Xi'an Shiyou Daxue Xuebao (Ziran Kexue Ban)/
Journal of Xi'an Shiyou University, Natural Sciences Edition
ISSN: 1673-064X
E-Publication: Online Open Access
Vol: 67 Issue 04 | 2024
DOI: 10.5281/zenodo.10953134

PHARMACOLOGICAL OUTCOME OF ROTENONE INDUCED PARKINSON'S DISEASE IN RATS MODEL OF PARKINSONISM

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Abstract

Background: Psychosis can be characterized by a disruption in behavior and thought processes, leading to significant distortion in mental capacity and organization of thought. This results in an impaired ability to perceive reality accurately or engage meaningfully with others. In patients with a psychiatric disorder psychotic features including delusions, hallucinations, and disorganized behavior. While traditional antipsychotics tackle positive symptoms, they fall short addressing negative and cognitive aspects, often with adverse effects. About one-third of patients remain unresponsive to current pharmacotherapy. Hence, there's a pressing need to pioneer novel molecules for psychosis treatment. Parkinson Disease is a worldwide neurodegenerative disorder with age being the main possible aspects. The disorder impacts between the ages of 65 and 69 about 0.5–1% of the inhabitants and above the age of 80 it impacts about 1–3% of the population (De Lau andBreteler2006; Toulouse and Sullivan 2008). In PD, in the substantia nigra and pars compacta there is significantly decline in dopaminergic neurons, as a subsequent in striatum reduced level of dopamine. As a result of this there is deficiency of dopamine and abnormalities in their functions. **Method**: In this study, rotenone was administered in animals at dose of 10 mg/kg for 28 days. **Results:** The outcome of recent experiment to observe the neurotoxic effects of the administration of rotenone-induced Parkinson's disease (PD) exhibited that administration of rotenone decreased food intake and body weight. It also revealed that locomotor activity and exploratory activity was significantly decreased by the administration of rotenone. The administration of rotenone exhibited impaired motor functions and

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coordination in Pole test and Inverted screen test. **Conclusion:** Present study revealed that administration of rotenone for a long term period induced Parkinsonism in rat's model of PD.

INTRODUCTION

Parkinson Disease is a worldwide neurodegenerative disorder with age being the main possible aspects. The disorder impacts between the ages of 65 and 69 about 0.5–1% of the inhabitants and above the age of 80 it impacts about 1–3% of the population (De Lau and Breteler 2006). In PD, in the substantia nigra and pars compacta there is significantly decline in dopaminergic neurons, as a subsequent in striatum reduced level of dopamine.

As a result of this there is deficiency of dopamine and abnormalities in their functions (Loonam *et al.,* 2003; Centonze *et al.,* 2004) motor coordination dysfunction, inability to maintain equilibrium, rigidity (Lotharius and Brundin 2002), and slowness of movement (Recchia *et al.,* 2004). In PD patients many neurological and biological changes have been recognized in the brain such as OS, free radical-aided impairment, inflammatory alterations, and mitochondrial dysfunction (Tseng *et al.,* 2016).

Oxidative stress is involved in the development of PD (Jiang T *et al.,* 2016). It is be associated with protein aggregation, cell cycle reactivation; apoptosis and mitochondrial dysfunction are identified in patient of PD (Tsang AH *et al.,* 2009). Oxidative stress also declines the glutathione (GSH) level. It also reduced the performance of glutathione peroxidase; catalase has also been noticed in PD patients (Sanders, and Greenamyre, 2013).

Various efforts were accomplished in rats to regenerate certain of the extreme domains of PD such as rotenone is major toxin to regenerate the main medical and behavioral symptoms of PD in animals such as motor impairment, dopaminergic deterioration, mitochondrial dysfunction, and neuroinflammation (Betarbet *et al.,* 2000). In 2000, Betarbet et al effectively regenerate major behavioral, biochemical and clinical signs of PD via rotenone in animals (Betarbet *et al.,* 2000).

Subsequent Betarbet et al.' investigation, scientist exhibited that rotenone possibly creates various clinical progressions such as inflammation (Ling, 2003), apoptotic cell death (Ahmadi *et al.,* 2003) autophagic impairment (Jang *et al.,* 2016) and microtubule depolarization (Passmore 2017) in rats alike to those happen in parkinsonian person brains. In addition, rotenone was also recognized to produce gradually functional and pathological alteration in the CNS of animals representing modification noticed in individual PD (Greene *et al.,* 2009).

Together support connection among the rotenone and PD, and strengthen the Greenamyre acceptance that rotenone may generate PD in individual as it done in trail rats (Adam, 2000).

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METHODS AND MATERIALS

Animals

Animals Study was designed on 24 male Albino wistar rats (120-180 gm), purchased from the Dow university of Health and Sciences, Karachi, Pakistan and housed in individual cages and allowed to acclimatize to their surrounding with temperature (25±2ºC) for one week. Animals had free access to a normal standard diet during acclimatizing time before starting experiment. All experimental animals were approved by Institutional Ethics and Animal Care Committee, and the procedure was carried out in accordance with the National Institute of Health Guide for care and Use of Laboratory.

Drugs

Rotenone (Sigma, St. Louis, USA) was dissolved in saline (0.9% NaCl) and administrated orally through a stainless steel feeding tube at dose of 10 mg/kg /day to the respective group animals. Drug was freshly prepared before starting the experiment. Saline (0.9%NaCl solution; 1ml/kg) was administrated to control animals.

Experimental Procedure

Twenty-four animals were randomly divided into two equal groups control and rotenone treated rats. Animals of control were administrated with saline (0.9% NaCl) and test group animals were administrated with rotenone (10 mg/kg/day) for 28 days by a stainless feeding tube orally. Food intake, change in growth rate and behavioral assessments were monitored on next day of 1st and 28th day of drug administration.

Behavioral Assessment

- **Food Intake**

Food intake was determined after the 24 hours of 1st day of the administration and then determined weekly. It was noted through measured the given diet individually in cage and by determining the leftover diet, food intake was noted.

- **Body Weight**

To determine the variation in body weight. The basket was kept on balance machine and

Each rat was permitted to place in the center of a basket and then notes the body weight of rats.

- **Home Cage Activity**

Home cage or activity cage box was used to evaluate the stimulatory activity. Size of the cage was 26 cm^3 and was made up of Perspex. Activity is conducted in 2 phase, 1st habituation phase and 2nd trail phase. In habituation phase, rat was placed in cage box to familiarize with environment about 10 mins. In trail phase, number of cage crossing was monitored for 5 mins after 10 min of habituation phase.

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- **Open Field Activity**

In a new environment for the evaluation of ambulatory or exploratory activity, we performed open field activity. The OFT is comprises of square wooden box (76 × 76 cm). Apparatus walls are 35cm tall which avoid the animal escaping. 25 squares of same dimension were drawn on the ground base. For determine the activity, animals were kept in the middle square and of the testing arena. The number of squares crossed by each animal was then meticulously observed and noted over a period of five mins. (Kaoud *et al.,* 2010)

- **Inverted Screen**

Neuromuscular strength of rats was determined by inverted screen test. The horizontal grid which is attached about 20 cm above the ground. With all paws rats were permitted to hold the grid, and then the grid was turns down. The latency to fall in second was noted about 30 secs (Kondziella, 1964).

- **Pole Test**

Motor coordination and bradykinesia in rats was determined by the help of pole test. Apparatus is composed of wooden pole which is 50 cm long and diameter is about 1cm. that directed to their cage. The rodents were kept at the top of a wooden pole facing upward direction. The training phase takes place two constant days. In training session rats were trained to turn to face downward and cross the pole in to their home cage. In test phase rats were exposed to five trails. The spent to orient downward and time to descend until it reaches the base of the home cage pole were monitored. Times were limited to 60 seconds (Hwang *et al.,* 2005)

Statistical Assessment

Results are represented as means ± SD. The software SPSS (version 16) software was used for assessment. Statistics was done via three-way ANOVA (repeated measures design). Tukey HSD method was performed for significance differences. Significance was attributed to findings with $p<0.05$.

RESULTS

Outcome of Rotenone Induced Parkinson on Food Intake in Rats.

Figure 1 represents the outcome of rotenone induced Parkinson on food intake in rats. Two-way ANOVA (repeated measures design), was accomplished to evaluated the results, the consequence of days ($F=0.835$, $df=1, 24$) were not statistically significant. While the consequence of rotenone ($F=67.737$, $df=1, 24$, $p<0.01$) and the interrelationship of rotenone and days ($F=47.563$, $df=3, 48$, $p<0.01$) were statistically significant. Tukey, s HSD test revealed that there was significantly ($p<0.01$) decrease in food intake after administration of rotenone on 28th day of administration.

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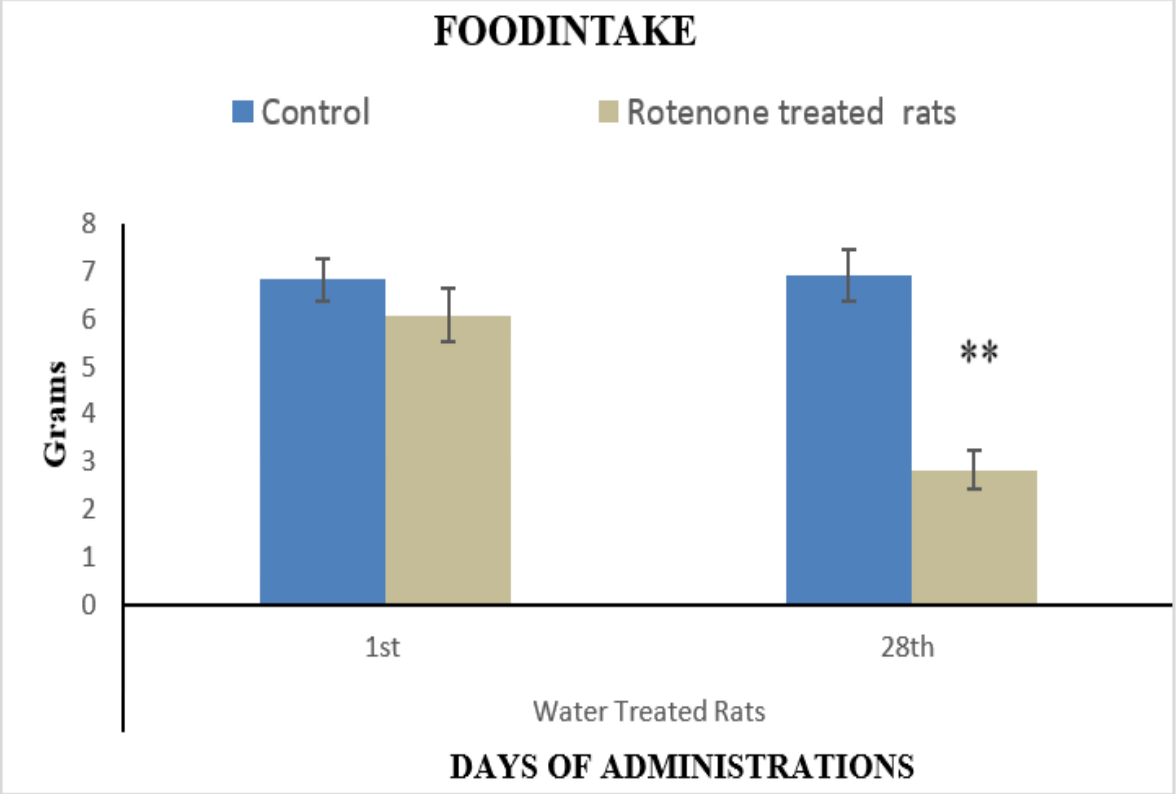

Figure 1: Outcome of Rotenone Induced Parkinson on Food Intake in Rats

Results: means ± SD (n=6).

Statistics done via Tukey HSD test, following two-way ANOVA (repeated measure design). When compared among saline inject or rotenone treated rats from 1st day of treatment symbolized by significance levels* $p < 0.05$, ** $p < 0.01$ when compared saline inject or rotenone treated animals marked by significance levels + $p < 0.05$, ++$p < 001$

Outcome of Rotenone Induced Parkinson on Body Weight in Rats.

Figure 2 represent the outcome of rotenone induced Parkinson on body weight in rats. Two-way ANOVA (repeated measures design) was accomplished to evaluated the results, the consequence of days ($F=0.125$, $df=1, 24$) were not statistically significant. While the consequences of rotenone ($F=372.940$, $df=1, 24$, $p<0.01$) and the interrelationship of rotenone and days ($F=165.980$, $df=3, 48$, $p<0.01$) were statistically significant. Tukey, s HSD test revealed that there was significantly decrease in body weight after administration of rotenone on 28th ($p<0.01$) day of administration.

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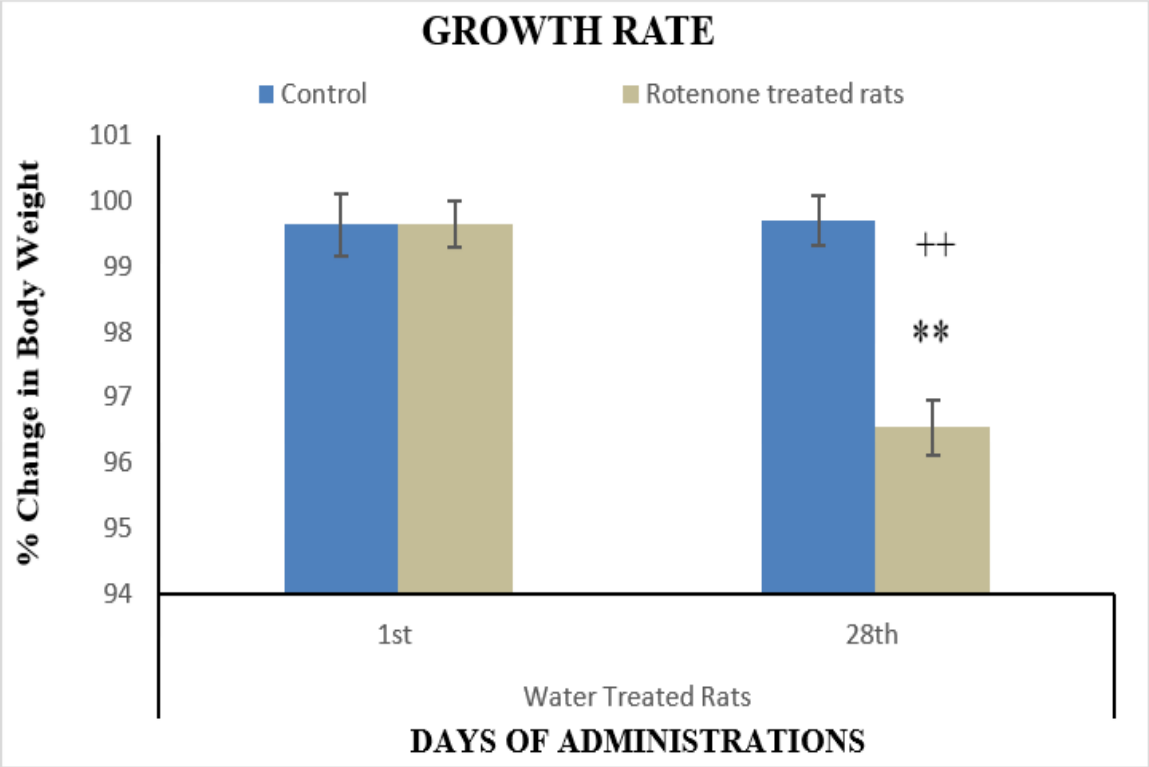

Figure 2: Outcome of Rotenone Induced Parkinson on Body Weight in Rats

Results: means ± SD (n=6).

Statistics done via Tukey HSD test, following two-way ANOVA (repeated measure design). When compared among saline inject or rotenone treated rats from 1st day of treatment symbolized by significance levels* $p < 0.05$, ** $p < 0.01$ when compared saline inject or rotenone treated animals marked by significance levels + $p < 0.05$, ++$p < 001$

Outcome of Rotenone Induced Parkinson on Locomotor Activity in Rats

Figure 3 represent the outcome of rotenone induced Parkinson on locomotor activity in rats. Two-way ANOVA (repeated measures design) was accomplished to evaluated the results, the consequence of days ($F=1.254$, df=1, 24) were not statistically significant. While the consequence of rotenone ($F=338.926$, df=1, 24, $p<0.01$) and the interrelationship of rotenone and days ($F=75.043$, df=3, 48, $p<0.01$) were statistically significant. Tukey, s HSD test revealed that there was significantly decreased in locomotor activity after administration of rotenone on 28th ($p<0.01$) day of administration.

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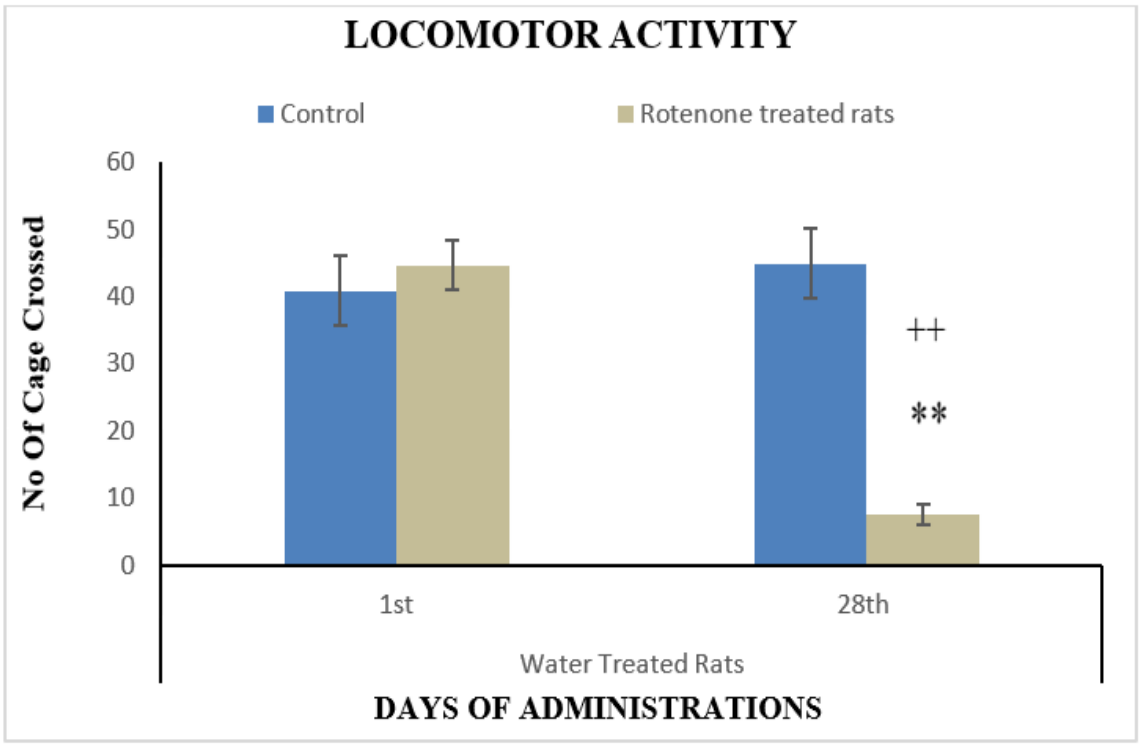

Figure 3: Outcome of Rotenone Induced Parkinson on Locomotor Activity in Rats

Results: means ± SD (n=6).

Statistics done via Tukey HSD test, following two-way ANOVA (repeated measure design). When compared among saline inject or rotenone treated rats from 1st day of treatment symbolized by significance levels* $p < 0.05$, ** $p < 0.01$ when compared saline inject or rotenone treated animals marked by s significance levels + $p < 0.05$, ++$p < 001$

Outcome of Rotenone Induced Parkinson on Open Field Activity in Rats

Figure 4 represent the outcome of rotenone induced Parkinson on open field activity in rats. Two-way ANOVA (repeated measures design) was accomplished to evaluated the results, the consequence of days ($F=3.146$, $df=1, 24$) were not statistically significant. While the outcome of rotenone ($F=396.000$, $df=1, 24$, $p<0.01$) and the interrelationship of rotenone and days ($F=203.440$, $df=3, 48$, $p<0.01$) were statistically significant. Tukey· s HSD test revealed that there was significantly decreased in exploratory activity after administration of rotenone on 28th ($p<0.01$) day of administration.

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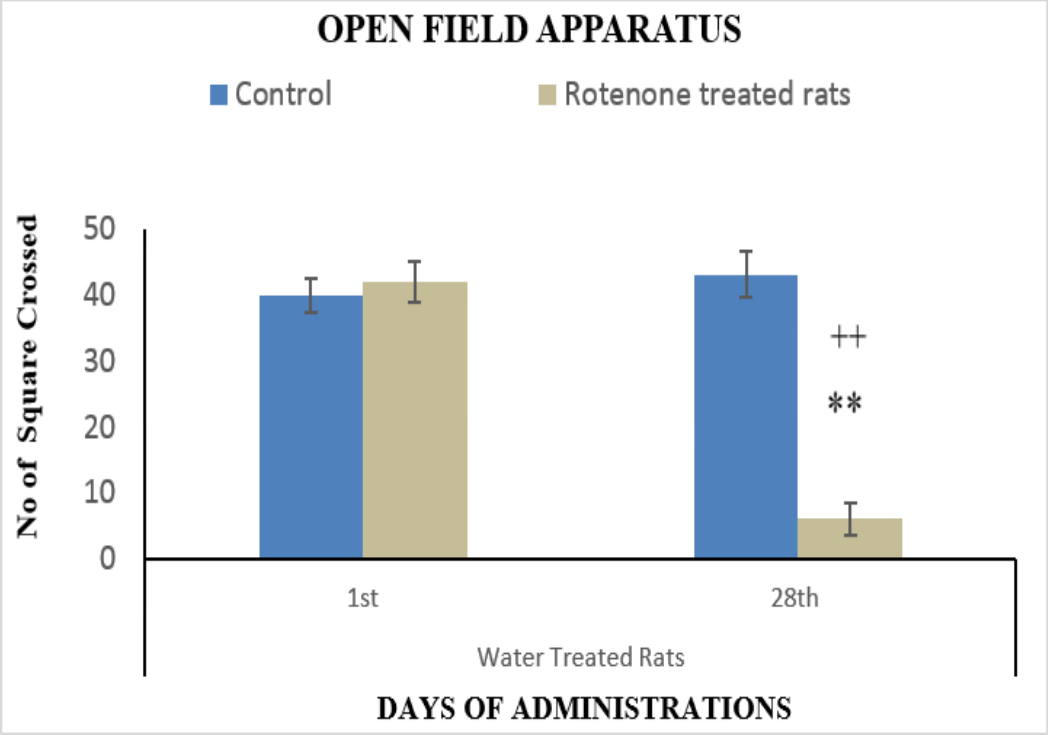

Figure 4: Outcome of Rotenone Induced Parkinson on Open Field Activity in Rats

Results: means ± SD (n=6).

Statistics done via Tukey HSD test, following two-way ANOVA (repeated measure design). When compared among saline inject or rotenone treated rats from 1st day of treatment symbolized by significance levels* $p < 0.05$, ** $p < 0.01$ when compared saline inject or rotenone treated animals marked by significance levels + $p < 0.05$, ++$p < 001$

Outcome of Rotenone Induced Parkinson on Motor Coordination in Rats.

Figure 5 represent the outcome of rotenone induced Parkinson on motor coordination by using pole test in rats. Two-way ANOVA (repeated measures design) was accomplished to evaluated the results, the consequence of days ($F=0.055$, $df=1, 24$) were not statistically significant. While the outcome of rotenone ($F=567.303$, $df=1, 24$, $p<0.01$) and the interrelationship of rotenone and days ($F=173.604$, $df=3, 48$, $p<0.01$) were statistically significant. Tukey, s HSD test revealed that there was significantly impaired motor coordination after administration of rotenone on 28^{th} ($p<0.01$) day of administration.

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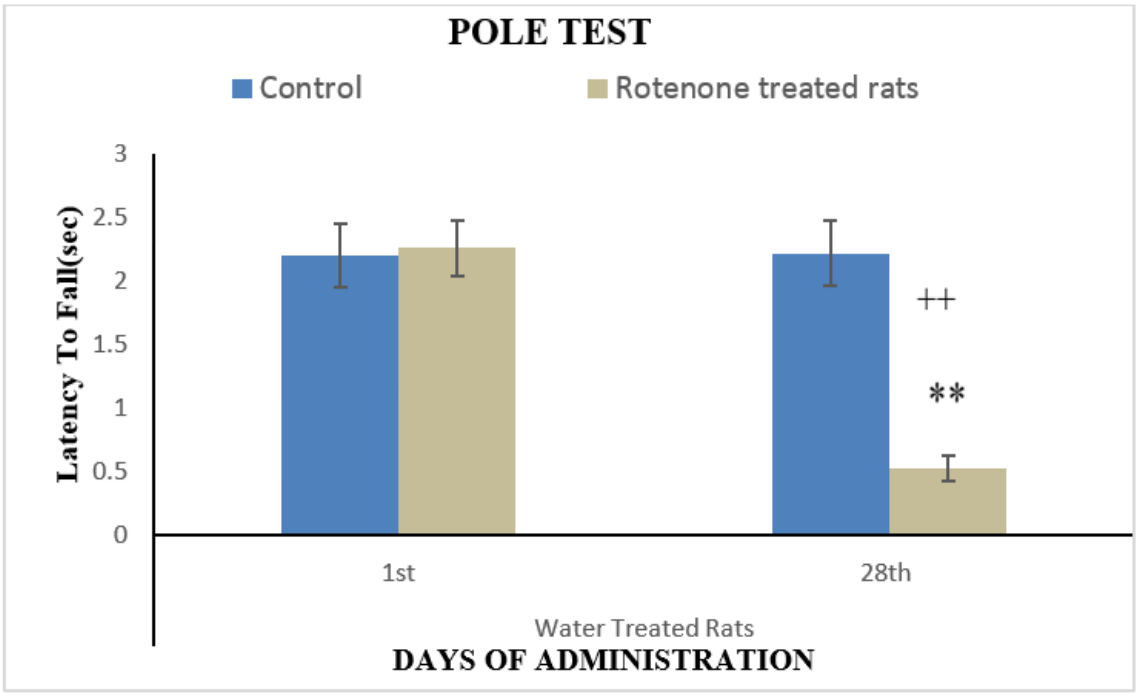

Figure 5: Outcome of Rotenone Induced Parkinson on Motor Coordination in Rats

Results: means ± SD (n=6).

Statistics done via Tukey HSD test, following two-way ANOVA (repeated measure design). When compared among saline inject or rotenone treated rats from 1st day of treatment symbolized by significance levels* $p < 0.05$, ** $p < 0.01$ when compared saline inject or rotenone treated animals marked by significance levels + $p < 0.05$, ++$p < 001$

Outcome of Rotenone Induced Parkinson on Muscular Strength in Rats

Figure 6 represent the outcome of rotenone induced Parkinson on muscular strength by using inverted screen test in rats. Two-way ANOVA (repeated measures design) was accomplished to evaluated the results, the consequence of days ($F=1.110$, $df=1, 24$) were not statistically significant. While the outcome of rotenone ($F=171.608$, $df=1, 24$, $p<0.01$) and the interrelationship of rotenone and days ($F=130.483$, $df=3, 48$, $p<0.01$) were statistically significant. Tukey, s HSD test revealed that there was significantly impaired muscular strength after administration of rotenone on 28^{th} ($p<0.01$) day.

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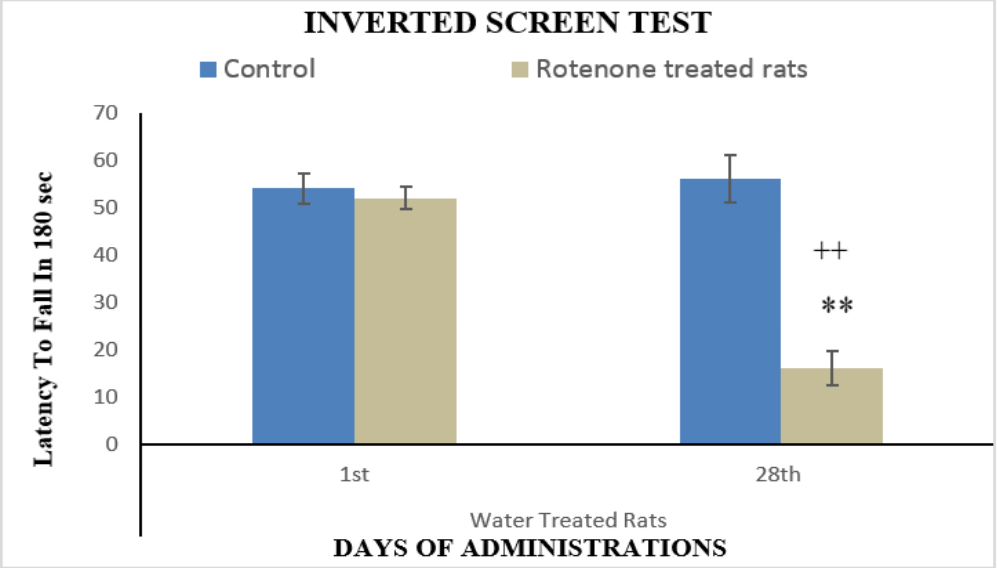

Figure 6: Outcome of Rotenone Induced Parkinson on Muscular Strength in Rats

Results: means ± SD (n=6).

Statistics done via Tukey HSD test, following two-way ANOVA (repeated measure design). When compared among saline inject or rotenone treated rats from 1st day of treatment symbolized by significance levels* $p < 0.05$, ** $p < 0.01$ when compared saline inject or rotenone treated animals marked by s

DISCUSSION

In current experiment, one of the models of PD that has been developed is the ROT-induced PD model to evaluate the diverse behavioral, biochemical and cellular changes. (Inden *et al.,* 2011). Outcome of our trails described that administration of rotenone significantly reduced food intake and body weight 28thday of administration. Previous literature exhibited that gastrointestinal dysfunction is greatest recurrently happened indications of PD along with prior overfilling and reduced weight, constipation during rotenone toxicity (Pfeiffer, 2003). The current results exhibited that rotenone administration significantly decreased food intake and body weight at 28th day of administrations. It also revealed that locomotor activity and exploratory activity was significantly decreased by decreased the no. of caged crossed and number of squares crossed by the administration of rotenone at 28th day of administration. The administration of rotenone exhibited impaired motor functions and coordination in wire grid test, Pole test, Inverted screen test and Beam walk test. At 28th day of administrations. The current study also revealed that rotenone administration significantly produced depression like symptom by decreased the Swimming time and increased Immobility time. The current study also revealed that rotenone administration was significantly decreased locomotor

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activity and exploratory activity by decrease the no. of squares crossed and deceased the number of caged crossed at 28th of administration in open field apparatus and home cage activity box respectively. Previous study supports our study that reduction in locomotion activity and exploratory activity during the open field test and home cage activity in rotenone-treated rats (Valdez *et al.,* 2019)

Present study showed that the administration of rotenone exhibited impaired motor functions and coordination in Pole test and inverted screen test by decreased the time of latency to fall at 28th of administrations. The current study also revealed that administration of rotenone was significantly decreased locomotor activity and exploratory activity by decrease the sum of squares crossed and caged crossed in open field apparatus and home cage activity box respectively. Previous study supports our study (Nehru *et al.,* 2008). It also revealed that locomotor activity and exploratory activity was notably increased by nutmeg extract at 7th and 14th day of administrations in rotenone treated rats. Present study showed that the administration of rotenone exhibited impaired motor functions and coordination in wire grid test, Pole test, Inverted screen test and Beam walk test by decreased the time of latency to fall. Past research also reported that nigrostriatal structures deterioration are related with movements and balance dysfunction (Betarbet *et al.,*2000), these symptoms are distinguished by hyperkinesias, tremor, stiffness, and *instability in body positions* (Casarrubea *et al.,*2010). The motor functions and coordination were significantly enhanced by the administration of nutmeg extract at 7th and 14th days of administrations in wire grid test, Pole test, Inverted screen test and Beam walk test respectively by increased the time of latency to fall.

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