

Original Research Article

Pioglitazone improves motor function and attenuates the central and peripheral alpha-synuclein burden in a rotenone-induced model of Parkinson's disease in rats

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Abstract

Purpose: To investigate the neuroprotective effect of Pioglitazone (PIO), a PPAR- γ agonist, in reducing central and peripheral α -synuclein (α -Syn) burden in rotenone-induced Parkinson disease (PD).

Methods: A total of 48 adult male Wistar rats were randomly and equally divided into six groups ($n = 8$). Group 1 was control, groups 2, 3, 4, 5, and 6 received rotenone to induce Parkinsonism (2.5 mg/kg, intraperitoneal every 48 h for 21 days). Groups 3, 4, 5, and 6 was treated with carboxyl methylcellulose, rasagiline (1 mg/kg/day), and pioglitazone at 10 and 20 mg/kg/day respectively. Oral treatments started three days before the first rotenone injection and continued throughout the study. Body weight was recorded on days 1, 7, 14, and 21. Behavioural assessments were performed on Day 22 (24 h after the final treatment dose) using rotarod and open field tests to evaluate locomotor activity, exploratory behavior, and motor coordination. α -Syn expression was quantified using brain immunohistochemistry (IHC) and serum enzyme-linked immunosorbent assay (ELISA).

Results: Rotenone administration successfully induced Parkinsonian evidenced by significant decrease in body weight, motor and behavioural impairments, higher cerebral α -syn accumulation, and lower α -syn serum levels ($p < 0.05$) compared to the control. Treatment with Pioglitazone significantly increased mean body weight, reduced cerebral α -syn accumulation and increased serum α -syn levels in a dose-dependent manner compared to group 2 (rotenone group; $p < 0.05$).

Conclusion: Pioglitazone significantly reversed symptoms of Parkinsonism induced by rotenone in a dose-dependent manner.

Keywords: Neuroprotection, Parkinson disease, Pioglitazone, Rotenone, α -Synuclein

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INTRODUCTION

Parkinson disease (PD) is a chronic and progressive neurodegenerative disorder characterized by irreversible degeneration of dopaminergic neurons within the substantia nigra pars compacta and intracellular accumulation of misfolded alpha-synuclein (α -syn) in the form of Lewy body inclusions [1]. Although, the

pathological hallmark of PD has traditionally been linked to the central nervous system, growing evidence suggests that α -syn pathology also involves peripheral tissues and biological fluids, supporting PD as a multisystem disorder [2]. Alpha-synuclein (α -syn) is present in central and peripheral compartments, and has emerged as a promising biomarker for evaluating disease-related pathological changes and monitoring

therapeutic responses [3]. Oxidative stress and neuroinflammatory mechanisms are also widely recognized as major contributors to neuronal dysfunction and disease progression, making them important therapeutic targets. Among the experimental models used to study pathogenesis of PD, rotenone-induced neurotoxicity is considered one of the most well-established approaches because it reproduces key clinical and pathological features of the disease, such as motor impairment, dopaminergic neuronal degeneration, mitochondrial dysfunction, and α -syn accumulation [5]. Due to its lipophilicity, rotenone readily penetrates the blood–brain barrier and inhibits mitochondrial complex I, leading to high production of reactive oxygen species (ROS), disruption of cellular bioenergetics, and progressive neuronal damage [6]. Also, rotenone model provides a reliable platform for evaluating potential neuroprotective therapies targeting disease-related pathological alterations. Pioglitazone (PIO), a peroxisome proliferator-activated receptor gamma (PPAR- γ) agonist, has gained considerable attention due to its antioxidant, anti-inflammatory, and neuroprotective effects demonstrated in experimental models of neurodegenerative disorders. Activation of PPAR- γ has been linked to reduced oxidative stress, regulation of inflammatory signaling pathways, preservation of mitochondrial function, and promotion of neuronal survival [7]. Therefore, this study investigated the neuroprotective effect of Pioglitazone (PIO) in rotenone-induced Parkinson disease (PD).

EXPERIMENTAL

Animals

A total of 48 Adult male Wistar rats (50 – 300 g) were housed at the Animal House of the College of Pharmacy, University of Babylon, under standard conditions (25 °C, 45 – 50 % relative humidity, and a regulated 12 h light / dark cycle), with unrestricted access to food and water *ad libitum* for 2 weeks to acclimatize. The rats were randomly allocated into six equal groups (n = 8) in each group. The study project was reviewed and approved by the scientific research ethical committee of the College of Pharmacy, University of Babylon (approval no. A-0062) and complied with the guide for care and use of laboratory animals [8].

Treatment

The animals were randomly allocated into six groups. Group 1 was control, groups 2, 3, 4, 5, and 6 received rotenone to induce Parkinsonism

(2.5 mg/kg, intraperitoneal every 48 h for 21 days). Groups 3 and 4 was treated with carboxyl methylcellulose (Xi'an Sonwu Biotech Co., Ltd., China), and rasagiline (1 mg/kg/day) respectively. Groups 5 and 6 received pioglitazone (Xi'an Sonwu Biotech Co., Ltd., China) at 10 and 20 mg/kg/day respectively. Oral treatment was initiated 3 days before the first rotenone injection and continued throughout the experimental period.

Evaluation of parameters/indices

Body weight

Body weight was recorded on day 1, 7, 14, and 21 in triplicate and presented in mean $\pm$ standard deviation (SD).

Behavioural assessments

Behavioural assessments were performed on day 22 (24 h after the final dose) using rotarod and open field tests. Each rat underwent three consecutive trials on the rotarod apparatus followed by a 10-minute open field test session. The sessions were video-recorded for offline analysis.

Open field test

Locomotor activity was quantified as the total number of grid line crossings during the test period. Rearing was defined as the total number of upright postures adopted by the rat while exploring its environment. Risk-taking behaviour was evaluated by recording the number of entries into the central zone of the arena. Grooming was measured as the cumulative time spent in self-grooming behaviour.

Rotarod test

Rats were required to maintain balance on a rotating cylinder at variable speeds, and performance was assessed by recording the number of revolutions completed.

Tissue collection and preparation

On day 22, each rat was sacrificed by cervical dislocation and the skull was opened posteriorly from the foramen magnum. The brain, cerebellum, and olfactory bulbs were carefully removed, and rinsed with phosphate-buffered saline (PBS). The brain tissues were carefully dissected, and immunohistochemical staining for α -syn aggregation was performed using standard streptavidin–biotin complex method.

Immunohistochemical detection of α -synuclein

Immunohistochemical staining was performed to assess α -syn expression and aggregation in brain tissue sections. Brain tissues were fixed in 10 % neutral buffered formalin, routinely processed, and embedded in paraffin wax. Serial coronal brain sections of 4–5 μ m thickness were prepared using a rotary microtome and carefully mounted on glass slides. Paraffin-embedded sections were de-paraffinized in xylene, rehydrated using graded ethanol series, and subjected to heat-induced antigen retrieval using 10 mM sodium citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with 3 % hydrogen peroxide for 10 min.

Sections were incubated overnight at 4 °C with a primary antibody against α -syn. After washing, sections were treated with a biotinylated secondary antibody and visualized using a diaminobenzidine (DAB) chromogen. Sections were counterstained with hematoxylin, dehydrated, and mounted for microscopic examination.

Quantitative analysis of immunostaining

Immunoreactivity was quantified using the Q-scoring system, determined by multiplying intensity of the staining by the percentage of positive cells (eq. 1). Resulting score was graded on a scale from 0 to 18. Staining intensity (multiplier) was graded as 0 (no staining), 1 (weak staining), 2 (moderate staining), and 3 (strong staining). Percentage of positive cells (factor) was mapped to a standardized 0 – 6 scale and graded as 0 (no cell stained), 1 (1 to 4 % cells stained), 2 (5 to 19 % cells stained), 3 (20 to 39 % cells stained), 4 (40 to 59 % cells stained), 5 (60 to 79 % cells stained) and 6 (80 to 100 % cells stained)

Q-score = Staining intensity (0-3) x Percentage factor (0 - 6) (1)

Serum alpha-synuclein analysis

Levels of α -syn were quantified from samples collected in gel separator tubes using a sandwich ELISA. The assay employed a biotinylated detection antibody with streptavidin-HRP amplification. Absorbance was measured spectrophotometrically, and concentrations were determined against a recombinant α -syn standard curve in pg/mL. Serum level of α -syn was measured using enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

Data was analyzed using Statistical Packages for Social Sciences version 26.0 (IBM Corp., Armonk, NY, USA). Data were expressed as mean $\pm$ standard deviation (SD), analyzed with one-way analysis of variance (ANOVA) followed by Tukey's Honest Significant Difference (HSD) post-hoc test for multiple comparisons using a two-tailed model.

Non-parametric data were analyzed using the Kruskal–Wallis test, followed by the Mann–Whitney U test for pairwise comparisons between groups. $P < 0.05$ was considered statistically significant.

RESULTS

Weight changes

Administration of Rotenone and CMC significantly reduced mean body weight at day 21 compared to control and group 4 ($p < 0.05$). However, treatment with PIO showed no significant difference in mean body weight on day 7, 14, and 21 compared to day 1 ($p > 0.05$).

Open field tests

Grooming Time

Grooming time was significantly reduced in groups 2 and 3 compared to control ($p < 0.05$). Furthermore, treatment with Rasagiline and PIO (10 and 20 mg/kg) significantly increased grooming time compared to Rotenone and control ($p < 0.05$; Figure 1).

Number of line crossing

Number of line crossings was significantly reduced ($p < 0.05$) in groups 2 and 3 compared to control ($p < 0.05$). Furthermore, number of crossing lines was significantly increased ($p < 0.05$) following treatment with Rasagiline and PIO. Also, group 6 showed significantly higher number of line crossings compared to group 5 ($p < 0.05$; Figure 2).

Number of rearing

The rearing frequency was significantly reduced ($p < 0.05$) in groups 2 and 3 but significantly increased ($p < 0.05$) after treatment with Rasagiline and PIO. However, PIO significantly increased rearing frequency in a dose-dependent manner ($p < 0.05$; Figure 3).

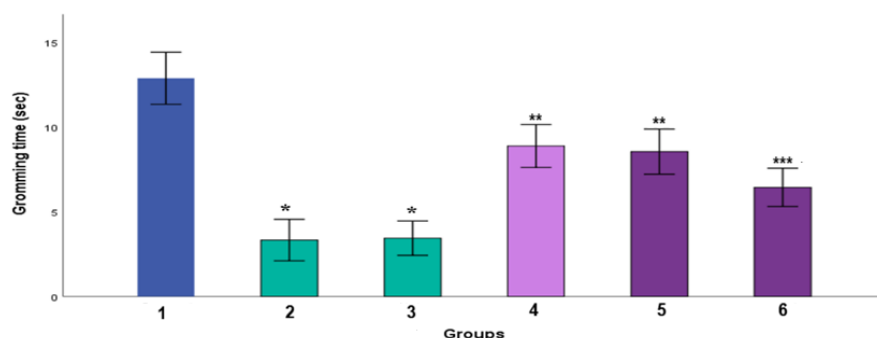


Figure 1: Grooming time in open field test. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data were expressed as mean $\pm$ SD. * P < 0.05 vs control, ** p < 0.05 vs control, groups 2, and 3; *** p < 0.05 vs control, groups 2, 3, 4, and 5

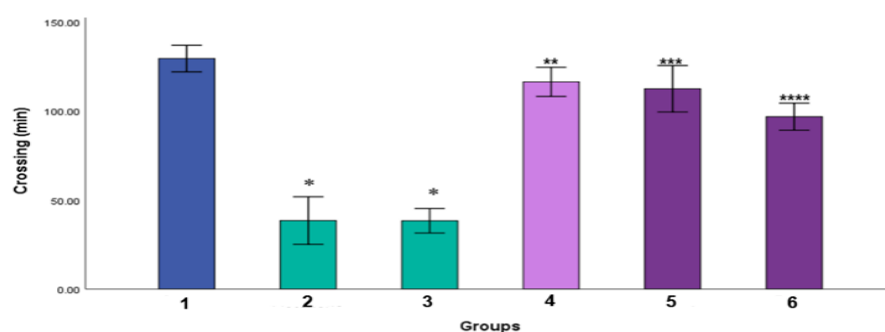


Figure 2: Number of line crossings in the open field test. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). * P < 0.05 compared to control, ** p < 0.05 vs groups 2, and 3; *** p < 0.05 vs groups 1, 2, and 3; **** p < 0.05 vs groups 1, 2, 3, 4, and 5

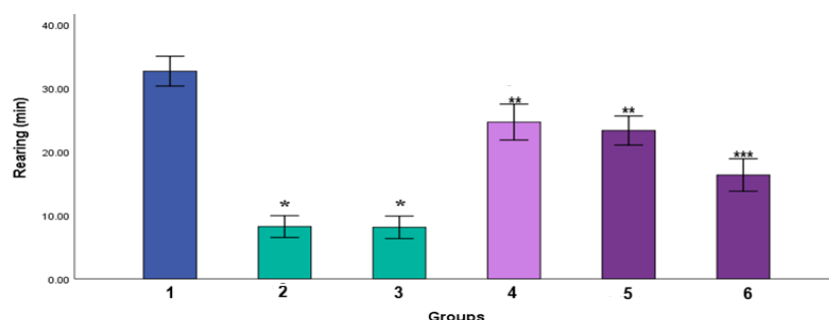


Figure 3: Number of rearings per min in the open field test. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data are expressed as mean $\pm$ SD. * p < 0.05 vs control, ** p < 0.05 vs groups 2, and 3; *** p < 0.05 vs groups 2, 3, 4, and 5

Number of visits to the center

The number of visits was significantly decreased in groups 2, and 3 compared to control (p < 0.05). However, Rasagiline and PIO significantly increased the number of visits compared to Rotenone and CMC (p < 0.05). Furthermore, group 5 showed significantly fewer visits than groups 4 and 5 (p < 0.05; Figure 4).

Rotenone aeration test

Number of Rotenoneations

Groups 2 and 3 showed significantly lower rotenoneations compared to control (p < 0.05). However, treatment with PIO significantly increased rotenoneations in a dose-dependent manner (p < 0.05; Figure 5).

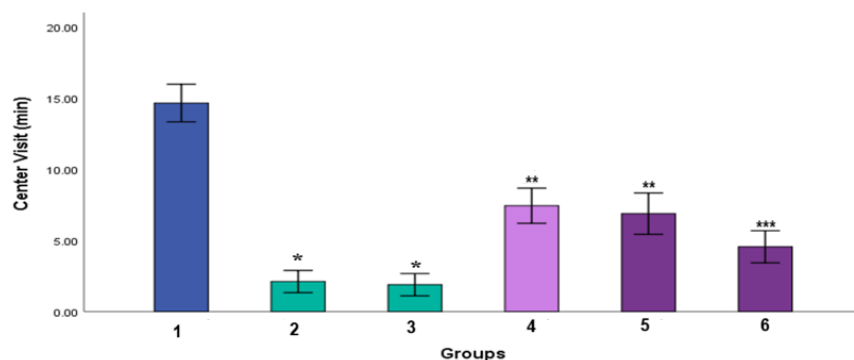


Figure 4: Number of visits to the center in the open field test. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data are expressed as mean $\pm$ SD. * $P < 0.05$ vs control, ** $p < 0.05$ vs groups 1, 2, and 3; *** $p < 0.05$ vs groups 1, 2, 3, 4, and 5

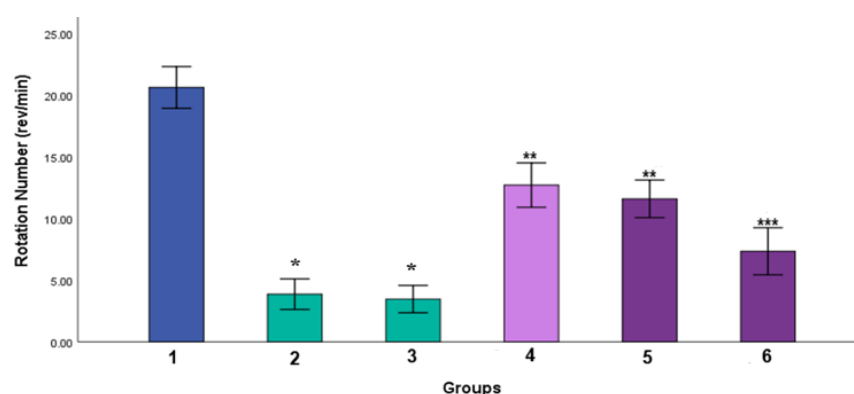


Figure 5: Number of Rotenoneations in the Rotenoneaerod test. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data were expressed as mean $\pm$ SD. * $P < 0.05$ vs control, ** $p < 0.05$ vs groups 1, 2, and 3; *** $p < 0.05$ vs groups 1, 2, 3, 4, and 5

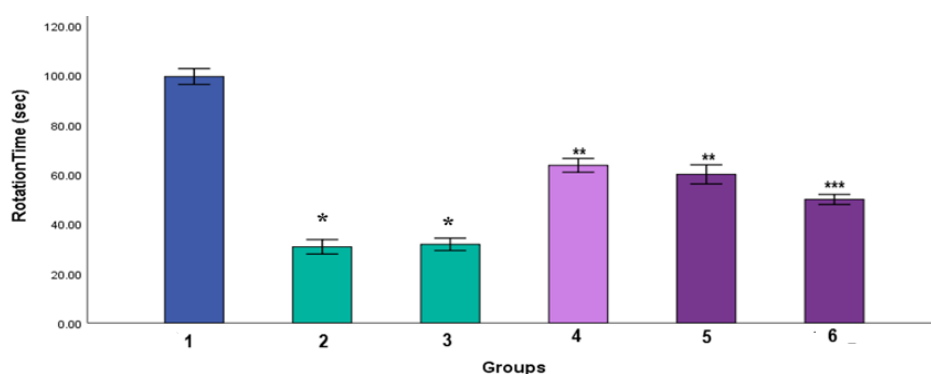


Figure 6: Time of Rotenoneation on the Rotenoneaerod (sec). Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data were expressed as mean $\pm$ SD. * $P < 0.05$ vs control, ** $p < 0.05$ vs groups 1, 2, and 3; *** $p < 0.05$ vs groups 1, 2, 3, 4, and 5

Time of rotenoneation

The time spent on the Rotenone-aerod apparatus was significantly decreased in groups 2 and 3 compared to control group ($p < 0.05$). However, treatment with PIO significantly

increased time of rotenoneation in a dose-dependent manner ($p < 0.05$; Figure 6).

Distance of rotenoneation

The motor coordination and balance of the rats were assessed using the distance of

rotenoneation. Distance of rotenoneation was significantly decreased ($p < 0.05$) in groups 2 and 3 compared to control. Treatment with rasagiline and doses of pioglitazone significantly increase distance travelled on the rotenonearod (Figure 7).

Alpha-synuclein in brain tissue

The immunohistochemical analysis revealed significant variations in α -syn expression across

different experimental groups. Control group exhibited a baseline score of zero, indicating no detectable α -syn pathology. In contrast, the α -syn IHC scores were significantly increased in groups 2 ($p < 0.05$). However, these scores were significantly decreased following treatment with Rasagiline and PIO ($p < 0.05$). Furthermore, α -syn expression in group 6 was significantly higher compared to group 4 and 5 ($p < 0.05$; Figure 8).

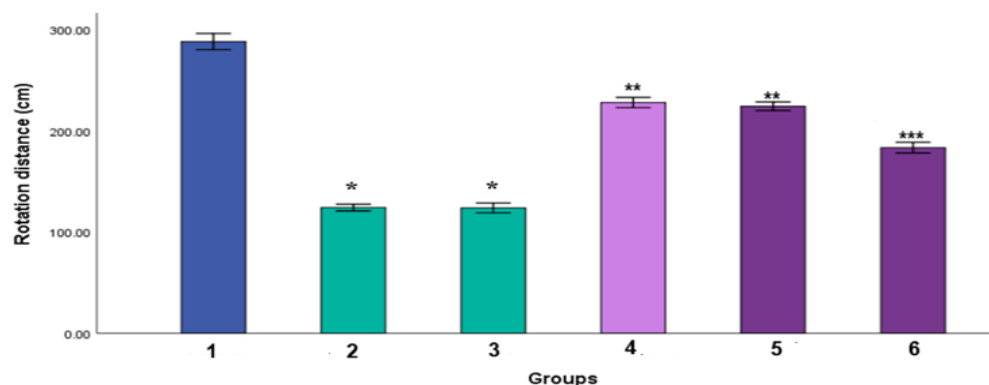


Figure 7: Distance of Rotenoneation (cm) on the Rotenonearod. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data were expressed as mean $\pm$ SD. * $P < 0.05$ vs control, ** $p < 0.05$ vs groups 1, 2, and 3; *** $p < 0.05$ vs groups 1, 2, 3, 4, and 5

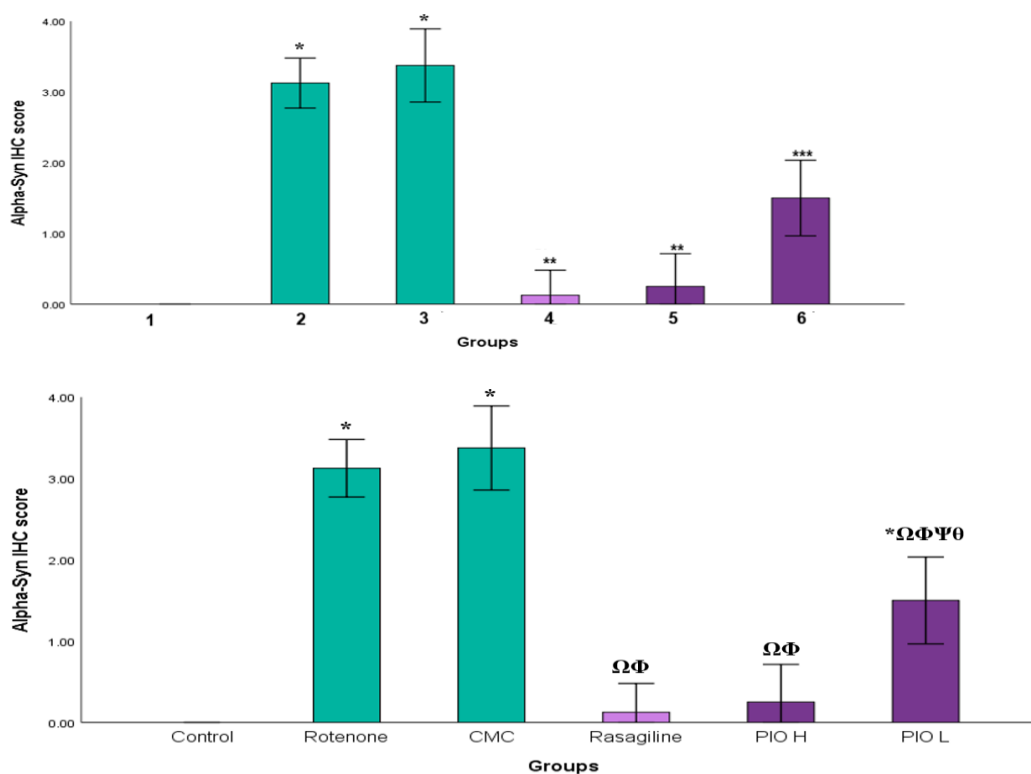


Figure 8: The α -syn IHC scores. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data were expressed as mean $\pm$ SD. * $P < 0.05$ vs control, ** $p < 0.05$ vs groups 2 and 3, *** $p < 0.05$ vs groups 1, 2, 3, 4, and 5

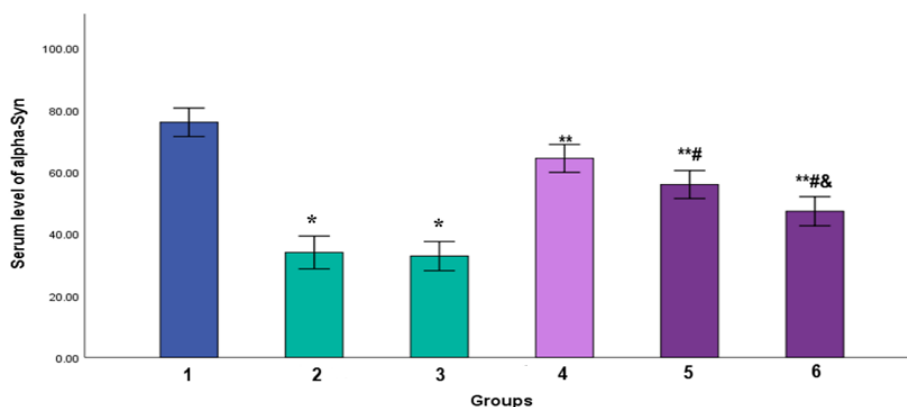


Figure 9: Serum α -syn levels. Group 1 (control), group 2 (Rotenone), group 3 (Rotenone + CMC), group 4 (Rotenone + Rasagiline), group 5 (10 mg/kg PIO), group 6 (20 mg/kg PIO). Data were expressed as mean $\pm$ SD. * $P < 0.05$ compared to control, ** $p < 0.05$ vs groups 1, 2, and 3; *** $p < 0.05$ vs groups 1, 2, 3, and 4; ***& $p < 0.05$ vs groups 1, 2, 3, 4, and 5

Serum levels of α -synuclein

Groups 2 and 3 showed significantly lower serum α -syn levels compared to control ($p < 0.05$). Groups 4, 5, and 6 showed significantly higher serum α -syn levels ($p < 0.05$). Furthermore, group 6 showed significantly lower α -syn levels compared to other groups ($p < 0.05$; Figure 9).

DISCUSSION

The rotenone-induced rat model used in this study is widely recognised as one of the most translationally relevant animal models of Parkinson's disease (PD), as it closely exemplifies several morphological, neurochemical, and neuropathological features observed in human PD. These include mitochondrial complex I inhibition, increased oxidative stress, α -synuclein aggregation, and the development of both motor and non-motor symptoms [9]. This present study demonstrated that pioglitazone exerted significant neuroprotective effect in rotenone-induced rat PD model. Pioglitazone significantly reduced α -synuclein burden not only in the central nervous system but also across peripheral tissues. Significant decrease in body weight following treatment with Rotenone and CMC represented strong clinical sign of systemic toxicity and metabolic dysfunction. Rotenone-induced inhibition of mitochondrial complex I significantly reduced adenosine triphosphate production and increased oxidative stress. This leads to gradual loss of muscle and negative energy balance, a condition often described as toxin-induced cachexia [10]. Furthermore, the comparable decline observed following administration of CMC indicated that the vehicle itself does not provide any protective or compensatory metabolic effects against rotenone [11].

Rasagiline and pioglitazone showed varying level of improvement in body weight and metabolic status. Treatment with Rasagiline maintained a growth pattern comparable to control group. This observation is consistent with studies showing that monoamine oxidase B (MAO-B) inhibitors reduce systemic oxidative stress and help maintain physiological stability [12]. Similarly, pioglitazone-treated groups exhibited a dose-dependent recovery in body weight. Pioglitazone likely mitigates weight loss through two main mechanisms. It promotes mitochondrial biogenesis via upregulation of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 α), leading to improved mitochondrial efficiency and compensating for energy deficits caused by Complex I inhibition. Also, it increases insulin sensitivity and metabolic function, leading to better glucose and lipid utilization, which counteracts the cachectic state [13]. Greater weight gain observed following treatment with Pioglitazone suggested that a certain level of PPAR- γ activation is necessary to effectively reverse the resulting metabolic burden by chronic rotenone exposure [14].

Behavioural changes confirmed that Rotenone administration successfully produced Parkinsonian-like impairments, evidenced by marked reduction in motor coordination (grooming), locomotor activity (line crossings), and exploratory behavior (rearing and center visit). These deficits indicated significant disruption of dopaminergic pathways involved in movement and motivation [15], while treatment with Rasagiline and Pioglitazone significantly ameliorated these impairments. Pioglitazone demonstrated a dose-dependent effect, with higher dose (20 mg/kg) showing higher efficacy

compared to the lower dose (10 mg/kg) across all behavioural parameters. Performance of Pioglitazone was comparable to Rasagiline in several measures, including line crossings and center visit [16]. This improvement may be attributed to the anti-inflammatory and mitochondrial protective properties, while Rasagiline primarily enhances dopaminergic transmission by preserving dopamine levels [17]. Also, rotenone administration produced significant motor impairments, confirming that Rotenone exposure triggers complex I mitochondrial inhibition and oxidative stress, leading to degeneration of dopaminergic neurons in the substantia nigra [18]. In contrast, the treatment with Rasagiline and Pioglitazone significantly improved motor performance, supporting their potential neuroprotective effects. Also, Pioglitazone at high dose demonstrated significantly greater improvements across all measured parameters compared to low dose.

Quantitative assessment of α -syn across experimental groups demonstrated inverse relationship between its level in peripheral blood and central nervous system (CNS) accumulation, supporting a sequestration-driven mechanism in parkinsonian pathology. In the rotenone-induced model, α -syn levels were significantly increased in brain tissue, while systemic concentrations were significantly reduced. This pattern suggested that neurotoxic effect promoted the aggregation of α -syn within the brain or disrupts its clearance into circulation [19]. Importantly, administration of Rasagiline significantly improved α -syn distribution, reflected by reduced brain levels and increased blood concentrations. This effect may be stimulated through activation of the Akt/Nrf2 signaling pathways, which protect against α -syn-related neural damage and cell death [20]. Treatment with pioglitazone (PIO) exhibited significantly decrease in brain α -syn accumulation with partial restoration of circulating levels. These beneficial effects were attributed to its activity as a PPAR- γ agonist, which promotes autophagic clearance of misfolded α -synuclein aggregates. This process may mitigate aggregation-induced neurotoxicity, improve mitochondrial function, attenuate oxidative stress-mediated neuronal damage, and ultimately enhance neuroprotection [21].

CONCLUSION

This study shows that pioglitazone effectively reduces accumulation of alpha-synuclein in the brain, restores systemic levels, improves motor performance and alleviates metabolic deterioration induced by rotenone exposure in a dose-dependent manner.

DECLARATIONS

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Use of Artificial intelligence/Large language models

The authors confirm that AI-based tools were used solely for language editing and manuscript polishing purposes (e.g., grammar, phrasing, and clarity). No AI tools were used to generate content, interpret data, or influence study design, results, or conclusions. All intellectual contributions, study analyses, and interpretations reported in the manuscript are the original work of the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

REFERENCES

1. Sayyaed A, Saraswat N, Vyawahare N, Kulkarni A. A detailed review of pathophysiology, epidemiology, cellular and molecular pathways involved in the development and prognosis of Parkinson's disease with insights into screening models. *Bull Natl Res Cent* 2023; 47: 70. doi: 10.1186/s42269-023-01047-4.
2. Ma C, Zhang W, Cao M. Role of the peripheral nervous system in Parkinson's disease pathology, diagnosis, and treatment. *Front Neurosci* 2021; 15: 598457. doi: 10.3389/fnins.2021.598457.
3. Basellini MJ, Kothuis JM, Comincini A, Pezzoli G, Cappelletti G, Mazzetti S. Pathological pathways and α -syn in parkinson's disease: a view from the periphery. *Front Biosci* 2023; 28(2): 15. doi: 10.31083/j.fbi2802015.
4. Çınar E, Tel BC, Şahin G. Neuroinflammation in Parkinson's disease and its treatment opportunities.

- Balkan Med J 2022; 39(5): 318-333. doi: 10.4274/balkanmedj.galenos.2022.2022-7-100.
5. Najafi N, Ghasemzadeh Rahbardo M, Hosseinzadeh H, Hayes AW, Karimi G. Chemical agents protective against rotenone-induced neurotoxicity. *Toxicol Environ Chem* 2022; 104(1): 149–175. doi: 10.1080/02772248.2022.2030341.
 6. Worth AJ, Basu SS, Snyder NW, Mesaros C, Blair IA. Inhibition of neuronal cell mitochondrial complex I with rotenone increases lipid β -oxidation, supporting acetyl-coenzyme A levels. *J Biol Chem* 2014; 289(39): 26895-26903. doi: 10.1074/jbc.M114.591354.
 7. Gray E, Ginty M, Kemp K, Scolding N, Wilkins A. The PPAR- γ agonist pioglitazone protects cortical neurons from inflammatory mediators via improvement in peroxisomal function. *J Neuroinflammation* 2012; 9: 63. doi: 10.1186/1742-2094-9-63.
 8. National Research Council. *Guide for the care and use of laboratory animals*, National Academies Press. Washington, DC; 2010.
 9. Landau R, Halperin R, Sullivan P, Zibly Z, Leibowitz A, Goldstein DS et al. The rat rotenone model reproduces the abnormal pattern of central catecholamine metabolism found in Parkinson's disease. *Dis Model Mech* 2022; 15(1): dmm049082. doi: 10.1242/dmm.049082.
 10. Rai SN and Singh P. Advancement in the modelling and therapeutics of Parkinson's disease. *J Chem Neuroanat* 2020; 104: 101752. doi: 10.1016/j.jchemneu.2019.101752.
 11. Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH et al. Mechanism of toxicity in rotenone models of Parkinson's disease. *J Neurosci* 2003; 23(34): 10756-10764. doi: 10.1523/JNEUROSCI.23-34-10756.
 12. Lecht S, Haroutiunian S, Hoffman A, Lazarovici P. Rasagiline – a novel MAO-B inhibitor in Parkinson's disease therapy. *Ther Clin Risk Manag* 2007; 3(3): 467–474. doi: 10.2147/tcrm.s12160420.
 13. Vázquez-González D, Corona JC. Pioglitazone enhances brain mitochondrial biogenesis and phase II detoxification capacity in neonatal rats with 6-OHDA-induced unilateral striatal lesions. *Front Neurosci* 2023; 28(17): 1186520. doi: 10.3389/fnins.2023.1186520.
 14. Titus C, Hoque MT, Bendayan R. PPAR agonists for the treatment of neuroinflammatory diseases. *PPAR Res* 2021; 2021: 1–19. doi: 10.1155/2021/8870852.
 15. Monir DM, Ahmed OG, Mahmoud ME, Abdel Hamid AA. Behavioral evaluation of rotenone model of Parkinson's disease in male Wistar rats. *J Appl Vet Sci* 2024; 9(2): 73–81. doi: 10.21608/javs.2024.269145.1316.
 16. Vázquez-González D, Corona JC. Pioglitazone enhances brain mitochondrial biogenesis and phase II detoxification capacity in neonatal rats with 6-OHDA-induced unilateral striatal lesions. *Front Neurosci* 2023; 17: 1186520. doi: 10.3389/fnins.2023.1186520.
 17. Oertel W, Schulz JB. Current and future treatments of Parkinson's disease. *Nat Rev Neurol* 2021; 17(1): 25–32. doi: 10.1038/s41582-020-00435-0.
 18. Sherer TB, Richardson JR, Testa CM, Seo BB, Panov AV, Yagi T et al. Mechanism of toxicity of pesticides acting at complex I: relevance to environmental etiologies of Parkinson's disease. *J Neurochem* 2007; 100(6): 1469-1479. doi: 10.1111/j.1471-4159.2006.04333.
 19. Bellini G, D'Antongiovanni V, Palermo G, Antonoli L, Fornai M, Ceravolo R. α -Synuclein in Parkinson's disease: From bench to bedside. *Med Res Rev* 2025; 45(3): 909-946. doi: 10.1002/med.22091.
 20. Pedersen CC, Maple-Grødem J, Lange J. A systematic review of biofluid phosphorylated α -synuclein in Parkinson's disease. *Parkinsonism Relat Disord* 2025; 132: 107240. doi: 10.1016/j.parkreldis.2024.107240.
 21. Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G, Ghiglieri V. A-syn in parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction. *Cell Death Dis* 2023; 14(3): 176. doi: 10.1038/s41419-023-05672-9.