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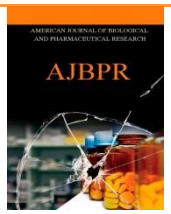

EVALUATION OF ANTI-PARKINSONIAN EFFECTS OF ETHANOLIC EXTRACT OF RHUBARB (*Rheum Emodin*) IN RATS

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ABSTRACT

Rhubarb (Da Huang) is dried rhizomes and roots of *Rhubarb palmatum* L, Rheum tangguticum Maxim. ex Balf, or Rheum officinale Baill from Polygonaceae family Rhubarb is a well-known traditional Chinese medicine; it has been used in China for thousands of years. Rhubarb anthraquinones are the major medicinal ingredients derived from rhubarb including emodin, aloe-emodin, chrysophanol, rhein, physcion, and danthron. These different anthraquinone derivatives alone or in combination play a therapeutic role in central nervous system diseases (CNSD), such as cerebral ischemic stroke, intracerebral hemorrhage, traumatic brain injury, brain tumor, Alzheimer's disease, depression, and others Modern pharmacological studies indicated that these anthraquinones possess a wide spectrum of pharmacological properties, such as anti-infammatory, antioxidant, antitumor, and antivirus. Results: In groups treated with ethanolic extract of Rhubarb *(rheum emodin*) 200 and 400mg/kg p.o.,) The anti-oxidative properties of EERE reduced the duration of the catalepsy and increased the locomotor activity along with motor coordination. The group treated with EERE 400 mg/kg showed normal locomotor activity and motor coordination without any cataleptic behavior when compared with haloperidol-treated group. Conclusion: In this research, the animals which were treated for 14 days with haloperidol showed severe cataleptic responses along with decreased locomotor and motor coordination. The anti-oxidative properties of EERE reduced the duration of the catalepsy and increased the locomotor activity along with motor coordination. The group treated with EERE 400 mg/kg showed normal locomotor activity and motor coordination without any cataleptic behavior when compared with haloperidol-treated group. The group treated with EERE 100, 200 mg/kg showed some cataleptic behavior when compared to EERE 400 mg/kg treated group.

INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive movement disorder that involves the malfunction and death of vital nerve cells in the brain, called neurons. Some of these dying neurons produce dopamine, a chemical that sends messages to the part of the brain that controls movement and coordination. As PD progresses, the amount of dopamine produced in the brain decreases, leaving a person unable to control movement normally. Parkinson's was originally described in 1817 by James Parkinson in his Essay on the Shaking Palsy. It is not considered a fatal disease and the way it progresses is different for each person. Primary motor signs of Parkinson's disease include tremor, slowness, rigidity and

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postural instability. Most people with Parkinson's also experience non-motor symptoms that may precede motor symptoms — and a PD diagnosis — by years. The most recognizable early symptoms include loss of sense of smell, constipation, mood and sleep disorders, and neurogenic orthostatic hypotension (low blood pressure when standing up) [1]

PD is a neurodegenerative disease. There is a loss of neurons (nerve cells) in certain areas of the brain, including a region called the substantia nigra, Latin for "black substance." The neurons in this region (which appear dark under a microscope) produce a neurotransmitter (a chemical messenger that allows neurons to communicate) called dopamine. Dopamine helps to regulate movement. As the number of cells in the substantia nigra decreases, there is less dopamine available in the brain. Dopamine is important to maintain normal movement patterns. This loss of dopamine is the reason that many treatments for PD are intended to increase dopamine levels in the brain. Treatment for PD will be explained in more detail in Chapter 4. Loss of neurons in other parts of the brain also occurs in PD, and accounts for some of the non-motor symptoms of the disease. In addition to decreases in dopamine and the cells that make dopamine, you might also read or hear about a protein called alpha-synuclein. Studies suggest that alpha-synuclein normally helps neurons communicate with each other. In PD, the protein clumps up in microscopic aggregates called Lewy (LOOee) bodies. Researchers believe that alpha-synuclein build-up contributes to the development of PD, and that it may be possible to develop new treatments that reverse this build-up [2]

Rhubarb (Da Huang) is dried rhizomes and roots of *Rhubarb palmatum* L, Rheum tangguticum Maxim. ex Balf, or Rheum officinale Baill from Polygonaceae family3 Rhubarb is a well-known traditional Chinese medicine; it has been used in China for thousands of years. Rhubarb anthraquinones are the major medicinal ingredients derived from rhubarb including emodin, aloe-emodin, chrysophanol, rhein, physcion, and danthron. These different anthraquinone derivatives alone or in combination play a therapeutic role in central nervous system diseases (CNSD), such as cerebral ischemic stroke, intracerebral hemorrhage, traumatic brain injury, brain tumor, Alzheimer's disease, depression, and others 4 Modern pharmacological studies indicated that these anthraquinones possess a wide spectrum of pharmacological properties,such as anti-infammatory, antioxidant, antitumor, and antivirus [5-11] Considering the available information of the plant, the present study was designed to evaluate the Anti-Cataleptic or Anti-Parkinsonian effect of Ethanolic extract of dried roots of *Rhubarb palmatum* L, Rheum tangguticum Maxim.

MATERIALS AND METHODS

Drugs and chemicals

Standard Drug: Haloperidol injection IP (serenace) manufactured by RPG life science Ltd. was used to induce Parkinsonism in rats and Levodopa and carbidopa tablet (syndopa 110) Sun Pharma Lab. Ltd. was used as standard drug.

Other Chemicals: Saline water, Ethanol (90%), DPPH, Ascorbic acid, HCL, 0.1 N NaOH, Chloroform, Ferric chloride, 40% Sodium Hydroxide. The chemicals used and other solutions were all of analytical grade. All drugs and reagents were prepared immediately before use

Collection of Plant materials

The medicinal plant Rhubarb *(rheum emodin*) Root powder has been purchased online form www.ayurvedacart.com website and plant was identified and Authenticated by Dr. P. G. Bansod, Department of Botany, Vidyabharti Mahavidyalaya Camp, Amravati. herbarium specimens were deposited in Department of Botany, Vidyabharti Mahavidyalaya Herbarium. The deposition number is not available.

Preparation of Plant extract

The dried root powder of Rhubarb *(rheum emodin*) 150 g Macerated with 350 mL of Ethanol .The mixture was shaken by an electrical shaker at room temperature for 48 h. After that time, the mixture was filtered and the solvent was removed on a rotary evaporator. After drying the residue at 70 °C in an electrical oven, a yellow powder was obtained.

Solubility analysis

The solubility analysis of ethanolic extract of Rheum emodin has been carried out using different solvents. Extract was found to be soluble in water and freely soluble in hot water.

Experimental animal

Experiments are performed in accordance with the committee for the purpose of control and supervision of experimental animals (CPCSEA) guidelines after the approval of the experimental protocol by the Institutional animals ethical committee (IAEC). Wistar rats weighing 150-250g are obtained from the animal house of Department of Pharmacology, Vidyabharti college of Pharmacy, Amravati. All the animals are acclimatized to the animal house prior to use. They are kept in cages in animal house with a 12hr light: 12hr dark cycle at temperature (25±1°C) with 50±55% of relative humidity. Animals are fed on pellets and tap water *ad libitum*. The maintenance of animals was done by following the rules made by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment, Forests and Climate Change, Government of India, New Delhi Registration number:-(1504/PO/RE/S/11/CPCSEA 9/8/2016). There is no

euthanasia methods used in this study, Animals are rehabilitated after experimentation.

Determination of Acute Toxicity

The acute toxicity of prepared extract was performed using OECD guideline 425 in Following manner.

Selection of Animal species & housing:

For the acute toxicity study the Female rats were used, as Female rats are more sensitive than Male rats. All the test animals were kept in separate cages at least 5 days before the commencement of toxicity test. Animals were maintained at 22 ± 3^0C in (12:12) light & Dark cycle with free access of Food and Water.

Preparation of doses

During each study procedure ,fresh aqueous solution of root extract of Rheum emodin was made and each time same volume of dose was administered by varying the concentration of the drug extract.

Test procedure

The required dose is administered in animal one at a time by using oral gavages The animals (Rats) were fasted overnight but water was not withdrawn. The fasted body weight of rat is determined and dose is calculated on body weight basis. After administration of Rheum emodin extract the food is withheld for further 3-4 h. For limit test 2000 mg/kg dose was administered in one animal and then the animal was observed for mortality for a period of 48hr,if the tested rat survived the test was continued by taking 4 more animals. In main test, dose of 1.75, 5.5, 17.5, 55, 175, 550, 2000 was selected and was administered in animal one at a time. The animal was observed for any toxic symptoms initially for 1hr. interval for 4 hrs, then periodically for up-to 14 days.

Determination of Antiparkinsons Activity

The Antiparkinson's potential of ethanolic roots extract of *Rheum emodin has* been carried out by using haloperidol induce model in wistar rat of either sex weighing 150-250 gm.

Induction of experimental parkinsonism

Wistar rats weighing 150-250g taken and haloperidol at a dose of 1mg/kg (intraperitonially) was administered chronically to the rats for a period of 14 days to induce PD. All the behavioural assessment was carried out on 4^{th} day, 8^{th} day and 14^{th} day of the study and the last behavioral quantification was done 24 hours after the last dose of Haloperidol. [12]

Behavioural assessment

Cataleptic Behavior

Bar Test

Catalepsy, defined as a reduced ability to initiate movement and a failure to correct abnormal posture, was measured by means of the bar test. To test of catalepsy, animals were positioned so that their hindquarters were on the bench, and their forelimbs rested on a 1 cm diameter horizontal bar, 6–9 cm above the bench. The length of time that animal maintained this position was recorded by stopwatch to a maximum of 180 s (mean of three consecutive trials; interval: 1 min). Animals would determine judge to be cataleptic if they maintained this position for 30 s or more.[13,14]

Motor Coordination

Despair Swim Test

Each animal was introduced into a pool (45 cm long; 22 cm wide diameter, and 20 cm high) filled with 10 cm deep water. The animals were allowed to make rotations. The number of rotations made per 3 min was recorded [13,14]

Locomotor Activity

Actophotometer

This test measures the exploration and the voluntary locomotion within an enclosed area. The objective value for the spontaneous motor activity was obtained using a photoactometer (INCO Ltd., India). The animal was placed individually into a 30 cm × 30 cm black metal chamber with a screen floor and a light-tight lid. Six beams of red light were focused 2 cm above the floor into photocells on the opposite side. Each beam interruption was registered as an event on the external counter. The light beam breaks were counted for 5 min. [15]

Statistical Analysis

The data were expressed as a mean ± SEM. Result were analysed statistically by one way ANOVA followed by DUNNETS TEST using Graphpad prism version 5. The difference was considered significant if< 0.05.

RESULTS

The animals treated with haloperidol (1 mg/kg, i.p,) alone for 14 days showed significant ($P < 0.01$) increase on 4th day, ($P < 0.01$) increase on 8th day, ($P < 0.01$) increase on 14th day in the cataleptic behavior when compared to Standard group. Animals treated with 100mg of EERE (250 mg/kg) along with haloperidol (1 mg/kg, i.p) for 14 days showed a significant ($P < 0.01$) decrease on 4th day, ($P < 0.01$) decrease on 8th day, ($P < 0.01$) increase on 14th day in the cataleptic behavior when compared to the inducing group. The animals treated with dose 200mg and 400mg of EERE along with haloperidol (1 mg/kg, i.p,) for 14 days showed a significant ($P < 0.01$) decrease on 4th day, ($P < 0.01$) decrease on 8th day, ($P < 0.001$) increase on 14th day in the cataleptic behavior when compared to the inducing group.

Catalepsy Test

Table 1. Effect of (EERE) Ethanolic Extract of Rheum Emodin on Catelepsy bar test in haloperidol induced catalepsy in rat

Group	Treatment and Doses (1mg/kg)	4 th day Cateleptic score No.seconds/3min.	8 th day Cateleptic score No.seconds/3min	14 th day Cateleptic score No.seconds/3min
Control	Control (oral) Distilled water	3.500 ± 0.1693	3.559±0.1996	3.817±0.3081
Negative control	Haloperidol (1mg/kg) in water for inj. Ip	7.66 ± 0.1333##	58.267± 2.683##	113.73 ± 6.2390##
Positive control	Standerd Syndopa (levodopa+ carbidopa) (10mg/kg i.p).	3.550 ± 0.1996	23.667 ± 0.5315	78.267 ±0.2963
4.	EERE (100mg/kg) Haloperidol (1mg/kg i.p.)	5.183± 0.3049**	47.867± 1.491**	95.750 ±0.2203**
5.	EERE.(200mg/kg) Haloperidol (1mg/kg i.p.)	4.367± 0.1687**	35.233± 0.9898**	85.117 ± 0.1400**
6.	EERE.(400mg/kg) Haloperidol (1mg/kg i.p)	3.683 ± 0.1721**	24.300 ± 0.5774	79.967 ± 0.1358**

Results are expressed as mean ± SEM (n=6). Data was analyzed by one way analysis of variance (ANOVA) followed by Dunnet test. **.indicates ($p<0.01$) compared to inducing and ## indicates ($p<0.01$) compared to standard.

Locomotor test

Table 2. Effects of (EERE) Ethanolic Extract of Rheum Emodin in Locomotar Activity determination using Actophotometer

Group	Treatment and doses	4 th day No. Of Counts/5 min	8 th day No. Of Counts/5 min	14 th day No. Of Counts/5 min
1.	Control (oral) Distilled water	217.60 ± 0.1966	238.50 ± 0.1966	238.68 ± 0.1856
2.	Haloperidol (1mg/kg in water for inj. i.p.) vehicle	103.27 ±0.2472##	82.883±0.1352##	30.317 ± 0.1922##
3.	Standard 'Syndopa' (levodopa + carbidopa)(10mg/kg,i.p)	153.40 ± 0.1291	132.62 ± 0.1721	90.517 ± 0.1973
4.	EERE (100mg/kg) Haloperidol (1mg/kg i.p.)	131.53 ± 0.1994**	93.250± 0.09916**	60.133 ± 0.1054**
5.	EERE.(200mg/kg) Haloperidol (1mg/kg i.p.)	147.57 ± 0.1687**	102.18± 0.07032**	72.400 ± 0.1633**
6.	EERE.(400mg/kg) Haloperidol (1mg/kg i.p)	150.47 ± 0.1706**	120.47 ± 0.1333**	80.117 ± 0.094**

Values are expressed as mean ± SEM, one-way ANOVA followed by Dunnet's test multiple comparison test, ** indicates *P<0.01* when compared to inducing. ## indicates(P< 0.01) when compared to standard.

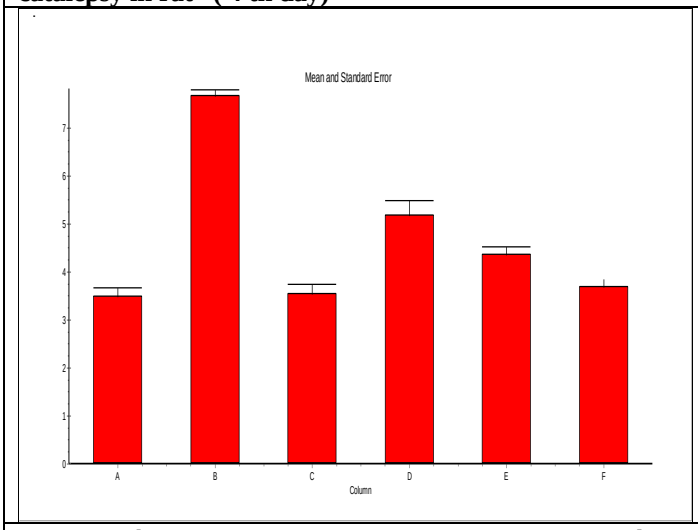
Table 3. Effects of (EERE) Ethanolic Extract of Rheum Emodin in Motar co- ordination determination using Despaire Swim Test.

Group	Treatment and doses	4th day No. Of Rotation/3min.	8 th day No. Of Rotation/3min.	14 th day No. Of Rotation/3min.
1.	Control (oral) Distilled water	8.250 ± 0.2952	9.850 ± 0.1910	10.983 ± 0.3609
2.	Haloperidol (1mg/kg in water for inj. i.p.) vehicle	4.350± 0.1708##	5.717 ± 0.2358##	6.483 ± 0.2372##
3.	Standard ' Syndopa' (levodopa + carbidopa),10mg/kg,i.p)	7.350 ± 0.1910	8.833 ± 0.2445	9.398 ±0.4849
4.	EERE (100mg/kg) Haloperidol (1mg/kg i.p.)	5.317 ± 0.1740**	6.317 ± 0.4377^{ns}	7.383 ± 0.3701**

5.	EERE.(200mg/kg) Haloperidol (1mg/kg i.p.)	5.717 ± 0.2182*	6.917 ± 0.3027*	7.850 ± 0.2997ns
6.	EERE.(400mg/kg) Haloperidol (1mg/kg i.p)	6.183 ± 0.2903**	7.433 ± 0.4080**	8.550 ± 0.2202**

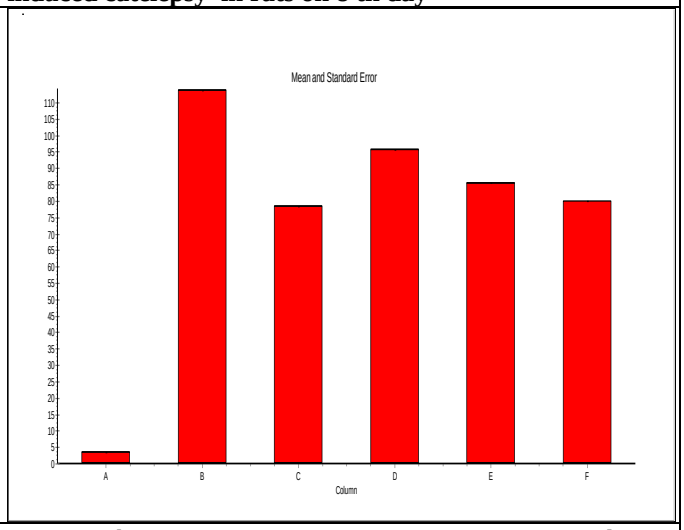
Values are expressed as mean ± SEM, one-way ANOVA followed by Dunnett's test multiple comparison test, ## indicates *P<0.01* when compared to standard. * indicates *P<0.05* when compare to Inducing. ** indicates *(P<0.01)* when compared to inducing group. Ns indicates non-significant.

Graph 1 : Effect of (EERE) Ethanolic Extract of Rheum Emodin on Catelepsy bar test in haloperidol induced catalepsy in rat (4 th day)



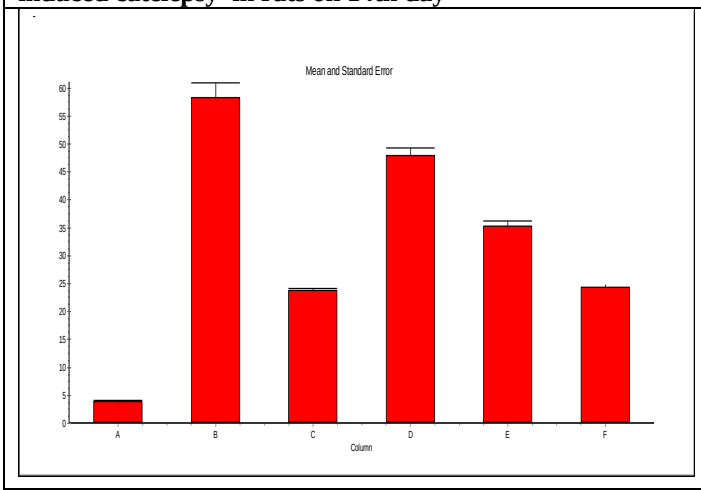
n = 6 Observations are mean ± SEM A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 2 : Representation of EERE treatment on the Catelepsy determination using bar test on haloperidol - induced catelepsy in rats on 8 th day



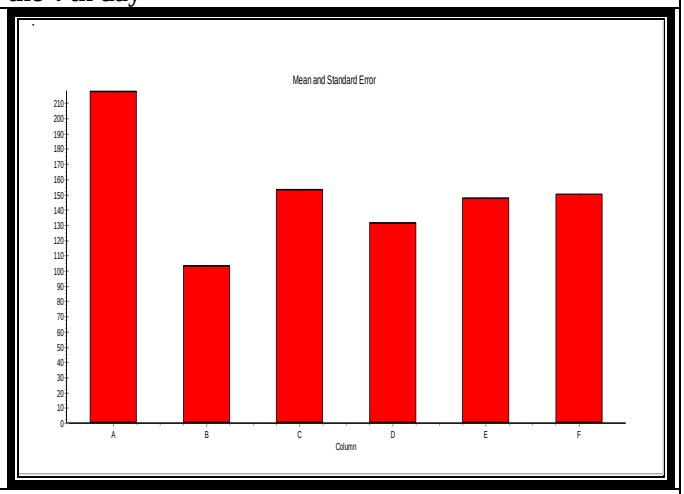
n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) (10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 3 : Representation of EERE treatment on the Catelepsy determination using bar test on haloperidol - induced catelepsy in rats on 14th day



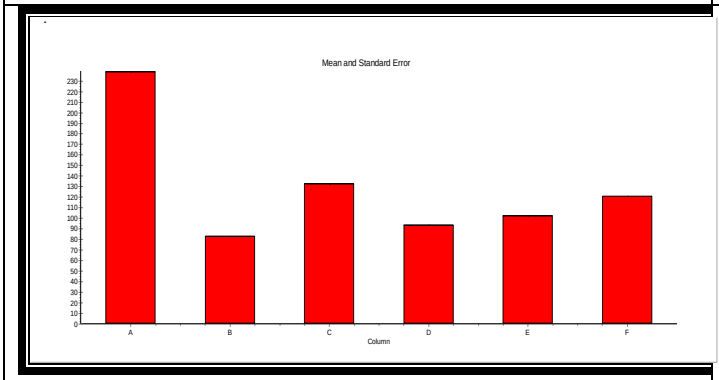
n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o); F- Extract EERE (400mg/kg/p.o)

Graph 4 : Representation of EERE treatment on Locomotar Activity determination using Actophotometer the 4 th day



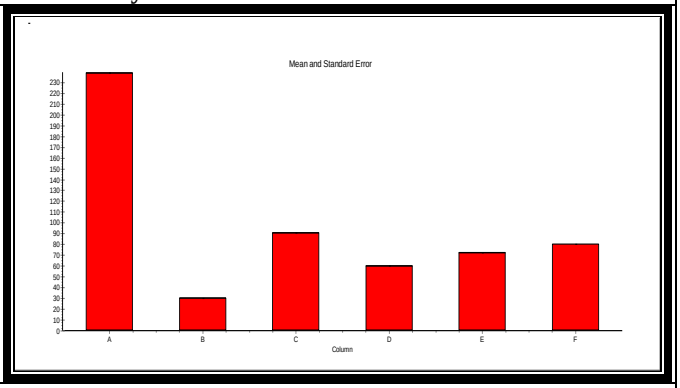
n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 5: Representation of EERE treatment on Locomotar Activity determination using Actophotometer the 8th day



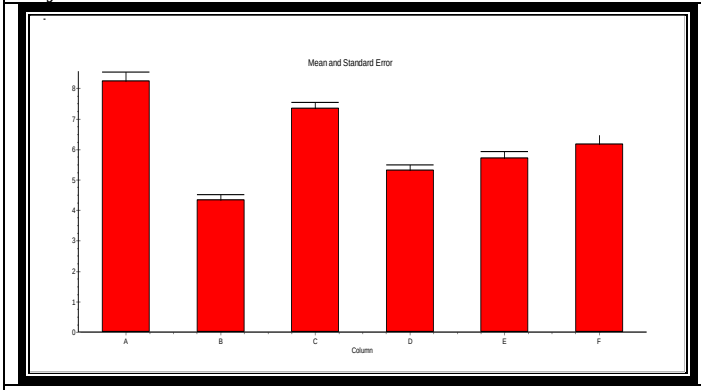
n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 6: Representation of EERE treatment on Locomotar Activity determination using Actophotometer the 14th day



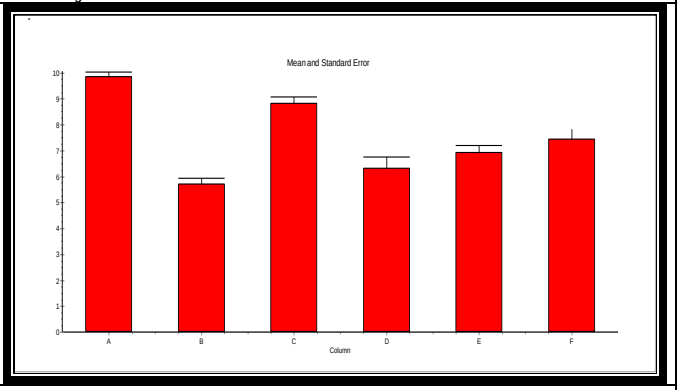
n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 7 : Representation of EERE treatment on Motar co- ordination determination using Despire Swim Test 8 th day



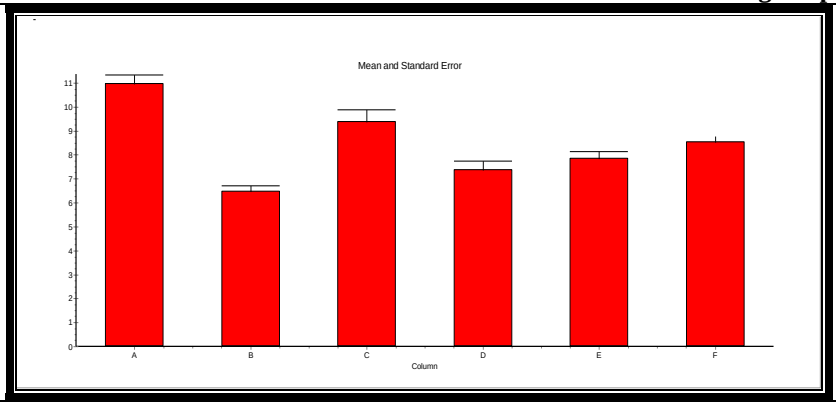
n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 8 : Representation of EERE treatment on Motar co- ordination determination using Despire Swim Test 4th day



n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Graph 9 : Representation of EERE treatment on Motar co-ordination determination using Despire Swim Test 14th day



n = 6 Observations are mean ± SEM; A- Control; B- Haloperidol 1mg/kg/i.p. ; C- Standard (levodopa+carbidopa) 10mg/kg/i.p.); D- Extract EERE (100mg/kg/p.o); E- Extract EERE (200mg/kg/p.o) F- Extract EERE (400mg/kg/p.o)

Animals treated with haloperidol (1 mg/kg, i.p,) alone for 14 days showed a significant ($P < 0.01$) decrease on 4th day, ($P < 0.0001$) decrease on 8th day, ($P < 0.0001$) decrease on 14th day in the locomotor activity when compared to Standard group. Animals treated with low dose of EERE (100 mg/kg) along with haloperidol (1 mg/kg, i.p) for 14 days showed a significant ($P < 0.01$) increase on 4th day, ($P < 0.01$) increase on 8th day, ($P < 0.01$) increase on 14th day in the locomotor activity when compared to Inducing group. Animals treated with moderate and high dose of EERE (200 mg/kg) (400mg/kg) along with haloperidol (1 mg/kg, i.p,) for 14 days showed a significant ($P < 0.01$) increase on 4th day, ($P < 0.01$) increase on 8th day, ($P < 0.0001$) increase on 14th day in the locomotor activity when compared to inducing group.

The animals treated with haloperidol (1 mg/kg, s.c.,) alone for 14 days showed a *($P < 0.01$)* decrease on 4th day, ($P < 0.01$) decrease on 8th day, significant ($P < 0.01$) decrease on 14th day in the number of rotations when compared to Standard group. The animals treated with 1ow dose of EERE (100 mg/kg) along with haloperidol (1 mg/kg, p.o,) for 14 days showed a significant ($P < 0.01$) increase on 4th day, non-significant increase on 8th day, non-significant increase on 14th day in the number of rotations when compared to Inducing group. The animals were treated with moderate dose of EERE (200 mg/kg) and along with haloperidol (1 mg/kg, i.p,) for 14 days showed a ($P < 0.05$) significant increase on 4th day, ($P < 0.05$) significant increase on 8th day, significant ($P < 0.05$) increase on 14th day in the number of rotations when compared to inducing group. Higher dose of EERE (400mg/kg) shows increase ($P<0.01$)on 4^{th} day, 8 th day and 14 th day when compared to inducing group.

DISCUSSION

In the present study, the animals which were treated for 14 days with haloperidol showed severe cataleptic responses along with decreased locomotor and motor coordination. The exact mechanism by which haloperidol increases free radical production was not clear. The enzymatic degradation by MAOs was associated with the production of hydrogen peroxide, which was readily converted to the hydroxyl radical in the presence of iron 16 Thus, it could initiate a destructive LPO cascade, but an increased dopamine (DA) turnover, leading to hydrogen peroxide production which might not be exclusively involved in the degeneration of oxidative stress .[17] The metabolites of haloperidol inhibit complex-I of the electron transport chain. The capability of the anti-psychotic drugs to clinically induce the extrapyramidal syndrome seems to correlate well with their inhibitory effect on the complex-I inhibition.[17] Whatever could have been be the mechanism of the unbalanced production of the reactive oxygen species and the oxidative stress by haloperidol, EERE was found to be effective in decreasing the oxidative stress in the haloperidol-treated animals. The anti-oxidative properties of EERE reduced the duration of the catalepsy and increased the locomotor activity along with motor coordination. The group treated with EERE 400mg/kg showed normal locomotor activity and motor coordination without any cataleptic behavior when compared with the haloperidol-treated group. The group treated with EERE 200mg/kg showed some cataleptic behavior when compared to EERE 400 mg/kg treated group.

CONCLUSION

In this research, the animals which were treated for 14 days with haloperidol showed severe cataleptic responses along with decreased locomotor and motor coordination. Further, the animals (haloperidol-treated) showed decreased levels of glutathione and catalase and increased levels of LPO products and superoxide dismutase as compared to the control animals. The anti-oxidative properties of EERE reduced the duration of the catalepsy and increased the locomotor activity along with motor coordination. The group treated with EERE 400 mg/kg showed normal locomotor activity and motor coordination without any cataleptic behavior when compared with haloperidol-treatedgroup. The group treated with EERE 100, 200 mg/kg showed some cataleptic behavior when compared to EERE 400 mg/kg treated group. Treatment with EERE (100, 200 and 400 mg/kg) decreased the elevated levels of LPO in the haloperidol-treated animals and elevated the cellular defense mechanisms such as glutathione, further suggesting the role of free radicals in the pathophysiology of the haloperidol induced extrapyramidal syndrome. The anti-oxidant activity of EERE could be possibly due to the direct scavenging of the superoxide radicals by the flavonoids which are known to be present in the ethanolic extract of *Rheum Emodin* From the present results, it can be concluded that EERE may prove to be a beneficial adjuvant in the treatment of drug-induced EPS effects and related disorders.

LIST OF ABBREVAITIONS

ANOVA :- Analysis of variance ; CPCSEA :- Committee for the Purpose of Control and Supervision of Experiments on Animals ; IAEC :- Institutional animals ethical committee

EERE :- Ethanolic extract of Rheum Emodin

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