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Neuroprotective Effect of *Scoparia dulcis* Plant Extract against Parkinson's Model of Excitotoxicity in Rats and Zebrafish Model

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ABSTRACT

Background: Herbal medicines have regularly kept up ubiquity for cultural and historical reasons and furthermore viewed as more secure as they started from natural sources. *Scoparia dulcis* is an Indian herbal plant species, extensively used traditionally for treating various disorders. However, it is unclear whether *Scoparia dulcis* can also offer protection against Parkinson disease and to determine if an aqueous whole plant extract of *Scoparia dulcis* has the potential for Neuroprotective activity against excitotoxicity in Parkinson's disease. **Methodology:** Acute toxicity study was first performed. Excitotoxicity were then induced using monosodium glutamate (MSG). MSG induced model was performed on wistar rats for a schedule of 1 week. On 8th day, readings of muscle grip strength and locomotor activity were recorded and on 9th day, biochemical parameters i.e., levels of dopamine, catalase and glutathione were analysed using UV-Vis spectrophotometer. MSG induced excitotoxicity model of Parkinson's disease in zebrafish was performed for 96 hrs resulted in alterations in swimming pattern measured through video recording system. **Results:** The maximum tolerated extract dose was more than 2g/kg in rats and 100mg/L in zebrafish. The extract was found to be neuroprotective as it reduces excitotoxicity score and prevents Parkinson disease. Treatment with the extract also counteracts the elevation of glutamate level as a result of MSG induced excitotoxicity. **Conclusion:** An aqueous whole plant extract of *Scoparia dulcis* has the potential for neuroprotective activity against excitotoxicity in Parkinson disease via NMDA antagonistic property.

INTRODUCTION

Neurodegenerative disease includes a great variety of circumstances which principally affect human neurons. Huntington's, Alzheimer's and Parkinson's disease are well known examples of neurodegenerative diseases. Neurodegenerative diseases are untreatable and making someone very weak as well as infirm that result in progressive degeneration and/or death of nerve cells. Thus, it becomes reasons for movement problems or mental functioning.[1] Parkinson's disease (PD) is a neurodegenerative disorder which was first depicted by James Parkinson in 1817, a British doctor who had produced and printed a paper which was referred as "the shaking palsy." In this paper, he put forward the significant side effects of the illness that was later bearded his name. It happens only when the nerve cells of the brain which was referred from the substantia nigra would become completely disabled or had died. Typically, these nerve cells develop a significant chemical, present in brain referred as dopamine. Dopamine is a chemical messenger which is responsible for delivering the signals in between substantia nigra with next "relay station" of the nervous system, the corpus striatum, to develop smooth and deliberate movement. Decrease of dopamine resulted in unusual nerve launching patterns inside the brain that cause weakened movement. Studies had indicated that most Parkinson's patients had lost in between 60 to 80 percent or more than that of dopamine producing neurons or never cells present in substantia nigra whenever the side effect or symptoms appear.[2] As soon as PD was first depicted in 1817, researchers had completed the causes and treatment for the prevention of the disease. In the mid 1960s, scientists built the principal key issue problem underlying the disorder in which decrease of brain neuro cells that develops a chemical compound referred as dopamine, which was significant for control and coordination of muscle movement activity. This finding prompted the first successful treatment for the prevention of PD and proposed methods for concocting new and much progressively successful treatments. Parkinson's exploration keeps on being a functioning intriguing discovery revealed each day.[3]

In recent times there is an increase in global utilization of herbal medicines in the treatment of various disease affecting humans. *Scoparia dulcis* is a rich source of flavones, terpenes and steroids, phenols, tannins, saponins, amino acids, coumarins, and carbohydrates. The principle chemical constituents included scopadulcic acids A and B, scopadulciol, scopadiol, scoparic acids A-C, scopadulin and betulinic acid. Other chemicals constituents included: acacetin, apigenin, amyrin, benzoxazin, benzoxazolinone, benzoxazolin, cirsitakaoside,

cirsimarin, coumaric acid, coixol, cynaroside, dulcinol daucosterol, dulcioic acid, glutinol, gentisic acid, hymenoxin, luteolin, linarin, mannitol, scutellarein, scoparinol, sitosterol, stigmasterol, scutellarin, taraxerol, vitexin and viceninand. *Scoparia dulcis* has principle physical and chemical properties and its capability to pass through the blood brain barrier which makes it a suitable candidate for therapy of neuroprevention in Parkinson's disease.[4]

Scoparia dulcis plant consists of a chemical constituent i.e., Gentisic acid (Benzenoid derivative), has shown anticonvulsant activity by inhibiting Ca^{2+} ion channel leading to decrease in Ca^{2+} ions inside the membrane which prevents excitotoxicity leading to epilepsy.[5] No research has yet been carried out on the above mentioned plant for Parkinson's disease treatment. Thus, the reason for selecting the compound from plant is its probability of having a neuroprotection activity in Parkinson's disease by anticonvulsant activity and antioxidant activity. The pathogenesis of cell degeneration in neurodegenerative diseases are dopamine depletion, oxidative stress, mitochondrial dysfunction, protein aggregation mysfolding, neuroinflammation, excitotoxicity, apoptosis and cell death pathway, loss of trophic factor. Immoderate release of glutamate from presynaptic nerve terminals and astrocytes into the extracellular spaces with resultant over stimulation of glutamate receptors mainly NMDA receptors which ultimately related to excitotoxicity. Several neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS dementia complex and Parkinson's disease observed because of neuronal injury which is mainly due to overstimulation of both ionotropic and metabotropic glutamate receptors. The concept of oxidative stress and antioxidants may be directly or indirectly involved in the pathogenic process of Parkinson's disease. Thus, with this present study an attempt to evaluate neuroprotective activity against excitotoxicity model of Parkinson's disease.

MATERIALS AND METHODS

Drugs and Chemicals

Scoparia dulcis (whole plant) powder (Govind Ayurved Bhavan, Dadar). Monosodium glutamate (MSG) was purchased from Himedia Lab., Dextromethorphan hydrochloride chewable tablets (Lastuss CT, FDC), Dopamine (Sigma Aldrich), 5,5-dithiobis[2-nitrobenzoic acid] (Sigma Aldrich).

Animals

The wistar rats of either sex, weighing 200-250g of 2-3 months old were procured from Bharat serums and vaccines, Thane and adult wild-type zebrafishes of both sexes weighing 0.5-1g of 4-6 months old were procured from Vikrant aquaculture, Bandra. The rats were brought to animal house and zebrafishes were brought to zebrafish facility of Dr.L.H. Hiranandani College of Pharmacy, Ulhasnagar-03. In animal house, these rats were acclimatized under standard conditions of husbandry, i.e., 24±10°C room temperature, 45-55 % relative humidity and 12:12 hr light/dark cycle whereas in zebrafish facility, these zebrafish were acclimatized under standard conditions, i.e., 28±5°C temperature, 7-8 optimum pH, 0.25-0.75ppt (parts per thousand) optimum conductivity and 14:10 hr light/dark cycle. In strict hygienic condition, the animals had free access to food and water supplied libitum. Before behavioural experiments, animals were acclimatized for at least two weeks. The study protocol was approved by the college's Institutional Animal Ethics Committee (IAEC) and the experiments were conducted as per the guidelines of CPCSEA. The study protocol number is PCOL/IAEC/2018/07 (rats) and PCOL/IAEC/2018/18 (zebrafish).

Preparation of AESD extract

Dried powder of *Scoparia dulcis* whole plant was procured from Govind Ayurved Bhavan, Dadar (W).and authenticated by Dr. Harshad Pandit, HOD of Botany Andheri. The authentication number of the plant is vvp p05260918. The dried powder of plant *Scoparia dulcis* was extracted with distilled water at a ratio of 1:3 in soxhlet apparatus at a temperature of 60°C for a period of 6 hr. The aqueous extract of *Scoparia dulcis* (AESD) obtained from soxhlet extraction was further subjected to rotary evaporator to get the concentrated AESD. The concentrated AESD was placed in hot air oven to get dry powder of the extract and the extract was collected and stored at -20°C when needed the extract was dissolved in sterile water used for further investigation. The observed yield was 15.7%.[6]

Physicochemical, Preliminary Phytochemical analysis and Confirmatory test

Physicochemical analysis of crude extract was performed, parameters such as total ash value, acid insoluble and water soluble ash value and loss on drying was performed.[7] Preliminary phytochemical test was carried out to identify the compounds present in AESD. The presence of gentisic acid in AESD was confirmed by confirmatory test.[8]

Acute toxicity study

Acute toxicity studies were performed on rats as well as zebrafishes. In rats, acute toxicity study of AESD was performed on 6 wistar rats weighing approximately 200-300g as per OECD guidelines 425. Rats were fasted overnight and then AESD was suspended in distilled water, administered orally with single maximum dose of 2000mg/kg. After dosing at least once during the first 30 min, periodically during the first 24 hrs, rats were observed individually, with special attention given on first 4 hrs and after daily up to 14 days.[9] Parameter to be observed: Behavioural (Alertness, Aggressiveness); Neurological (Convulsion, Ataxia, Grip strength); Autonomic (Eyes, Salivation) Food intake and body weight were also measured. Rats were sacrificed at the end of the study. In zebrafish, acute toxicity study was performed as per OECD guidelines 203. 8 fishes were exposed to the AESD solution at a maximum dose of 100mg/L for a period of 96 hrs. Parameters evaluated are erratic swimming patterns like vertical swimming, sideway swimming, upside down, arrow like swimming (darting behaviour)and rigidity of fins. The fate of zebrafish was rehabilitation.[10]

***In vivo* studies:** To evaluate neuroprotective activity of AESD by using monosodium glutamate (MSG) induced excitotoxicity model in rats and zebrafish.

MSG induced Excitotoxicity

In rats

The experimental group consists of 30 wistar rats. The study was carried out for a period of 7 days. These rats were randomized and divided into 5 groups, where each group consists of 6 rats. First group was treated with vehicle i.e. 1%CMC at a dose of 5ml/kg peroral administration. Except vehicle group, all the remaining four groups was treated with MSG at a dose of 2000mg/kg i.p. In third group, after 1 hr treatment of MSG, standard i.e., Dextromethorphan was treated at a dose of 30mg/kg peroral administration. In fourth and fifth group, AESD was treated at a dose of 400mg/kg and 1000mg/kg per oral administration following one hour treatment of MSG administration. On 8th day, Behavioural parameters such as muscle grip strength by rotarod apparatus and locomotor activity by actophotometer was determined. On 9th day, rats of all the groups were sacrificed by exposure to CO_2 chamber and brains were dissected. Straitum part was identified and dipped in Tris buffer solution. Straitum was homogenized with a ratio of 1:15 (1g brain: 15 ml Tris buffer solution)

in handheld homogenizer at a speed of 5000rpm for 10min to get a brain homogenate. Brain homogenate obtained was subjected to cooling refrigerated centrifuge machine at 12000rpm for 5 min to get sediment and supernatant. The sediment was discarded and supernatant was collected and stored at 4°C and biochemical parameters such as dopamine, catalase and glutathione were analyzed.[11]

Dopamine

Approximately 20 mg of unadulterated chemical dopamine was precisely weighed and mixed with 20 ml distilled water to develop 1000 ppm (1000 µg/ml) concentration which can be referred as stock solution. An aliquot or approx. amount of 0.2, 0.4, 0.6, 0.8 and 1.0 ml from the stock solution would be transferred into a sequence of 25 ml standard volumetric jars or flasks to create 8, 16, 24, 32 and 40 ppm (µg/ml) concentrations. In next step, 1 ml of 4 N hydrochloric acid (HCL) with 1 ml of 0.02 N brominating mixture to every flask or jar was added. The volumetric flask or jar would be shaken well and put in a safe spot for 5 min to create a complete bromination. At that time, 1 ml of 0.1 N potassium iodide would be added to every flask or jar, which was diluted to 25 ml with distilled or refined water. The yellow coloured solution developed with dopamine was measured against distilled water at 280 nm as a blank. A calibration curve was obtained by plotting or placing concentration of dopamine on X-axis with absorbance of concentrations of dopamine on Y-axis. Further, 1 ml of supernatant of rat brain was transferred to 25ml flask. In next step, 1 ml of 4 N hydrochloric acid (HCL) with 1 ml of 0.02 N brominating mixture to every flask or jar was added. The volumetric flask or jar would be shaken well and put in a safe spot for 5min for to create a complete bromination. At that time, 1 ml of 0.1 N potassium iodide was added to every flask or jar, which was diluted to 25 ml with distilled or refined water. The yellow coloured solution developed with supernatant was measured against distilled water at 280 nm as a blank. Amount of dopamine present in supernatant of rat brain homogenate was read from calibration curve.[12]

Catalase

The analysis mixture was developed which consisted of 50 µl of 1 M Tris–HCl buffer with pH 8.0 in which 5 mM EDTA, 900 µl of 10 mM H_2O_2, 30 µl of distilled water and 20 µl of the brain tissue supernatant was added. The rate of decay of hydrogen peroxide was anaylsed spectrophotometrically at 240 nm in UV-Vis spectrophotometer.[13]

Glutathione

The supernatant (0.5ml) of the brain was added to 4 ml ice-cold of 0.1 mM solution of 5,5-dithiobis[2-nitrobenzoic acid] (DTNB) dissolved in 1M phosphate buffer of pH 8. The absorbance was analysed at 412 nm in a UV-Vis spectrophotometer.[13]

In zebrafish:

The experimental group consists of 40 adult wildtype zebrafishes. The study was carried out for a period of 96 hrs. Zebrafish were randomized and divided into 5 groups. Each group consists of 8 fishes. In first group, fishes were exposed to 10% DMSO solution. Fishes were exposed to 30µg/ml MSG solution[14] in second group for 30 min. In third, fourth and fifth group, Fishes were first exposed to Dextromethorphan (30µg/ml),[15] AESD (40µg/ml and 100µg/ml) for 30 min and thereafter fishes were placed in freshwater for 15 min. After 15 min, the fishes were exposed to MSG solution at a dose of 30µg/ml for 30 min. After 96 hrs, Behavioural parameters such as latency to travel from one fixed point to another, time spent near the bottom of the tank, complete immobility time and erratic swimming were analysed in experimentation tank. The experimentation tank consists of 5L fresh aerated water, divided into two equal parts horizontally and vertical lines were drawn on tank at 5cm apart.[16]

Statistical analysis

The results of anti-Parkinson's activity were expressed as MEAN ± SEM of 6 animals in every group. Results were analysed statistically using one–way ANOVA followed by Tukey's multiple comparison tests; all groups were compared with disease control group and $P<0.05$, $P<0.01$ was considered significant. GraphPad Prism was the software used for statistical analysis.

RESULTS AND DISCUSSION

The present study was performed to carry out the phytochemical and pharmacological evaluation of aqueous extract of *Scoparia dulcis* (AESD). The results were presented in tables and graph format. The result displayed include physicochemical, phytochemical evaluation and confirmatory test for AESD, acute toxicity study for AESD, neuroprotective activity of AESD and pharmacological effect of AESD on MSG induced excitotoxicity in rats and zebrafish.

Physicochemical and Preliminary Phytochemical analysis

As per phytochemical test AESD showed presence of alkaloids, carbohydrates, flavonoids, glycoside, phenol and proteins. Results obtained for physicochemical parameter and confirmatory test mention in Table 1 and Table 2.

Table No. 1: Physicochemical parameter evaluation of AESD

TOTAL ASH VALUE	ACID INSOLUBLE ASH VALUE	WATER SOLUBLE ASH VALUE	LOSS ON DRYING
10.2%	1.5%	3.4%	0.9%

Table No. 2: Confirmatory test of Gentisic acid present in AESD

TEST	OBSERVATION	INFERENCE
Benzenoid Derivative Test (For Gentisic acid): Add 1ml Bromine to Aqueous Extract.	No Colour change observed	Gentisic acid is present

Acute toxicity study

In rats, AESD was found safe at 2000mg/kg bodyweight. There was no death of animals during or after 14 days. The parameter such as alertness, aggressiveness was found to be normal in mice. Parameter such as ataxia, convulsion and muscle grip strength were found to be absent in rats. Autonomic (eye, salivation) parameter and bodyweight of mice were found to be normal in mice. In zebrafish, the maximum tolerable dose was found to be 100mg/L. Erratic swimming was found to be absent in zebra fishes.

MSG induced Excitotoxicity in rats

Behavioural parameters: Results of rotarod test and actophotometer were mentioned in Table 3 and Figure 1 and 2.

Table No. 3: Muscle grip strength by rotarod and locomotor activity by Actophotometer

GROUPS	TIME IN SEC. (TO FALL FROM ROTAROD	SCORE OF LOCOMOTOR ACTIVITY
Vehicle	54.662424±1.869	200.5±2.94
Toxic (MSG-2g/kg i.p)	9.66±0.652***	71.33±0.93***
Standard (Dextromethorphan-30mg/kg p.o)	51±1.433***	194.66±1.217***
AESD (400mg/kg p.o)	32±0.8164***	153.16±1.558***
AESD (1000mg/kg p.o)	48.16±1.234***	187.83±1.786***

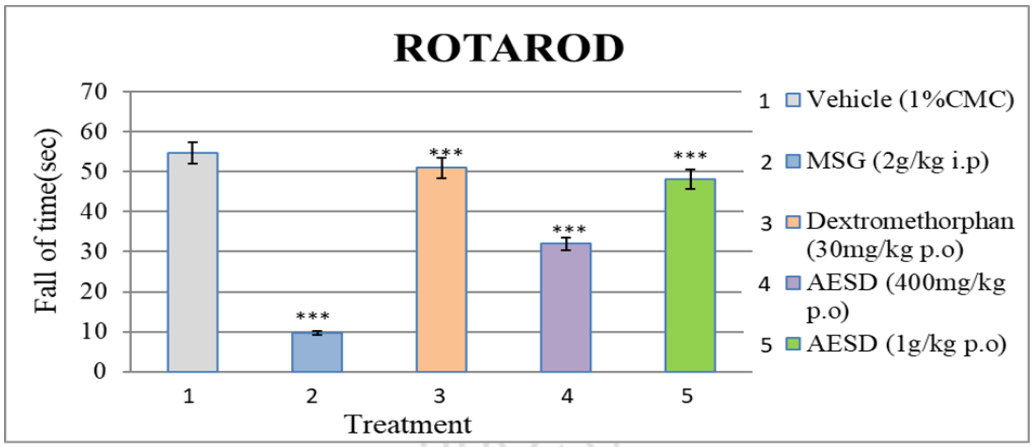

Figure No. 1: Muscle grip strength by rotarod

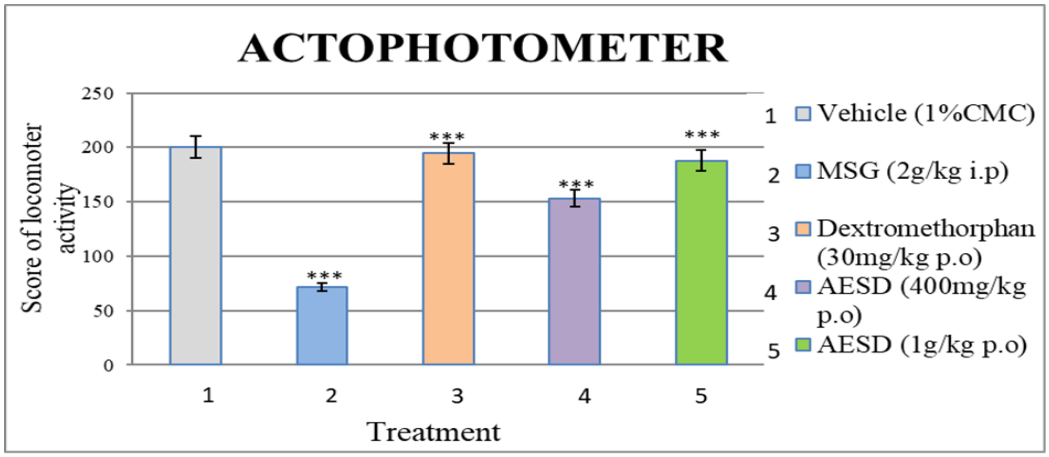

Figure No. 2: Locomotor activity by Actophotometer

Biochemical parameters estimations: Results of dopamine, catalase and glutathione were mentioned in Table 4 and Figure 3-5.

Table No. 4: Observed levels of Dopamine, Catalase, Glutathione

GROUPS	DOPAMINE (mg/g PROTEIN)	CATALASE (U/mg PROTEIN)	GLUTATHIONE (µg/mg PROTEIN)
Vehicle	5.82±0.045	73.706±3.89	25.44±1.889
Toxic (MSG-2g/kg i.p)	2.07±0.057***	20.948±1.76***	4.17±0.583**
Standard (Dextromethorphan-30mg/kg p.o)	5.78±0.037***	72.268±3.416***	24.28±4.104***
AESD (400mg/kg p.o)	3.14±0.028***	32.324±0.527*	12.64±0.467***
AESD (1000mg/kg p.o)	5.67±0.026***	62.821±1.989***	23.78±0.788***

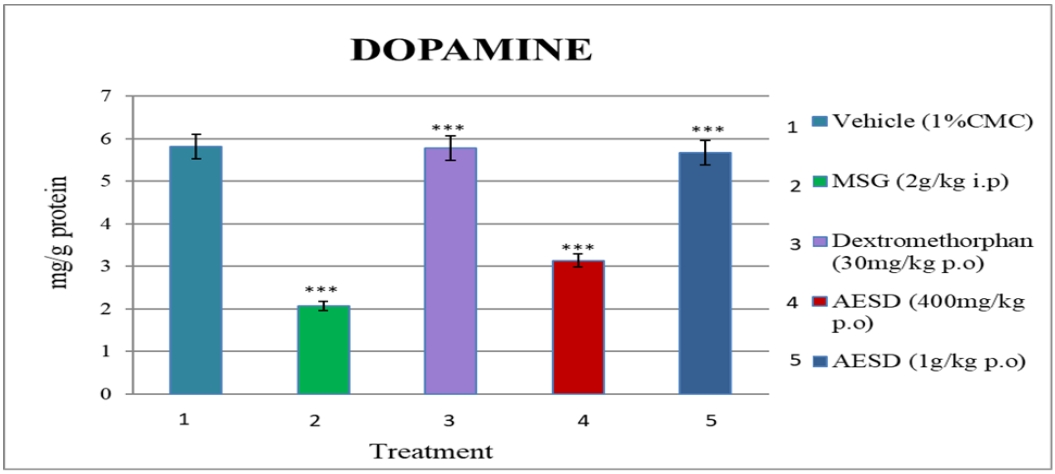

Figure No. 3: Dopamine level estimation

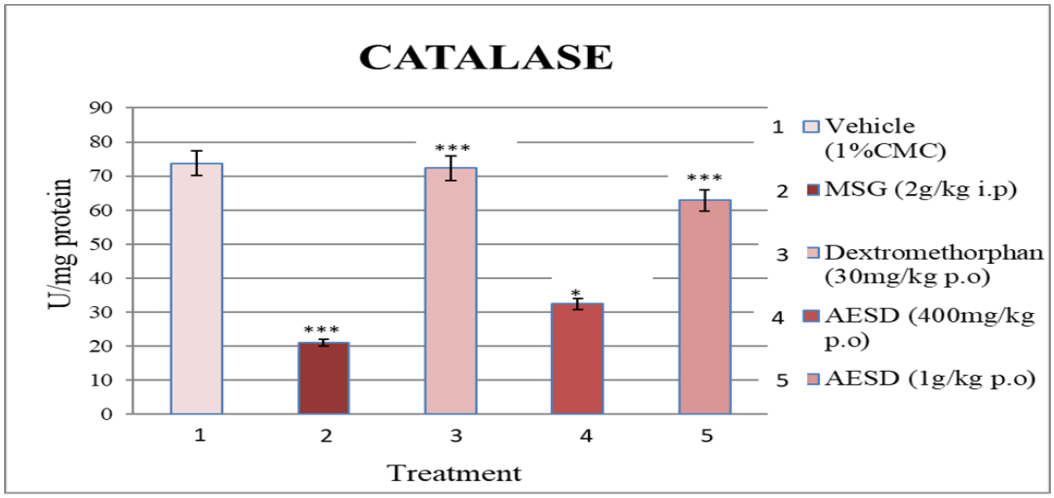

Figure No. 4: Catalase level estimation

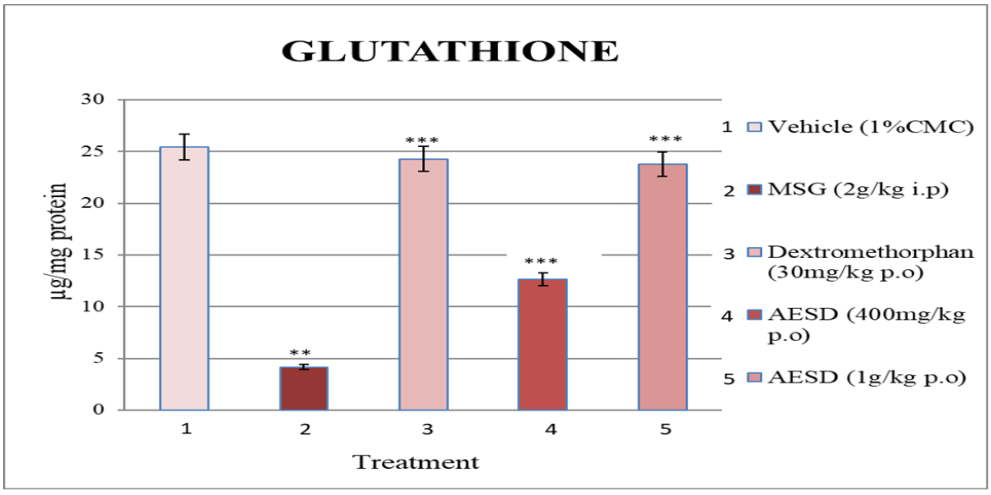

Figure No. 5: Glutathione level estimation

MSG induced Excitotoxicity in zebrafish: Results of behavioural parameters were mentioned in Table 5 and Figure 6-9.

Table No. 5: Behavioural parameters in zebrafish

GROUPS	LATENCY TO TRAVEL FROM ONE FIXED POINT TO ANOTHER	TIME SPENT NEAR THE BOTTOM OF TANK	COMPLETE IMMOBILITY TIME	ERRATIC SWIMMING
Vehicle (10% DMSO)	2.75±0.25	1.35±0.69	0	0
MSG (30µg/ml)	13.65±0.49***	50.37±4.72***	18.25±1.08***	12±0.96***
Dextromethorphan (30µg/ml))	3.62±0.32***	5.25±1.01***	0.37±0.26***	1±0.37***
AESD (40µg/ml)	7.25±0.36**	23.12±2.38***	2.25±0.45***	6.5±0.37*
AESD (100µg/ml)	3.87±0.39***	6.87±0.69***	0.25±0.16***	2.12±0.39***

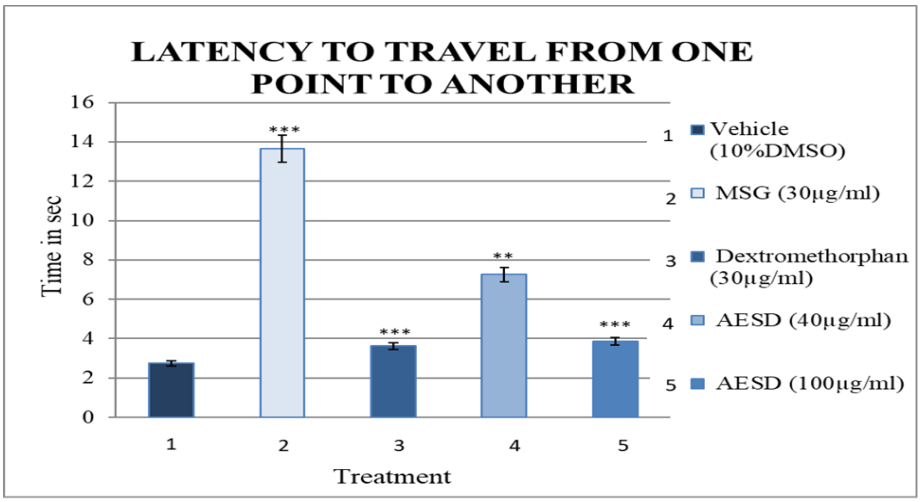

Figure No. 6: Latency to travel from one point to another

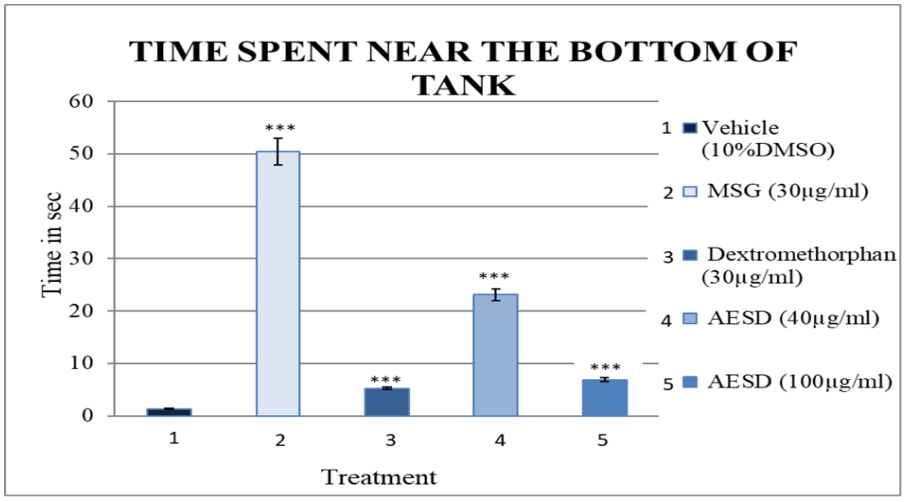

Figure No. 7: Time spent near the bottom of the tank

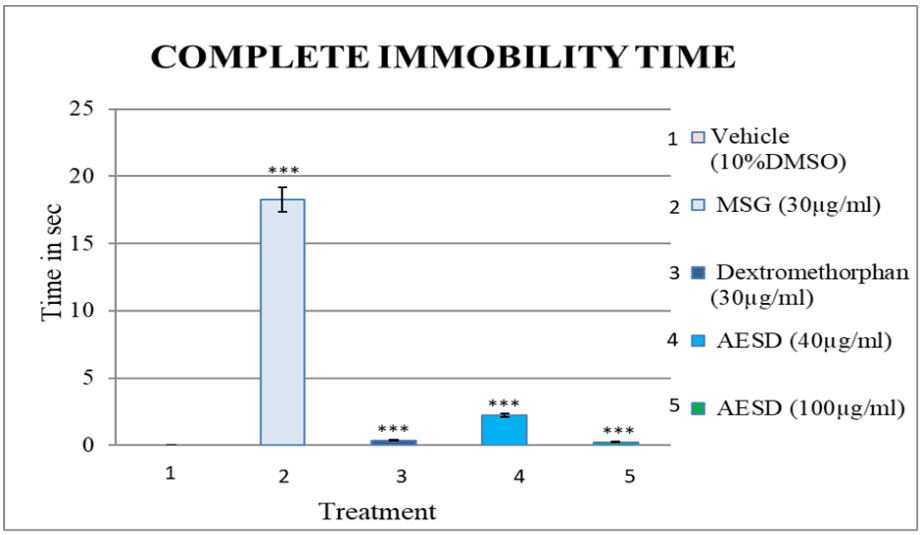

Figure No. 8: Complete immobility time

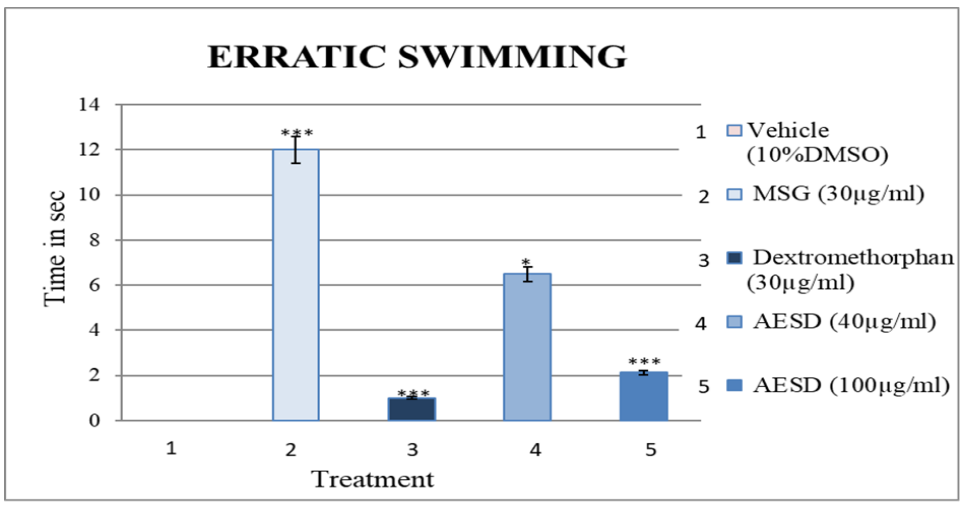

Figure No. 9: Erratic swimming

DISCUSSION

Herbal medicines have regularly kept up ubiquity for cultural and historical reasons and furthermore viewed as more secure as they started from natural sources. The research plant (*Scoparia dulcis*) consists of a chemical constituent i.e., Gentisic acid (Benzenoid derivative), has shown anticonvulsant activity by inhibiting Ca^{2+} ion channel leading to decrease in Ca^{2+} ions inside the membrane which prevents excitotoxicity leading to epilepsy. Thus, the reason for selecting the compound from plant was its probability of having a neuroprotection activity in Parkinson's disease by NMDA antagonistic activity. The present study was an attempt to evaluate neuroprotective activity against excitotoxicity model of Parkinson's disease in rats and zebrafish.

In this study, monosodium glutamate (MSG) induced excitotoxicity was performed on wistar rats as well as on adult zebrafish. MSG induced excitotoxicity was used to study behavioural changes in rats accompanied by assessment of biochemical parameters, such as dopamine (neurotransmitter), catalase and glutathione (antioxidant enzymes). The study further involved the assessment of the activity of the aqueous extract of *Scoparia dulcis* (AESD) against excitotoxicity induced by MSG which was evaluated by the behavioural parameters in zebrafish.

Acute toxicity of AESD did not show any toxic or deleterious effects up to 2000mg/kg per oral dose administration indicating AESD is nontoxic up to a maximum dose of 2000mg/kg in rats whereas acute toxicity in zebrafish did not show any toxic effects up to a maximum dose of 100mg/L.

Glutamate is the main neurotransmitter responsible for excitotoxicity mechanism. Glutamate binds to NMDA receptor present on neuronal cell surface, leading to increase in Ca^{2+} inside the cell membrane. Excess release of glutamate leads to overstimulation of NMDA receptors which was created by sodium salt of MSG resulted to excitotoxicity. Over initiation of NMDA receptor alongside other glutamate or glycine receptors which imbalances the maintenance of calcium homeostasis, which was the key principle transmitter of glutamate-resulted to excitotoxic damage to neuron. Dextromethorphan, an established opioid agonist works moreover as an NMDA receptor antagonist. Subsequently, in the present research, we had used dextromethorphan as a standard against MSG-induced excitotoxicity. The accumulation or gathering of elevated intracellular calcium together included elevated level

of sodium low level with potassium which intracellularly stimulates a cascade of cytoplasmic, membrane with nuclear events resulting in mitochondrial dysfunction and free radical formation leads to excitotoxicity.

In the present study, we had focused upon exploring the potential of AESD (400mg/kg and1000mg/kg) for the anti-Parkinsonian activity using excitotoxicity model. Excitotoxicity was induced in rats with the help of MSG (2gm/kg) and in zebrafish by MSG (30µg/ml). Dextromethorphan an established neuroprotective agent was used as a standard in the present research study.

MSG leads to behavioural changes in parameters which are referred as low/decreased locomotor or motor activity and less muscle grip strength. The MSG intake leads in aggressive nature, diarrhoea with hyper activeness in every animals.

The MSG principally reduced locomotor motor activity in comparison with healthy animals. Therapy with AESD at doses of 400 and 1000 mg/kg which also included standard, dextromethorphan which principally altered the MSG-resulted reduction in locomotor activity. The mechanism behind MSG to alter locomotor activity is by having effect-causing disruption to the dopamine nerve cells by producing free radicals. Therefore, it can be concluded that dextromethorphan and AESD is responsible for preventing the harmful effect by MSG for preventing the damage by NMDA receptor antagonist property.

Therapy of MSG principally reduced the period to fall from rotarod apparatus when compared with normal healthy animal group. This harmful effect was caused by overstimulation of glutamate pathway resulting to excitotoxic neuronal death. Therapy with AESD and standard dextromethorphan principally elevated the period of falling from the rotating rod apparatus when compared with MSG treated induction group. Thus, the alteration of MSG-induction leading to low muscle grip activity and therapy with AESD can referred to NMDA receptor antagonist activity, which showed protection for excitotoxicity.

Treatment with AESD and standard dextromethorphan significantly reduced the levels of dopamine (neurotransmitter), catalase and glutathione (antioxidant enzymes) in rats whereas prevents behavioural parameters like latency to travel from one point to another, time spent near the bottom of the tank, complete immobility time and erratic swimming in zebrafish. Therefore, it concludes that AESD and dextromethorphan prevents MSG induced excitotoxicity.

CONCLUSION

By this study, we conclude that the aqueous extract of *Scoparia dulcis* (AESD) was found to be neuroprotective as it reduces excitotoxicity score and prevents Parkinson disease. Treatment with the extract also counteracts the elevation of glutamate level as a result of MSG induced excitotoxicity. An AESD has the potential for neuroprotective activity against excitotoxicity model in Parkinson disease via NMDA antagonistic property.

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CONFLICTS OF INTEREST

None

ABBREVIATIONS

MSG- Monosodium glutamate

NMDA-N-methyl-D-aspartate

AESD-Aqueous extract of *Scoparia dulcis*

IAEC-Institutional animal ethics committee

PD- Parkinson;s disease

CPCSEA-Committee for the purpose of control and supervision on animals

AIDS-Acquired immunodeficiency virus

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