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Research Article

Cerebellar vs. Cerebral Neurodegeneration: MPTP-Induced Parkinson's Disease Model in Swiss Albino Mice

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Abstract

Neurodegenerative diseases are severe conditions that affect human health by disrupting neuronal structure and function. Among the most common neurodegenerative diseases are Parkinson's disease (PD), Alzheimer's disease (AD), and multiple sclerosis (MS). PD is characterized by the degeneration of dopaminergic neurons and the aggregation of alpha-synuclein. MPTP is a widely used neurotoxin to replicate Parkinsonian symptoms in animal models. This study investigates the effects of MPTP on the cerebrum and cerebellum of mice, focusing on oxidative stress markers and neurotransmitter alterations. Mice were administered 14 mg/kg MPTP via intraperitoneal injection in four doses at 2-hour intervals, following Jackson-Lewis & Przedborski's protocol [Figure 1]. The results demonstrate that MPTP induces oxidative stress and neurotransmitter depletion in both the cerebrum and cerebellum, leading to neurodegeneration. The findings suggest that MPTP not only impacts the motor function controlled by the cerebellum but also affects cognitive regions in the cerebrum.

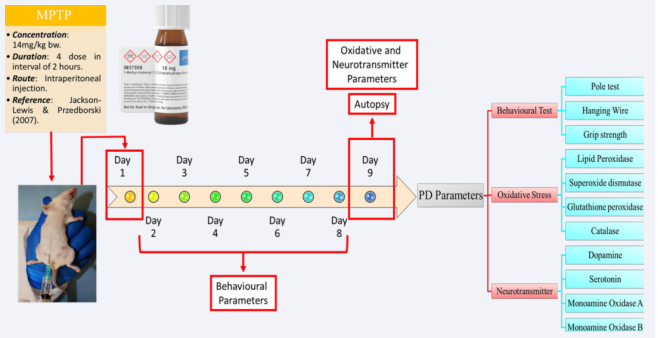

Figure 1 Graphical Abstract.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects the motor system, resulting in symptoms such as bradykinesia, tremors, muscle rigidity, and postural instability [1]. The underlying pathology involves the degeneration of dopaminergic neurons in the substantia nigra, a region of the brain that plays a critical role in the regulation of movement. The depletion of dopamine in the brain, particularly in the striatum, disrupts normal motor control and leads to the characteristic motor deficits observed in PD patients. While the exact cause of PD remains unknown, genetic, environmental, and age-related factors are considered to contribute to its development [2].

To study Parkinson's disease, researchers often use animal models to simulate the disease's neurodegenerative processes. One of the most widely used neurotoxins to create a Parkinsonian model is 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) [3]. MPTP itself is not toxic, but when administered, it crosses the blood-brain barrier and is metabolized by monoamine oxidase-B (MAO-B) into 1-methyl-4-phenylpyridinium (MPP+), a toxic metabolite. MPP+ selectively targets dopaminergic neurons in the substantia nigra, leading to neuronal death, oxidative stress, and a significant reduction in dopamine levels, which mimics the neurodegenerative and motor symptoms of Parkinson's disease [4].

In this study, we aim to investigate the effects of MPTP on two brain regions: the cerebrum and the cerebellum. The cerebrum, particularly the motor cortex, is involved in planning and executing voluntary movements. The cerebellum, on the other hand, is responsible for fine motor coordination, balance, and muscle tone regulation. Although the cerebellum has not been traditionally associated with Parkinson's disease as closely as the basal ganglia, recent research has suggested that it may play a role in compensating for motor deficits, and its dysfunction can contribute to the movement abnormalities seen in PD. Therefore, understanding how MPTP affects these two brain regions could provide new insights into the broader neurological impact of Parkinson's disease.

By administering MPTP to Swiss albino mice, we seek to

model the neurodegenerative processes seen in PD and analyse oxidative stress and neurotransmitter depletion in both the cerebrum and cerebellum. Our goal is to determine which brain region is more vulnerable to MPTP-induced neurotoxicity and how this correlates with motor deficits observed in Parkinson's disease models. This study will focus on evaluating the effects of MPTP on oxidative stress markers, such as lipid peroxidation (LPO), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), as well as on neurotransmitters like dopamine, serotonin monoamine oxidase – A (MAO-A) and monoamine oxidase - B (MAO-B). Through this investigation, we aim to provide a better understanding of the relationship between these brain regions and Parkinson's disease pathology.

MATERIALS AND METHODOLOGY

Chemical

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was procured from Merck M0896 Sigma-Aldrich named as 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride.

Animal Model and MPTP Administration

Male Swiss albino mice (8–10 weeks old, weighing 20–25g) were used for the experiment. The animals were procured from the animal house approved by Ethical Committee CPCSEA Registration number: IAEC/2022/I/5 and housed in a controlled environment (12-hour light/dark cycle, with ad libitum food and water). The experimental group received MPTP injections (14 mg/kg body weight) intraperitoneally in four doses, administered at 2-hour intervals [3]. The control group received normal saline 0.9% NaCl solution injections in the same pattern.

Behavioural parameters

To assess motor function and neuromuscular coordination in Swiss albino mice, the following behavioral tests were conducted:

Grip Strength: This test was done to evaluate forelimb muscle strength in mice. During this test, the mice were gently held by the base of their tails and allowed to grip a horizontal metal bar (diameter: 2 mm) with their forelimbs. Once the mouse had a firm grip, the mouse was slowly pulled backward until it released the bar. The time each mouse was able to maintain its grip was recorded in seconds [2]. Three trials were conducted for each mouse, and the mean value was used for analysis. A reduction in grip strength indicates motor impairment. Percent decrease in grip strength was calculated as follows -

$$\frac{Time \text{ taken}}{Total\ Time \text{ taken}} \times 100$$

Hanging Wire: This test was done to assess endurance, neuromuscular strength, and coordination. During this test, the mice were placed on a wire mesh that was inverted to a height of 50 cm above a soft surface. Mice naturally cling to the wire when inverted, and the time taken for each mouse to fall from the wire was recorded. Mice were given three trials, and the maximum duration each mouse held onto the wire was recorded in seconds. The mean of three trials was calculated. A lower hanging time reflects muscle weakness and coordination deficits [2].

Pole Test: This test was done to assess bradykinesia and motor coordination. During this test, a vertical wooden pole (50 cm in height, 1 cm in diameter) was used. Each mouse was placed head-up near the top of the pole, and the time taken for the mouse to turn and descend to the base was recorded in seconds. This test evaluates motor skills, particularly agility and coordination. The average time taken across three trials was calculated. Prolonged descent times indicate motor dysfunction typically associated with Parkinsonism [5].

Below given are oxidative stress and neurotransmitter parameters that were performed after autopsy:

Brain Homogenate Preparation

After behavioral testing, the mice were euthanized, and their cerebrum and cerebellum were carefully dissected on ice. The tissues were homogenized for biochemical analysis of oxidative stress markers and neurotransmitter levels [6].

Oxidative Stress/ Antioxidants

To assess the oxidative stress levels in the cerebrum and cerebellum of the mice, the following biochemical assays were performed on brain homogenates:

Lipid Peroxidase: Lipid peroxidase (LPO) activity was estimated to measure the level of malondialdehyde (MDA), a product of lipid peroxidation, as an indicator of oxidative damage to lipids, by the method of Ohkawa et al [7]. Brain tissue homogenates were mixed with thiobarbituric acid (TBA) reagent and incubated in a boiling water bath for 60 minutes. The resulting pink-colored MDA-TBA complex was measured spectrophotometrically at 532 nm. Lipid peroxidation was expressed as nmol of MDA/mg of protein.

Catalase: To measure the activity of catalase, an enzyme that catalyzes the breakdown of hydrogen peroxide into water and oxygen, by the method of Aebi et al [8]. The decomposition of hydrogen peroxide (H_2O_2) was measured spectrophotometrically at 240 nm over a 1-minute period in brain tissue homogenates. Catalase activity was expressed as μmol of H_2O_2 decomposed per minute per mg of protein.

Superoxide Dismutase: The activity of superoxide dismutase was estimated by the method of Markland and Markland, which catalyzes the dismutation of superoxide radicals. The assay was based on the inhibition of pyrogallol autooxidation by SOD. Brain homogenates were incubated with pyrogallol, and the absorbance was recorded at 420 nm. The decrease in the rate of pyrogallol oxidation was used to calculate SOD activity. SOD activity was expressed as U/mg protein, where one unit is the amount of enzyme required to inhibit the oxidation of pyrogallol by 50%.

Glutathione Peroxidase: To measure the activity of

GPx, an enzyme that reduces hydrogen peroxide by oxidizing glutathione, by the method of Paglia and Valentine et al [9]. The reaction mixture contained brain tissue homogenates, reduced glutathione (GSH), H_2O_2, and NADPH. The decrease in NADPH absorbance was measured spectrophotometrically at 340 nm. GPx activity was expressed as µmol of NADPH oxidized per minute per mg of protein.

Neurotransmitter

To determine the neurotransmitter levels in the cerebrum and cerebellum, the following assays were used:

Dopamine: The quantification of dopamine by the utilization of an iodine solution involves using a colorimetric technique that relies on the oxidation of dopamine by iodine under acidic circumstances, resulting in the formation of a pigmented substance [10]. The enzyme activity was expressed as nmol per mg of protein.

Serotonin: The Schlumfjf method is based on the idea of converting serotonin into its fluorescent derivative, which may subsequently be measured using a spectrofluorometer. The technique described in this study utilizes the inherent fluorescence properties of serotonin derivatives that are produced through the reaction between o-phthaldialdehyde (OPA) and a sulfhydryl molecule, specifically 2-mercaptoethanol. The content of serotonin in the sample can be determined by measuring the resultant fluorescent molecule at specified wavelengths. Lastly, the enzyme activity was expressed as nmol per mg of protein [10].

Monoamine Oxidase – A and B: The activity of monoamine oxidase – A and B (MAO-A and MAO-B) was estimated by the method of Charles and McEwen. Brain homogenates were incubated with the substrates, and the enzymatic activity was measured by the production of metabolites. The rate of substrate oxidation was monitored using a spectrophotometer at 280 nm for MAO-A and 297 nm for MAO-B. MAO-A and MAO-B activities were expressed as nmol substrate metabolized/min/mg protein [11].

Statistical Analysis

All data were expressed as the mean ± standard error of the mean (SEM). Statistical significance between control and MPTP-induced groups was determined using one-way ANOVA followed by Tukey's post-hoc test. A p-value of less than 0.05 was considered statistically significant (*).

RESULTS

Behavioural Parameters

Mice treated with MPTP displayed significant reductions in motor function compared to the control group, as seen in the grip strength, hanging wire, and pole tests. Table 1 provides a summary of the behavioral performance.

Table 1: Effect of MPTP on behavioural activity of Swiss albino mice

Groups\ Parameters	Grip Strength	Hanging Wire	Pole Test
Control	16.7±1.7	70.07±6.6	26.8±1.6
MPTP - Induced	8.9±2.6*	15.6±1.03*	44.5±5.5*

Values are expressed as Mean ±Standard Error. * Significant difference from control ($p<0.05$).

Grip Strength: The grip strength test revealed a significant reduction in forelimb muscle strength in MPTP-induced mice compared to the control group [Table 1]. Grip strength is primarily controlled by the motor cortex and spinal cord, but the cerebellum also plays a crucial role in coordinating muscle movements. The significant decrease in grip strength in MPTP-treated mice suggests that motor coordination and muscle strength, which involve cerebellar function, are severely affected.

Hanging Wire: The hanging wire test evaluates neuromuscular coordination and endurance. It shows a significant ($p<0.05$) decrease in the MPTP-treated group as compared to the control [Table 1]. The pronounced reduction in performance in MPTP-treated mice indicates impaired neuromuscular function, which is associated with cerebellar dysfunction since the cerebellum is essential for maintaining balance and coordination.

Pole Test: The pole test assesses motor coordination and balance, both of which are heavily dependent on the cerebellum. And showed a significant ($p<0.05$) increase in the MPTP-treated group as compared to the control [Table 1]. The increased descent time in MPTP-treated mice reflects impaired motor coordination and balance, reinforcing the cerebellum's critical role in these functions.

Oxidative Stress/ Antioxidants

Administration of MPTP to the mice leads to an elevation in ROS and oxidative stress levels. The present study showed a significant ($p<0.05$) decline in the activity of catalase, glutathione peroxidase, and superoxide dismutase whereas significant ($p<0.05$) escalation in the activity of lipid peroxidase.

Lipid Peroxidase: The level of Lipid peroxidase shows a significant ($p<0.05$) increase in the cerebrum, and cerebellum [Table 2]. Elevated lipid peroxidation indicates oxidative damage. The higher LPO in the cerebellum suggests greater oxidative stress and cellular damage in this region compared to the cerebrum, highlighting the cerebellum's increased vulnerability to MPTP-induced oxidative damage.

Catalase: CAT helps decompose hydrogen peroxide, a reactive oxygen species. The level of catalase shows a significant ($p<0.05$) decrease in the cerebrum, and cerebellum [Table 2]. The greater decrease in CAT activity in the cerebellum indicates a reduced capacity to manage oxidative stress, making it more susceptible to damage.

Superoxide Dismutase: SOD is an enzyme that helps neutralize superoxide radicals. The level of Superoxide dismutase shows a significant ($p<0.05$) decrease in the cerebrum, and

cerebellum [Table 2]. The more significant reduction in SOD activity in the cerebellum suggests a higher level of oxidative stress and reduced ability to counteract oxidative damage in this region.

Glutathione Peroxidase: GPx reduces hydrogen peroxide and organic peroxides. The level of Glutathione peroxidase shows a significant ($p<0.05$) decrease in the cerebrum, and cerebellum [Table 2]. The more significant decline in GPx activity in the cerebellum suggests diminished antioxidant defenses in this region, contributing to its increased vulnerability to oxidative stress.

Neurotransmitter

Administration of MPTP to the mice leads to alteration in neurochemical levels. Dopamine, and Serotonin levels showed a significant ($p<0.05$) decline in the cerebrum, and cerebellum. Monoamine oxidase-A showed significant ($p<0.05$) increment in the cerebrum, and cerebellum and Monoamine Oxidase-B showed a significant ($p<0.05$) increment in cerebellum.

Dopamine and Serotonin: Both the level of Dopamine and Serotonin showed a significant ($p<0.05$) decrease in the cerebrum, and cerebellum (Table 3). The cerebellum has fewer dopamine and serotonin neurons compared to the cerebrum, making it more sensitive to decreases in neurotransmitter levels. The severe reduction in these neurotransmitters in the cerebellum reflects its high sensitivity to MPTP-induced neurotoxicity.

Monoamine Oxidase: *Monoamine Oxidase – A*: The level of MAO-A shows a significant ($p<0.05$) increase in the cerebrum, and cerebellum [Table 3]. Elevated MAO activity indicates increased neurotransmitter degradation.

Monoamine Oxidase – B: The level of MAO-B shows a significant ($p<0.05$) increase in cerebellum [Table 3]. The higher MAO-B activity in the cerebellum suggests more extensive neurochemical changes and neurotoxicity in this region compared to the cerebrum.

DISCUSSION

The present study was performed to analyze the effects of MPTP on various behavioural parameters, oxidative stress, and neurotransmitters assay in different areas of the brain. According to the results, there was a significant ($p<0.05$) decrease in the level of pole test, hanging wire and grip strength behavior activity after 1 day of treatment of MPTP. Grip strength help in motor coordination and to assess central nervous system (CNS) disorder. In present study the activity of grip strength decline significantly ($p<0.05$) in comparison to control [Table 1], Similar results were depicted by other researchers, Bagga et al. [12], reported a significant decline in the activity of grip strength with a MPTP dose of 25 mg/kg body weight (intraperitoneal) administration for 8 days.

Pole test describes the movement of basal ganglia part and hanging wire able to show the muscle coordination. Moreover, in present study they were seen to give significant decline the activity of both pole test and hanging wire behaviour [Table 1]. Similar results were observed by Zhang et al [13]. Who reported a significant elevation in the level of Pole test and hanging wire activity with exposure to MPTP (30 mg/kg body weight intraperitoneal 1 h) for 8 days to C57BL mice.

An important pathophysiological role in the emergence of neurodegenerative illnesses is played by oxidative stress, which is an imbalance between the generation of harmful reactive oxygen species (ROS) and the body's natural antioxidant defense mechanism. Lipid peroxidation, DNA damage, inflammation, and consequent cell death are all caused by lipid oxidation, which also causes cellular and tissue damage by covalent bonds. Presently, there shown a significant ($p<0.05$) increase in the level of lipid peroxidase after 1 day of treatment of MPTP in the cerebrum, and cerebellum [Table 2]. Similar results were observed by Rehman et al. [14], who reported a significant elevation in the level of lipid peroxidase activity with exposure to MPTP (30 mg/kg body weight intraperitoneal) for 5 days to C57BL mice. Similarly, Sugumar et al. [15], reported a significant elevation in the activity of lipid peroxidase with exposure to MPTP (40 mg/kg body weight intraperitoneal) in an interval of 16 hours to C57BL mice. LPO levels were found to be elevated in the frontal cortex of Parkinson`s affected patients [16]. In contrast, the level of superoxide dismutase, catalase, and glutathione peroxidase declined in Parkinson`s cases [17].

Catalase helps to protect against reactive oxygen species [18]. Moreover, inhibition of catalase leads to an elevation in

Table 2: Effect of MPTP on oxidative stress in brain of Swiss albino mice

Groups\Parameters + Brain areas	Lipid Peroxidase		Catalase		Superoxide Dismutase		Glutathione Peroxidase	
	Cerebrum	Cerebellum	Cerebrum	Cerebellum	Cerebrum	Cerebellum	Cerebrum	Cerebellum
Control	0.01±0.009	1.7±0.02	90.07±1.6	226.8±10.7	647.5±9.9	164±10.3	2.06±0.02	4.6±0.02
MPTP- Induced	1.2±0.02*	323.2±2.21736*	0.4±0.02*	41.3±0.02*	38.7±5.004*	56.3±4.3*	0.04±0.02*	2.2±0.4*

Values are expressed as Mean ±Standard Error. * Significant difference from control ($p<0.05$).

Table 3: Effect of MPTP on neurotransmitter level in brain of Swiss albino mice

Groups\Parameters + Brain areas	Dopamine		Serotonin		Monoamine Oxidase - A		Monoamine Oxidase - B	
	Cerebrum	Cerebellum	Cerebrum	Cerebellum	Cerebrum	Cerebellum	Cerebrum	Cerebellum
Control	1.2±0.07	1.2±0.2	2.03±0.02	1.05±0.02	0.07±0.01	0.07±0.02	0.1±0.02	0.1±0.02
MPTP- Induced	0.3±0.02*	0.1±0.02*	1.02±0.01*	0.9±0.02*	1.05±0.005*	0.4±0.05*	0.2±0.05	2.9±0.3*

Values are expressed as Mean ±Standard Error. * Significant difference from control ($p<0.05$).

reactive oxygen species and oxidative stress [19]. Hence, catalase is significant in maintaining the oxidative balance. In the present study, the level of catalase is significantly ($p<0.05$) decreased in the cerebrum, and cerebellum as compared to the control [Table 2]. Similar results were quoted by Ardah et al. [20], the level of catalase and superoxide dismutase decreased significantly in MPTP as compared to saline as control with the exposure of MPTP dose (25 mg/kg body weight intraperitoneal) for 5 days to C57BL mice. Superoxide dismutase has the ability to counteract the destructive level of reactive oxygen species [21]. Furthermore, in the present study, the level of superoxide dismutase significantly ($p<0.05$) decreased in the cerebrum, and cerebellum by MPTP as compared to control [Table 2]. For superoxide dismutase similar results were showed by Wang et al, [22], with an MPTP dose (30 mg/kg/day body weight intraperitoneal) for 5 days to C57BL mice. Lastly, Glutathione peroxidase is significant in the conversion of glutathione to oxidized glutathione disulfide and glutathione reductase that reduced to further glutathione disulfide and leads to the formation of glutathione [23]. This is how GPx maintains the oxidative balance and decreases the level of Hydrogen peroxide [24]. Therefore, reduction in the level of glutathione peroxidase leads to increased oxidative stress and in the present study, the level of glutathione peroxidase is significantly ($p<0.05$) decreased by MPTP as compared to control [Table 2]. Also, a significantly decreased level of GPx was noted by Chang et al, [25], with an MPTP dose (20 mg/kg body weight intraperitoneal) for 5 days with every 4-hour interval to C57BL mice. Hence the antioxidant levels can maintain the redox balance.

Dopamine is the most significant neurochemical which maintains homeostasis and is also a precursor of other catecholamine. It is basically a feel-good chemical moreover its declination leads to depression or degeneration of dopaminergic neurons and its elevation leads to favourable conditions in the central nervous system [26]. Our results showed a significant ($p<0.05$) decrease in the level of dopamine in the cerebrum, and cerebellum by MPTP dose as compared to control [Table 3]. Similar results were shown by Zhang et al. [27], decreased level of dopamine in MPTP as compared to the control and the dose given of MPTP was (30 mg/kg/day body weight intraperitoneal) for 5 days to C57BL mice. Furthermore similar to the level of dopamine, serotonin also significantly ($p<0.05$) decreased in the cerebrum, and cerebellum by MPTP as compared to the control [Table 3]. Janakiraman et al. [28], reported the decline levels of both dopamine and serotonin in the MPTP model with a dose of (25 mg/kg body weight intraperitoneal) for 5 weeks in mice. The last, neurotransmitter is Monoamine oxidase – A and B. Monoamine is an enzyme that breaks the neurotransmitters, and Monoamine inhibitors drugs prevent the action of the monoamine enzyme [29]. So inhibiting the action of the monoamine enzyme will increase the level of neurotransmitters that is capable to release into the synapse and their increase cause an action potential. MAO – A breaks down serotonin, norepinephrine, melatonin, and epinephrine and is majorly found in the liver. And MAO – B is found in blood platelets and in the brain, which breaks down dopamine [30]. In the present study, the level of MAO – A is significantly ($p<0.05$) increased in the cerebrum, and cerebellum [Table 3], and the level of MAO – B is significantly ($p<0.05$) increased in the cerebellum [Table 3]. On the basis of this study, we can conclude that MPTP affects behavioural aspects of animals, neurotransmitter levels, and posed oxidative stress levels in mice at the tested dose levels. Therefore, this dose can be used to develop the PD mice model and this model can be further used to perform various therapeutical studies for Parkinson`s disease.

CONCLUSION

The present study concludes that 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), administered at a dosage of 14 mg/kg body weight in four doses at 2-hour intervals, induces significant neurotoxic effects, particularly in the cerebellum, as compared to the cerebrum. The results show a pronounced decline in motor function in MPTP-treated mice, as evidenced by reduced grip strength, shorter hanging wire time, and longer pole test descent times, reflecting marked motor impairment. When compared to control mice, MPTP-treated mice exhibited significant oxidative stress, with lipid peroxidation levels being considerably higher in the cerebellum (323.2 ± 2.2 nmol MDA/mg protein) compared to the cerebrum (1.2 ± 0.02 nmol MDA/mg protein). This suggests that the cerebellum experiences greater oxidative damage. Additionally, antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) showed more drastic reductions in activity in the cerebellum than in the cerebrum, indicating that the cerebellum's ability to counteract oxidative stress is more severely compromised.

Neurotransmitter analysis further supports this observation, as dopamine and serotonin levels were significantly lower in the cerebellum than in the cerebrum following MPTP exposure. Dopamine levels in the cerebellum dropped to 0.1 ± 0.02 ng/mg protein compared to 0.3 ± 0.02 ng/mg protein in the cerebrum, while serotonin levels also followed a similar trend. Monoamine oxidase-B (MAO-B) activity, which is associated with the breakdown of dopamine, was markedly elevated in the cerebellum compared to the cerebrum, further indicating the cerebellum's heightened neurochemical vulnerability.

Comparing these results to the control group, where both brain regions maintained normal oxidative stress levels, antioxidant activity, and neurotransmitter levels, it is evident that the cerebellum is more susceptible to MPTP-induced neurotoxicity than the cerebrum. The greater oxidative damage, reduced antioxidant defenses, and more pronounced neurotransmitter depletion in the cerebellum make it the brain region most affected by MPTP. This finding is critical as it highlights the cerebellum's significant involvement in motor dysfunction in Parkinson's disease and suggests a novel area for targeted research and therapeutic development in addressing neurodegenerative disorders.

Credit Authorship Contribution Statement

Kanika Bhardwaj: Design, Conception, and Experimentation, Analysis of the result, Interpretation, Drafted manuscript and critically revised manuscript. Author gave final approval and agrees to be accountable for all aspects of the work ensuring integrity and accuracy.

Ethical Approval

Male Swiss Albino mice weighing around 28 ± 2 grams were procured from the animal house approved by Ethical Committee CPCSEA Registration number: IAEC/2022/I/5.

Data Availability

The author confirms that data supporting the findings of this study are available within the article in the form of figures and tables.

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