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EXPLORATION OF ANTI-PARKINSON ACTIVITY OF AQUEOUS EXTRACT OF *Barleria prionitis* WITH ANTIOXIDANT POTENTIAL IN MPTP AND ROTENONE INDUCED PARKINSON RAT MODELS

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ABSTRACT

Introduction: The plant *Barleria prionitis* (family: Acanthaceae) is a traditional herb it is widely distributed in India and it has important medicinal value. The aim of present research work was to evaluate the anti-parkinsonrole of aqueous extract of *Barleria prionitis* (AEBP). **Methods:** The anti-parkinson activity of AEBP was evaluated using MPTP induced Parkinson mice and Rotenone induced Parkinson rat models. Levodopa was served as reference standard for both animal models. **Results:** Extracts treated groups showed higher *in vivo* antioxidant and anti-parkinson activities. They also showed higher activity in neurotransmitters level. AEBP exhibited similar anti-parkinson activity that of standard but with lesser magnitude. **Conclusion:** The result may be attributed to the chemical constituents namely iridoid glycosides existing in it which may be because of their specific or increasing effect that enhanced anti-parkinson activity and provided scientific evidence of the ethnomedicinal futures of *Barleria prionitis*. These findings could justify the inclusion of this plant in the management of parkinson's disease.

Keywords: Levodopa; *In vivo*; Neurotransmitters; Ethnomedicine, Dopamine, GABA

INTRODUCTION

Parkinson Disease (PD) is the one of the neurodegenerative disorder which is widespread in global and ranking in second chronic neurodegenerative disorder in the world, after Alzheimer´s Disease (AD), and is estimated to affect about 2% of the population over 60 years of age. The disease generally affects persons aged 55–64 years, although occasionally much younger individuals are affected. Although the causes for worsening of dopaminergic neurons in Parkinson's disease are not well understood, the degeneration of these dopaminergic neurons leads to four cardinal, debilitating symptoms: resting tremor, muscular rigidity, bradykinesia and postural imbalance **[1, 2]**. Pathologically the hallmark of Parkinson disease are the severe loss of dopaminergic neuron in the substantianigra pars compacta and the presence of proteinaceous inclusion called lewy bodies, which is mainly composed of fibrillar α-synuclein and ubiquitinated protein with in some remaining nigral neurons **[3, 4]**. The plant *Barleriaprionitis* (BP) is under the family of Acanthaceae an ayurvedic medicinal plantit is having important medical belongings. The plant BP contains Iridoids, Barlerin, Acetyl barlerin, β-sitosterol, Prioniside, Barlerinoside, verbascoside, 7-methoxy diderroside, Anthroquinones, Flavonoids. The plant used for Stomach disorder, Urinary infections, fever, Tooth ache, Diuretic, Jaundice, Asthma, Arthritis, Inflammation, Migraine, Dropsy, Leprosy. But there is no scientific report on antiparkinsonism activity of BP. So that current research is designed to evaluate the antiparkinson effect of BP.

MATERIALS AND METHODS

Collection and authentication of plant

The whole plant of BP were collected from the surrounding areas of Erode district, Tamilnadu, India during the month of December and authenticated by Botanical survey of India (BSI) southern circle, Coimbatore, Tamil Nadu. The authentication certificate number is No.BSI/SRC/5/23/2016-14/TECH/2108.

Soon after collection the aerial parts were cleaned, driened in shade and crumpled to a coarse powder, stored in an air tight glass container, until further use. The above powder was extracted with water for 48 h at room temperature. After extraction the extracts were evaporated by using rotary evaporator and dried at room temperature **[5, 6]**. The obtained extract was used for the *in vivo* study.

Experimental animals

Male Swiss albino mice 3 month of age, and 25-30 g body weight and Male Sprague-Dawley (SD) rats 50 days of age, and 80-100 g body weight were offered by KMCHCollege of Pharmacy, Coimbatore. All the rats were maintained at room temperature and allowed to acclimate in standard conditions less than 12h light/ 12h dark cycle in the animal house. Animals were fed with commercial pellet food and water ad libitum freely throughout the study. The experimental procedure was approved by IAEC (Institution of Animal Ethical Committee).

Preparation of Benzerazide and Levodopa

12mg/kg of levodopa and 3 mg/kg of Benzerazide was dissolved in distilled water. Levodopa and benzerazide was freshly prepared daily (7 days) and given via *i.p* to the standard group.

Preparation of AEBP

200 mg/kg and 400 mg/kg were dissolved in distilled water and it was prepared freshly and given via oral route to group IV& V respectively for 7 days.

Experimental Induction of Parkinson

Preparation and induction of MPTP solution

The MPTP was purchased from sigma chemicals, Mumbai, India and was stored according to the manufacturer label (37^0C) to prevent its decomposition. The MPTP solution was freshly prepared at 25 mg/kg. The MPTP was dissolved in 0.9% sodium chloride solution and injected i.p at the dose of 25 mg/kg body weight on 7 day. MPTP solution is stable only for a period of 24 hours at 4^0C.

Preparation and induction of Rotenone solution

The Rotenone was purchased from sigma chemicals, Mumbai, India and was stored according to the manufacturer label (-20^0C) to prevent its decomposition. The Rotenone solution was freshly prepared at 3 mg/kg. The Rotenone was dissolved in DMSO and adjusts to pH 7.4 with potassium hydroxide. Rotenone injected i.p at the dose of 3 mg/kg body weight, 7 days. The solution should be used immediately after preparation. Rotenone solution is stable only for a period of 24 hours at 25^0C.

Experimental design for MPTP induced parkinson mice

Group I: Vehicle control (normal saline *i. p*) for 7 days

Group II: Only MPTP (25 mg/kg, *i.p*) for 7 days

Group III: MPTP + Standard [Levodopa 12 mg/kg + Benzerazide 3mg/kg*i.p*] for 7 days

Group IV: MPTP + AEBP (200 mg/kg, *p.o*) for 7 days

Group V: MPTP + AEBP (400 mg/kg, *p.o*) for 7 days

Experimental design for Rotenone induced Parkinson rats

Group I: Vehicle control (normal saline *i.p*) for 7 days

Group II: Only Rotenone (3 mg/kg, *i.p*) for 7 days

Group III: Rotenone + Standard [Levodopa 12 mg/kg + Benzerazide 3mg/kg*i.p*] for 7 days

Group IV: Rotenone + AEBP (200 mg/kg, *p.o*) for 7 days

Group V: Rotenone + AEBP (400 mg/kg, *p.o*) for 7 days

Estimation of behavioral parameters

The behavioral parameters such as motor co-ordination test (rota rod test), locomotor activity (actophotometer), depression (tail suspension test and forced swimming test) and alertness (hole board test) were evaluated by standard procedure followed by previous literature on 3rd, 5th and 7th day of treatment **[7-9]**.

Estimation of brain neurotransmitter and antioxidants level

After the treatment period all the animals were sacrificed and isolated brain were used for estimation of neurotransmitter (Serotonin, GABA and Dopamine) and *in vivo* antioxidants (reduced glutathione (GSH), proteins and lipid peroxidation). Brain homogenate was prepared by using HCl – Butanol solution for neurotransmitter level estimation and ice-cold TCA for antioxidant level estimation, standard procedure followed by literature **[10-15]**.

Statistical analysis

The statistical analysis was carried out by using PRISM version 5 software. The data's of all data were analyzed using means of one way ANOVA followed by Dunnett's test. The results were expressed as mean ±SEM.

RESULTS AND DISCUSSION

MPTP was commonly used as a PD model in rats. The MPTP is actions as a lipophilic protoxin which crosses the BBB and transformed into 1-methyl-4-phenyl-pyridinium (MPP+) the toxic metabolite through serotonergic neurons and astrocytes via monoamine oxidase-B. MPP+ is formerly unrestricted into the extracellular interplanetary and collected through the DA transporter (DAT) to DA neurons, producing a bilateral deterioration of the nigrostriatal tract. MPP+ generates neurodegeneration by the blockade of electron transport chain enzyme complexes I, III, and IV. Supplementary issues control MPTP toxicity including iron, countenance of the reactive

oxygen species (ROS), vesicular monoamine transporter, and apoptosis.

Exposure to the pesticide rotenone is accompanying to an augmented risk of PD in epidemiological reports and has been adapted for PD models. Rotenone is extremely lipophilic and travels across the BBB and spread into neurons wherever it constrains complex I of the mitochondrial breathing chain and produces neuro-degeneration of SN neurons; however, reports of its selectivity for neurotoxicity are variable. MPTP and rotenone causes significant overt and subtle behavioural manifestations. Present study reveals quantitative behavioural responses within short spans of7 days in MPTP and rotenone induced animals with the administration of AEBP at the doses 200mg/kg and 400mg/kg. Present study was evaluated on 3rd, 5th and 7th day of treatment.

Muscular co-ordination was evaluated by rota rod performance test and observed that the retention time on rota rod was significantly decreased in MPTP and rotenone control as associated to the normal control group. Levodopa/benzerazide and AEBP 400mg/kg significantly improved the muscle grip strength on 7th day **(Table 1)**.

In the evaluation of locomotor activity using actophotometer, the MPTP and rotenone control showed a significant reduction in the locomotor activity as associated to the vehicle control and the drug treated groups significantly dose dependently restored the locomotion **(Table 2)**.

Behaviour despair swim test was authenticated as a tool to assess drugs with supposed antidepressant properties. In the present study, MPTP and rotenone control showed a significant grow in total immobility time as associated to normal control. Levodopa/benzerazide and AEBP at 400mg/kg significantly reduced total immobility time and enhanced the struggling behaviour on 5th and 7th day **(Table 3)**. Tail suspension test has been is a ccustomed examine for broadcast possible antidepressant drugs. In the present study, MPTP and rotenone control showed a significant increase in total immobility time as associated to normal control. Levodopa/benzerazide and AEBP at 400mg/kg significantly reduced total immobility time and enhanced the struggling behaviour on 5th and 7th day **(Table 4)**.

The hole board test designated that the skull plunging behaviour was sensitive to variations in the expressive state of the animal, and recommended that the appearance of an anxiolytic state might be reproduced by an upsurge in head-dipping

behaviour. The results exposed that here remained an important reduction in the amount of skull dippings in MPTP and rotenone control group as associated to the normal control group. Levodopa/benzerazide and AEBP at 400mg/kg has a significant result on 7th day **(Table 5)**.In the estimation of protein, the MPTP and control group showed a significant proliferation in the total protein of brain tissue. With respect to other groups, the effect of AEBP 400mg/kg dose on total protein was more when associated with MPTP and rotenone control in brain tissues.

MPTP and rotenone persuaded oxidative pressure consequences in augmented level of malondialdehyde (MDA) and lipid hydroperoxides, a biomarker of oxidative pressure injury of neurons. GSH in conjunction with the reductant nicotinamide adenine dinucleotide phosphate reduced (NADPH), can reduce lipid peroxidase, free radicals, and H_2O_2. Thus, reduction in GSH level results in cumulative free radical load, it activate oxidative pressure persuaded neurodegeneration. From the obtained results, it could be said that the administration of AEBP for 7 successive days reduced the LPO level and increased the GSH level aids in decreasing the oxidative stress **(Table 6)**. PD is related with multifaceted neurophysiologic and neurochemical variations. In the present study, MPTP and rotenone control showed a significant reduction in DA, 5-HT, GABA, when associated to the normal control group. AEBP at 400mg/kg showed a significant proliferation in DA, 5-HT, GABA when associated to MPTP and rotenone control group **(Table 7)**.

Table 1: Effect of AEBP on muscle grip strength

Groups	Time spent on Rota rod (sec)		
	Day 3	Day 5	Day 7
Vehicle control (SD rats)	129±1.1547	129±1.4456	130±1
ROTENONE	43.667±1.2019***	60±1.5275***	69.333±0.88192***
ROTENONE + Levodopa/benzerazide	58±2.0817***	81.333±1.2019***	118.67±1.2024***
ROTENONE + AEBP (200 mg/kg)	47.667±2.6034***	62.333±0.88192***	95±1.1547***
ROTENONE + AEBP (400 mg/kg)	53±2.0817***	76.333±0.88192***	111.33±3.5277***
Vehicle control (Mice)	178±0.57735	179±1	178.67±0.88192
MPTP	44.667±1.3333***	62±1.1547***	71.333±1.2019***
MPTP+ Levodopa/benzerazide	59±2.0817***	84.667±1.7638***	120.67±1.3333***
MPTP + AEBP (200 mg/kg)	47±1.5275***	67±1.5275***	94.667±1.2019***
MPTP + AEBP (400 mg/kg)	53.333±2.4037***	81±2.0817***	111.67±1.7638***

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

Table 2: Effect of AEBP on Spontaneous locomotor activity

Groups	Locomotive score		
	Day 3	Day 5	Day 7
Vehicle control (SD rats)	392.33±4.4096	412±2.0817	396±1.1547
ROTENONE	157.33±1.2019***	173.33±1.8559***	195.67±1.421**
ROTENONE + Levodopa/benzerazide	176±1.1621***	228.33±1.453***	258.33±2.0276***
ROTENONE + AEBP (200 mg/kg)	169±1.7321***	198±2.0817***	224.33±2.9059***
ROTENONE +AEBP (400 mg/kg)	178.33±2.0276***	212.33±2.1732***	246.33±2.1858***
Vehicle control (Mice)	384±3.6056	394±1.1547	386.33±1.2019
MPTP	145±2.3094***	162.67±2.0276***	186.33±1.2019***
MPTP+ Levodopa/benzerazide	166.33±2.6034***	217.33±0.88192***	246.33±0.88192***
MPTP + AEBP (200 mg/kg)	155.33±1.453***	184.67±2.0276***	215.67±1.2019***
MPTP +AEBP (400 mg/kg)	162±1***	198±1.5275***	236.67±1.8559***

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

Table 3: Effect of AEBP on depression

Groups	Immobility time (sec)		
	Day 3	Day 5	Day 7
Vehicle control (SD rats)	55±1.1547	52±1.2308	53±1.1522
ROTENONE	128.67±2.0276***	130.33±2.4037***	132.67±1.453***
ROTENONE + Levodopa/benzerazide	125.33±1.362***	107.33±2.3333***	90±1***
ROTENONE + AEBP (200 mg/kg)	133.33±2.6034***	125.33±2.3333***	121.33±1.2019***
ROTENONE +AEBP (400 mg/kg)	135.67±0.88192***	119.67±1.2169***	99.667±1.2273***
Vehicle control (Mice)	52.333±2.6034	47.667±0.88192	48.667±1.3333
MPTP	125±1.7321***	130.33±1.7638***	131.33±2.3333***
MPTP+ Levodopa/benzerazide	117.67±1.3333***	101±1.1547***	85.333±1.7638***
MPTP + AEBP (200 mg/kg)	127.67±2.848***	120.67±0.88192***	118.67±2.7285***
MPTP +AEBP (400 mg/kg)	127±1***	116.33±0.88192***	93.333±2.4037***

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

Table 4: Effect of AEBP on depression

Groups	Immobility time (sec)		
	Day 3	Day 5	Day 7
Vehicle control (SD rats)	58±1.1547	54.333±1.453	55±1.1547
ROTENONE	132.67±1.7638***	135±1.5275***	136±2.0817***
ROTENONE + Levodopa/benzerazide	127.33±1.8559***	108.33±1.453***	92±2.3094***
ROTENONE + AEBP (200 mg/kg)	136.67±1.2019***	126.67±0.88192***	124±1.5275***
ROTENONE +AEBP (400 mg/kg)	132.00±1.5275***	122.67±1.2019***	102.67±2.7285***
Vehicle control (Mice)	54.667±1.2019	52.667±1.8559	53±1.5275
MPTP	129.67±1.3333***	132.67±0.88192***	131±1.1547***
MPTP+ Levodopa/benzerazide	123.00±2.0817***	103.67±1.7638***	87.667±0.88192***
MPTP + AEBP (200 mg/kg)	132.67±0.88192***	123.33±1.453***	121.33±1.453***
MPTP +AEBP (400 mg/kg)	128.33±1.7638***	118.33±1.453***	96±1.5275***

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

Table 5: Effect of AEBP on alertness

Groups	No. of head dippings		
	Day 3	Day 5	Day 7
Vehicle control (SD rats)	32±1.5275	32±1.1547	29±1.1547
ROTENONE	21.667±1.2019**	20.333±1.2019***	14±1.1547***
ROTENONE + Levodopa/benzerazide	23±1**	23±1.7321**	27.333±0.66667ns
ROTENONE + AEBP (200 mg/kg)	13.667±1.7638***	12.667±0.88192***	11.667±1.7638***
ROTENONE +AEBP (400 mg/kg)	16±1.1547***	20.333±0.88192***	23.333±0.88192***
Vehicle control (Mice)	36±1.1547	36±1.1547	33.667±1.3333
MPTP	22±1.1547	22.333±1.453**	18.333±1.7638***
MPTP+ Levodopa/benzerazide	23±1.1547	24±2.0817**	31.333±0.88192ns
MPTP + AEBP (200 mg/kg)	18.333±1.7638	18±1.7321***	15.333±1.2019***
MPTP +AEBP (400 mg/kg)	23.333±1.453	24.333±2.4037**	27.333±1.2019*

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

Table 6: Effect of AEBP on total protein in brain tissueEffect of AEBP on IN VIVO antioxidants of brain of ROTENONE induced parkinsonic mice

Groups	TOTAL PROTEIN (mg/100mg of tissue)	GSH (Glutathione µg/mg protein)	LPO (nmol of MDA/mg protein)
Vehicle control (SD rats)	5.43±0.011547	5.0733±0.043716	3.7267±0.012018
ROTENONE	2.17±0.011547***	2.1267±0.027285***	4.93±0.011547***
ROTENONE+ Levodopa/benzerazide	4.09±0.011547***	4.39±0.026458***	3.9217±0.0035277***
ROTENONE + AEBP (200 mg/kg)	2.8333±0.01453***	2.9233±0.035277***	4.1167±0.017638***
ROTENONE +AEBP (400 mg/kg)	3.8733±0.043716***	3.9833±0.020276***	3.7067±0.0088192ns
Vehicle control (Mice)	3.3533±0.020276	6.4933±0.0014529	6.1547±0.058894
MPTP	4.4533±0.013333***	2.34±0.055678***	11.436±0.0067415***
MPTP+ Levodopa/benzerazide	3.8267±0.0088192***	4.225±0.056589***	7.2437±0.0014529***
MPTP + AEBP (200 mg/kg)	4.0833±0.043716***	3.2367±0.063857***	9.055±0.0062452***
MPTP +AEBP (400 mg/kg)	3.6067±0.035277***	4.1457±0.056004***	7.5247±0.007513***

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

Table 7: Effect of AEBP on brain neurotransmitters of ROTENONE induced parkinsonic mice

Groups	DOPAMINE(ng/g tissue)	SEROTONINE(ng/g tissue)	GABA(ng/g tissue)
vehicle control (SD rats)	373.33±1.453	379.33±0.88192	213.67±2.313
ROTENONE	174.33±1.308***	189.67±1.2019***	125.33±1.1147***
ROTENONE + Levodopa/benzerazide	292.67±1.6612***	286.33±1.107***	154.33±1.220***
ROTENONE + AEBP (200 mg/kg)	187.67±2701***	205.67±0.88192***	142.33±2.0276***
ROTENONE +AEBP (400 mg/kg)	228.67±1.321***	220.33±0.116***	155.33±1.7638***
Vehicle control (Mice)	367.67±11.289	357.67±2.848	203±1.5275
MPTP	188±1.1547	174.33±1.453	109.33±2.4037
MPTP+ Levodopa/benzerazide	287±5.5076	273±2.0817	142±1.7321
MPTP + AEBP (200 mg/kg)	198.33±4.3333	192.67±0.88192	128.33±1.8559
MPTP +AEBP (400 mg/kg)	217±2.3094	206±1.1547	138.67±1.3333

Data is expressed as mean ± SEM; n=6, One way ANOVA followed by Dunnett's test; ns = non-significant; normal control compared with Rotenone and MPTP group; Rotenone and MPTP group compared with treatment group;* p<0.05, ** p<0.01, *** p<0.001).

CONCLUSION

From the present study, it can be concluded that the aqueous extract of BP showed important anti-parkinsonism action in MPTP and rotenone model correspondingly. The possible mechanism of this plant reduced lipid peroxidation owing to the occurrence of flavonoids, polyphenols and glycosides. All the Parameters of extract treated group animals have exposed improved consequences once associated with MPTP and rotenone-induced group and the standard L-dopa treated group. These results deliver an initial indication for its potential as Neuro-protective medication, including Parkinson's disease prevention and improvement of symptoms.

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