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EVALUATION OF PHYTOCHEMICALS AND NEUROLEPTIC POTENTIAL OF LEAVES EXTRACT OF *ADENIUM OBESUM*

Pulkit Sharma*[1]; Dr. Shmmon Ahmad[2]; Ashok Kumar[2]
*[1]Research Scholar, Glocal College of Pharmacy, Glocal University, Saharanpur (UP), India
[2]Faculty, Glocal College of Pharmacy, Glocal University, Saharanpur (UP), India

Corresponding Author:
Pulkit Sharma
Research Scholar, Glocal College of Pharmacy, Glocal University, Saharanpur (UP), India
Email: sharmapulkittalk2@gmail.com

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ABSTRACT:
The term psychosis refers to illnesses that impair the mind and cause a loss of touch with reality. The present research focuses on screening of phytochemicals and neuroleptic potential of leaves extract of *Adenium Obesum* in animal models. Leaves of *Adenium obesum* were obtained from the Saharanpur, UP region and these were identified and authenticated by a botanist at BSI, (Prayagraj) Allahabad. The leaves were washed making dust-free and dried at room temperature or shade. The dried leaves were rendered into coarse powders and then finally into fine ones. The powder was weighed and soaked into hydroalcoholic solution consisting ethanol+ distilled water (1:1) for fifteen days with gradual stirrings. A rotating evaporator is used to dry the brownish until a semisolid extract was obtained. Animal House, Department of Pharmacy, Glocal University Saharanpur (UP) was provided Wistar rats of either sex weighing 130–160g. Animals were divided in 4 groups (n=6) i.e., group1 administered only normal saline daily for 21 days, group 2 administered pregabalin (10mg/kg) orally, for 21 days, group 3 administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 200mg/kg orally, for 21 days and group 4 administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 400mg/kg orally up to 21 days. Screening of phytochemicals and then neuroleptic activity of *Adenium Obesum* by screening models i.e., Apomorphine-induced stereotypy, Haloperidol-induced catalepsy and Climbing behavior test was evaluated. In results, *Adenium obesum* has prominent neuroprotective effect at lower and higher doses (200mg/kg & 400mg/kg). But response was based on dose levels. It exhibited a significant neuroprotective behavior it might be due to better release of constituents from the leaves of *Adenium obesum* plant. In conclusion, *Adenium obesum* has potential neuroprotective behaviour at the all the doses used but highest was observed at higher dose of ethanolic extract that might be due to better solubility and constituents release from the *A. obesum* leaves in extraction. Future research suggests, to identify and isolate the responsible element for the pharmacological potential and make the suitable dosage form.

Keywords: *Adenium obesum*, phytochemicals, neuroleptic, apomorphine-induced stereotypy, haloperidol-induced catalepsy.

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INTRODUCTION

The term psychosis refers to illnesses that impair the mind and cause a loss of touch with reality. Psychosis symptoms include delusions (incorrect beliefs) and hallucinations- seeing or hearing something that do not exist (Schizophrenia, Mental Health Information, 2022). Psychotic symptoms, like delusions and hallucinations, can appear gradually and develop over time, or they might appear suddenly. People suffering from psychosis may be unaware that their sensations are abnormal. What is going on in their heads is extremely real to them (Antipsychotic medications, 2022). Approximately 1% of the individuals will develop psychosis or schizophrenia during their lives (NICE Clinical Guidelines, 2014).

According to World Health Organization (WHO), Schizophrenia affects around 24 million people globally, or one in every 300 people (0.32 percent). Adults have a rate of 1 in 222 (0.45 percent). It is not as widespread as other mental illnesses. Onset occurs most frequently in late adolescence and at the age of twenties, and it occurs earlier in males than in women. Schizophrenia is typically linked with considerable distress and impairment in important areas of life such as individual, family, social, education, occupational, and other (Schizophrenia, WHO, 2022). Early onset is linked to lower outcomes, while early intervention is linked to better outcomes. In children, psychosis is extremely rare (McGrath et al. 2004) Psychosis affects about 3% of the general population over their lifetime, with psychosis due to a general health condition accounting for 0.21 percent (Perala et al. 2007). Pathogenesis of schizophrenia has been due to abnormalities in secretion of neurotransmission. It denotes the neurotransmitter imbalances i.e., dopamine, serotonin, & glutamate. Other thoughts indicate aspartate, glycine & GABA to schizophrenia's neurochemical dysregulation (Lavretsky et al. 2008).

Plant Description

Although *Adenium obesum* species first appeared in Africa, they have since spread throughout the rest of the tropics and subtropics. The chosen plant species can be found in both Asia and Africa. Several species of the preferred plant can be found in Oman. The Sultanate of Oman, for instance, is home to the desert rose. All parts of a given species are used to treat a wide range of illnesses. Several plant species have been singled out for commercial cultivation due to their medicinal value (Akhtar et al., 2017).

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Fig 1. *Adenium obesum* plant

Taxonomy

Kingdom- Plantae
Subkingdom- Tracheobionta
Division- Magnoliophyta
Class- Magnoliopsida
Order- Gentianales
Family- Apocynaceae
Genus- *Adenium*
Species- *obesum*

Chemical constituents

Multiple chemical classes were identified in a locally cultivated AO whole plant, and the number of compounds increased with plant age (Malebo et al., 2009). Carbohydrates, flavonoids, cardiac glycosides, flavonoids, terpenoids, and pregnanes were all identified in the selected plant during the phytochemical examination. The bulk of the isolated chemicals from the chosen plant had physiological effects. Previous studies of the selected plant have resulted in the extraction and identification of a total of 53 compounds. Many of these plants are hazardous, while others have been shown to have useful biological properties like antiviral, anticancer, and cytotoxic activities (Amin et al. 2013).

Stem and bark exhibited the chemical constituents as Betulin and Rosmarinic Acid. Stem showed 3,5,7,3,4,5-Hexahydroxy flavone and 5,7,3,4-Tetrahydroxy flavone whereas leaves confirmed for various chemical constituents i.e., Honghelin, Obeside-B & C (Amin et al. 2013; Hossain et al. 2013)

The present research focuses on screening of phytochemicals and neuroleptic potential of leaves extract of *Adenium Obesum* in animal models.

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MATERIALS AND METHODS

Experimental requirements

Fresh leaves of *Adenium obesum*, pregabalin, apomorphine, haloperidol, Wistar rats of either sex, rotatory evaporator/ water bath, ethanol, distilled water, beaker, conical flask.

Collection, identification & authentication of plant

Leaves of *Adenium obesum* were obtained from the Saharanpur, UP region and these were identified and authenticated by a botanist. The leaves were washed making dust-free and dried at room temperature or shade. The dried leaves were rendered into coarse powders and then finally into fine ones. The powder was weighed and soaked into hydroalcoholic solution consisting ethanol+ distilled water (1:1) for fifteen days with gradual stirrings. A rotating evaporator is used to dry the brownish until a semisolid extract was obtained. The yield of the leaf extract was calculated as a percentage.

$$\text{percent yield} = \frac{\text{actual yield}}{\text{theoretical yield}} \times 100\%$$

Preparation of animals

Animal House, Department of Pharmacy, Glocal University Saharanpur (UP) was provided Wistar rats of either sex weighing 130–160g. The animals are kept in good health, with room temperatures of 25°C and a 12-hour light/dark cycle. The relative humidity is kept at 44-56 percent, and the rats are provided a regular rodent diet and free access to water. The animals were kept on fasting but have free access to water until 1 hour before study begins (Bhajoni et al. 2016).

Experimental protocols

All the rats are divided into 4 groups (n=6) as followings-

Group 1: Rats are administered only normal saline daily for 21 days.

Group 2: Rats are administered pregabalin (10mg/kg) orally, for 21 days.

Group 3: Rats are administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 200mg/kg orally, for 21 days.

Group 4: Rats are administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 400mg/kg orally up to 21 days.

Protocols

1. **Apomorphine induced stereotypy**

Group I serving as the control group, receiving normal saline (p. o.). Pregabalin (10mg/kg, i. p.) was given to Group II as a drug control. HLAO (200mg/kg) was given to Group III and group IV as given HLAO (400mg/kg, prior 1 hr administration of apomorphine (5mg/kg). The stereotyped behavior is a result of stereotyping. The rats were housed in individual cages

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and watched for 10 seconds. After treatment with APO, intervals that allows you to track the behavioral effects of apomorphine over time, the presence or absence of movement, rearing, sniffing, licking, and chewing will observe at every 10, 20, 30, 45, 60 & 90 min (Amos et al. 2003).

They were scored as per the severity of stereotyped activity-

0 for asleep

1 for energetic

2 for predominantly activeness (with intervals of sniffing & rearing)

3 for fixed stereotyped behavior (sniffing, rearing with locomotor activity)

5 for stereotyped activity (bursts of licking, biting)

6 for persistent licking of cage grids

7 for consistent biting of cage grids

8,9 for constant stereotyped activity

2. Haloperidol induced catalepsy model

Group I serving as the control group, receiving normal saline. The HLAO was given to Group III and IV, animals at doses of 200 & 400mg/kg, (orally) 60 minutes before the Haloperidol (1mg/kg) was given. Thus, the max. potential score for a single rat would be 3.5, indicating total catatonia. The total catatonia score will be calculated at every 10, 20, 30, 45, 60 & 90 min (Praveen & Brij, 2005; Kulkarni, 1999).

They were scored as per the severity of catatonic response-

Stage I (Score 0)- If rats move normally when placed on table

Stage II (Score 0.5)- If rats move only when touched or pushed

Stage III (Score 0.5)- If a rat placed on the table with front paws occasionally on a 3cm high frame fails to correct the posture in 10 seconds (for each paw, total of 1 for this stage)

Stage IV (Score 0.5) a rat placed on the table with front paws alternately on a 9cm block fails to remove (total 1 for this stage).

3. Climbing behavior

Each rat is made to hand individually on cage of vertical wire-stick (width 12cm; height of 14cm) for the determination of climbing behavior every 10 minutes for ½ hr and evaluated as follows:

Rats were individually habituated in the vertical wire-stick cage for 30 minutes before apomorphine induction to reduce scoring error owing to exploratory behavior (Vogel, 2008; Durg et al. 2015).

0= If 4 paws on the floor

1: If forefeet holding the bars

2: If four feet holding the bars.

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3.1 Statistical analysis

Statistical data were analyzed by ANOVA i.e., by 2-tailed t- test. Readings were expressed as Mean±SEM. The data was analyzed using Sigma Stat pro3.3. The results were noted as statistically marked at $p \leq 0.05$.

RESULTS AND DISCUSSION

Apomorphine induced stereotypy

In apomorphine induced stereotypy score model, total 4 groups of rats were used to screen out neuroleptic potential in contrast to standard and control group. Group 1 was kept as control that was served normal saline only. Group 2 was treated with standard neuroprotective drug- Pregabalin (10mg/kg) whereas, group 3 & 4 was administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 200mg/kg & 400mg/kg, respectively. Stereotype response was recorded at 10, 20, 30, 45, 60 and 90 minutes.

When stereotype score was seen in control group as 2.29±0.29* and 3.12±0.12** at 10 min and 90 min respectively. In all the groups of animals, the *A. obesum* showed excellent neuroprotective behavior when observed in comparison with control and apomorphine control groups. At 60 min, pregabalin group showed stereotype score as 93.12±0.28*** and HLAO as 2.39±0.29** and 98.81±0.52** at the dose of 200mg/kg and 400mg/kg, respectively.

Table 1. Stereotyped score estimation

Treatment	Stereotype Score (Mean ± SEM)					
	10 min	**20 min**	**30 min**	**45 min**	**60 min**	**90 min**
Vehicle	2.29±0.29*	3.64±0.30**	4.29±0.32**	4.67±0.26**	4.43±0.38**	3.12±0.12**
Pregabalin (10mg/kg)	1.23.49±0.17**	1.19±0.24**	1.15±0.20**	1.03±0.26**	0.93±0.28***	0.82±0.29**
HLAO (200mg/kg)	2.81±0.43**	2.73±0.12***	2.64±0.32**	2.52±0.22**	2.39±0.29**	2.10±0.23***
HLAO (400mg/kg)	1.97±0.29**	1.47±0.10**	1.10±0.23***	1.04±0.71***	0.98±0.52**	0.93±0.57**

Significance level was represented by *; P<0.05
n=6; readings were given in Mean± SEM

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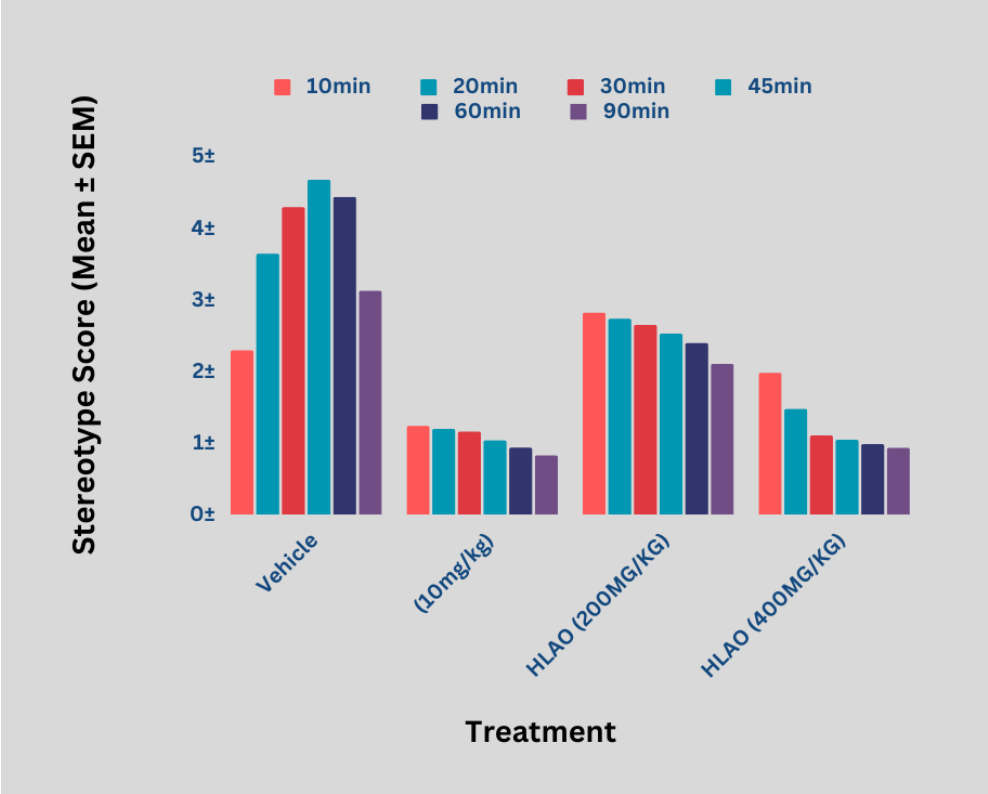

Fig 2. Graphical data of Stereotyped score estimation

Haloperidol induced catalepsy

In Haloperidol induced catalepsy model, total 4 groups of rats were used to screen out neuroleptic potential in contrast to standard and control group. Group 1 was kept as control that was served normal saline. Group 2 was treated with standard neuroprotective drug-Pregabalin (10mg/kg) whereas, group 3 & 4 was administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 200mg/kg & 400mg/kg, respectively. Catalepsy response was recorded at 10, 20, 30, 45, 60 and 90 minutes.

The maximum inhibitory catalepsy score was seen in group 3 treated with pregabalin, as 27.39±1.13** at 90 min which so far from the apomorphine treated animals. HLAO showed catalepsy score as 49.45±1.39** and 32.51±1.38** at the dose of 200mg/kg & 400mg/kg, respectively at 90 min, that are nearer to standard group when compared with all other group of animals.

Previous studies indicate, highest catalepsy score was recorded at 60 min in apomorphine treated group as 78.23±1.29***. Catalepsy inhibitory role was observed in all the AI extracts but it was highest in ethanolic and lowest in methanolic.

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Table 2. Catalepsy score determination

Treatment	Catalepsy score (Mean ± SEM)					
	10 min	**20 min**	**30 min**	**45 min**	**60 min**	**90 min**
Vehicle	66±1.29**	72.93±1.28**	72.28±1.17**	68.25±1.34**	73.41±1.20**	75.39±1.31**
Pregabalin (10mg/kg)	53.16±1.22**	53.28±1.33**	56.24±1.19**	46.38±1.37**	38.20±1.47**	27.39±1.13**
HLAO (200mg/kg)	54.28±1.19**	57.43±1.62**	56.24±1.61**	53.27±1.19**	51.48±1.30**	49.45±1.39**
HLAO (400mg/kg)	57.37±1.10**	52.54±1.38**	47.40±1.27***	42.72±1.62**	39.42±1.37**	32.51±1.38**

Significance level was represented by *; P<0.05
n=6; readings were given in Mean± SEM

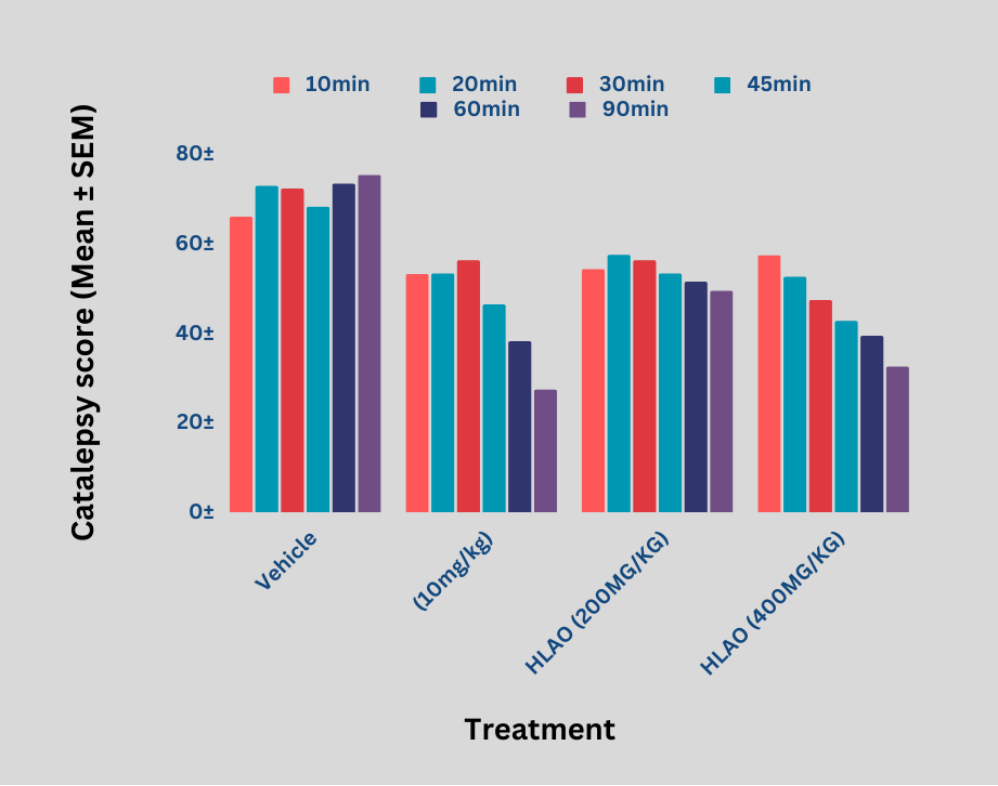

Fig 3. Graphical data of Catalepsy score determination

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Apomorphine induced climbing behaviour

In apomorphine induced climbing model, total 4 groups of rats were used to screen out neuroleptic potential in contrast to standard and control group. Group 1 was kept as control that was served normal saline. Group 2 was treated with standard neuroprotective drug-Pregabalin (10mg/kg) whereas, group 3 & 4 was administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 200mg/kg & 400mg/kg, respectively. Climbing time was recorded at 30 minutes.

Climbing time was noted as 17.26±0.29* in normal saline treated rats. Similarly, cumulative climbing index was observed 18.39±0.11* in control. Climbing time was significantly found decreased as 6.19±0.17** and cumulative climbing index as 7.46±0.53** which was lowest among all the treatments. A significant inhibitory role was seen in hydroalcoholic leaves extract of *Adenium obesum* (400mg/kg) as 8.79±0.33*** when compared with other control.

Table 3. Apomorphine induced climbing behaviour estimation

Treatment	Climbing time (30 min)	Cumulative climbing index
Vehicle	17.26±0.29*	18.39±0.11*
Pregabalin (10mg/kg)	6.19±0.17**	7.46±0.53**
HLAO (200mg/kg)	14.27±0.17**	15.37±0.28**
HLAO (400mg/kg)	8.79±0.33***	8.94±0.35**

Significance level was represented by *; P<0.05
n=6; readings were given in Mean± SEM

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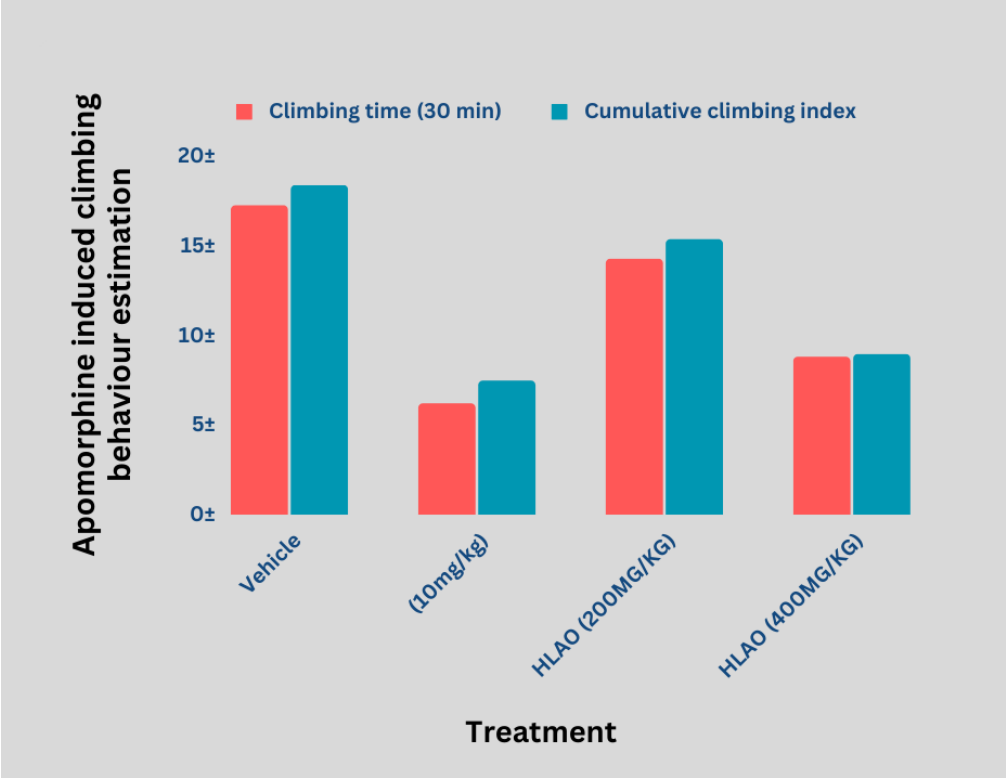

Fig 4. Graphical data of Apomorphine induced climbing behaviour estimation

Pole climbing behaviour score

In pole climbing model, total 4 groups of rats were used to screen out neuroleptic potential in contrast to standard and control group. Group 1 was kept as control that was served normal saline. Group 2 was treated with standard neuroprotective drug- Pregabalin (10mg/kg) whereas, group 3 & 4 was administered hydroalcoholic leaves extract of *Adenium obesum* (HLAO) at dose of 200mg/kg & 400mg/kg, respectively. Climbing score out of 5 was recorded at 10, 20 and 30 minutes.

Similarly, since climbing time reduction, climbing score was noted out of 5. In 30 min, climbing score was found as 1.63±0.34*** and 0.62±0.25*** in the hydroalcoholic leaves extract of *Adenium obesum* at dose of 200mg/kg and 400mg/kg, respectively and which was lowest when compared with control as 4.38±0.29** in 30 min.

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Table 4. Pole climbing score estimation

Treatment	Climbing Score out of 5		
	10 min	20 min	30 min
Vehicle	2.38±0.26**	3.22±0.38**	4.38±0.29**
Pregabalin (10mg/kg)	1.29±0.27***	1.07±0.17*	0.44±0.31***
HLAO (200mg/kg)	2.56±0.39**	2.42±0.25***	1.63±0.34***
HLAO (400mg/kg)	2.48±0.32**	1.64±0.33***	0.62±0.25***

Significance level was represented by *; P<0.05
n=6; readings were given in Mean± SEM

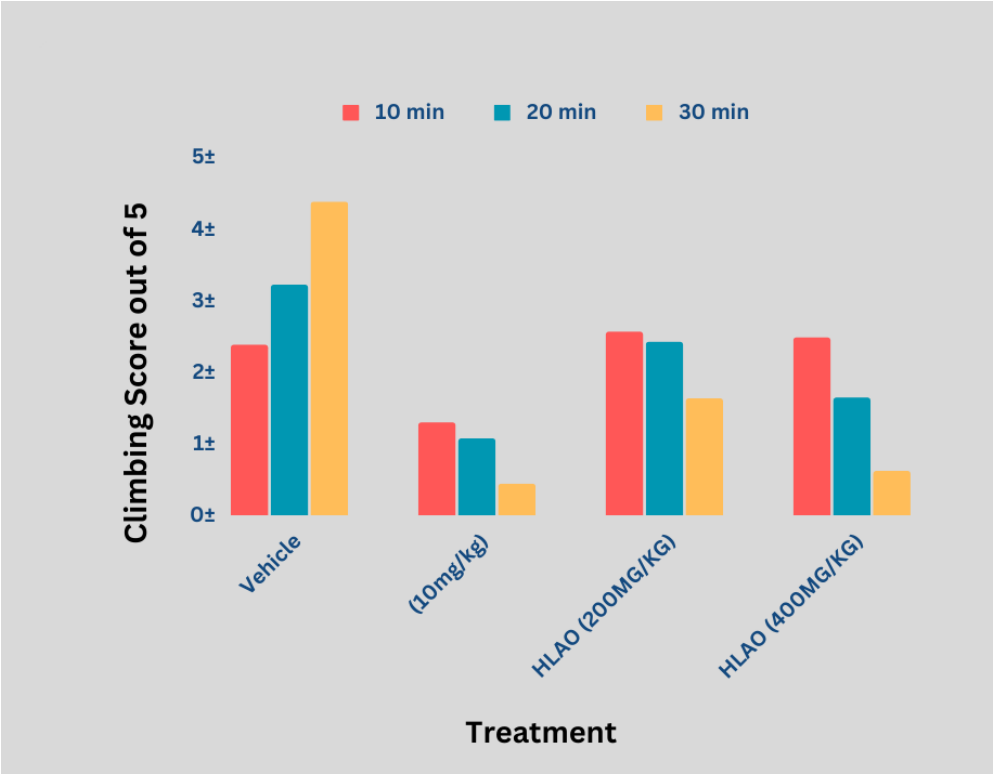

Fig 5. Graphical data of Pole climbing score estimation

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In previous studies, inhibitory action in the levels of neurotransmitters was found maximum in pregabalin treated animals as 1500±0.12*** when compared with APO control group as 2900±0.32** in the case of dopamine. Similarly, a prominent reduction in levels of noradrenalin and serotonin was estimated.

In results, *Adenium obesum* has prominent neuroprotective effect at lower and higher doses (200mg/kg & 400mg/kg). But response was based on dose levels. It exhibited a significant neuroprotective behavior it might be due to better release of constituents from the leaves of *Adenium obesum* plant.

In mice and rats, peripheral injection of apomorphine causes increased movement and stereotyped behavior. Neuroleptic activity has been linked to medicines that inhibit climbing and stereotyped behavior in mice. Blockade of dopamine D2 and serotonin receptors is also recommended in the treatment of psychosis (Durg et al. 2006). There was a link between the results and a better decrease at high dose embelin. However, low doses of AI did reduce climbing behavior in a time-dependent way, but did result in significant reductions in estimated neurotransmitter levels (Vogel, 2008). Its neuroprotective action may be believed due to inhibitory effect on the release of catecholamines (CAs) and various neurotransmitters such as dopamine, noradrenaline and serotonin (5-HT).

CONCLUSION

Adenium obesum inhibited apomorphine onset climbing & stereotyped behaviour in mice, and these effects may be partially mitigated by dopaminergic & serotonergic pathway inhibition and noradrenergic neuron inhibiting activity. To understand the precise manner of its antipsychotic activity, more research is needed (Durg et al. 2017).

It would be very impactful with easier, way of curing ulcer due to its wide availability and action. It would be a great change towards allopathic medicines to counter the gastric problems and heal the life of millions. It may also be refined that its production would be reasonable in terms of cost with relatively strong usefulness. It would be great deal for stability of formulation that would be done further. It will sustain the induction of ulcer and heal if already demonstrated its symptoms. Whereas, action produced 400mg/kg/kg was dominant. As psychoses and mania are most become commonest form of mental disability, so it may demonstrate an economic and pharmacological impact in modulating behavioral of humans. Its mode of action- evaluation is important to confirm its actual neuroprotective action pathway. It is well available and no cost is payable as *A. obesum* is widely available throughout the India and world.

In conclusion, *Adenium obesum* has potential neuroprotective behaviour at the all the doses used but highest was observed at higher dose of ethanolic extract that might be due to better

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solubility and constituents release from the *A. obesum* leaves in extraction. HLAO at the dose of 400mg/kg when administered orally, showed much nearer neuroleptic behaviour when compared with the standard drug pregabalin (10mg/kg). It significantly modulated the neuroprotective action in rodents.

Future research suggests, to identify and isolate the responsible element for the pharmacological potential and make the suitable dosage form the make available in the market and society in the cure of this deadly affective mental disorder. Its action was comparable with Pregabalin at the dose of 400mg/kg.

As *A. obesum* has already been proved as a versatile plant for various medical conditions to heal. This study also exhibited the positive neuroprotection behavior of *A. obesum* plant when tested in Wistar rats. The herbal extract was administered orally while pregabalin was given intraperitoneally prior pharmacological study.

FUNDING

Nil.

CONFLICT OF INTEREST

None.

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