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Research Article

NEUROPROTECTIVE EFFECTS OF BIOSYNTHESIZED SILVER NANOPARTICLES USING DIOSMIN IN A ROTENONE-INDUCED PARKINSON'S DISEASE RAT MODEL

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ABSTRACT

This study investigated the neuroprotective potential of silver nanoparticles (AgNPs) synthesized using Diosmin against rotenone-induced behavioral and motor impairments in a male Wistar rat model of Parkinson's disease (PD). Thirty-six male Wistar rats were randomly divided into six groups of six animals each. Group I served as the vehicle control, while Group II received intraperitoneal rotenone (0.5 mg/kg body weight). Groups III, IV, and V were co-treated with rotenone and orally administered biosynthesized AgNPs at doses of 5, 10, and 20 mg/kg, respectively, for 60 days. Group VI received AgNPs alone (20 mg/kg). Motor and behavioral performance was assessed using open field, rotarod, hanging wire, and narrow beam walking tests, among others. Rats treated with rotenone exhibited significant behavioral deficits and impaired motor coordination compared with controls ($p < 0.001$). Co-administration of Diosmin-based AgNPs markedly improved locomotor activity, balance, and muscle strength, restoring performance parameters close to normal levels. These findings suggest that diosmin-mediated AgNPs could serve as promising therapeutic agents for managing Parkinsonian neurodegeneration

Keywords: Rotenone, Parkinson's disease, Diosmin, Silver nanoparticles, Behavioral analysis.

INTRODUCTION

Parkinson's disease is a progressive neurodegenerative condition characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the consequent depletion of dopamine in the striatum. This loss results in hallmark motor impairments such as tremors, rigidity, bradykinesia, and postural instability (Kalia and Lang, 2015). Among various experimental models, chronic exposure to rotenone which is a natural pesticide and mitochondrial complex I inhibitor has been widely used to reproduce the neuropathological and behavioral features of PD in rodents (Betarbet *et al*. 2000). Rotenone induces mitochondrial dysfunction, oxidative stress, α-synuclein aggregation, and neuroinflammation, all of which mimic the pathological cascade seen in human PD (Gao *et al*. 2003). Despite decades of research, existing pharmacotherapies such as levodopa and dopamine agonists mainly alleviate symptoms but fail to prevent or reverse neurodegeneration (Connolly and Lang, 2014). Consequently, there is a critical need to identify natural or synthetic compounds capable of offering neuroprotection by targeting oxidative stress and neuroinflammatory pathways.

Flavonoids, a large group of naturally occurring polyphenolic compounds, have emerged as promising neuroprotective candidates due to their strong antioxidant and anti-inflammatory properties (Panche *et al*. 2016). Diosmin, a citrus-derived flavonoid glycoside, has demonstrated beneficial effects in several neurodegenerative models by reducing oxidative stress, modulating apoptosis-related proteins, and enhancing endogenous antioxidant enzyme activities (Albrahim and Binobead, 2018; Bhatia *et al*. 2021). In a rotenone-induced PD model, diosmin improved motor performance and protected dopaminergic neurons by downregulating proinflammatory mediators and restoring antioxidant balance (Sridevi *et al*. 2020). In recent years,

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nanotechnology-based approaches have gained attention for improving drug delivery and bioavailability of natural compounds in neurological disorders. Among various nanomaterials, silver nanoparticles (AgNPs) are widely studied for their strong antioxidant, anti-inflammatory, and antimicrobial properties (Prabhu and Poulose, 2012). Green synthesis of AgNPs using plant metabolites or bioactive compounds enhances their stability, biocompatibility, and therapeutic efficiency while minimizing potential toxicity (Kumar *et al*. 2019). Combining the bioactive potential of Diosmin with nanosilver synthesis offers a novel strategy for developing efficient neuroprotective agents. Therefore, the present study investigates the neuroprotective efficacy of biosynthesized silver nanoparticles using Diosmin against rotenone-induced behavioral and motor impairments in male Wistar rats.

MATERIALS AND METHODS

Animal design

Adult male Wistar albino rats weighing 150–180 g were obtained from a registered breeder and maintained under standard laboratory conditions at Vinayaka Mission's College of Pharmacy, Salem, India. The animals were housed in polypropylene cages with a 12-hour light/dark cycle, temperature of 25 ± 2 °C, and relative humidity of 55 ± 5%. Standard pellet diet and water were provided *ad libitum*. All animal handling procedures followed the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and were approved by the Institutional Animal Ethics Committee (Approval No: P.COL/13/2017/IAEC/VMCP).

Drugs and chemicals

Rotenone and Diosmin were purchased from Sigma-Aldrich**.** All other chemicals used were of analytical grade. Solvents were freshly prepared before use. The biosynthesis of silver nanoparticles was carried out using Diosmin as the reducing and stabilizing agent.

Biosynthesis of silver nanoparticles using diosmin

A 1 mM aqueous solution of silver nitrate ($AgNO_3$) was prepared, and 0.1% Diosmin solution was slowly added under constant stirring at room temperature. The mixture was incubated under dark conditions to avoid photoreduction. The formation of Ag-NPs was monitored visually by observing a color change from pale yellow to brown and confirmed spectrophotometrically at 420 nm using a UV–Vis spectrophotometer. The synthesized nanoparticles were centrifuged at 12,000 rpm for 20 min, washed three times with distilled water to remove unreacted residues, and dried at 60 °C. The dried powder was stored for further use. Characterization of the Ag-NPs was performed using UV–Vis spectroscopy, FTIR analysis, and scanning electron microscopy to determine particle size and morphology

Experimental design

The animals were equally divided into six experimental groups. Each group contains six animals. Group I (Control): Received vehicle (sunflower oil, 0.5 mL/kg, i.p.). Group II: Received rotenone (0.5 mg/kg body weight/day, i.p.) for 60 days. Group III: Received Rotenone plus Diosmin-Ag-NPs (5 mg/kg/day, orally). Group IV: Received Rotenone plus Diosmin-Ag-NPs (10 mg/kg/day, orally). Group V: Received Rotenone plus Diosmin-Ag-NPs (20 mg/kg/day, orally). Group VI: Received Diosmin-AgNPs (20 mg/kg/day, orally) alone. All treatments were continued for 60 days. Behavioral evaluations were conducted at the end of the treatment period

Behavioural assessment methods

Behavioral tests were conducted to evaluate locomotor activity, motor coordination, balance, and neuromuscular strength in rotenone-induced Parkinsonian rats. All experiments were performed at the same time each day under controlled laboratory conditions. Prior to testing, animals were acclimatized for seven days and trained for each behavioral paradigm to minimize stress and variability.

Open field test

The open field test was used to assess spontaneous locomotor and exploratory behavior. Each rat was placed in the corner of a square wooden arena (100 × 100 × 40 cm) divided into 25 equal squares. The apparatus was illuminated with a 100-W bulb positioned 150 cm above the center. Animals were observed for five minutes, and the number of squares crossed (central and peripheral), rearing frequency, and grooming episodes were recorded (Ghatan *et al*. 1998; Fernagut *et al*. 2002). The apparatus was cleaned with 70% ethanol between trials to prevent odor cues.

Narrow beam walking

Motor coordination and balance were evaluated using a narrow wooden beam (1 m long, 1 cm wide) elevated 100 cm above the floor. Each rat was placed at one end of the beam and allowed to traverse to a goal box at the opposite end. The time taken to cross the beam and the number of foot slips were recorded (Crabbe *et al*. 2003; Fleming *et al*. 2004). Each animal underwent three consecutive trials, and the mean value was used for statistical analysis.

Rotarod Performance Test

The rotarod test measured balance and motor coordination. Rats were placed on a rotating rod apparatus (diameter: 25 mm; speed: 4–40 rpm). The latency to fall from the rotating rod was recorded for three consecutive trials (Caston *et al*. 1995; Gerlai *et al*. 1996). Training sessions were conducted

for two days before testing to ensure consistent performance.

Hanging Wire Test

Neuromuscular strength was assessed using a wire grid apparatus suspended 50 cm above a soft surface. Each rat was allowed to grip the wire with all four paws, and the grid was gently inverted. The time taken for the animal to fall was measured, with a cutoff time of 300 seconds (Mohanasundari *et al*. 2006). Each rat was tested in triplicate, and the mean hanging time was recorded.

Swim test

Motor coordination and muscular endurance were evaluated using a transparent tank (40 × 25 × 16 cm) filled with water at 27 ± 2 °C. Each rat was placed in the tank for 10 minutes, and swimming behavior was rated on a 1–4 scale as described by Muralikrishnan and Mohanakumar (1998). Animals were towel-dried and returned to their cages after testing

Stride length (Footprint) analysis

Gait performance was evaluated by coating the fore- and hindpaws with non-toxic ink and allowing the rat to walk along a narrow runway (50 cm long, 4.5 cm wide) lined with white paper. The stride length was calculated as the mean distance between consecutive prints of the same limb, excluding the first and last few steps (D'Hooge *et al*. 1999). Three successful runs per animal were averaged.

Akinesia

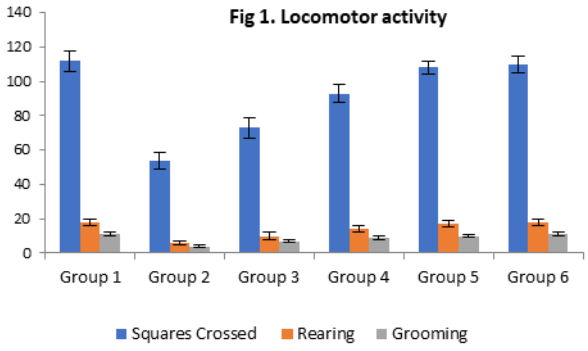
Akinesia, the delay in initiating movement, was measured by placing each rat on a flat platform (40 × 40 × 30 cm) and recording the latency (in seconds) to move all four limbs. A maximum cutoff time of 180 seconds was applied (Muralikrishnan and Mohanakumar, 1998). Each trial was repeated six times per animal.

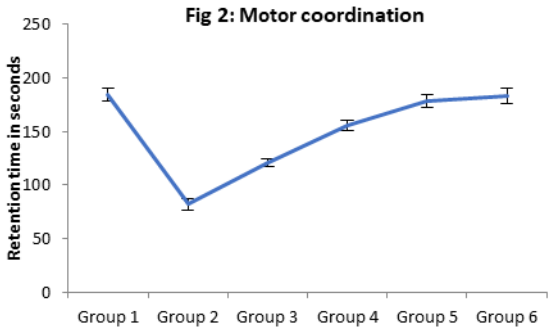
Catalepsy

Cataleptic behavior was evaluated by gently placing both forepaws of the rat on a horizontal wooden bar positioned 5 cm above the floor. The duration for which the animal maintained the imposed posture without moving was recorded (Muralikrishnan and Mohanakumar, 1998). Each rat was tested six times, and the mean catalepsy time was calculated.

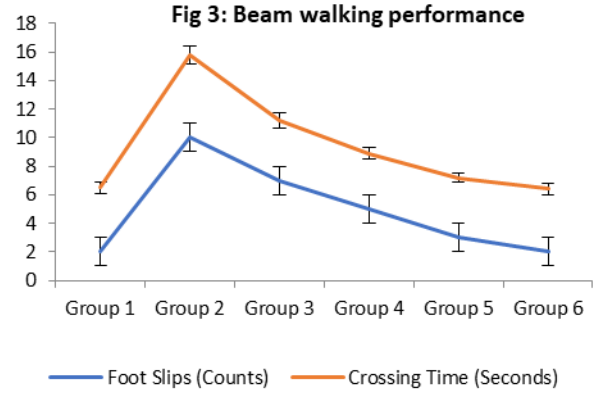
RESULT AND DISCUSSION

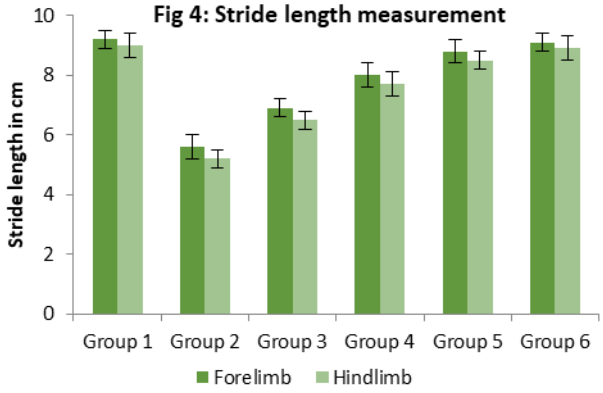
The alterations in locomotor activity among experimental rats are summarized in Figure 1. Control rats exhibited the highest levels of activity, with 112 ± 6 squares crossed, 18 ± 2 rearings, and 11 ± 1 grooming episodes, representing normal exploratory behavior. In contrast, rotenone-treated rats (Group II) demonstrated a significant reduction ($p < 0.001$) in these parameters, recording only 54 ± 5, 6 ± 1, and 4 ± 1, respectively, indicating severe locomotor impairment. Co-treatment with biosynthesized Ag-NPs using Diosmin significantly improved locomotor performance in a dose-dependent manner, with the 20 mg/kg group (108 ± 4, 17 ± 2, 10 ± 1) showing near-normal activity comparable to controls. Ag-NPs alone produced no behavioral alterations. The changes in motor coordination among the experimental groups are presented in Figure 2. Rats in the control group maintained normal balance and coordination, remaining on the rotarod for 185 ± 6 seconds. In contrast, rotenone-treated rats (Group II) showed a marked reduction ($p < 0.001$*) in retention time, averaging 82 ± 5 seconds, indicating significant impairment of motor coordination. Co-treatment with biosynthesized Ag-NPs using Diosmin improved performance in a dose-dependent manner. Groups administered 5, 10, and 20 mg/kg b.wt of Ag-NPs recorded retention times of 121 ± 4, 156 ± 5, and 178 ± 6 seconds, respectively, showing progressive restoration of balance and motor ability. The beam walking performance of experimental rats is presented in Figure 3. Control rats showed stable motor coordination with 2 ± 1-foot slips and a beam-crossing time of 6.5 ± 0.4 s. Rotenone-treated rats exhibited significant impairment ($p < 0.001$*), with 10 ± 1-foot slips and an extended crossing time of 15.8 ± 0.6 s. Co-treatment with biosynthesized Ag-NPs using Diosmin improved performance in a dose-dependent manner. Rats receiving 20 mg/kg Ag-NPs demonstrated near-normal balance, recording 3 ± 1-foot slips and 7.2 ± 0.3 s crossing time, closely matching control values.

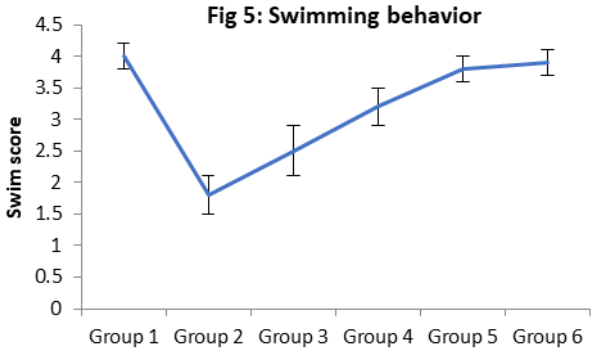


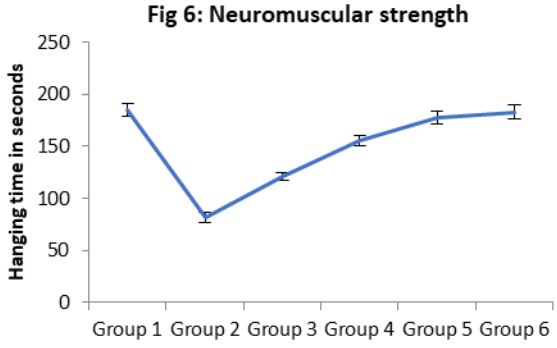


The effects of biosynthesized Ag-NPs using Diosmin on gait performance are summarized in Figure 4. Control rats exhibited normal stride lengths of 9.2 ± 0.3 cm (forelimb) and 9.0 ± 0.4 cm (hindlimb). Rotenone-treated rats showed a significant reduction ($p < 0.001$*), with stride lengths of 5.6 ± 0.4 cm and 5.2 ± 0.3 cm, indicating motor impairment. Co-treatment with Diosmin-Ag-NPs improved stride length in a dose-dependent manner. The 20 mg/kg group displayed nearly normal values (8.8 ± 0.4 cm, 8.5 ± 0.3 cm), demonstrating effective recovery of gait function. The motor ability of experimental rats assessed by the swim test is presented in Fig 5. Control rats exhibited normal swimming behavior with a score of 4.0 ± 0.2, whereas rotenone-treated rats showed a significant reduction ($p < 0.001$*), recording a score of 1.8 ± 0.3, indicating poor motor coordination. Co-treatment with biosynthesized Ag-NPs using Diosmin improved swimming performance in a dose-dependent manner. The 20 mg/kg group achieved a score of 3.8 ± 0.2, closely resembling the control group, demonstrating enhanced neuromuscular function and recovery from rotenone-induced motor deficits. The results of the hanging wire test evaluating neuromuscular strength are presented in Figure 6. Control rats maintained normal grip strength with a hanging time of 185 ± 6 s, while rotenone-treated rats exhibited a significant reduction ($p < 0.001$*), remaining suspended for only 82 ± 5 s. Co-treatment with biosynthesized Ag-NPs using Diosmin markedly improved muscle strength in a dose-dependent manner. Rats receiving 20 mg/kg Ag-NPs displayed a hanging time of 178 ± 6 s, nearly equivalent to the control group, indicating effective restoration of neuromuscular function.

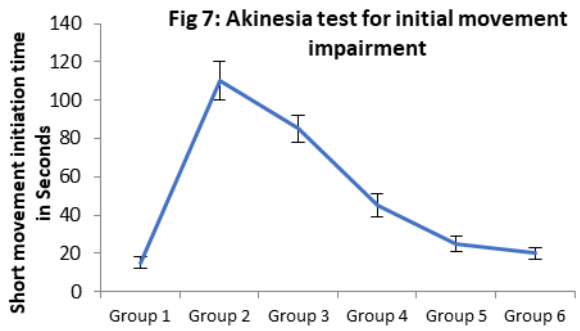


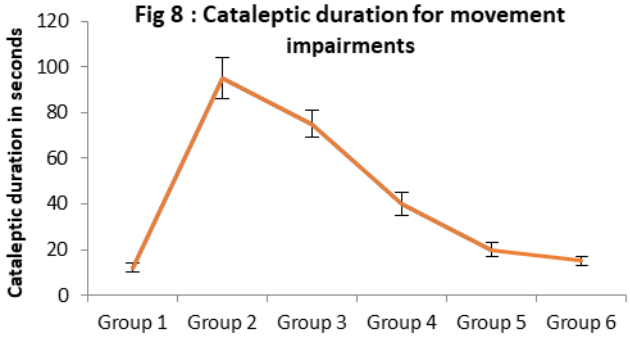






The akinesia test results indicating initial movement impairment are shown in Figure 7. Control rats exhibited a short movement initiation time of 15 ± 3 s, whereas rotenone-treated rats demonstrated a marked delay ($p < 0.001$*), with a latency of 110 ± 10 s, confirming severe motor initiation deficits. Co-treatment with biosynthesized Ag-NPs using Diosmin significantly reduced latency in a dose-dependent manner. The 20 mg/kg group showed near-normal movement with 25 ± 4 s, indicating effective reversal of rotenone-induced akinesia. The effects of biosynthesized Ag-NPs using Diosmin on rotenone-induced movement impairments are presented in Figure 8. Control rats exhibited normal motor response with a catalepsy duration of 12 ± 2 s, while rotenone-treated rats showed a significant increase ($p < 0.001$*), remaining immobile for 95 ± 9 s. Co-treatment with Diosmin-Ag-NPs reduced the cataleptic duration in a dose-dependent manner. The 20 mg/kg group demonstrated a marked recovery with 20 ± 3 s, approaching control levels and indicating effective improvement in motor coordination and flexibility.





Behavioral evaluations are crucial in Parkinson's disease research as they reveal the extent of dopaminergic dysfunction in the nigrostriatal pathway (Tillerson & Miller, 2003). In this study, rotenone exposure produced marked motor and coordination impairments, validating its neurotoxic effect. Co-treatment with biosynthesized silver nanoparticles (AgNPs) using Diosmin significantly improved behavioral outcomes, indicating a strong neuroprotective role of this formulation. Rotenone administration caused a notable decline in locomotor and exploratory activity, as reflected by reduced square crossings, rearing, and grooming frequencies. These findings correspond to dopamine depletion and basal ganglia dysfunction (Fernagut *et al*. 2002). Similar behavioral suppression was previously observed by Meredith and Kang (2006), where oxidative stress following rotenone exposure led to decreased spontaneous movement. The restoration of locomotor activity in Diosmin-Ag-NP-treated rats suggests that the flavonoid component enhanced mitochondrial function and reduced reactive oxygen species consistent with the antioxidant and neuroprotective effects reported by Sridevi *et al*. (2020) and Albrahim and Binobead (2018). Rotarod performance was markedly reduced in rotenone-treated rats, confirming motor coordination loss and balance impairment. Comparable findings have been documented by Rozas *et al*. (1998) in PD toxin models. Diosmin-Ag-NP co-treatment increased latency to fall in a dose-dependent manner, indicating protection of the nigrostriatal neurons. Similar recovery of rotarod performance through antioxidant therapy was demonstrated by Mohanasundari *et al*. (2006). The improved retention time here reflects the combined antioxidative and anti-inflammatory mechanisms of Diosmin (Bhatia *et al*. 2021).

In the narrow beam walking test, rotenone induced significant motor imbalance, with increased foot slips and crossing time (Crabbe *et al*. 2003). Co-treatment with Diosmin-Ag-NPs markedly reduced these impairments, confirming restoration of cerebellar coordination. Kumar *et al*. (2019) also reported enhanced balance and neural recovery using green-synthesized nanoparticles, supporting the present findings. Similarly, the swim and hanging wire tests revealed severe motor fatigue and muscle weakness in rotenone-treated rats. Diosmin-Ag-NPs improved swimming behavior and grip strength, indicating enhanced neuromuscular function. These results align with the findings of Anandhan *et al*. (2012), who showed that polyphenolic antioxidants protect dopaminergic neurons and improve endurance. Stride length, a sensitive marker of Parkinsonian gait, was shortened after rotenone exposure, as also described by Fernagut *et al*. (2002). Treatment with Diosmin-Ag-NPs significantly improved stride length, indicating recovery of motor control. Furthermore, akinesia and catalepsy tests confirmed severe bradykinesia and rigidity in rotenone-treated rats, which were effectively reversed by Diosmin-Ag-NPs, consistent with Schober (2004) and Albrahim and Binobead (2018).

CONCLUSION

The present study demonstrates that biosynthesized silver nanoparticles using Diosmin effectively protect against rotenone-induced behavioral and motor impairments in rats. Co-treatment significantly improved locomotor activity, coordination, gait, and neuromuscular strength in a dose-dependent manner. These beneficial effects can be attributed to the potent antioxidant and anti-inflammatory properties of Diosmin, enhanced by the nanoscale bioavailability of AgNPs. The results suggest that Diosmin-functionalized AgNPs provide substantial neuroprotection by preserving dopaminergic function and reducing oxidative stress, highlighting their therapeutic potential as a novel, biocompatible strategy for managing Parkinson's disease and related neurodegenerative disorders.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

All animal handling procedures followed the guidelines of the Committee for the Purpose of Control and Supervision

of Experiments on Animals (CPCSEA) and were approved by the Institutional Animal Ethics Committee (Approval No: P.COL/13/2017/IAEC/VMCP).

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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