COLLOQUIA ERUDITA 2026; 1: 29–30

PROCEEDINGS ABSTRACT

Pioglitazone improves the 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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Received: 28 March 2026; Revised: 27 May 2026; Accepted: 17 June 2026; Published: 18 June 2026

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta and the widespread accumulation of alpha-synuclein (α-Syn); an intracellular aggregation-prone protein. The resulting dopamine deficiency in the basal ganglia gives rise to the hallmark motor features of PD, including resting tremor, bradykinesia, gait disturbances, hypophonia, muscle rigidity, postural instability, and dysarthria. This study has investigated the neuroprotective potential of pioglitazone (PIO; a peroxisome proliferator-activated receptor gamma agonist) in attenuating the α-Syn burden and intracellular dysfunction in a rotenone-induced model of PD in rats. To this end, 48 adult male albino Wistar rats were randomly allocated into six groups: a healthy control group, a rotenone-induced PD model group, a vehicle-treated group receiving carboxymethylcellulose as well as rotenone (similarly to the PD model group), a rasagiline-treated group (receiving rasagiline at a dose of 1 mg/kg/day) that also received rotenone (as in the PD model group), and two PIO-treated groups receiving PIO at doses of 10 or 20 mg/kg/day in combination with rotenone (as in the PD model group). Parkinsonism was induced through the intraperitoneal administration of rotenone at a dose of 2.5 mg/kg every 48 h, for 21 days. Oral treatments were initiated 3 days before the first rotenone injection and were continued throughout the experimental period. Body weight was recorded on days 0, 7, 14, and 21. Behavioural assessments were performed on day 22 (24 h after the final treatment dose) using rotarod and open-field tests so as to evaluate locomotor activity, exploratory behavior, and motor coordination. The α-Syn expression was further quantified *via* brain immunohistochemistry and serum ELISA. The rotenone-induced Parkinsonian-like changes were evidenced by an 8.18% reduction in body weight (compared to a 20.35% increase in the control group; $p<0.05$) as well as by a substantial drop in behavioural performance ($p<0.05$) compared to that of the control group. Marked reductions were observed in grooming time (74.17%), number of crossing lines (70.33%), number of rearing episodes (74.84%), and number of visits to the center (85.62%). Motor performance was markedly decreased by rotenone, with decreases observed in the number of rotations (81.23%), the rotation time (69.10%), and the distance of rotation (56.90%) relatively to those of the control group. Addi-

Abbood G. S., Alzubaidi F. A., Mousa M. J.: Pioglitazone improves the motor function and attenuates the central and peripheral alpha-synuclein burden in a rotenone-induced model of Parkinson's disease in rats. *Colloq. Erud.* 1: 29–30 (2026).
https://doi.org/10.5281/zenodo.20748074

This proceedings abstract is published in *Colloquia Erudita – Volume 1: Proceedings of the 3rd International Babylon Conference on Clinical and Experimental Pharmacological Research (Hillah; June 29–30, 2026)*; a volume of proceedings edited by Rafal J. Al-Saigh, Argyro Kyriakaki, and Apostolos Zarros.

tionally, increased cerebral α-Syn accumulation (p<0.05) and a 50.09% decrease in the serum α-Syn levels (p<0.05) were recorded in the rotenone-induced PD model group compared to those of the control group. Treatment with PIO exhibited dose-dependent protective effects: high-dose PIO administration significantly improved body weight, resulting in a 12.28% increase of the latter compared to 6.78% and 7.30% increases in the low-dose PIO and the rasagiline groups, respectively. Moreover, the high-dose PIO administration resulted in remarkable increases in the rats' behavioural performance in terms of grooming time (157.06%), crossing lines (192.82%), rearing (183.82%), and center visits (226.54%) as compared to those of the PD model group (p<0.05). Additionally, motor performance was markedly enhanced by the high-dose PIO, as evidenced by an increase in rotation number (199.48%), rotation time (95.12%), and rotation distance (80.59%) relatively to the rotenone-treated PD model group (p<0.05). Finally, the cerebral α-Syn accumulation was found to be reduced by 25.0%, 50.0%, and 75.0% in the low-dose PIO, the high-dose PIO, and the rasagiline groups, respectively (p<0.05), while serum α-Syn levels were found to be increased by 13.11%, 38.27%, and 76.73%, respectively, in these same groups and as compared to the rotenone-induced PD model group's levels (p<0.05). In conclusion, PIO exerted dose-dependent neuroprotective effects on the assessed rotenone-induced Parkinsonism, improving motor performance and reducing central α-Syn burden, with the higher dose producing effects comparable to those of rasagiline.

Keywords

α-Syn; neuroprotection; Parkinson's disease; pioglitazone; rotenone

Acknowledgements

The authors gratefully acknowledge the College of Pharmacy of the University of Babylon for its support.

Conflicts of interest statement

None to declare.

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