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Evaluation of Anti-Catatonic Effect of Stem Extracts of *Securinega leucopyrus* on Haloperidol Induced Catatonia in Rats

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Abstract

The present study was undertaken to evaluate the anti-catatonic activity of methanolic and aqueous extracts of *Securinega leucopyrus* on haloperidol induced catatonia in rats. The study comprises of five groups (Negative control, Positive control, Standard, Aqueous stem extract, Methanolic stem extract), each containing five animals. Animals in groups I, III, IV & V were administered with haloperidol to produce extra pyramidal side effects. The severity of the catatonia was evaluated by block method and is scored. The methanolic (SLME) and aqueous (SLAE) extracts have shown significant anti-catatonic effect at a dose of 100mg/kg, p.o., showing an overall p value<0.05 when compared to other groups. SLME has more ability to reduce the extra pyramidal effects than SLAE. The results suggest that both the extracts can be used for anti-catatonic activity.

Keywords

Securinega leucopyrus, Catatonia, Haloperidol, Block method, Parkinson's disease.

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INTRODUCTION

Parkinson's disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the system. It is a progressive mortality disorder, occurs due to loss of dopaminergic neurons running from substantia nigra to corpus striatum. These dopaminergic neurons are inhibitory neurons that act on D2 receptor of cholinergic neurons in the corpus striatum, thus loss of inhibition causes hyperactivity of these cholinergic neurons[1]. Use of typical antipsychotic drugs like phenothiazine (chlorpromazine or perphenazine), haloperidol or non-psychotic drugs such as steroids, disulfiram, ciprofloxacin, several benzodiazepines, as well as drugs of abuse, including phencyclidine, cannabis, mescaline, LSD, cocaine will produce extra pyramidal side effects (catatonic symptoms) like tremors, muscular rigidity and bradykinesia[2]. The major clinical symptom of Parkinson's disease include

difficulty to move and change the posture (akinesia and rigidity) and tremors. So by this parameter we could observe the severity of catatonia. Haloperidol induced catalepsy i.e., a state of akinesia with muscular rigidity in animals, is one of the established model for screening the drugs for antiparkinson's effect.

Securinega leucopyrus (Family: Euphorbiaceae), popularly known as Bush weed and Indian Snowberry. It is a commonly found in India, Sri Lanka and Burma. It is a perennial shrub that grows up to 5 m in height. The genus Securinega is a native of Madagascar and the Mascarene Islands in Indian Ocean. There are about 45 species present in this genus. In the year 1789, Securinega was first described as a genus. Securinega was a genus in the family Phyllanthaceae, later it is changed to the family Euphorbiaceae.

It is used topically in paste form for healing of chronic and non-healing wounds[3]. The leaves of the plant contain germicidal properties. The decoction of leaves is used to dress the cancerous wounds and also used externally in the treatment of piles. The juice or paste of the leaves along with tobacco is used to destroy worms in sores. It is used as popular veterinary medicine. The leaves are used to extract the extraneous materials from body tissues without surgery[4]. Leaves are boiled and taken twice a day for stomach aches. The roots are used in the treatment of testicular enlargement and in the cure of edema. The whole plant is used for the cure of cancer in the sole of the foot. It is also used in the treatment of abdominal lumps and liver hypertrophy and portal hypertension. The bark of stem is used for tooth ache[5].

Fig 1: Stem of *Securinega leucopyrus*

Phytochemicals:

The aqueous & methanolic stem extracts of *Securinega leucopyrus* possess the following chemical constituents.

Table 1: Phytochemicals present in SLME & SLAE

S.No.	Phytoconstitutents	Methanolic extract	Aqueous extract
1	**Alkaloids**	+	+
2	**Unsaturated sterols**	+	+
3	**Saponins**	+	-
4	**Glycosides**	+	+
5	**Phenolics**	+	+
6	**Terpenoids**	+	+
7	**Tannins**	+	+
8	**Flavonoids**	+	+
9	**Carbohydrates**	+	+
10	**Proteins**	+	+

'+' indicates presence of phytochemicals; '-'indicates absence of phytochemicals

MATERIALS AND METHODS

Collection & Authentication of Plant Material:

The stem of the plant, *Securinega leucopyrus (Willd.) Muell.* was collected from the medicinal garden of Chalapathi Institute of Pharmaceutical Sciences, Guntur. The plant material was identified and authenticated by Dr. M. Raghu Ram, Department of Botany, Acharya Nagarjuna University, Guntur.

Preparation of Extract:

The stem of *Securinega leucopyrus* was shade dried and was powdered in a mechanical grinder. The collected powder was extracted with water & methanol by using Soxhlet apparatus. The extraction was carried out for 72 hrs. Excess solvent was removed by the solvent evaporation.

Experimental Animals:

SD rats of either sex weighing between 200-300 gm were used. Animals were maintained under standard conditions in an animal house approved by Committee for the Control and Supervision of Experiments on Animals (CPCSEA Reg. No.: 1048 / a / 07 / CPCSEA). The animals were housed in Poly propylene cages and maintained at 25±2°C under 12 h light / dark cycle and were fed with standard animal pellet feed (Hindustan lever limited) and water *ad libitum.* The animals were allowed to acclimatize to laboratory conditions for 48 h before starting the experiment.

Haloperidol Induced Catatonia in SD Rats:

Haloperidol {4-(4-chlorophenyl)-1-(4-(4-flurophenyl)-4-oxobutyl)-4-piperidinol} is widely used antipsychotic drug and it shares some structural similarities with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). MPTP is identified as the toxic agent present in heroin and responsible for neurodegenerative condition similar to Parkinson's disease. MPTP is commonly used to induce Parkinsonism in experimental animals. Haloperidol is metabolized in liver, it undergoes oxidation to pyridinium metabolite, 4-(4-chlorophenyl)-1-(4-(4-fluorophenyl)-4-oxobutyl)-pyridinium (HPP+) which shares some structural similarities and toxic actions with pyridinium metabolite of MPTP 1-methyl-4-phenylpyridine (MPP+). This suggests that HPP+ might produce neurological effects similar to MPTP. Therefore, in the present study haloperidol is used to induce Parkinsonism in rats. Haloperidol is known to produce extra pyramidal side effects in man. These effects, such as akinesia, rigidity and tremors, are called Parkinson's-like because in Parkinson's disease the major clinical symptoms include difficulty to move and change posture (akinesia and rigidity) and tremors. These effects of antipsychotic drugs are due to excessive blockade of dopamine receptors in the extra pyramidal motor system. Therefore, butyrophenones [haloperidol (or) trifluperidol] are commonly used to produce Parkinson's-like extra pyramidal symptoms in laboratory animals and to study anti-parkinsonian drugs[6].

Experimental Design:

The anti-parkinsonism activity of the aqueous and methanolic stem extracts of *Securinega leucopyrus* was investigated using the haloperidol induced catatonia method [Haloperidol is widely used to induce Parkinsonism like condition at a dose 0.5 to 4 mg/kg daily for a week in rats]. The test animals were randomly chosen and divided into four groups having five rats in each as follows:

Treatment Schedule of Different Groups

1. **Group I (Negative Control)**: Haloperidol (4mg/kg, p.o once/day x 1 week)
2. **Group II (Positive Control)**: Saline solution (0.9%,)
3. **Group III (Standard)**: Syndopa plus [7][(Levodopa+ carbidopa) (10mg/kg, p.o, once/day x 1 week)] +Haloperidol
4. **Group IV (Test I)**: Aqueous stem extract of *Securinega leucopyrus* [SLAE- 100mg/kg p.o x 1 week] +Haloperidol
5. **Group V (Test II)**: Methanolic stem extract of *Securinega leucopyrus* [SLME- 100mg/kg p.o x 1 week] +Haloperidol

All the animals of the groups were treated with respective drugs 30 minutes prior to haloperidol administration for 7 days of experimental period.

EVALUATION OF ANTIPARKINSON'S ACTIVITY

Measurement of Catalepsy by Block Method:

Two wooden blocks were taken. One is 3cm high and the other is 9cm high. Catalepsy of rat was measured by a scoring method given below[8-10]. Severity of catatonic response was recorded as follows:

TABLE 2: Scoring for Catatonia

Stages	Description/Behavior	Score
Stage- I	Rat moves normally when placed on the table	0
Stage- II	Rat moves only when touched or pushed	0.5
Stage –III	Rat placed on the table with front paws set alternatively on 3cm high block fails to correct the posture in 10 sec, score=0.5 for each paw with a total of 1 for this stage.	1
Stage –IV	Rat fails to remove when the front paws are placed alternatively on 9cm block, score= 1 for each paw, a total score of 2 for this stage.	2

Thus for a single rat, the maximum possible score would be 3.5 revealing total catatonia. Severity of catatonia was observed at 30, 60, 90,120 & 240 min after haloperidol administration. Plot a graph, time along on X-axis and catatonic scores along the Y-axis.

Figure-2: Catatonia-Stage-III

Figure-3: Catatonia-Stage-IV

STATISTICAL ANALYSIS

The values are represented as mean ± S.E.M, and statistical significance between treated and control groups was analyzed using of ANOVA.

RESULTS AND DISCUSSION

Effect of stem extracts of *Securinega leucopyrus* on cataleptic activity:

Haloperidol induced a time dependent increase in cataleptic state in rats, as compared to vehicle treated groups. Maximum catalepsy score was noted at a time interval of 120-180 min. all the groups i.e. standard (L-dopa + carbidopa), SLME and SLAE showed significant ($P<0.05$) reduction in scores at all time periods. The average scores for the standard and the test drugs were reduced to that of the Haloperidol group (Group I).

TABLE 3: Effect of stem extracts of *Securinega leucopyrus* on haloperidol-induced Parkinsonism (catalepsy)

S.No	Group	Treatment	Degree of catatonic response(in min)				
			30	60	90	120	240
1.	I	Haloperidol	0.66±0.07	1.83±0.09	2.81±0.08	3.54±0.06	2.80±0.20
2.	III	Standard + haloperidol	0.32±0.02	0.50±0.02	0.33±0.02	0.27±0.02	0.32±0.01
3.	IV	SLAE + haloperidol	0.34±0.02	0.52±0.02	0.34±0.02	0.25±0.02	0.32±0.01
4.	V	SLME + haloperidol	0.33±0.02	0.51±0.02	0.33±0.02	0.24±0.02	0.32±0.02

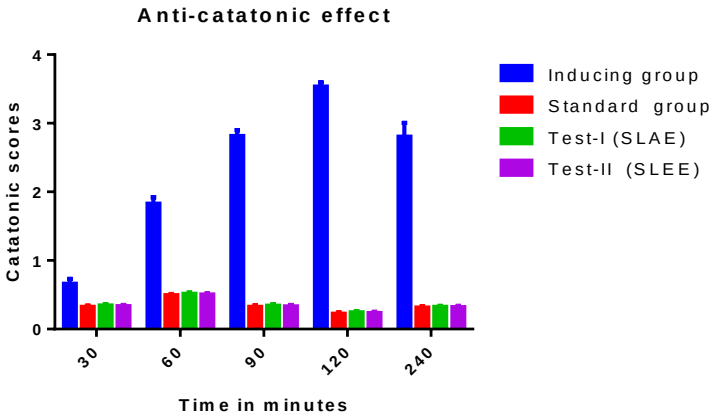

Figure 4: Effect of stem extracts of *Securinega leucopyrus* on haloperidol-induced Parkinsonism (catalepsy). Values are expressed as Mean ± SE, *p < 0.05* vs. control (n = 5 animals).

CONCLUSION

Pharmacological screening of methanolic and aqueous extracts of *Securinega leucopyrus* showed anti-catatonic activity. The methanolic extract was found to have a good activity than aqueous extract and has the potential to be used as anti-catatonic activity. The chemical constituents like saponins and flavonoids in *Securinega leucopyrus* gives a hope for further research in the area of neurodegeneration.

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