of fully matured zebrafish have a much lower number of dopaminergic neurones than other parts of their brains. Research has shown that the sensory and motor behavioural characteristics of zebrafish undergo transient alterations due to this reduction in dopaminergic neurones. This study also employed the Tg (dat:tom20MLS:mCherry) strain of zebrafish to demonstrate a significant increase in the proportion of fragmented mitochondria in zebrafish that received injections of MPTP. Gene expression analysis supports the results, indicating that mitophagy is the mechanism responsible for dopaminergic cell death. This, in turn, leads to increased mitochondrial fission and a more fragmented structure of the mitochondria, which helps us better understand how chemically induced mitochondrial dysfunction contributes to dopaminergic neurone degeneration and other Parkinson's disease-related disorders [113].

Rotenone, 6-hydroxydopamine (6HD), and MPP+/MPTP are three chemicals that function as mechanistic instruments for the identification of vulnerability pathways in dopaminergic neurones that result in Parkinsonism. Rotenone, MPP+, and, it is probable, 6HD inhibits the mitochondrial electron transport chain at Complex I, thereby disrupting energy generation and metal metabolism and increasing ROS formation [114–116]. Sewell and Cozzi [117] identified MPTP as a chemical contaminant in a synthetic heroin preparation. MPTP is efficiently transported across the blood–brain barrier and absorbed by astrocytes. Subsequently, it is converted to MPP+ by monoamine oxidase B and released into the extracellular space. Dopaminergic neurones absorb MPP+, the toxic metabolite of MPTP, through the dopamine transporter. MPP+ is present in two organelles: the mitochondrial matrix and catecholamine storage vesicles. MPP+ in mitochondria inhibits ETC Complex I, releases iron from heme–iron and iron–sulphur cofactors, and increases ROS production. The accumulation of MPP+ in intracellular vesicles results in the release of dopamine, which can either be oxidised to 6HD or undergo autoxidation to form dopamine semiquinone. This process is catalysed by free iron and hydrogen peroxide [118]. Aminochrome, a precursor to neuromelanin, is produced through autoxidation of both 6HD and dopamine semiquinone. This intermediate functions as an inhibitor of Complex I. Mitochondria acquire damage and endure recycling during this process. Inhibitor studies and human genetic research indicate that mitophagy, or the autophagy of mitochondria, facilitates mitochondrial regeneration and mitigates cytotoxicity. Terron et al. [119] have observed the occurrence of ER stress, dysregulation of calcium sequestration by mitochondria, and proteasome activity. MPP+ selectively induces the demise of dopaminergic neurones, which leads to Parkinsonian symptoms in younger individuals. Due to the idiosyncratic or unknown nature of its primary causes, this condition is named "Parkinsonism" rather than Parkinson's disease (PD). The jicama vine and other plants, which evolved this mechanism to eliminate insects and other herbivores, likely produced rotenone, which functions as a potent inhibitor of Complex I [117]. Rotenone is employed as an insecticide in agriculture and has been linked to an increased risk of Parkinson's disease in labourers who administer it [120]. Rotenone, like MPTP, induces mitophagy, endoplasmic reticulum stress, and mitochondrial injury [121]. In cultured neurones that have been exposed to rotenone, the protective effects of enhancing mitophagy have been demonstrated. Numerous mutations in PD risk genes, including *PARK2*, *PINK1*, *GBA*, and *KAT8*, have been demonstrated to impair autophagy. Additionally, lysosomal activity is influenced by mutations in *TMEM175*, *CTSB*, *ATP6V0A1*, and *GALC*. This suggests that the mitophagy and the degradation of Lewy bodies may contribute to the prevention or progression of Parkinson's disease in vivo. Lewy bodies may mitigate the development or progression of Parkinson's disease in vivo.

4.2.3. Rotenone

Known for its capacity to produce symptoms that closely match those of PD, rotenone is a neurotoxic ketone that is naturally generated by lancepods and utilised as an herbicide, pesticide, and piscicide. Its capacity to easily cross the blood–brain barrier (BBB) and build up within mitochondria allows it to directly penetrate the central nervous system (CNS) and accomplish this goal [122]. It is common practice to employ the herbicide rotenone to cause PD-like symptoms in zebrafish as an animal model of the disease. In response to rotenone exposure, zebrafish displayed olfactory abnormalities, anxiety-like behaviour, and motor impairment. The rotenone group's lower dopamine levels might be the cause of these PD-like symptoms [123]. Rotenone-treated zebrafish showed a 30% decrease in dopamine production and impaired dopamine absorption, leading to behavioural abnormalities, including decreased locomotor activity, cognitive function, and motor skills impairment, that resemble PD symptoms [124].

4.2.4. Paraquat

Research indicates that the polar herbicide paraquat (PQ) damages dopaminergic neurones oxidatively, leading to aberrant behaviour in vivo and the onset of PD. It is well recognised that prolonged exposure to paraquat may change human dopaminergic systems, increasing the risk of PD. According to Kim et al. [125], zebrafish larvae exposed to paraquat poisoning exhibit impaired motor responsiveness, aberrant brain activity, and behavioural abnormalities. Low-dose PQ therapy (0.04 ppm, less than the recommended daily exposure for humans) caused neurodegenerative symptoms and motor impairments in 18-hpf embryonic zebrafish at different developmental stages. At different developmental stages, there was a drop in GSH levels, an increase in lipid peroxidation, and apoptosis, respectively. These findings suggest that paraquat disrupts the cholinergic system via oxidative stress, which leads to Parkinsonian-like motor abnormalities in later life [126]. Paraquat disrupts dopaminergic signalling and mitochondrial function, according to in vivo PD research using the zebrafish model [123].

As a conclusion, one useful tool for understanding the pathophysiological process of PD in zebrafish is the use of environmental neurotoxins in research on the illness. However, the use of the neurotoxin-induced zebrafish model has several limitations that need to be recognised despite its effectiveness and advantages. Danio rerio has emerged as a crucial platform, especially in the field of neurodevelopmental research, demonstrating the significant contribution the translational medicine era has made to scientific advancement. Zebrafish have played a significant role in helping to understand the aetiology of neurological disorders such as Huntington's disease, Alzheimer's disease, and PD. Because of its short life cycle, ease of genetic alteration, and transparent embryos, it is more amenable to molecular research than rodents and primates. Research in biology, neurology, pharmacology, and toxicology now makes extensive use of zebrafish because they are a great model for studying neurobehavioral features that are relevant to humans.

4.3. MPTP mechanism of action in Zebrafish model

The mechanism of MPTP toxicity in zebrafish parallels that in humans [21] supporting its extensive application as a model in Parkinson's disease research. The primary challenge in researching PD is the blood–brain barrier (BBB) [127], which selectively regulates the entry of substances into the central nervous system. The evaluation of potential therapeutic medications is complicated by the highly selective nature of the blood–brain barrier [127]. The identification of MPTP offers a potential pathway in PD research, as this compound can easily cross the BBB. MPTP is generally administered to adult zebrafish through intraperitoneal or intracerebral injection, whereas zebrafish larvae and embryos are exposed to MPTP through direct immersion in aqueous solutions containing the compound [61].

MPTP is metabolised in glial cells by monoamine oxidase B (MAO B) after successfully crossing the zebrafish BBB; this enzyme is located on the outer mitochondrial membrane. This mechanism enables the conversion of MPTP into its active metabolite, MPP+ [61]. Due to its structural similarity to dopamine, MPP+ is subsequently taken up by dopaminergic neurones through the dopamine transporter protein (DAT) [128]. The dopamine transporter (DAT) is a transmembrane protein located in the presynaptic area of dopaminergic neurones, playing a crucial role in the modulation of dopamine neurotransmission [129]. The MPTP neurotoxin causes DAT to misidentify the harmful MPP+ as dopamine, thereby enabling its transport into dopaminergic neurones [61, 128].

MPP+ accumulates in the mitochondria of neurones, where it inhibits the mitochondrial electron transport chain by binding to complex I [130]. The interaction of MPP+ with complex I disrupts the electron transport chain, leading to insufficient ATP synthesis and increased ROS production (Perier & Vila, 2012; Robea et al., 2020) [63, 131]. Energy deficiency and increased levels of reactive oxygen species (ROS) progressively result in oxidative stress, protein dysfunction, lipid peroxidation, and ultimately contribute to the death of dopaminergic neurones [63, 131].

4.4. Neuro-behavioural changes after MPTP exposure

After exposure to MPTP, zebrafish display symptoms and behaviours linked to PD, especially motor signs. Zebrafish produced through MPTP exhibit movement deficits characterised by decreased swimming speed and atypical swimming behaviour, analogous to bradykinesia-like symptoms observed in humans. Zebrafish also demonstrate extended periods spent at the bottom of the tank, along with an increase in freezing behaviours, signifying a notable reduction in locomotor activity. Zebrafish exposed to MPTP demonstrated reduced responsiveness to tactile stimuli, marked by lethargic trunk and tail reflexes [132, 133]. The sensory impairment can be linked to reduced striatal dopamine levels, leading to disrupted striatal function [134]. The behavioural changes observed in zebrafish during their development as a model organism provide important indicators that differentiate normal zebrafish from those displaying Parkinsonian characteristics. Optimised and standardised behavioural evaluations are essential for improving the accuracy and reliability of zebrafish models, like rodent models, and are increasingly relevant in Parkinson's disease research [15].

5. Bibliometric analysis of MPTP PD model research in a 10-year time window

The study of the evolution and organisation of knowledge in scientific disciplines is known as bibliometrics. It is a popular method for determining the topics, hotspots, and boundaries of a certain area of study [135]. This study compiles pertinent works on a certain topic and statistically examines the topic's historical emphasis, present state of development, and potential future directions [136]. To our knowledge, there has not yet been a published bibliometric examination of the MPTP model of PD. In the present research, we use bibliometric analysis to examine the current trends and hotspots of PD publications connected to MPTP during the last ten years.

5.1. Methodology

5.1.1. Data sources

A bibliometric analysis of English-language articles retrieved via PubMed using the search term "MPTP model of Parkinson's Disease" yielded 23 documents published between 2014 and 2023, across 20 distinct sources. These publications involved 160 authors in total. All sources fall within Bradford's Law zones, indicating a broad yet balanced distribution of literature across core and peripheral journals in the field. The metadata were downloaded and saved as .csv format.

5.1.2. Data analysis

Bibliometrix [137] is a quantitative bibliometric analysis software that runs on R. This package includes Biblioshiny, a web interface for Bibliometrix. We used R Studio Version 2022.07.2+576 (RStudio, PBC, Boston, MA, USA) to install and load the Bibliometrix package. This resulted in the R console's "biblioshiny()" command loading the Biblioshiny package. Both programmes' specific algorithms and procedures were described elsewhere [137, 138]. We submitted the obtained information to the Biblioshiny interface for analysis. Three parameters were analysed: the authors' keywords, publishing sources, and general outputs (publication trends and partnerships). Before the study began, terms that had similar meanings were combined. We downloaded and stored the analysis's visual results in.png format.

5.2. Results and analysis

5.2.1. Analysis of publication outputs, growth trends, and scientific collaborations

As shown in **Table 3**, the bibliometric data spans a decade (2014–2023) and comprises 23 documents published across 20 sources, with an annual growth rate of 8.01%, indicating steady scholarly interest. Despite this, the average citations per document remain at zero, suggesting limited impact or recent publication. The documents have an average age of 6.83 years, yet only one reference is recorded—an unusually low figure that may reflect a data reporting issue. Content-wise, there are 136 Keywords Plus and 62 Author's Keywords, highlighting broader thematic indexing than author-driven terms. Authorship is highly collaborative, with 160 authors contributing and only one single-authored document; the average number of co-authors per document is 7.17. However, international collaboration is notably absent (0%), which may hinder global visibility. The document types include 22 journal articles and 1 evaluation study, showing a predominance of traditional scholarly outputs with limited methodological diversity. Overall, while the field shows signs of growth and collaboration, its low citation rate and lack of international engagement suggest opportunities for greater outreach and impact (**Figure 4** and **Figure 5**).

Table 3 • Main information of the selected articles gathered by Biblioshiny.

Description	Results
Main information about data	
Timespan	2014–2023
Sources (Journals, Books, etc.)	20
Documents	23
Annual Growth Rate %	8.01
Document Average Age	6.83
Average citations per doc	0
References	1
Document contents	
Keywords Plus (ID)	136
Author's Keywords (DE)	62
Authors	
Authors	160
Authors of single-authored docs	1
Authors' collaboration	
Single-authored docs	1
Co-authors per doc	7.17
International co-authorships %	0
Document types	
Evaluation study	1
Journal article	22

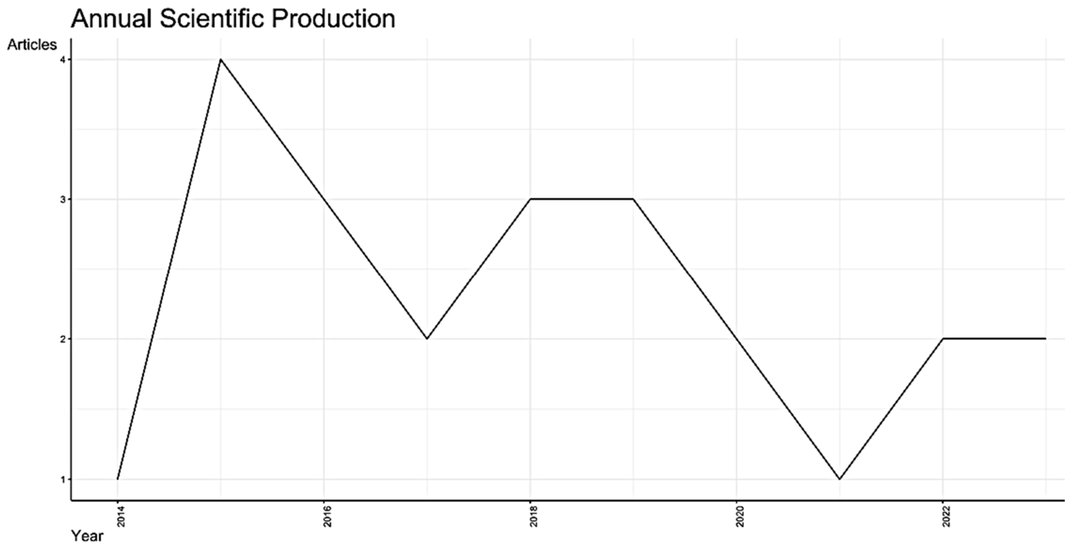

Figure 4 • The total number of annual publications. The year 2014 had the greatest publication output.

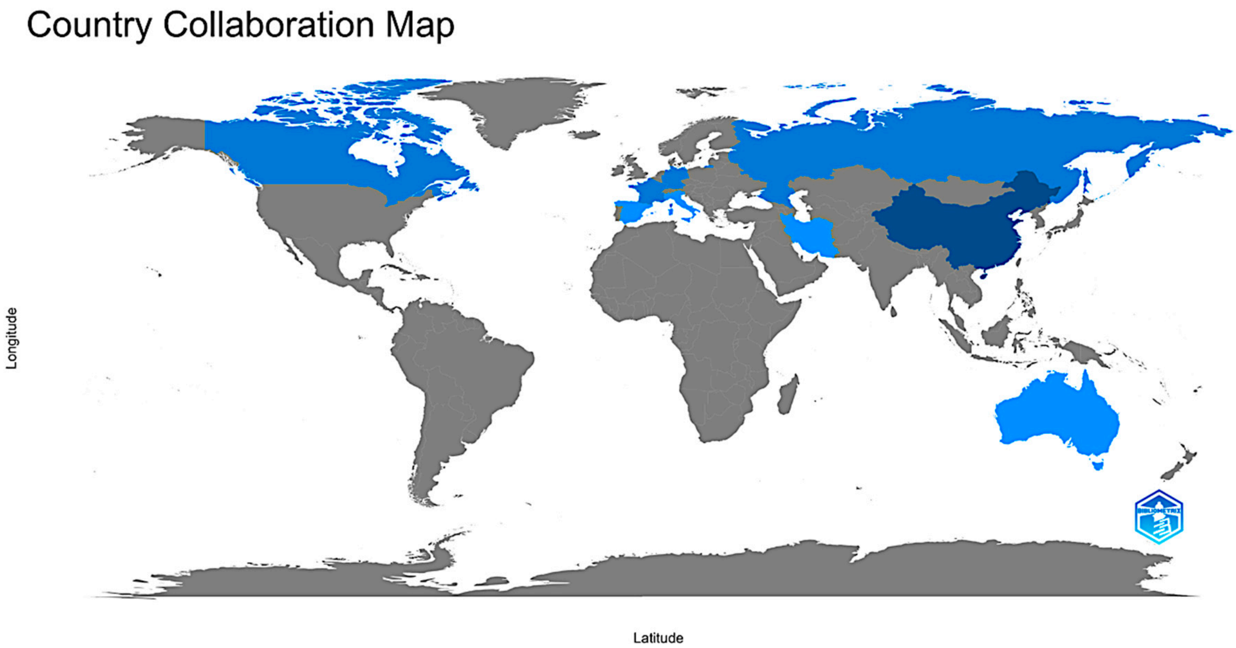

Figure 5 • Scientific collaboration world map. Countries with a darker blue shade have a higher number of publications.

5.2.2. Analysis of publication sources

Bibliometric analysis identified a total of 23 journals that had published MPTP PD model articles from 2014 to 2023. The top 10 journals publishing articles in this research field are presented in **Figure 6**. The Annals of Neurology journal was the journal that published the highest volume of MTPT PD model research, with two articles, followed by other journals which published only one article each, including Basic and Clinical Neuroscience, Behavioral Brain Research, and Biology (**Figure 6**). According to the Bradford's Law of Scattering, the core sources for this research field are Annals of Neurology, Laboratory Investigations, and The Journal of Nutrition (**Figure 7**).

5.2.3. Analysis of keywords

Keywords assigned by the authors in their articles are especially useful for bibliometric analysis when investigating the hotspots and trends of a specific research field. By performing keyword analysis, we revealed the top 10 most frequent keywords used by the authors for the MPTP-PD model research (**Figure 8**). Of 136 keywords, "animals" and "disease model" were used most frequently, with 20 and 18 occurrences, respectively, followed by "male" with 14 occurrences. Several keywords related to the PD model, including "mice", "MPTP", "dopaminergic", and "substantia nigra", were also identified as frequent words, with ten, nine, seven and sex occurrences, respectively. In parallel with the upward publication trend, cumulative occurrences of the keywords also increased (**Figure 8**). The most noticeable increments are "MPTP" and "Animals" with around 20 cumulative occurrences out of all analysed articles.

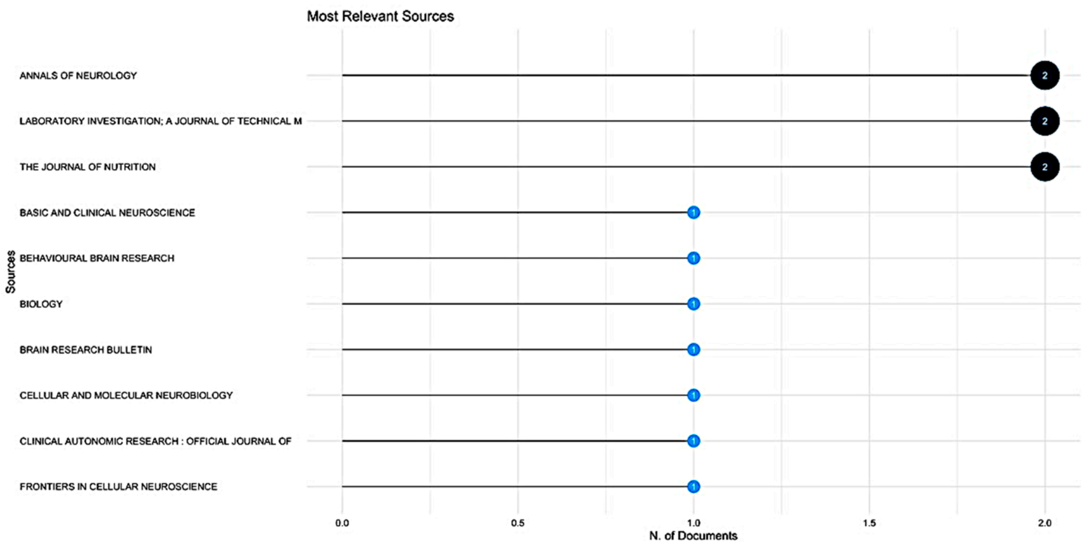

Figure 6 • Top 10 journals that published MPTP PD MODEL-related articles from 2014 to 2023.

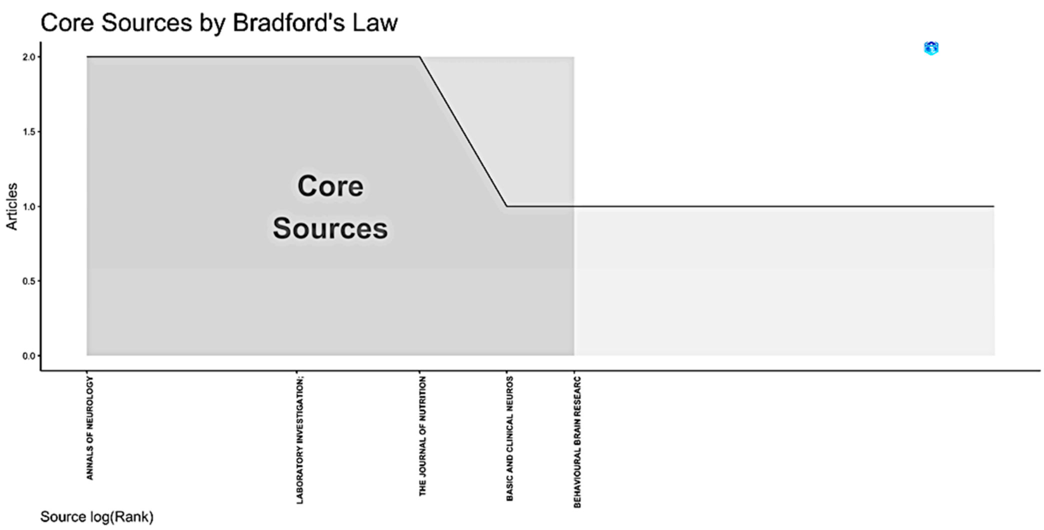

Figure 7 • Core publication sources clustering through Bradford's Law.

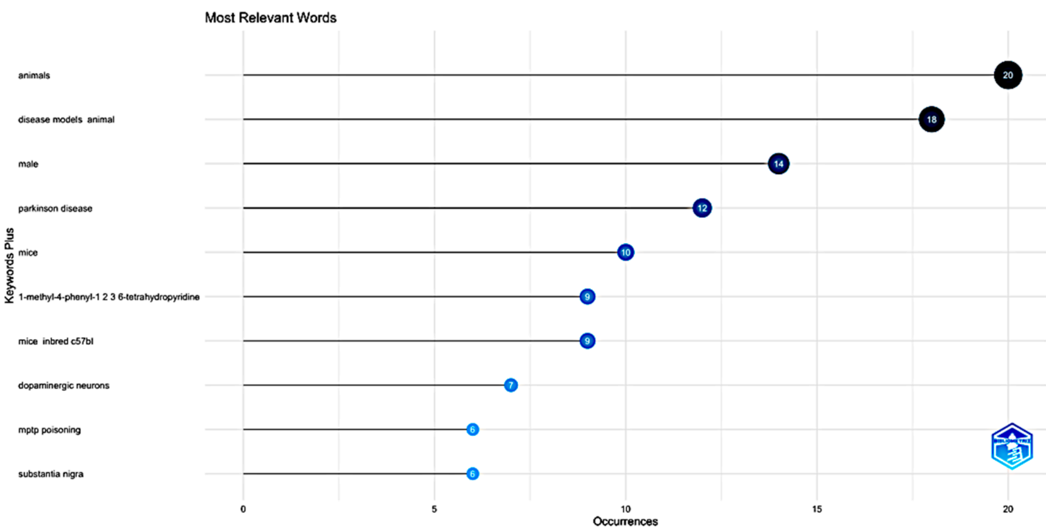

Figure 8 • Top 10 most frequent keywords used by authors for their MPTP-PD model articles.

Figure 9 displays the network of the top 50 keywords based on a co-occurrence analysis of keywords. While node colours show clusters and the correlation between nodes, node sizes show the frequency of terms. Following the completion of the study, the keywords are grouped into three primary clusters that show the criteria that were taken into consideration and the reasons for splitting the keywords. The biggest and most node-rich cluster is the red one. In addition to HMGB1-related phrases like "animals," "MPTP," and "disease model," this cluster contains PD-related terms like "Parkinson's disease," "tyrosine hydroxylase," and "$\alpha\alpha$-synuclein." The blue cluster contains the MPTP model-related terms "oxidative stress," "substantia nigra," "microglia," and "mice inbred." Meanwhile, the green and purple clusters have a mechanical relationship with anti-PD medications and the MPTP PD Model, respectively.

Figure 10 visualises the trends in key terminology within Parkinson's disease research, specifically focusing on studies using MPTP-induced models in mice that were published between 2015 and 2021. The data confirms that research centred on dopaminergic neurons was the most prominent. The persistent high frequency of terms like mice and MPTP poisoning underscores the dominance of this particular animal model. The inclusion of humans reflects the translational goal, while the presence of the word male indicates a significant focus on studying males within this model system. The "Top 1" ranking suggests "dopaminergic neurons" was the single most frequently occurring term over this period. The actual chart (**Figure 10**, **Figure 11** and **Figure 12**) shows how the usage frequency of each term evolved over the six years. This image captures the enduring core themes and methodologies in a significant segment of Parkinson's disease preclinical research during the late 2010s and early 2020s, highlighting the centrality of dopaminergic neuron studies using MPTP mouse models, often focused on males, with an eye towards human application.

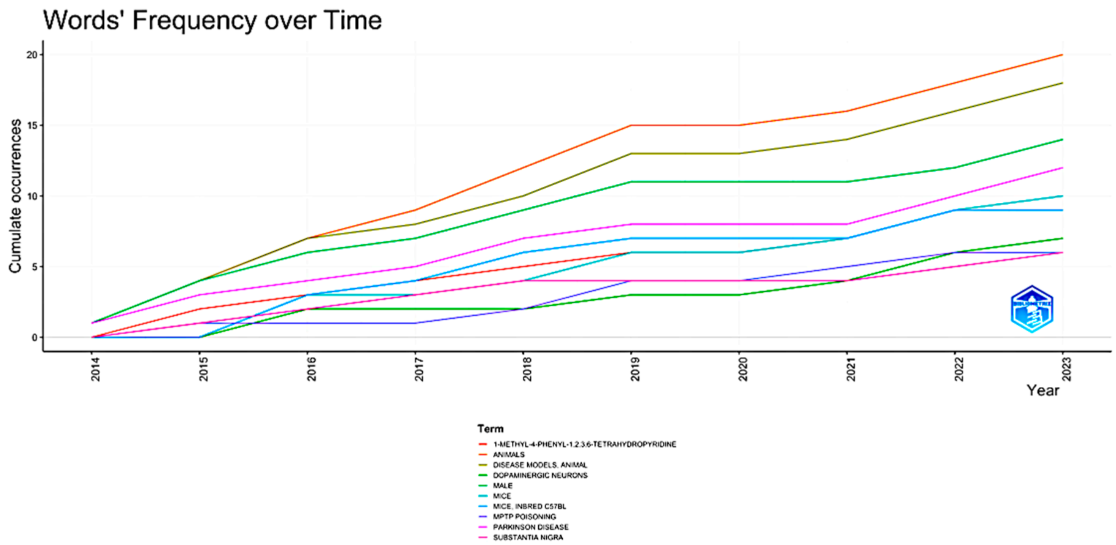

Figure 9 • Cumulative keyword occurrences from 2014 to 2023.

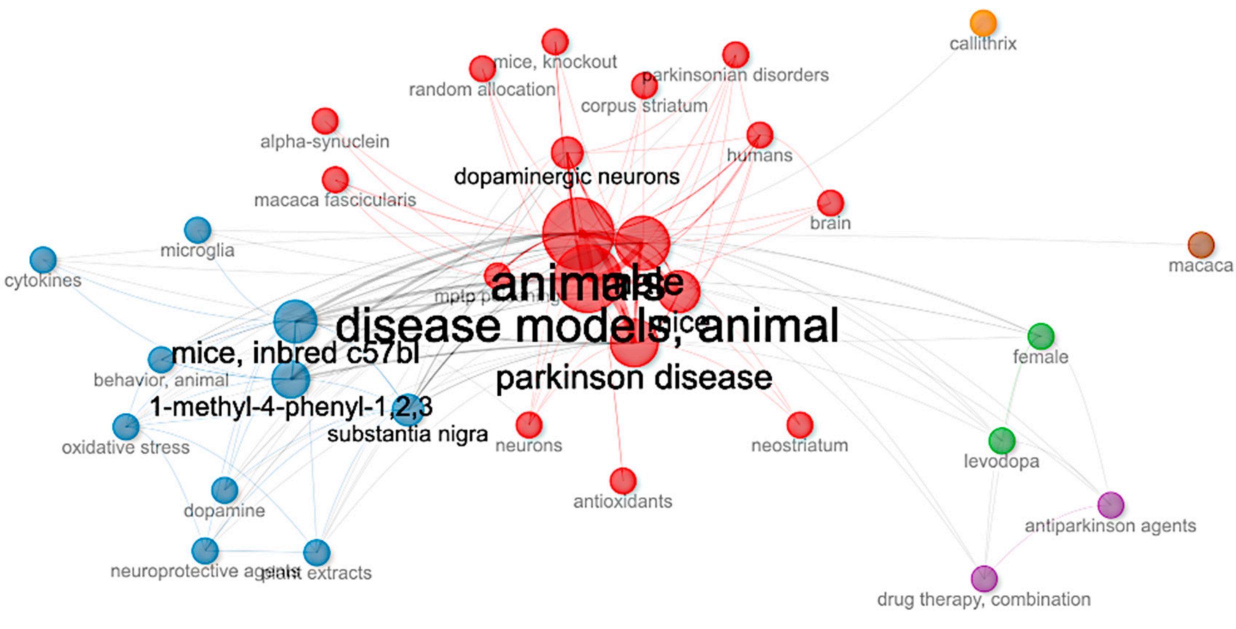

Figure 10 • Co-occurrence network of the topics discussed. Nodes with the same colour indicate topics under the same cluster.

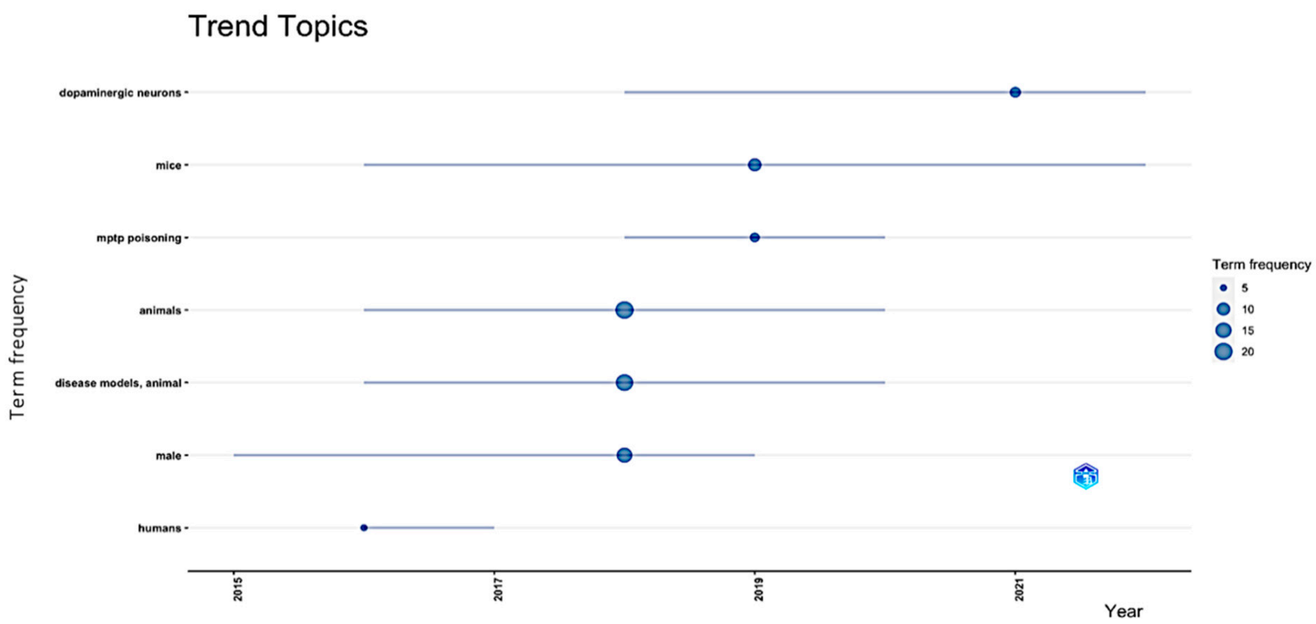

Figure 11 • Trending topics' occurrence over the years.

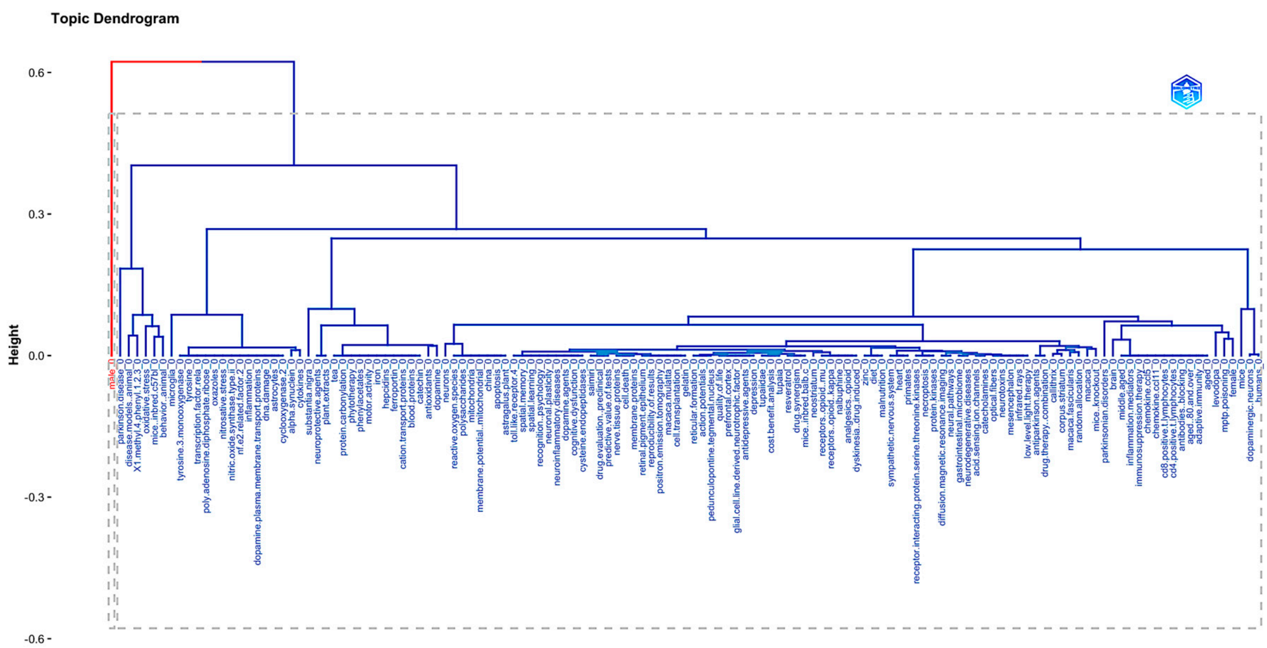

Figure 12 • Dendrogram with factorial analysis.

Finally, the above dendrogram represents the results of a bibliometric analysis based on research articles related to the MPTP model of Parkinson's disease. It visualises the hierarchical clustering of keywords or research topics extracted from the literature, with the vertical axis indicating the degree of dissimilarity between them. The clustering reveals distinct thematic groupings: one includes terms such as "tyrosine 3-monooxygenase" and "monoamine oxidase," reflecting molecular and genetic aspects, while another comprises "MPTP poisoning," "dopaminergic neurons," and "Parkinsonism," highlighting neurodegenerative mechanisms. The central portion features a broader range of terms covering clinical, cellular, and imaging-related research. The dendrogram structure, particularly the cut off near 0.6, indicates the presence of two major thematic clusters, providing a clear overview of the conceptual landscape in MPTP-based Parkinson's disease research over the past decade.

5.2.4. Limitations

Table 4 below lists the fields critical for basic identification and retrieval (Abstract, Author, DOI, Title, Journal, Publication Year, Language, Document Type, Affiliation, Total Citations), with 0% missing data. This is indicative of excellent curation of essential bibliographic information, ensuring the reliability of the search, attribution, and basic analysis. There is a category for Problematic Keyword Coverage with Author Keywords (DE), of which 34.78% of the data were missing (8/23 records). This is a significant gap, as author-provided keywords are vital for topic discovery and precision searching. For the category Keywords Plus (ID), 13.04% of the data were missing (3/23). While better than DE, this still limits automated topic mapping and literature mining. Additionally, for the category Critical Gaps in Scholarly Context, four fields are 100% missing (23/23 records). Regarding the Cited References (CR), all citation data is absent, preventing the following analyses: citation network analysis, impact factor calculations, and literature backtracking. Furthermore, for the Corresponding Author (RP), no contact details were found, hindering collaboration or data requests. Issues determining the number of Cited References (NR) prevent bibliometric studies (e.g., citation density trends). Missing data for Science Categories (WC) eliminates subject-area classification, making disciplinary analysis impossible. In such cases, the dataset is usable for basic queries but severely limited for scholarly analysis (bibliometrics, network studies, or replication). Data Quality Tiering falls under the following categories: Tier 1 (0% missing) indicates that the research is a trustworthy source of foundational metadata; Tier 2 (DE/ID) suggests that it should be used with caution for content-based tasks; and Tier 3 (CR/RP/NR/WC) indicates that it is unusable for advanced research contexts. The Potential Causes include legacy records lacking digitised references, non-academic sources (e.g., reports, preprints) without structured metadata, and aggregation errors during data ingestion. This dataset excels in terms of descriptive metadata but fails to capture scholarly context. It is fit for basic discovery but not for citation analysis, subject mapping, or reproducibility studies. Addressing the 100% missing fields should be the primary focus for enhancement.

This bibliometric study has limitations despite its scientific implications. First, the findings of this research were solely relevant to this criterion, since the chosen articles exclusively originated from the PubMed database. Results from combining publications from other sources, including Web of Science and Scopus, might be more thorough. Second, articles produced in languages other than English were not included in this study. It is challenging to integrate multilingual articles, as proper synonym keyword merging requires a comprehensive pre-analysis screening. Including publications authored by scholars from various native cultures is fascinating, too, since it may provide insights from a variety of perspectives.

6. Discussion and perspectives

With an emphasis on PD, this article highlights the usefulness of zebrafish as a realistic model for testing new drugs created to treat various neurological conditions. The article examines recent advancements in the research of PD pathophysiology using zebrafish models. These models either incorporate pathogenic genes associated with human neurodegenerative disorders or reduce the activity of the relevant zebrafish genes. These changes lead to observable morphological, physiological, and biochemical problems in certain neurone types reported in various animal and human models.

Table 4 • Missing data table.

Metadata	Description	Missing counts	Missing %	Status
AB	Abstract	0	0.00	Excellent
C1	Affiliation	0	0.00	Excellent
AU	Author	0	0.00	Excellent
DI	DOI	0	0.00	Excellent
DT	Document Type	0	0.00	Excellent
SO	Journal	0	0.00	Excellent
LA	Language	0	0.00	Excellent
PY	Publication Year	0	0.00	Excellent
TI	Title	0	0.00	Excellent
TC	Total Citation	0	0.00	Excellent
ID	Keywords Plus	13.04	13.04	Acceptable
DE	Keywords	8	34.78	Poor
CR	Cited References	23	100.00	Completely missing
RP	Corresponding Author	23	100.00	Completely missing
NR	Number of Cited References	23	100.00	Completely missing
WC	Science Categories	23	100.00	Completely missing

AB = Abstract, C1 = Affiliation, AU = Author, DI = Digital Object Identifier (DOI), DT = Document Type, SO = Source (Journal), LA = Language, PY = Publication Year, TI = Title, TC = Total Citations, ID = Keywords Plus, DE = Author Keywords, CR = Cited References, RP = Reprint Author (Corresponding Author), NR = Number of Cited References, WC = Web of Science Categories (Science Categories).

Although there are still many issues when it comes to accurately simulating complicated human illnesses like Parkinson's disease in animal models, using a variety of animal models may assist to mitigate these issues. The zebrafish, a relatively recent model organism, provides a variety of models that examine different facets of Parkinson's disease. Chemical techniques may easily cause zebrafish to exhibit disease-like conditions, although they might not accurately mimic every facet of the illness. However, several well-established chemically generated Parkinson's disease models provide solid research bases, while other recent approaches have promise but need to be researched further. It is interesting to note that when exposed to the same substances, zebrafish models usually show effects that are comparable to those of mammalian models, proving that zebrafish are suitable for this purpose. The zebrafish is quickly becoming a popular model organism due to developments in genome-editing technology and the application of sophisticated imaging methods. The zebrafish is a model for disorders that has the potential to provide new discoveries in neurodegenerative diseases and other related domains because of its wide range of behavioural paradigms and high-throughput screening capabilities. The use of many animal models may help to overcome the inherent limitations of animal models when it comes to simulating complex human illnesses like Parkinson's disease. The zebrafish provides a variety of models that explore different aspects of Parkinson's disease in this regard.

Research utilising adult zebrafish, Danio rerio, as a model for human neurological diseases has proven advantageous for drug development and the study of genetic disorders. Zebrafish serve as an effective model for assessing medicinal efficacy in a high-throughput, in vivo context; this has been attributed to their notable genetic similarity to humans, economical care requirements, relatively swift breeding cycles, and considerable embryo production. Currently, most research utilising zebrafish models for PD induces the condition in larval or embryonic specimens due to the ease of administration, with developmental progression occurring within a few days. The utilisation of early-stage organisms limits the applicability of zebrafish as models for adult diseases, especially those related to age-associated neurodegeneration. Researchers have recently sought to improve the use of zebrafish as models for Parkinson's disease. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is recognised as a prodrug that, upon administration, encapsulates the biochemical processes and symptoms associated with Parkinson's disease. The use of MPTP in an adult zebrafish model may advance research in Parkinson's disease. This article highlights recent research on this model, comparing it with the human variant of Parkinson's disease.

The lack of experimentation on adult zebrafish suggests inconsistencies in procedural setups and fish characteristics, which may result in variability in behavioural and neurochemical observations. The application of MPTP in zebrafish is increasingly recognised as a valuable research avenue for animal models of Parkinson's disease. Various research groups, including ours [72, 139, 140], are contributing essential insights that may facilitate the development of a more standardised model. The age, gender, and strain of zebrafish used in experiments demonstrate considerable variability. In zebrafish, the term "adult" typically denotes the achievement of sexual maturity, which occurs at around 3 months of age [141]. The ageing process in zebrafish is being studied and is linked to functional changes [142], which may impact study outcomes and make comparisons of findings unsuitable.

Zebrafish models exhibit specific characteristics of Parkinsonism due to anatomical, biochemical, and cellular pathological similarities to human systems. Nonetheless, they may not fully capture the diversity present in the aetiology of human Parkinson's disease [143]. The mechanisms of disease induction in these fish fail to sufficiently account for the gradual and progressive features of human Parkinson's disease. Parkinson's disease in humans is characterised by the progressive degeneration of dopaminergic neurones and the accumulation of alpha-synuclein over time. Zebrafish models demonstrate accelerated symptom onset after toxin exposure, thereby complicating the exploration of long-term, age-related factors in Parkinson's disease [144]. There are notable differences in the pharmacokinetics of drug metabolism, the characteristics of the blood–brain barrier, and drug responses when comparing zebrafish and humans. As a result, findings from drug testing may not directly translate and necessitate validation in mammalian models before proceeding with further development [144, 145]. Zebrafish models offer significant benefits, including accelerated development, optical transparency, and potential for genetic modification. These models are particularly useful for investigating the basic mechanisms of neurodegeneration and for performing drug screening [146]. Integrating insights from zebrafish with other animal models and human studies is crucial for a comprehensive understanding of Parkinson's disease. The homology of the catecholamine cascade indicates that neurotoxin models in zebrafish are advantageous for the development of effective therapeutics for Parkinson's disease. This discussion focuses on the use of the neurotoxin 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a model for Parkinson's disease, highlighting its straightforward administration in zebrafish.

While MPTP neurotoxin clearly contributes to the manifestation of Parkinson's disease symptoms in zebrafish, several challenges related to its application warrant attention. Previous studies utilising the MPTP-induced paradigm have demonstrated that the effects of this neurotoxin are transient (Sarath Babu et al., 2016; Godoy et al., 2020; Wasel et al., 2020) [20, 133, 147]. In summary, the neurochemical changes resulting from MPTP injection caused a temporary dysfunction of dopaminergic neurones. Continuous exposure to MPTP is required in the zebrafish model to sustain the effects of MPTP. The different methods of administering MPTP to zebrafish models may lead to inconsistencies in dosage and exposure duration. For example, despite equivalent dosages, a lesser amount of MPTP will arrive at the target area when delivered intraperitoneally compared to intracerebellar injection, due to the increased travel distance. A similar example is observed in zebrafish embryos or larvae. The immersion-induced MPTP may lead to varying levels of compound absorption in individual embryos or larvae. Careful precautions are essential, as this issue may influence the interpretation of results and the overall success of the research. Despite these challenges, MPTP has provided significant insights into the development of zebrafish as a model for Parkinson's disease. The combination of gene knockdown and MPTP exposure has enabled the investigation of the relationships between genetic and environmental factors in the onset of Parkinson's disease. This neurotoxin has enabled substantial discoveries, allowing researchers to enhance their understanding of the mechanisms and pathology of Parkinson's disease.

The toxic mechanism of MPTP and its conversion to MPP+ offers a valuable framework for the development of animal models of Parkinson's disease in research, as it replicates several key pathological characteristics of the disorder [148]. The progression of MPTP-induced Parkinsonism generally occurs more rapidly and severely than that of idiopathic Parkinson's disease in humans. MPTP is not considered a causative factor in idiopathic Parkinson's disease among human patients. MPTP, despite its limitations, has demonstrated significant value in Parkinson's disease research due to its pharmacodynamic properties in neural tissues [15]. MPTP is beneficial as it accurately mimics the effects on catecholaminergic production, as well as behavioural and motor deficits. Most MPTP zebrafish models predominantly employ fish in early developmental stages. The zebrafish embryonic model of Parkinson's disease is preferred mainly because of the straightforward nature of MPTP induction, which can be readily dissolved in tank water at appropriate dilutions. Embryonic zebrafish can absorb the neurotoxin MPTP through their gill capillaries, leading to irreversible neurological deficits within a few hours. Numerous studies have utilised this method, allowing fish to reach sexual maturity after incubation in MPTP during the larval developmental phase [15, 72].

Many questions remain and articulating them could encourage experimenters to seek answers. Is sporadic Parkinson's disease caused by toxicants that penetrate the brain, or does it have its origins in the gut, as proposed by certain researchers? The narrative suggests that unidentified toxicants may penetrate the blood–brain barrier and interfere with the interconnected pathways of glutathione and metal disposition. What explains the variations in mechanistic evaluations of rotenone, MPP+, and 6HD, given their shared inhibition of Complex I in mitochondria? Do sporadic Parkinson's disease and non-Lewy body Parkinsonism share common etiological factors, and what is the relevance of Lewy bodies in this context? What is the role of neuromelanin? Does it serve a protective function, or does it act as a repository for readily oxidised catecholamines that were utilised as neurotransmitters before the evolution of long-lived animals? What explains the relative deficiency of metallothionein and glutathione in healthy neurones? Do they interfere with neurotransmission, which relies on zinc mobilisation, or is this simply another instance of neurones depending on astrocytes, which contain substantial amounts of metallothionein and glutathione, for protection? Is there a specific reductase enzyme that reduces oxidised sulfhydryl groups in metallothionein to restore functionality? Does this reaction also utilise GSH? What roles do MTF1 and MTF2 play in transcriptional regulation and resilience to threats? In conclusion, a notable question emerges: Is there a therapeutic strategy to prevent neurodegeneration after a substantial loss of neurones has occurred and symptoms have presented? Should resources be directed towards the identification of causes and the prevention of neurodegenerative diseases instead? Neurodegenerative diseases display variability; nonetheless, they consistently lead to the degeneration of neuronal groups. Parkinson's disease and Parkinsonism are environmental disorders marked by the selective degeneration of dopaminergic neurones in the substantia nigra, noted in individuals exposed to agents like rotenone or MPTP, as well as in animals administered these substances or 6-hydroxydopamine (6HD). This disease allows for the identification of environmental causes through chemical methods to reveal neuronal vulnerabilities. The observation that metallothionein genes were markedly induced by seven neurotoxicants, including rotenone, 6HD, MPP+, and methylmercury, indicates a potential connection between the metal disposition pathway and the glutathione pathway. Metallothionein detects reactive oxygen species (ROS), oxidised glutathione (GSSG), and free metals, including iron, and subsequently responds by releasing zinc ions. MTF1 binds to free zinc and activates the transcription of genes that adapt to stress, such as metallothionein and reductases. Neurones have restricted levels of GSH and low amounts of metallothionein, limiting their ability to tolerate free iron and reactive oxygen species (ROS). Neurones, especially large striatal dopaminergic neurones, necessitate considerable aerobic metabolism, resulting in significant production of reactive oxygen species (ROS). Low levels of glutathione (GSH) and metallothionein seem to make neurones vulnerable to disruptions in these metabolic pathways, increasing their dependence on astrocytes for protective assistance. Neurones typically exhibit deficiencies in metallothionein and glutathione.

7. Conclusions and future directions

The emergence of translational medicine has become a notable factor in the scientific community. Danio rerio has created a new framework in neurodevelopmental research, producing notable findings and advancements. Several neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, and Huntington's disease, have benefited from this species. Zebrafish, noted for its transparent embryos, ease of genetic manipulation, and short lifespan, has facilitated molecular research, particularly in omics, in ways that primates and rodents have not been able to accomplish.

The principle of precision medicine, combined with a comprehensive understanding of the omics (genomics, proteomics, metabolomics) of a disease, may improve healthcare practitioners' capacity to tailor therapies for individual patients. This patient-centred approach aims to achieve optimal therapeutic outcomes through individualised assessment of each patient. Considering that most cases of Parkinson's disease are classified as sporadic (non-hereditary) [149], comprehending precision medicine is essential for determining the most suitable therapeutic strategy for individual patients with Parkinson's disease. Extensive investigations of Parkinson's disease are conducted annually to explore its aetiology and pathophysiology; however, researchers still face considerable challenges in understanding this condition, especially at the molecular genomic and proteomic levels. Zebrafish has been established as the optimal model for Parkinson's disease research, especially in studies necessitating molecular analysis. The integration of MPTP with adult zebrafish has produced animal models that demonstrate measurable and observable alterations associated with human Parkinson's disease [81]. The advancement of this field is impeded by the lack of universally accepted and standardised protocols for the application of MPTP in adult zebrafish. There is variability in delivery routes, dosing of MPTP, tissue analysis techniques, and movement analysis methods [15].

The emphasis of treatments for Parkinson's disease has shifted towards symptom management due to the persistent difficulty in identifying a cure. The use of zebrafish as a model organism offers opportunities to improve our comprehension of the mechanisms underlying Parkinson's disease and to discover novel treatment alternatives. Zebrafish serve as an effective and cost-efficient model organism for studying neurological disorders, such as Parkinson's disease. The investigation of zebrafish models, combined with a deeper understanding of Parkinson's disease pathophysiology, may provide new insights and potential therapies for this complex condition.

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The authors declares that they have no competing interests.

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