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SESAMOL AMELIORATES THE MOTOR BEHAVIOR IN ROTENONE-INDUCED RAT MODEL OF PARKINSON'S DISEASE

ROHINI.D[1] AND VIJAYALAKSHMI.K*[2]

[1] Research scholar, Department of Biochemistry, Bharathi Women's College, Chennai, Tamil Nadu, India.
[2] Associate Professor, Department of Biochemistry, Bharathi Women's College, Chennai, Tamil Nadu, India.

ABSTRACT

Parkinson's disease is attributed to oxidative and inflammatory stress manifesting motor, cognitive and behavioral anomalies. Although current therapies focus on the restoration of dopamine levels, prevention or disease-modifying remedies are immediately needed. In this context, experiments were performed in male Wistar rats. They were segregated into five groups (n= 6): Group 1- vehicle (DMSO in corn oil intraperitoneal + saline intraperitoneal), Group 2- rotenone (3 mg/kg.B.wt intraperitoneal), Group 3- rotenone + sesamol (50 mg/kg.B.wt intraperitoneal), Group 4- rotenone + sesamol + L-DOPA (10 mg/kg.B.wt oral), Group 5- rotenone + L-DOPA were administered for 60 days. The body weight was noted periodically. Motor activity was assessed on 60th day by pole test, ladder climbing test and open field test. Administration of rotenone caused impaired ability to initiate movement. Significant reversal was observed with the administration of sesamol ($P<0.01$), L-DOPA ($P<0.05$) when compared to group 2. The maximal restoration in behavioral changes was observed in group 4 that received sesamol + L-DOPA combination ($P<0.001$) when compared to group 2. The results suggest that sesamol can be helpful in the management of motor behavior in Parkinson's disease, but treatment along with L-DOPA is more effective.

KEYWORDS: ***Parkinson's disease, rotenone, sesamol, L-DOPA***

VIJAYALAKSHMI.K*

Associate Professor, Department of Biochemistry, Bharathi Women's College, Chennai, Tamil Nadu, India.

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INTRODUCTION

Parkinson's disease (PD) is one of the debilitating neurodegenerative movement disease and its current cure focuses mainly on symptomatic treatment.[1] PD is primarily characterized by bradykinesia, rigidity, akinesia, resting tremor, postural instability and also associated with non-motor features.[2] Epidemiological study shows that the prevalence of PD in industrialized countries is usually estimated at 0.3% of the whole population and at 1% of people over 60 years of age.[3] It is difficult to diagnose PD at an early stage in human beings because the appearance of symptoms occurs only at 80% striatum dopamine depletion.[4] Motor impairment observed in PD patients appears to be the most prominent point of concern when recommending medicine or planning treatment. Animal models allow us to study the pathology of PD tracking physical and behavioral alterations. Among the available animal models, rotenone (ROT) ($C_{23}H_{22}O_6$) model depicts the classical features of PD due to its use as an organic pesticide.[5] ROT, commonly used as a specific inhibitor of mitochondrial complex I and the widely used pesticide to kill insects and nuisance fish in lakes.[6,7] ROT, an environmental neurotoxicant produced the consistent model of PD that recapitulates many key features of pathology and pathogenesis which are used in testing experimental therapeutics and to examine gene-environment interactions.[8] ROT model also enhances the oxidative stress and neuroinflammation in the nigrostriatal dopaminergic pathway.[9] L-DOPA ($C_9H_{11}NO_4$) is a kind of nerve transmitter which increases the dopamine content and obtains the therapy efficacy for the treatment of PD.[10] Repeated pulsatile stimulation of striatum dopamine receptors with L-DOPA treatment induces motor response complications.[11] The main goal for future cure of PD is the discovery and development of neuroprotective medications to terminate the disease progression and to reduce the toxicity of L-DOPA. Thus natural antioxidants could be helpful in the management of PD. Anti-parkinsonian drug is important to cross the blood-brain barrier. Sesamol (SES) ($C_7H_6O_3$) is a major constituent of *Sesamum indicum* seed and is a flowering plant of the genus *Sesamum* of the Pedaliaceae family.[12] SES is an effective antioxidant which guards the cells from free radical damage.[13] SES is known to have beneficial effects on cognitive impairment and depression.[14,15] SES also employed for the treatment of diabetes-associated blood-brain barrier dysfunction.[16] Therefore, SES has the capacity to cross the blood-brain barrier. In our earlier study of SES, an antioxidant antagonized ROT-induced cell death in SH-SY5Y neuronal cells has been demonstrated.[17] In this manuscript, we extended our studies to explore the possible neuroprotective effect of SES in the behavior impairments induced by ROT model of PD in rats

MATERIALS AND METHODS

Materials

Rotenone, sesamol, L-DOPA, dimethyl sulphoxide were purchased from Sigma Aldrich (St.Louis, Missouri, USA). All other chemicals used were of analytical grade.

Animals

Male Wistar rats (150-180 g) were used for the study. Rats were maintained at a temperature of 24±2ºC, in a 12 h dark/12 h light cycle, with food and water *ad libitum*. Rats were acclimatized to laboratory conditions before the test. The studies were carried out with the guidelines given by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (India). The Institution Animal Ethical Committee of Sathyabama University, Chennai approved the protocol of the study (SU/CLATR/IAEC/VI/034/2016).

Experimental design

The rats were divided into 5 groups, each containing 6 rats.

Group I: Vehicle (DMSO in corn oil intraperitoneal + Saline intraperitoneal) for 60 days.

Group II: Rotenone (3 mg/kg.B.wt intraperitoneal) for 60 days.

Group III: Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + Sesamol (50 mg/kg.B.wt intraperitoneal) for 60 days.

Group IV: Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + Sesamol (50 mg/kg.B.wt intraperitoneal) + L-DOPA (10 mg/kg.B.wt oral) for 60 days.

Group V: Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + L-DOPA (10 mg/kg.B.wt oral) for 60 days.

Body weight

Each rat was weighed prior to the experiments and during the course of study.

Neurobehavioral analysis

Rats were evaluated regarding locomotor disturbance through blinded investigators who monitored the following neurobehavioral analysis on 60th day of the experiment. All the test was videotaped and the videos were replayed for analysis of the following test.

Pole test

The pole test is usually performed to detect bradykinesia.[18] Pole test has also been used to evaluate the movement disorder caused by striatum dopamine depletion and motor coordination in the PD model.[19,20] The rats were located head up on top of a vertical wooden pole. The base of the pole was positioned in the home cage. When located on the pole, rats turn themselves downward and descend the length of the pole back in their home cage. The rats received 2 days of training that consisted of 5 trials for each session. On the assessment day, the rats received 5 trials, total time to descend was measured. The mean of the 5 trials was noted and compared.

Ladder climbing test

Catalepsy is the common incidence in PD due to the stiffness of muscles. The experimental rats were exposed to ladder climbing test to evaluate the catalepsy.[21] The ladder was inclined at 45^{o}. The rung space was not altered throughout the experimental period. The experimental rats were trained to climb the ladder for 3 days before the test and the average performance for five times was recorded and compared.

Open field test

Open field apparatus was constructed for detecting the spontaneous locomotor behavior and abnormal involuntary movements.[22] Open field apparatus consisted of a square arena with high walls. The entire apparatus was painted black except for 6 mm thick white lines that divided the floor into 16 squares. A central square was drawn on the middle of open field. The rats were centrally located in the open field apparatus and were allowed to walk without restraint inside the area for 5 minutes and the behavioral aspects were noted and compared.

- Ambulation frequency: Number of grid lines the rat crossed with all four paws.
- Rearing frequency: Number of times the rat stood on its hind limbs.
- Grooming frequency: Number of times the rat groomed facial region and licked/ washed/ scratched the various parts of the body.

Rats were exposed to the apparatus for habituation for two consecutive days. The open field apparatus was cleaned with 5% alcohol solution before behavioral testing to eradicate possible bias due to the smell left by previous rats.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS version 20 from IBM. The results were expressed as mean±SD. One-way analysis of variance was applied to the data and the significance of the results was derived by running post hoc test. The $p<0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

The effect of drug treatment on the body weight of experimental rats is shown in (Fig 1). It was observed that the body weight significantly ($p<0.001$) decreased due to ROT administration when compared to the vehicle group which coincides with the result of Binienda, *et al*.[23] Significant reversal was noted in ROT-induced groups treated with SES ($p<0.001$), SES + L-DOPA combination ($p<0.001$) and L-DOPA ($p<0.001$) when compared to ROT-induced group. SES, a potent antioxidant, was able to attenuate the decline in the body weight caused by ROT administration.[24] Behavioral outcome measures are essential to evaluate the potential therapeutic treatments in preclinical trials for many neurodegenerative diseases. The key symptoms of PD involves delayed motor initiative, slow performance of voluntary movements, rapid fatigue, disorders in performance of associated muscles.[25] The common feature of all toxin-induced models of PD is their ability to produce oxidative stress and cause cell death in dopamine neuronal populations.[26] In the pole test, on 60th day, all rats in each group showed variable time to reach the bottom of the pole (Fig 2). There was extremely significant ($p<0.001$) increase in time taken by ROT-induced group to reach the bottom of the pole when compared to the vehicle group. Significant reversal was noted in ROT-induced groups treated with SES ($p<0.01$) and L-DOPA ($p<0.05$). SES with its potential therapeutic benefits has decreased the time to reach the bottom of the pole.[27] The maximal decrease in time was observed in the group that received SES + L-DOPA combination ($p<0.001$) compared to ROT-induced group. It has been noted that dopamine depletion in the striatum produces profound deficits in response time in rats which may be related to the motor dysfunction commonly seen in PD.[28] Current results are in accord with the previous reports that dopamine level and motor deficits in PD model have been mitigated by antioxidant supplementation.[29,30,31] In the ladder climbing test, on 60th day, all rats in each group showed variable time to climb the ladder (Fig 3). The time taken to climb the ladder significantly ($p<0.001$) increasedROT-induced group compared to the vehicle group. Significant reversal was noted in ROT-induced groups treated with SES ($p<0.01$) and L-DOPA ($p<0.05$). Khadira Sereen *et al*. reported SES as an anti-Parkinson compound.[32] The maximal decrease in time was observed in the group that received SES + L-DOPA combination ($p<0.001$) compared to ROT-induced group. Xiong, *et al*. observed that edaravone, a powerful free radical scavenger, abolished ROT-induced catalepsy.[33] In the open field test, on 60th day, all rats in each group showed a variable frequency of ambulation, rearing and grooming. The ambulation frequency (Fig 4) was significantly ($p<0.001$) decreased in ROT-induced group as compared to the vehicle group. Amano, *et al*. reported the correlation of ambulation and PD.[34] Significant reversal was noted in ROT-induced groups treated with SES ($p<0.01$) and L-DOPA ($p<0.05$). The maximal increase in ambulation frequency was observed in the group that received SES + L-DOPA combination ($p<0.001$) compared to ROT-induced group.There was significant decrease in rearing frequency (Fig 5) in ROT-induced group ($p<0.001$) when compared with the vehicle group which coincides with the result of Sereniki, *et al*.[35] Significant reversal was noted in ROT-induced groups treated with SES ($p<0.01$) and L-DOPA ($p<0.05$). The maximal increase in rearing frequency was observed in the group that received SES + L-DOPA combination ($p<0.001$) compared to ROT-induced group. There was significant decrease in grooming frequency (Fig 6) in ROT-induced group ($p<0.001$) when compared with the vehicle group. Pelosi, *et al*. reported that grooming frequency has been affected by alterations of the dopamine system and it helps to screen PD in animal models.[36] Significant reversal was noted in ROT-induced groups treated with SES ($p<0.01$) and L-DOPA ($p<0.05$). The maximal increase in grooming frequency was observed in the group that received SES + L-DOPA combination ($p<0.001$) compared to ROT-induced group. Ximenes, *et al*. observed that the neuroprotective action of valproic acid reversed the 6-hydroxy dopamine induced behavioral changes as evaluated by the open field test.[37] Widespread history of PD therapies is considered symptomatic with no actual effects on pathology progression. Moreover, current therapies of PD are based primarily on dopamine replacement, providing temporary improvement in motor impairment. Earlier studies were trying to reach a neuroprotective agent that can guard the damaged neurons in PD.[38] In this study, we have used a plant derived compound namely SES helps to counteract the pathogenesis of PD without any undesirable effects, due to its antioxidant properties

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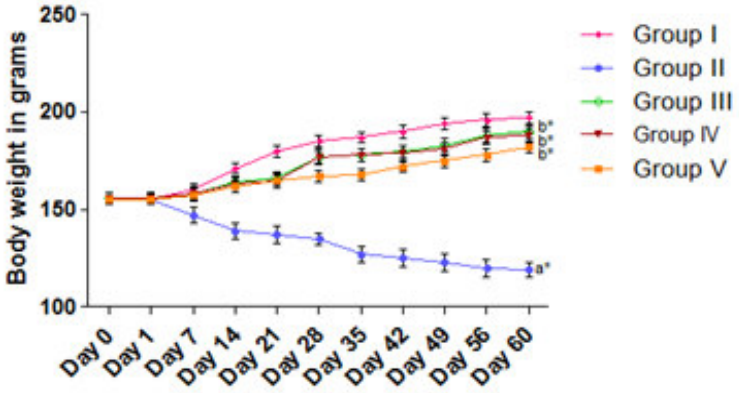

Figure 1 shows the body weight of experimental rats. Each value is expressed as mean ± SD, n=6. Group I: Vehicle-treated rats, Group II: Rotenone-induced rats (3 mg/kg.B.wt), Group III: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt) + Sesamol (50 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p<0.001. Comparison: a- as compared with Group I; b- as compared with Group II

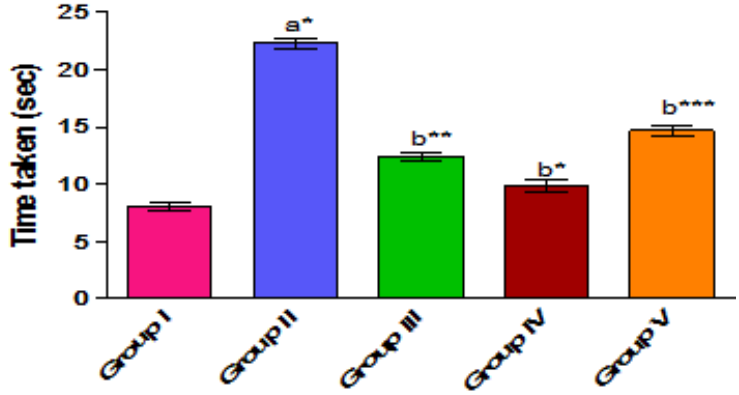

Figure 2 shows the behavioral activity (pole test) of experimental rats. Each value is expressed as mean ± SD, n=6. Group I: Vehicle-treated rats, Group II: Rotenone-induced rats (3 mg/kg.B.wt), Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p<0.001, **p<0.01, ***p<0.05. Comparison: a- as compared with Group I; b- as compared with Group II.

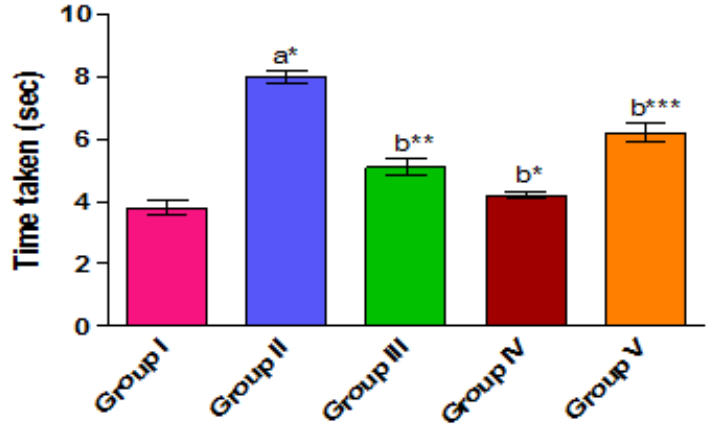

Figure 3 shows the behavioral activity (ladder climbing test) of experimental rats. Each value is expressed as mean ± SD, n=6. Group I: Vehicle-treated rats, Group II: Rotenone-induced rats (3 mg/kg.B.wt), Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p<0.001, **p<0.01, ***p<0.05. Comparison: a- as compared with Group I; b- as compared with Group II.

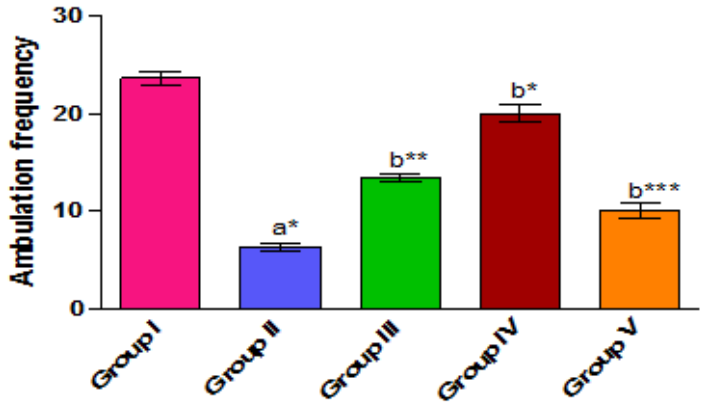

Figure 4 shows the ambulation frequency (open field test) of experimental rats. Each value is expressed as mean ± SD, n=6. Group I: Vehicle-treated rats, Group II: Rotenone-induced rats (3 mg/kg.B.wt), Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p<0.001, **p<0.01, ***p<0.05. Comparison: a- as compared with Group I; b- as compared with Group II

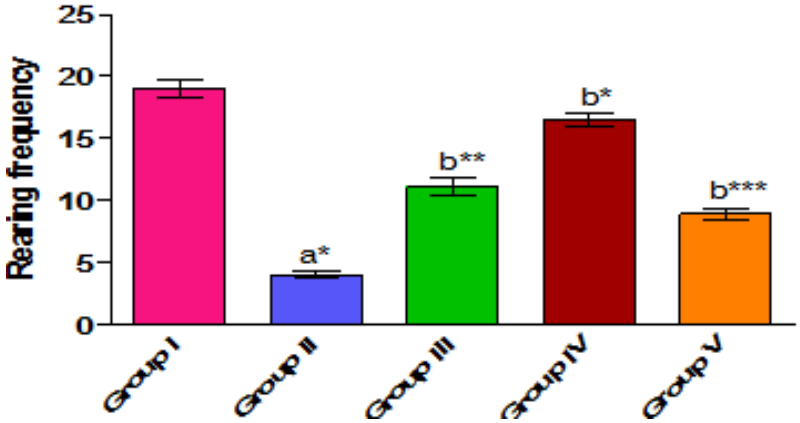

Figure 5 shows the rearing frequency (open field test) of experimental rats. Each value is expressed as mean ± SD, n=6. Group I: Vehicle-treated rats, Group II: Rotenone-induced rats (3 mg/kg.B.wt), Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p<0.001, **p<0.01, ***p<0.05. Comparison: a- as compared with Group I; b- as compared with Group II.

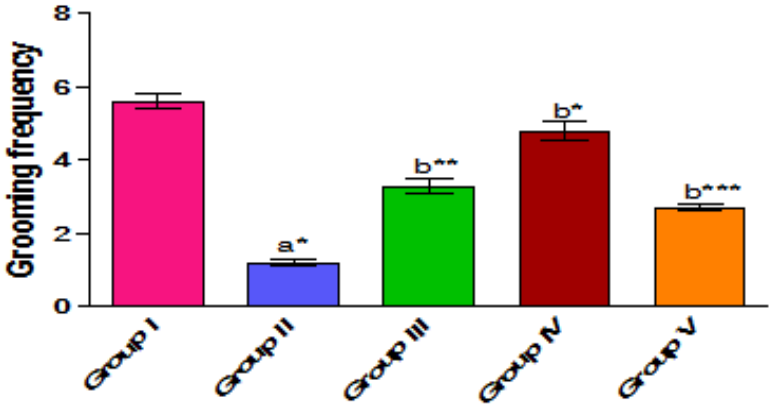

Figure 6 shows the grooming frequency (open field test) of experimental rats. Each value is expressed as mean ± SD, n=6. Group I: Vehicle-treated rats, Group II: Rotenone-induced rats (3 mg/kg.B.wt), Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt), Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt), Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt). Statistical significance: *p<0.001, **p<0.01, ***p<0.05. Comparison: a- as compared with Group I; b- as compared with Group II.

CONCLUSION

From the findings of the present study, SES was considered to possess a beneficial outcome in motor behavior along with L-DOPA against PD in ROT-induced rat model. Antioxidant therapy is a major concern in PD. Hence, we propose to strengthen the antioxidant potential of SES along with L-DOPA. Thus, the present work brought out new insights for the treatment of PD. However, *in vivo* study on the molecular basis is yet to be carried out to ascertain its potential.

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CONFLICTS OF INTERESTS

Conflict of interest declared none

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Reviewers of this article

Dr. L. Suguna

Scientist , Dept. of Biochemistry, Central Research Institute , Adyar ,Chennai , Tamilnadu , India.

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Associate Professor,Nalanda Institute of Pharmaceutical Sciences, Sattenapalli, Guntur, Andrapradesh, India

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