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# INVESTIGATION OF PROTATIVE EFFECT OF *P*-CYMENE ON ROTENONE INDUCED PARKINSON'S DISEASE IN ALBINO WISTAR RATS

Shivani Sisodia, Lalit Parihar*, Ramji Gupta, Mohmmad Rashid, Sanjar Alam
R V Northland Institute, Dadri, Gautambudh Nagar, Up, India
Corresponding author email id lalitpparihar@gmail.com

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**Abstract**

**Objective** :- This study was designed to evaluate the effect of P-Cymene on Parkinson's disease (PD) induced via Rotenone in wistar albino rats. At the moment, it is thought that oxidative stress, neuron inflammation and apoptosis are plays key role in the induction of PD.

**Method :-** For the study the animals were separated into five groups with six animals in each groups: Normal control; Toxic (Rotenone dose 1.5 mg/kg); *p*-Cymene + Rotenone [I]; *p*-Cymene + Rotenone [II]; Ropinirole + Rotenone. Daily dose of rotenone was given for 28 days. Various neurobehavioral tests including Beam crossing task (BCT), Rotarod Test, Forced swim test (FST), Morris water maze (MWM) and Catalepsy test were also performed to establish the antiparkinsonian effect of *p*-Cymene. After 24 hrs. of the last dosing the weights of all animals were weighed individually before sacrificing the animals after scarifying all the biochemical parameter were estimated in terms of TBARS, GSH, Catalase, and SOD in the brain tissue.

**Results** :- On assessment of neurobehavioral test (Beam crossing task, Morris water maze, rotarod apparatus, Forced swim test, Morris water maze and Catalepsy behavioural Test**)** shows the activity of rotenone treated group was significantly reduced and on the treatment groups p-Cymene (25 and 50 mg/kg i.p.) it shows significant improvement in the neurobehavioural parameters. On biochemical parameters estimation results shows significant decrease in GSH, SOD, catalase and ache level in the rotenone treated rat groups which was significantly increase on the treatment groups p-Cymene (25 and 50 mg/kg i.p.). In case of TBARS estimation it shows significant increase in rotenone treated rat groups which was significantly decrease on the treatment groups p-Cymene (25 and 50 mg/kg).

**Conclusion :-** According to the result ,it was concluded that the treatment of rotenone results in considerable oxidative stress & brain damage, while the administration of p-Cymene showed significant protective effect against PD in rats due to its robust antioxidant and positive results on neurobehavioral parameters.

**Keywords:-** Neurodegenerative diseases, Parkinson's disease, *p*-Cymene, Rotenone.

**Introduction**:- Neurodegenerative Dise**ase**s- It is a type of disease where an extensive degeneration of neuron and neuronal cell death occurs. The nervous systems are made with the help of neurons and there is a difficulty in regeneration of cells when the damage or death occurs. This is due to the inability in generating new cells by the body. Some of the neurodegenerative diseases are alzheimers, sclerosis, huntingtons and Parkinsons. (Sherer, Betarbet et al. 2007, Drolet, Cannon et al. 2009, Armstrong and Okun 2020) (de Santana, Guimarães et al. 2015)

Parkinson's disease (PD) is a class of neurodegenerative illnesses caused by loss of dopaminergic (DA-ergic) neurons from the basal ganglia's substantia nigra pars compacta (SNpc) region, which is in charge of motor coordination. (Favre and Powell 2014, Cicolini, Jing et al. 2016) Parkinson's disease is a neurological ailment that progresses over time and is caused by the degeneration of brain nerve cells. Deficits both non-motor and motor are caused by this illness. (Claiborne 1985) Rigidity, resting tremor, and bradykinesia are the indications of motor impairments. (Xu, Begley et al. 2016, Kavuri, Sivanesan et al. 2020) Depression, sleeplessness, and cognitive impairment are the non-motor indicators and symptoms. Parkinson's disease is caused by a gradual loss of dopamine (DA) as a result of the nigrostriatal dopaminergic pathway degenerating. (Armstrong and Okun 2020) In its early stages, Parkinson's disease makes it difficult to conduct coordinated movements. As the illness advances, depression, cognitive impairment, and neurogenic impairment—which leads to the loss of bladder control are also experienced. (Patassini, Begley et al. 2015)

p-cymene It is an aromatic chemical molecule that occurs naturally in the environment. It belongs to the class of alkylbenzenes and is associated with monoterpenes. Its molecular structure is made up of a benzene ring that has methyl and isopropyl atoms para-substituted into it. (Bashkatova, Alam et al. 2004) Despite the fact that p-cymene does not dissolve in water, it may be dissolved in organic solvents (Ellman 1959). It has shown essential oils & majority of their constituent parts have antioxidant action. (Favre and Powell 2014) A monoterpene, it is a key element in oils of several species of plant. *In vivo*, p-cymene possesses antioxidant activity and may protect neurons in the brain. The creation of a new therapy approach for a variety of disorders in which ROS plays a significant pathophysiological part may benefit from this substance.It is also known as p-isopropyl toluene, is a type of monocyclic monoterpene molecule. (Bonnet and Houeto 1999) It is often the primary component in the essential oils of fragrant plants like Protium (*Burseraceae*),

Artemisia (*Asteraceae*), Ocimum, Origanum, Eucalyptus, Thymus, and (*Lamiaceae*). It also found naturally in > 200 foods, including carrots, cinnamon, orange grapefruit juice, strawberries, tangerine, butter, nutmeg, as well as a number of spices .p-cymene chemical name is 1-methyl-4-(1-methylethyl) benzene. (Ellman 1959, Claiborne 1985) It is a synthetic alkyl-isoprenoid aromatic substance with two isomers, m-cymene (alkyl categories are meta) and o-cymene (alkyl categories are ortho). This chemical is a building block for chief volatile mixtures like carvacrol & thymol, which have a wide range of biological effects. (Asiri 2010) It is a useful industrial byproduct that is used to make herbicides, fungicides, fragrances, perfumes, and some predecessors of common antioxidants like p-cresol. When used as a flavoring agent. (Matheson and Spencer 2000)

## METHODS

**Animals:** Thirty albino rats of 180-200 gm weight were procured from, AHF, R. V. Northland Institute, G-Noida. The rats were housed in polypropylene cages with standard laboratory settings (room temperature 21±1°C, humidity 40±10%), in as per the recommendations set out by the IAEC. The rats were fed a regular meal that was balanced and included water. The Institutional Animal Ethical Committee authorized the project with protocol no is RVNI/IAEC/22-23/10.

**Material:** P-cymene (Sigma), rotenone (Sigma), and Ropinirole (Torrent Pharmaceutical) were used in the study.

**Experimental design;-** Rotenone was used for the induction of PD in rats which was administered subcutaneously and p- cymene was administered as a treatment drug via intra peritoneal rout. Thirty animals were divided into five groups, each consisting of six individuals (n=6). Group I (vehicle control) received normal saline (1 ml/kg, PO), Group II received Toxic drug (Rotenone) (1.5 mg/kg, S.C), Group III received P -cymene (25 mg/kg. i.p)+ Rotenone (1.5 mg/kg s.c), Group IV received P -cymene (50 mg/kg .i.p) + Rotenone (1.5 mg/kg, i.p.) and Group V receive Ropinirole (0.5 mg/kg i.p.) + Rotenone (1.5 mg/kg, s.c.) for 28 days. All animals underwent the behavioural assessment tests**.** After 24 hours of last dosing brain tissue was collected and washed in the normal saline and used for the biochemical analysis.

### Neurobehavioral Test

B**eam crossing task (BCT):** On days 28$^{th}$ day rats was exposed to a trial of its capacity to organize its developments. Rodents' coordinated movements were reviewed on a scale from 0 to 4 in view of how much falls in every preliminary. The creature that could undoubtedly cross the bar got a score of 0. Creatures were doled out scores of 1, 2, and 3, separately, demonstrating gentle, moderate, and serious incapacity. The creatures were bombing and walking simply on the bar got a score of 4. (Ohkawa, Ohishi et al. 1979, Patassini, Begley et al. 2015, Ishola, Balogun et al. 2020, Kaji, Matsui-Yuasa et al. 2020)

**Morris water maze (MWM):** The MWM task was conducted for learning and memory (Qin, Qiu et al. 2021). The MWM apparatus was a rounded water flask with a 110 cm width and a 60 cm height that was 30 cm bottomless and occupied with aquatic that was 26 ± 2 °C. The pool was split into four fictitious quadrants: N (North), W (West), E (East), & S (South). In the centre of the southwest quadrant, in the same location in the middle of each trial a black circular platform with a diameter of 10 cm was positioned 2 cm under water's surface. Three trials per day were conducted on the MWM errands for five straight days. The concealed platform was only visible to the rats for a maximum of 60 seconds (the cut off period), and they were only permitted to stay there for 30 seconds. A stopwatch was applied to time how long it took the rat to find the escape platform. The animal was gently led to the secret platform and given 30 seconds to explore it if it couldn't find it after 60 seconds. For five days straight, each rat had a daily session consisting of three trials. The time it took to track down the covered stage in the water labyrinth, or escape latency time (ELT), was utilized as a measure of learning (Prasad and Hung 2020, Qin, Qiu et al. 2021)**.** The platform was taken out of the tank on day 5 and the rats then participated in a spatial probe experiment in which they had 45 seconds to find the platform. The amount of time spent in the platform's 2 (40 cm diameter) annulus was measured (Ishola, et al. 2020)(Ellman 1959, Panov, Dikalov et al. 2005, Hardie 2011)

**Forced swim test (FST):** To survey the burdensome way of behaving of rodents, a constrained swim test was conducted. Rodents were put in the tank interestingly during the preparation stage, where they are uncovered for 15 minutes. The ensuing openness happens 24 hours after the fact and goes on for 5 minutes. Rodents are tried for a solitary 6-minute experience, of which the initial 2 minutes are utilized for rehashed openness and the last 4 minutes are utilized for the genuine test, which decides the length of idleness**.** (Ohkawa,

Ohishi et al. 1979, Panov, Dikalov et al. 2005, Vázquez-Manrique, Farina et al. 2016, Zeng, Geng et al. 2018, Miyazaki, Isooka et al. 2020)

**Rotarod Test:-** The rotarod apparatus is a revolving rod with five divisions where five animals can be placed at a time throughout the research. It is 70 cm long and 3 cm in diameter, and it is 50 cm above the floor. Prior to evaluation, each albino rat was put through five trials at a rotational speed of seven revolutions per minute. For almost seven minutes, the control albino rat stays attached to the rod. The time of the fall off time was recorded while the treated rats were maintained on the spinning rod at regular intervals. The exam had a 7-minute cutoff time. (Matheson and Spencer 2000, Ono, Hasegawa et al. 2004, Cicolini, Jing et al. 2016, Handley, Reid et al. 2017, Fikry, Saleh et al. 2022)

**Catalepsy behavioural Test:** The rat's forepaws were located on a flat bar that was 9 cm overhead the bench superficial to measure its catalepsy behaviour. The definition of catalepsy was an immovable stance with both forepaws on the bar. A maximum of 180 seconds was recorded during the catalepsy's duration. Each observation day had three trials, with the mean of the three trials being taken into account for analysis. (Patassini, Begley et al. 2015, Fikry, Saleh et al. 2022)

**2. Biochemical estimations in brain tissue**

**a) TBARS -** The tissue homogenate was eliminated and 1 ml of the way of life medium was centrifuged at 10,000 rpm. It was then given 0.5 ml (30 percent TCA) & 0.5 ml of 0.8 percent TBA. The test tubes were put in a shaking water shower at 80OC for 30 minutes with aluminum foils on top of them. The test tube will be eliminated after 30 minutes and kept up in the super cold water for 10 minutes. From that point onward, it went through 15-minute centrifugation at 3000 rpm. and absorbance was taken at 540 nm. (Ohkawa, Ohishi et al. 1979)

b) **Reduced Glutathione (GSH);-**.A known amount of brain tissue, weighing between 300 to 600 mg, will be homogenized in 5-8 ml (0.02 M EDTA) prior mixed with 4.0 ml of water. 1 ml of 50% TCA was mixed after thorough mixing the mixture was agitated sporadically for 10 min by vortex mixer. The mixture was put into centrifuge tubes after 10 minutes, washed with EDTA & centrifugation at 6000 rpm for fifteen minutes. After centrifugation, 4.0 ml of 0.4 M Tris buffer was added to 2 ml of the supernatant (pH 8.9). After thoroughly blending

the whole solution, 0.1 ml (0.01M DTNB) was added. Within 5 minutes after adding DTNB, the absorbance was measured at 412 nm. (Ohkawa, Ohishi et al. 1979, Favre and Powell 2014)

**c) Catalase:-** The proportion of 1:10 w/v was utilized to homogenize the tissue in a 50 Mm/L potassium phosphate (pH 7.4). For 20 minutes the homogenization was turned in a cool rotator at 10,000 rpm & 4 °C. In the supernatant that was gathered after centrifugation, catalase movement was tried. A cuvette holding 2.95ml of 19 m M/L arrangements of H2O2 made in potassium phosphate support was loaded up with the remaining (50 l). For three minutes, the varieties in absorbance were seen at 240 nm frequency at 1-minute stretches. Catalase separates H2O2, decreasing absorbance when it is available.(Claiborne 1985, Bonnet and Houeto 1999, Fikry, Saleh et al. 2022)

**d) Superoxide Dismutase (SOD):-** Grass action in the muck was analyzed by halting the pyrogallol autoxidation. To the Tris HCl cushion, 100 ml of cytosolic leftovers were added (pH 8.5). A similar cushion will be utilized to titrate the 3ml last volume. The absorbance was taken at 420 nm (Ellman 1959).

**3. Body Weight Measurement;-**On days 1, and 28 the animal's body weight was measured prior to dosing with p-Cymene and Rotenone compounds. Up until the last group of animals was put to death on day 29, the weighting continued. The weights of the animals were computed on each dosage day.(Claiborne 1985)

**4. AChE activity measurement;-** This test was carried out in accordance with the procedure that was outlined by Ellman et al. Spectrophotometry is used in this approach to determine the rate at which thiocholine is produced, and acetylcholine is hydrolyzed thanks to the catalytic activity of AChE. After being homogenized in (0.1 M) buffer with a pH of 8.0, the brain contents of rats were centrifuged at 14,000 rpm and 4 ° C for five minutes. After that, 0.2 mL of the found supernatant was placed in to the cuvette, which already contained 2.8 mL of phosphate buffer with a concentration of 0.1 M and 100 L of Ellman's reagent with a concentration of 0.01 M (5,5'-dithiobis-2-nitrobenzoic acid). As a result, the absorption was determined at a wavelength of 412 nm. The next step was to add 20 L of the substrate, which was acetylthiocholine iodide. After two minutes of incubation at 30 degrees Celsius , the result of the thiocholine with dithiobis-nitrobenzoic acid was

identified by measuring the absorbance per minute at a wavelength of 412 nanometers for a period of ten minutes at intervals of two minutes (Fikry, Saleh et al. 2022).

**Statistical analysis :-** The data was shown as mean ± SD. Tukey's t-test was run after an ANOVA, and a p-value of less than 0.05 was deemed significant.

## RESULT

### Neurobehavioral tests

On assessment of neurobehavioral test (Beam crossing task, Morris water maze, rotarod apparatus, Forced swim test, Morris water maze and Catalepsy behavioural Test**)**, shows the activity of rotenone treated group was significantly reduced and on the treatment groups p-Cymene (25 and 50 mg/kg i.p.) it shows significant improvement in the neuro behavioural parameters. When compare with the ropinirole there is also improvement but there is no significant defferance between p cymene 50mg/kg ip and ropinirole treated groups.

### Neurobehavioral observation test in different groups :-

**Table 1 Neurobehavioral parameters data showing mean ± SD.**

| **Groups** | **Beam crossing test** Mean ± SD | **Rotarod test** Mean ± SD | **Forced swim test FST** Mean ± SD | **Morris water maze** Mean ± SD | **Catalepsy behavioural Test** Mean ± SD |
|---|---|---|---|---|---|
| Control | 4±0.25 | 119.1±5.5 | 55.5±1.70 | 24.3±3.4 | 28.6±2.5 |
| Rotenone | 0.8±0.7 | 43.8±1.6 | 108.5±1.707 | 57±2.9 | 159.3±4.7 |
| p-Cymene 25 + Rotenone | 2.3±0.5$^{s}$ | 109.3±0.512 | 93.6±0.47 | 46±4.04 | 125.8±7.35 |
| p-Cymene 25 + Rotenone | 3.5±0.54 | 112.8±0.196$^{\#}$ | 48.6±0.43 | 32.5±1.70 | 45.8±2.3 |
| Ropinirole + Rotenone | 3.3±0.51 | 106.7±0.28 | 46.3±0.74 | 32.16±1.3 | 28.5±2.07 |

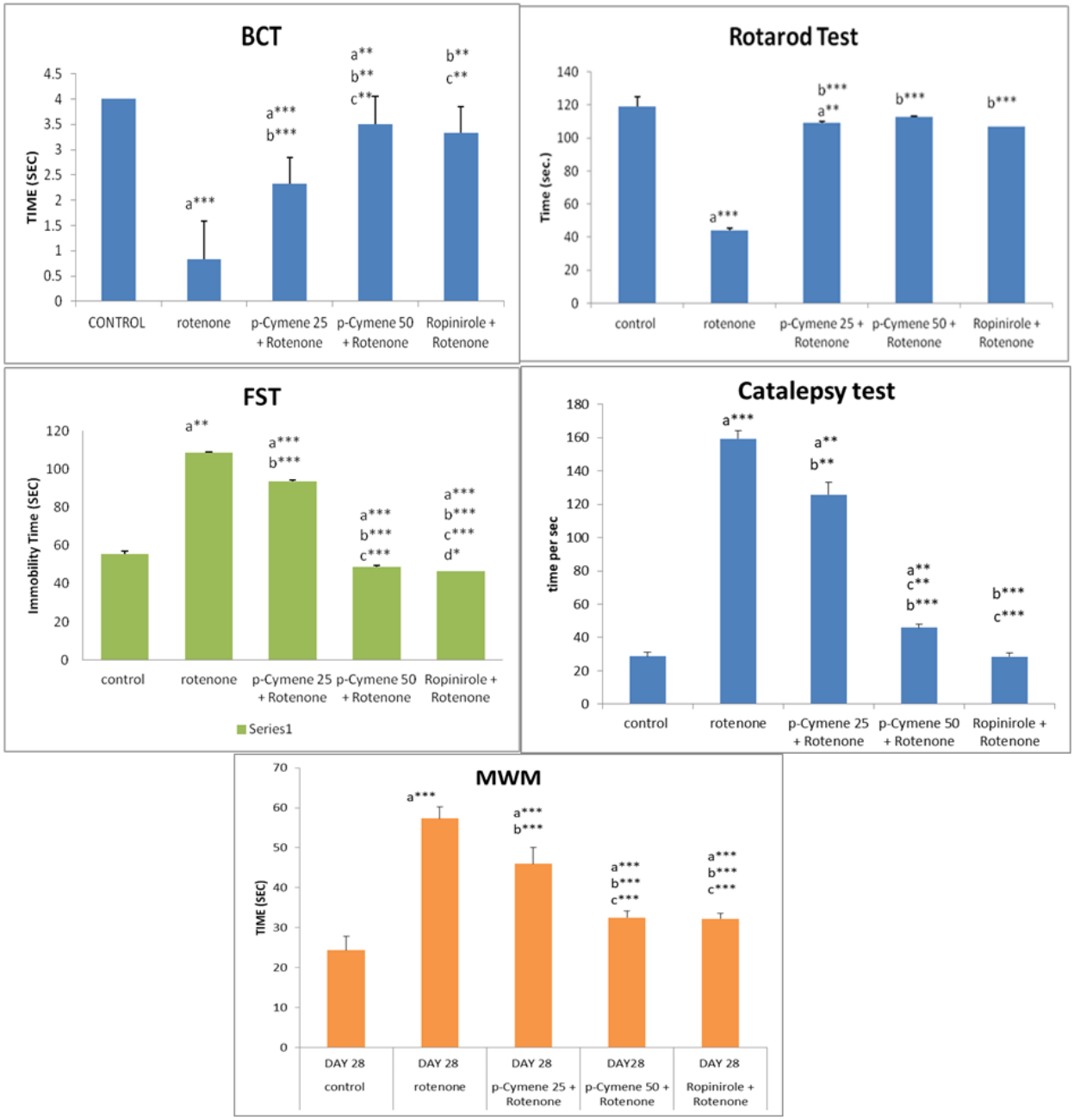


Figure 1 Effect of p-Cymene on neurobehavioral parameters in rotenone induced Parkinson's in experimental animal rat. All values are expressed as Mean ± SD. ***p < 0.001, **p<0.01,* p<0.05. a *vs.* control, b *vs.* rotenone, c *vs.* p-Cymene 25 + Rotenone, d *vs.* p-Cymene 25 + Rotenone.

**Biochemical observation in brain tissue of different groups**

On assessment of biochemical parameters estimation results shows significant decrease in GSH, SOD, catalase and ache level in the rotenone treated rat groups which was significantly increase on the treatment groups p-Cymene (25 and 50 mg/kg i.p.). When compare with the ropinirole there is also improvement. In case of TBARS estimation it shows significant increase in rotenone treated rat groups which was significantly decrease on the treatment groups p-Cymene (25 and 50 mg/kg).

**Table 2 Biochemical parameters data showing mean ± SD.**

| **Groups** | **TBARS (nmol of MDA/mg protein)** MEAN ± SD | **GSH (µmol of GSH/mg of protein)** MEAN ± SD | **CAT (nmol of H2O2\min\mg protein)** MEAN ± SD | **SOD (U/per mg of protein)** MEAN ± SD |
|---|---|---|---|---|
| Control | 0.237±0.12 | 5.1±0.6 | 6.7±0.86 | 2.6±0.19 |
| Rotenone | 1.53±0.1 | 2.8±0.34 | 1.45±0.32 | 0.35±0.20 |
| p-Cymene 25 + Rotenone | 1.17±0.108 | 3.3±0.31 | 3.1±0.67 | 0.57±0.13 |
| p-Cymene 25 + Rotenone | 0.38±0.21 | 4.26±0.30 | 4.8±0.29 | 1.76±0.15 |
| Ropinirole + Rotenone | 0.34±0.204 | 4.6±0.3 | 5.3±0.89 | 1.96±0.23 |

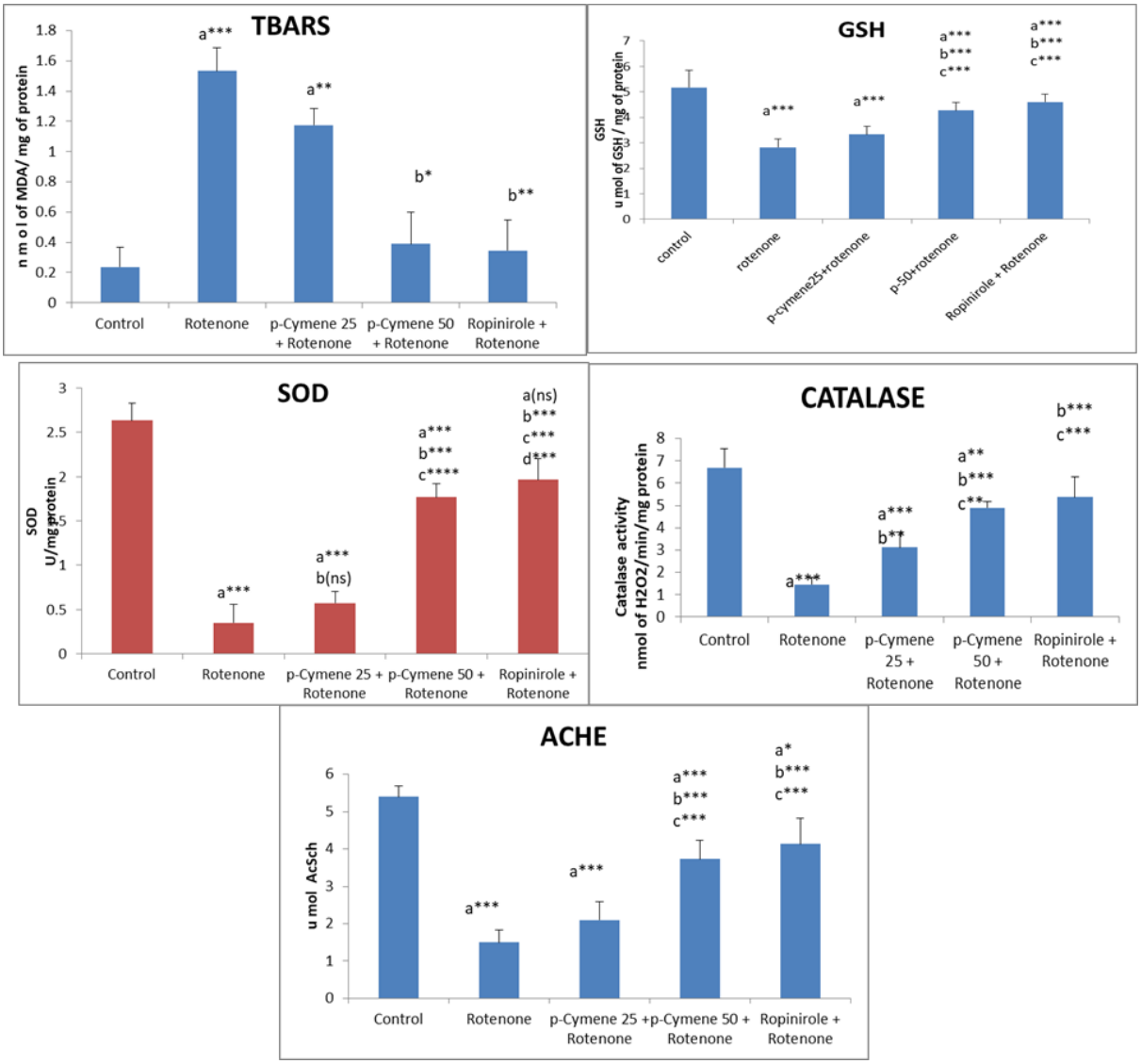


**Figure 2** Effect of p-Cymene on biochemical parameters in rotenone induced Parkinson's in experimental animal rat. All values are expressed as Mean ± SD. ***p < 0.001, **p<0.01, * p<0.05. a *vs.* control, b *vs.* rotenone, c *vs.* p-Cymene 25 + Rotenone, d *vs*. p-Cymene 50 + Rotenone.

## Conclusions

On the evaluation of various neurobehavioral and biochemical estimation p-cymene shows protective effects especially at 50 mg/kg dose. It helps in regulating the neuro behavioural parameters and also showed oxidative stress reducing activity. Its showed positive effect on excitotoxicity parameter. So we can conclude and suggest this drug will be a good option for the treatment of Parkinson's and further study required for the better understandings in future.

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**Conflicts of Interest** There is no any conflict of interest amoung the authors.

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