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Research Article

EFFECT OF SESAMOL IN ROTENONE INDUCED RAT MODEL OF PARKINSON'S DISEASE- BIOCHEMICAL AND HISTOPATHOLOGICAL EVIDENCES

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ABSTRACT

Objective: To investigate the protective effect of sesamol in rotenone-induced rat model of Parkinson's disease by biochemical and histopathological studies. Male Wistar albino rats were subjected to study for 60 days (n=6: I- vehicle control, II- rotenone (3 mg/kg.B.wt intraperitoneal), III- rotenone + sesamol (50 mg/kg.B.wt intraperitoneal), IV- rotenone + sesamol + L-DOPA (10 mg/kg.B.wt oral), V- rotenone + L-DOPA).The organs (brain, liver, kidney, heart and spleen) of experimental rats were weighed. Biochemical parameters like urea, uric acid, creatinine, blood urea nitrogen, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, total protein, albumin and globulin were determined. The histopathology of liver, kidney, heart, spleen and intestine were performed. Sesamol administration has attenuated the alterations caused by rotenone. These results suggest that sesamol can be a potential therapeutic for the treatment of Parkinson's disease by serving as a neuroprotective compound.

INTRODUCTION

Ageing lead to an increased prevalence of neurodegenerative diseases. Ageing is also the greatest risk factor for developing Parkinson's disease (PD) with 4-5 % of population [1]. PD is the devastating neurological disorder characterized by the degeneration of dopaminergic neurons which affect aged, young adults and even children [2]. Oxidative stress is an important etiology of PD [3]. Neuroinflammation plays an active role in the pathogenesis of PD[4]. Environmental and genetic factors are interlinked with the progressive loss of dopaminergic neurons [5]. Environmental exposures like pesticides also lead to the appearance of biochemical and behavioral alterations[6]. Rotenone (ROT) is considered to produce the nearest symptoms found in human patients suffering with PD [7].

ROT is a common insecticide used to kill fish and its administration can evoke the symptoms of PD in various models [8,9]. ROT exposure inhibits complex I and causes highly selective dopaminergic neuronal cell death and alpha synuclein aggregation[10]. The loss of dopaminergic neurons causes the over activity of sub thalamic nucleus and globuspallidus which lead to movement disorders [11]. ROT is considered as the best model for PD research[12]. Intraperitoneal administration of ROT resulted in accumulation of misfolded proteins, decreased the level of reactive proteins and caused the striatal dopaminergic terminals degeneration [8,13]. ROT exposure can cause hypokinetic multisystem degeneration [14]. Few researchers [15-17] have observed the potential link between pesticide exposure and increased risk for PD. Therefore, researchers over the world developed an interest to prevent and treat these pathologies. Natural compounds with a wide range of biological activities and therapeutic potentials are employed. Sesame oil derived from *Sesamumindicum* L. consists of non- fat antioxidants including sesamol (SES) (3,4-methylenedioxyphenol) [18].SES with its antioxidant potential capable of providing resistant to oxidative deterioration[19] and lipid peroxidation[20]. The protective effect of SES was observed in rats with mitochondrial oxidative stress and hepatic injury [21]. SES was also found to be effective on radiation-induced cytotoxicity [22]. Biochemical and histopathological evidences revealed the potential role of SES in 6-hydroxy dopamine induced rats [23]. SES attenuated the biochemical and cellular alterations caused by 3-nitropropionic acid in the rat model of Huntington's disease [24]. SES was also found to have a favorable anticandidal potential [25]. In our previous study [26], we have observed the effect of SES in ameliorating the motor impairment induced by ROT.

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MATERIALS AND METHODS

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

Animals

Male Wistar albino rats (150-180 g) were used in 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*. 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.
GroupIII:Co-treatment Rotenone (3 mg/kg.B.wt intraperitoneal) + Sesamol (50 mg/kg.B.wt intraperitoneal) for 60 days.
GroupIV: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.

Organ weight

The weight of organs (brain, liver, kidney, heart and spleen) were noted inexperimental rats

Biochemical parameters

The biochemical parameters such as urea[27] uric acid [28], creatinine[29], blood urea nitrogen[30], aspartate transaminase (AST)[31], alanine transaminase (ALT)[31], alkaline phosphatase (ALP)[32], lactate dehydrogenase (LDH)[33], total protein[34], albumin and globulin[35]were determined by standard procedures.

Histopathological analysis

Tissue samples (liver, kidney, heart, spleen and intestine) obtained from the experimental rats were fixed in 10% formalin for 3-6 hours. The tissue sections were embedded in paraffin wax at 5-6 µm thickness and the sections were stained with Hematoxylin-Eosin solution and viewed under light microscope [36].

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

Table 1 shows the weight of organs (brain, liver, kidney, heart and spleen) in experimental rats. ROT is highly lipophilic and thus can readily access all organs [37].

GROUPS	BRAIN (g)	LIVER (g)	KIDNEY (g)	HEART (g)	SPLEEN (g)
Group I	1.28±0.08	6.53±0.22	1.22±0.06	0.58±0.04	0.33±0.02
Group II	1.25±0.10 aNS	6.49±0.21 aNS	1.23±0.06 aNS	0.56±0.03 aNS	0.30±0.03 aNS
Group III	1.27±0.09 bNS	6.52±0.20 bNS	1.23±0.05 bNS	0.58±0.04 bNS	0.32±0.03 bNS
Group IV	1.28±0.09 bNS	6.52±0.25 bNS	1.20±0.04 bNS	0.55±0.03 bNS	0.33±0.02 bNS
Group V	1.26±0.10 bNS	6.51±0.23 bNS	1.22±0.05 bNS	0.58±0.03 bNS	0.35±0.03 bNS

Table 1: Shows the weight of organs in 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, NS- Non Significant. Comparison: a- as compared with Group I; b- as compared with Group II.

Table 2 shows the levels of serum urea, uric acid, creatinine and blood urea nitrogen in experimental rats. It was observed that the levels of serum urea, uric acid, creatinine and blood urea nitrogen were significantly increased ($p<0.001$) in ROT-induced rats when compared to the vehicle-treated rats. Significant reversal was noted in ROT-induced rats treated with SES ($p<0.001$), SES + L-DOPA ($p<0.01$) and L-DOPA ($p<0.05$).To investigate the molecular mechanisms in PD, ROT model is highly employed because it reproduces the exact gene-environment interactions[38]. The renoprotective effect of SES was observed by the renal dysfunction indicators such as creatinine and blood urea nitrogen in acute kidney injured rats[39]. The subcutaneous administration of ROT led to extensive peripheral organ toxicity [40].

Table 2 Shows the levels of serum urea, uric acid, creatinine and blood urea nitrogen in 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, NS- Non Significant. Comparison: a- as compared with Group I; b- as compared with Group II.

GROUPS	UREA (mg/dl)	URIC ACID (mg/dl)	CREATININE (mg/dl)	BLOOD UREA NITROGEN (mg/dl)
Group I	45.09±0.35	1.30±0.09	0.70±0.04	19.31±1.3
Group II	72.12±1.73a*	2.19±0.10a*	1.13±0.07a*	47.12±1.97a*
Group III	48.07±0.39b*	1.42±0.08b*	0.74±0.03b*	22.60±1.3b*
Group IV	53.00±0.22b**	1.57±0.08b**	0.82±0.04b**	25.67±1.5b**
Group V	62.00±0.31b***	1.99±0.09b***	1.02±0.03b***	39.25±1.68b***

Table 3 shows the activities of AST, ALT, ALP and LDH in serum of experimental rats. The activities of serum AST, ALT, ALP and LDH were significantly increased ($p<0.001$) in ROT-induced rats when compared to the vehicle-treated rats. Significant reversal was noted in their activities with SES ($p<0.001$), SES + L-DOPA ($p<0.01$) and L-DOPA ($p<0.05$). Elevated levels of AST and ALT were established in ROT induced liver injury rats [41]. Liver can be directly or indirectly affected by a primary central dopaminergic defect[42]. ROT administration developed a hypocaloric status in liver with condensation of cytoplasm [43]. SES played a vital defensive role in the hepatodysfunction by its antioxidant property [44].SES has normalized the serum levels of AST, ALT and also ameliorated the iron-intoxicated histological changes in liver of mice[45].

Table 3 Shows the activities of aspartate transaminase, alanine transaminase, alkaline phosphatase and lactate dehydrogenase in serum 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, NS- Non Significant. Comparison: a- as compared with Group I; b- as compared with Group II.

Groups	Aspartate transaminase (IU/L)	Alanine transaminase (IU/L)	Alkaline phosphatase (IU/L)	Lactate dehydrogenase (IU/L)
Group I	41.33±0.23	32.50±0.69	60.50±0.64	216.18±1.99
Group II	56.83±0.33 a*	47.33±0.77a*	77.00±0.62 a*	271.00±1.78a*
Group III	44.50±0.48 b*	33.50±0.59b*	62.83±0.56b*	220.00±1.98b*
Group IV	48.83±0.45 b**	37.33±0.75b**	69.17±0.71b**	233.00±1.89b**
Group V	52.33±0.39 b***	41.00±0.72b***	72.00± 0.89b***	262.00±1.92b***

Table 4 shows the levels of total protein, albumin and globulin in serum of experimental rats. The levels of total protein, albumin and globulin were significantly increased ($p<0.001$) in ROT-induced rats when compared to the vehicle-treated rats. Significant reversal was noted in their levels with SES ($p<0.001$), SES + L-DOPA ($p<0.001$) and L-DOPA ($p<0.01$).SES has also played beneficiary role in stress model of depression [46].

We have also noted the histopathology of mid brain where SES has provided neuroprotection in ROT-induced rat model of PD [47]. The histopathology of liver of experimental rats is shown infigure 1. Liver section of vehicle-treated rats (Group I) reveals the normal architecture whereas ROT-induced rats (Group II) shows vacuolar degeneration. SES treated rats (Group III) shows the recovery from vacuolar degeneration. SES + L-DOPA treated rats (Group IV) shows reduction in vacuolar degeneration. L-DOPA treated rats (Group V) shows pathological changes as in Group II rats. ROT, an insecticide when induced intraperitoneal developed injury in liver tissue through lipid peroxidation [48].

Table 4 Shows the levels of total protein, albumin and globulin in serum 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, NS- Non Significant. Comparison: a- as compared with Group I; b- as compared with Group II.

Groups	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)
Group I	7.35±0.27	4.89±0.30	2.45±0.19
Group II	13.12±0.70a*	8.56±0.33a*	4.52±0.25a*
Group III	7.81±0.29b*	4.92±0.28b*	2.88±0.16b*
Group IV	7.88±0.24b*	4.96±0.37b*	2.90±0.17b*
Group V	9.35±0.36b**	5.72±0.31b**	3.60±0.24b**

The protective effect of sesame oil in rats with oxidative stress and hepatic injury was studied [49]. SES has attenuated the hepatic injury and played a dominant role against oxidative stress [50].

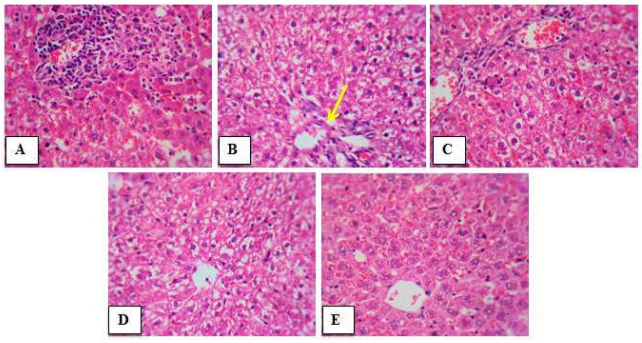

Figure 1 Shows the histopathology of liver in experimental rats: A- Group I: Vehicle-treated rats reveals the normal architecture, B- Group II: Rotenone-induced rats (3 mg/kg.B.wt) shows vacuolar degeneration (indicated by arrow), C- Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt) shows the recovery from vacuolar degeneration, D- Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt) shows reduction in vacuolar degeneration, E- Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows pathological changes as Group II rats. Magnification- 40X

The histopathology of kidney of experimental rats is shown infigure 2. Kidney section of vehicle-treated rats (Group I) reveals the normal architecture whereas ROT-induced rats (Group II) shows vacuolar degeneration. SES treated rats (Group III) shows the recovery from vacuolar degeneration. SES + L-DOPA treated rats (Group IV) shows reduction in vacuolar degeneration. L-DOPA treated rats (Group V) shows pathological changes as in Group II rats.ROT administration resulted in nephrotoxicity via oxidative damage and apoptosis in renal cells [51]. The renoprotective effect of SES in ferric nitrilotriacetate induced renal injurywas observed [52].

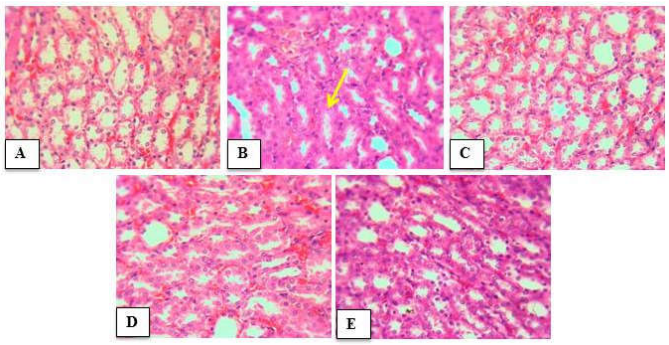

Figure 2 Shows the histopathology of kidney in experimental rats: A- Group I: Vehicle-treated rats reveals the normal architecture, B- Group II: Rotenone-induced rats (3 mg/kg.B.wt) shows vacuolar degeneration (indicated by arrow), C- Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt) shows the recovery from vacuolar degeneration, D- Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt) shows reduction in vacuolar degeneration, E- Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows pathological changes as Group II rats. Magnification- 40X

The histopathology of heart of experimental rats is depicted in figure 3. Heart section of vehicle-treated rats (Group I) reveals the normal architecture whereas ROT-induced rats (Group II) shows mild inflammation and mild myocardial damage. SES treated rats (Group III) shows the recovery from mild inflammation and mild myocardial damage. SES + L-DOPA treated rats (Group IV) shows reduction in mild inflammation and mild myocardial damage. L-DOPA treated rats (Group V) shows pathological changes as of Group II rats.SES also found to have vascular protective effect in the multifactoral heart disease atherosclerosis [53].

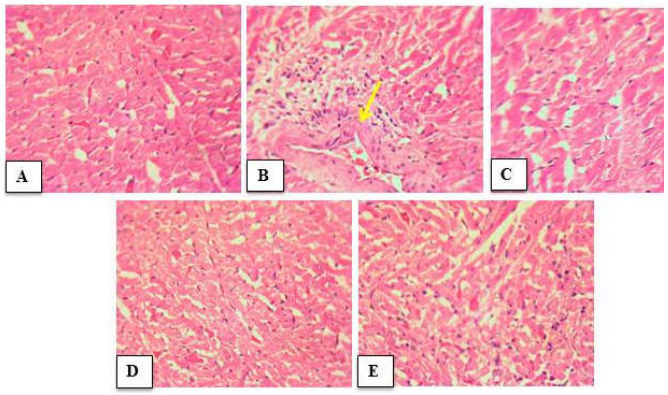

Figure 3 Shows the histopathology of heart in experimental rats : A- Group I: Vehicle-treated rats reveals the normal architecture, B- Group II: Rotenone-induced rats (3 mg/kg.B.wt) shows mild inflammation and mild myocardial damage (indicated by arrow), C- Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt) shows the recovery from mild inflammation and mild myocardial damage, D- Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt) shows reduction in mild inflammation and mild myocardial damage, E- Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows pathological changes as Group II rats. Magnification- 40X

The histopathology of spleen of experimental rats is observed in figure 4. Spleen section of vehicle-treated rats (Group I) reveals the normal architecture whereas ROT-induced rats (Group II) shows mild inflammation. SES treated rats (Group III) shows the recovery from inflammation. SES + L-DOPA treated rats (Group IV) shows reduction in inflammation. L-DOPA treated rats (Group V) shows pathological changes as of Group II rats.

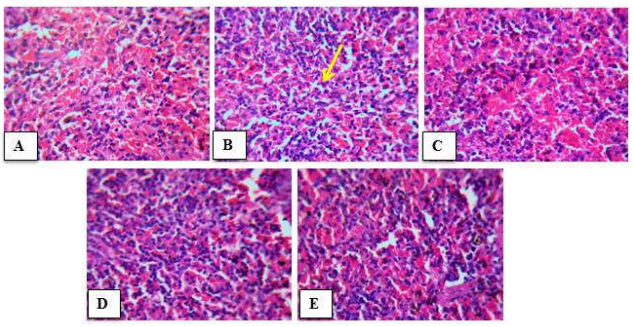

Figure 4 Shows the histopathology of spleen in experimental rats: A- Group I: Vehicle-treated rats reveals the normal architecture, B- Group II: Rotenone-induced rats (3 mg/kg.B.wt) shows mild inflammation (indicated by arrow), C- Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt) shows the recovery from inflammation, D- Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt) shows reduction in inflammation, E- Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows pathological changes as Group II rats. Magnification- 40X

The histopathology of intestine of experimental rats is noted infigure 5. Intestine section of vehicle-treated rats (Group I) reveals the normal architecture whereas ROT-induced rats (Group II) shows mild inflammation. SES treated rats (Group III) shows the recovery from inflammation. SES + L-DOPA treated rats (Group IV) shows reduction in inflammation. L-DOPA treated rats (Group V) shows pathological changes as of Group II rats. The biochemical and histopathological evidences revealed that SES can serve as a novel therapeutic compound in 6-hydroxy dopamine induced model of PD**[54]**.

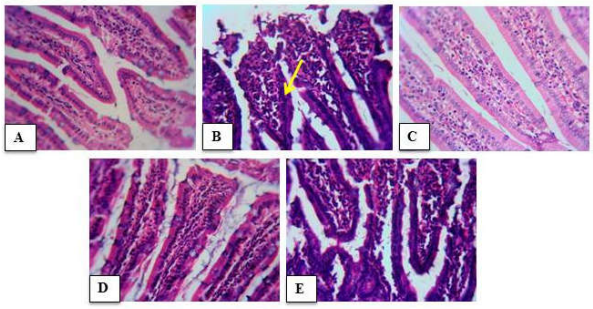

Figure 5 Shows the histopathology of intestine in experimental rats: A- Group I: Vehicle-treated rats reveals the normal architecture, B- Group II: Rotenone-induced rats (3 mg/kg.B.wt) shows mild inflammation (indicated by arrow), C- Group III: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt) shows the recovery from inflammation, D- Group IV: Rotenone (3 mg/kg.B.wt)+ Sesamol (50 mg/kg.B.wt)+ L-DOPA (10 mg/kg.B.wt) shows reduction in inflammation, E- Group V: Rotenone (3 mg/kg.B.wt) + L-DOPA (10 mg/kg.B.wt) shows pathological changes as Group II rats. Magnification- 40X

ROT was also investigated in SH-SY5Y cells and found that ROT-induced cell death by reactive oxygen species generation and mitochondrial dysfunction which was ameliorated by SES treatment [55].Thenatural compound SES has therapeutic benefits against PD and can be employed in clinical studies [56].

CONCLUSION

The results of this study confirm that the administration of ROT in rats induced biochemical and histopathological alterations mimicking those found in PD patients. Co-treatment with SES produced significant protection against these alterations. This opens up new avenues for the use of natural compounds in the management of PD.

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Abbreviations

PD, Parkinson's disease; ROT, Rotenone; L-DOPA, L-dihydroxy phenylalanine; SES, Sesamol; DMSO, Dimethyl sulphoxide; CPCSEA, Committee for the Purpose of Control and Supervision of Experiments on Animals.AST, Aspartate transaminase; ALT, Alanine Transaminase; ALP, Alkaline phosphatase; LDH, Lactate dehydrogenase.

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