

**EFFECT OF *CALOTROPIS GIGANTEA* ON CLONIDINE AND HALOPERIDOL INDUCED CATALEPSY**

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**Summary**

Catalepsy is a condition in which the animal is not able to correct an externally imposed posture. The present study was undertaken to investigate the anticataleptic effect of methanolic extract of roots of *Calotropis gigantea* R.Br. (CG) in clonidine and haloperidol induced catalepsy in mice. Methanolic extract of roots of *Calotropis gigantea* R.Br. significantly ( $p < 0.01$ ) reduced the cataleptic score in clonidine induced catalepsy in mice at 100, 200, 400 mg/kg, p.o., whereas there was no significant reduction in cataleptic score in the haloperidol induced catalepsy in mice. The results indicate that the methanolic extract of roots of *Calotropis gigantea* probably has antihistaminic activity.

**Keywords:** Catalepsy, antihistaminic, Clonidine, Haloperidol, *Calotropis gigantea*.

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## Introduction

Catalepsy is a sign of extrapyramidal side effect of drugs that inhibit dopaminergic transmission or increase histamine release in the brain (1). Clonidine is presynaptic  $\alpha_2$  – adrenoceptor agonist, induces dose-dependent catalepsy in mice by release of histamine from mast cells in brain. This cataleptic effect is inhibited by histamine H<sub>1</sub> receptor antagonists but not by H<sub>2</sub> receptor antagonist (2). Brain histamine does play a definite role in the production of the extra pyramidal motor symptoms of catalepsy. Therefore it has been suggested that the cataleptic effect of clonidine in the mouse be mediated by histamine (via H<sub>1</sub> receptors), which is released from the brain mast cells in response to stimulation of  $\alpha_2$  adrenoreceptors by clonidine (2). Neuroleptic-induced catalepsy has long been used as an animal model for screening drugs for Parkinsonism (3). There is considerable evidence that blockade of DA transmission produces catalepsy (3, 4) in rats and extrapyramidal side effects in humans (5). The objective of the present study was to evaluate the anticataleptic efficacy of methanolic extract of roots of *Calotropis gigantea* (CG) in clonidine and haloperidol-induced catalepsy in mice.

## Material and methods

### Plant material

Standardized methanolic dry extract of roots of *Calotropis gigantea* was gifted by Amsar Pvt. Ltd., Batch No. 6386, F/D No.586 Indore (M.P.) India along with certificate of analysis.

### Animals

Adult male Swiss albino mice (25-30 g) housed under standard laboratory conditions, in groups of five each. Laboratory animal handling and experimental procedures were performed in accordance with the guidelines of CPCSEA and experimental protocol was approved by Institutional Animal Ethics Committee (198/99/CPCSEA).

### Drugs and chemicals

Clonidine (Neon Lab. Ltd., India), Haloperidol (Sun Pharma. Ltd., India), Chlorpheniramine maleate (Aventis Pharma Ltd., India) were purchased from commercial source.

### Effect on Clonidine-Induced Catalepsy in mice (6, 7, 8)

Bar test was used to study the effect of CG on Clonidine induced catalepsy. Mice were divided into five groups (n=5). Animals belonging to group I served as control and were administered the distilled water (10 ml/kg, p.o.). Animals belonging to group II received Chlorpheniramine maleate (10 mg/kg, i.p.). Animals belonging to groups III, IV and V received three doses of CG (100, 200 and 400 mg/kg, p.o., respectively). All the groups received Clonidine (1 mg/kg, s.c.), 1 hr after the respective treatment. The forepaws of mice were placed on a horizontal bar (1 cm in diameter, 3 cm above the table) and the time required to remove the paws from bar was noted for each animal. The duration of catalepsy was measured at 15, 30, 60, 90, 120, 150 and 180 min.

### Effect on haloperidol-induced catalepsy in mice (6, 7, 8)

Bar test was used to study the effect of test drugs on the haloperidol-induced catalepsy in mice. Mice were divided into five groups (n=5). Animals belonging to group I served as control and were administered the distilled water (10 ml/kg, i.p.). The animal belonging to group II received Chlorpheniramine maleate (10 mg/kg, i.p.). Animals belonging to groups III, IV and V received three doses of CG (100, 200 and 400 mg/kg, p.o., respectively).

All the groups received Haloperidol (1 mg/kg, i.p), 1 hr after the respective treatment and the duration of catalepsy was measured at 15, 30, 60, 90, 120, 150 and 180 min.

### Statistical analysis

The data was presented as Mean  $\pm$  SEM. The data was analyzed by one-way ANOVA followed by Dunnett's test.  $p < 0.05$  and  $p < 0.01$  was considered significant.

## Results

### Clonidine-Induced-Catalepsy in mice

Clonidine (1 mg/kg, s.c.) produced catalepsy in mice, which remained for 2 hr. The vehicle treated group showed maximum duration of catalepsy ( $221.0 \pm 5.01$  sec.) at 120 minute after the administration clonidine. There was significant inhibition ( $p < 0.05$ ) of clonidine induced catalepsy in the animals pretreated with CG (100 200, 400 mg/kg, p.o., respectively) and the duration of catalepsy was found to be  $133.6 \pm 3.12$ ,  $89.2 \pm 4.97$  and  $77.0 \pm 2.42$  seconds, respectively, at 120 minute after the administration clonidine. Chlorpheniramine maleate (10 mg/kg, i.p.) significantly inhibited ( $p < 0.01$ ) clonidine induced catalepsy in mice at 120 minute after the administration of clonidine.

**Table No. 1: Effect of CG on Clonidine-induced catalepsy in mice.**

Group	Duration of catalepsy (sec) Mean $\pm$ SEM at						
	15 min	30 min	60 Min	90 min	120 min	150 min	180 min
I	29.8 $\pm$ 1.85	73.4 $\pm$ 5.45	104.4 $\pm$ 2.06	199.4 $\pm$ 20.40	221.0 $\pm$ 5.01	206.4 $\pm$ 4.38	191.2 $\pm$ 2.22
II	10.4 $\pm$ 1.43**	21.6 $\pm$ 1.81**	52.0 $\pm$ 2.50**	57.2 $\pm$ 2.81**	62.6 $\pm$ 2.97**	63.8 $\pm$ 4.38**	68.2 $\pm$ 1.49**
III	25.4 $\pm$ 3.95	62.0 $\pm$ 3.17*	92.0 $\pm$ 4.72**	110.0 $\pm$ 2.96**	133.6 $\pm$ 3.12**	105.9 $\pm$ 3.45**	97.8 $\pm$ 2.79**
IV	18.4 $\pm$ 3.53*	59.2 $\pm$ 3.12**	65.4 $\pm$ 1.86**	79.4 $\pm$ 5.42**	89.2 $\pm$ 4.97**	80.4 $\pm$ 4.57**	74.0 $\pm$ 2.58**
V	16.4 $\pm$ 2.61*	55.0 $\pm$ 3.20**	60.0 $\pm$ 2.90**	70.6 $\pm$ 4.56**	77.0 $\pm$ 2.42**	72.0 $\pm$ 3.82**	70.0 $\pm$ 1.93**

Data are expressed as Mean  $\pm$  S.E.M,  $n = 5$  in each group, Statistical analysis done by one way ANOVA followed by Dunnett's test. \* $p < 0.05$ , \*\* $p < 0.01$ , compared to control group.

### Haloperidol-Induced catalepsy in mice

CG did not inhibit haloperidol induced catalepsy in mice (Table 2).

Table No. 2: Effect of CG on Haloperidol-induced catalepsy in mice.

Group	Duration of catalepsy (sec) Mean $\pm$ SEM at						
	15 min	30 min	60 min	90 min	120 min	150 min	180 min
I	77.0 $\pm$ 4.52	104.6 $\pm$ 3.40	157.6 $\pm$ 2.94	185.0 $\pm$ 5.55	224.4 $\pm$ 5.75	245.8 $\pm$ 5.69	275.6 $\pm$ 5.76
II	79.2 $\pm$ 4.72	98.0 $\pm$ 6.44	158.6 $\pm$ 10.07	194.2 $\pm$ 5.33	206.4 $\pm$ 6.99	233.4 $\pm$ 8.17	280.2 $\pm$ 5.94
III	70.0 $\pm$ 3.99	96.8 $\pm$ 3.44	171.2 $\pm$ 6.40	177.0 $\pm$ 4.72	211.4 $\pm$ 7.98	245.2 $\pm$ 8.68	281.0 $\pm$ 8.38
IV	75.4 $\pm$ 4.32	113.4 $\pm$ 8.00	147.0 $\pm$ 6.04	178.0 $\pm$ 6.30	202.8 $\pm$ 5.81	245.6 $\pm$ 11.90	286.0 $\pm$ 6.08
V	70.0 $\pm$ 7.90	121.6 $\pm$ 3.29	141.4 $\pm$ 4.98	174.2 $\pm$ 4.03	199.4 $\pm$ 10.20	235.4 $\pm$ 7.73	289.4 $\pm$ 5.18

Data are expressed as Mean  $\pm$  S.E.M, n = 5 in each group, Statistical analysis done by one way ANOVA followed by Dunnett's test.

### Discussion

In the present study, the methanolic extract of roots of *Calotropis gigantea* in all the doses showed a significant reduction in the cataleptic scores in the clonidine-induced catalepsy model in mice. However it did not inhibit the haloperidol induced catalepsy in mice.

Several drugs are known to induce catalepsy in animals. The neuroleptic agents induce catalepsy by inhibiting dopamine D<sub>2</sub> receptors in the substantia nigra (3). Uvnas (1969) studied the mast cell degranulation and its correlation with the release of histamine after administration of mast cell degranulating agent, Compound 48/80 (9). Chopra and Dandiya (1975) studied the relative role of acetylcholine and histamine in perphenazine-induced catalepsy and suggested that anticholinergic activity of antidepressant might be due to an increase in dopamine content in brain or their ability to inhibit release of acetylcholine (10). They also showed that different stages of catalepsy appear to be directly correlated with brain histamine content. Clonidine releases histamine from mast cells in a similar manner to a selective liberator like compound 48/80 (11).

Typical neuroleptic-induced catalepsy has been linked to a blockade of postsynaptic striatal dopamine D<sub>1</sub> and D<sub>2</sub> receptors (3, 5). Despite this evidence, dysfunction of several other neurotransmitters such as acetylcholine (12), GABA (13) and serotonin (14), have also been implicated. In addition to dysfunction of various neurotransmitters in catalepsy, many clinical and preclinical studies have suggested the involvement of reactive oxygen species in haloperidol induced toxicity (15, 16).

The results of the present study indicate that the methanolic extract of roots of *Calotropis gigantea* inhibited the clonidine-induced catalepsy and did not inhibit the haloperidol induced catalepsy. The cataleptic effect of clonidine in the mice is mediated by histamine release from mast cells and hence it can be concluded that the methanolic extract of roots of *Calotropis gigantea* possesses antihistaminic activity. The effect of this extract on clonidine-induced catalepsy is probably due to mast cell stabilizing property. However it does not possess antidopaminergic and antiserotonergic activity.

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