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Research Article

Evaluation of Sedative and Hypnotic Activity of Ethanolic Extract of *Plumeria obtusa* Flowers in Experimental Mice

Naik Durga*, Ashoka Shenoy M.

Nandkumar Shinde College of Pharmacy, Aghur, Vaijapur 423701 Dist.-Aurangabad, Maharashtra

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ABSTRACT

The current study aimed to assess the sedative and hypnotic effects of the ethanolic extract of *Plumeria obtusa* flowers (POEE) in mice using the hole board test and potentiation of pentobarbital-induced sleeping time test model. The extract's effects on sedative and hypnotic-related behaviors were evaluated by counting the number of head dips in the hole board test after being given at two doses of 100 mg/kg and 200 mg/kg. The duration of sleep and its initiation were noted in the potentiation of the pentobarbital-induced sleeping time test. In the hole board test, POEE-treated animals significantly reduced the number of head dips when compared to control mice, suggesting sedative action. Similarly, POEE administration produced a longer duration of sleep action in the pentobarbital-induced sleeping time test potentiation, confirming its hypnotic potential. The 200 mg/kg dose was more effective than the 100 mg/kg dose, and the effects were dose-dependent. These findings strongly suggest that *Plumeria obtusa* flower ethanolic extract effectively induces sedative and hypnotic-related behaviors in experimental mice, indicating that it may be used to treat sleep-related disorders.

INTRODUCTION

Sleep disruptions are prevalent in older persons and frequently happen without any medical issues, they are increasingly being connected to negative health effects^[1]. Nearly 50% of older individuals suffer from major conditions including sleep apnea and insomnia and many of them have trouble falling asleep and staying asleep as their sleep-

wake cycle becomes disturbed with age^[2]. These problems are addressed by sedative-hypnotic medications which relax the nervous system and make it easier to fall asleep and stay asleep. While hypnotics mimics natural sleep, sedatives lessen agitation without causing sleep. Sedative-hypnotics can provide these effects as central

***Corresponding Author:** Naik Durga

Address: Department of Pharmacology, Srinivas College of Pharmacy, Mangalore-574143.

Email ✉: naikdurga3103@gmail.com

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nervous system depressants without affecting mood or pain threshold^[3]. In India, insomnia is linked to serious comorbidities including diabetes and cardiovascular disease making it life threatening health concern^[4]. More than 90% of Indians, according to recent research, do not get enough sleep, and many of them claim that their ability to function at work is adversely affected by their sleep, yet few of them seek medical assistance. Insomnia and other sleep disorders go untreated because of the social stigma associated with mental health issues. Traditional sedative-hypnotic drugs, such as benzodiazepines and non-benzodiazepine sedatives have been used extensively to treat insomnia; however, their efficacy is constrained by tolerance problems, addiction risks, and side effects, which has sparked interest in alternative therapy^[3]. Herbal remedies are becoming more popular due to their low risk of adverse effects and possible ability to treat sleeplessness. Several plants including *Plumeria obtusa*, *Valeriana officinalis*, and *Piper methysticum* have demonstrated sedative-hypnotics properties. Rich in flavonoids such as apigenin, quercetin, and rutin *Plumeria obtusa* has long been used to treat insomnia and other conditions involving the central nervous system. It primarily acts on GABAergic pathways that are connected to calming effects. Its sedative-hypnotic properties are not well supported by scientific research, despite its well-established use in traditional medicine. Therefore, the purpose of this research is to investigate the efficacy of *Plumeria obtusa* flower extracts in sedative-hypnotic activity via experimental models^[5].

METHODOLOGY:

Materials:

Chemicals such as Diazepam, and Pentobarbital of pure analytical grade were procured from E. Merck (India) Ltd, Mumbai, and all other chemicals and reagents of pure analytical grade were procured from local suppliers. Diazepam was

used as a standard drug for comparison in behavioral experiments. The experiment was performed as described in the standard bibliography, kinds of literature, and textbooks.

Plant Collection and Extraction:

The flower of *Plumeria obtusa* used for the present studies was collected from Mangalore, Karnataka, in May 2024. It was authenticated by Dr. Siddaraju M.N. (Assistant Professor and Research Guide, Department of Botany, and University College Mangalore). Fresh *Plumeria obtusa* flowers were collected locally. The flowers were cut into small pieces. About 500g of the flower's samples was macerated with 1.5 L of ethanol followed by frequent shaking for at least 3-7 days at room temperature. The obtained mixture was strained and filtered. The remaining residues were then discarded. The extracts obtained were stored in the refrigerator till further use^[6].

Phytochemical Screening:

The ethanolic extract of *Plumeria obtusa* (POEE) was qualitatively investigated for the presence of different phytochemicals according to the standard procedures^[7].

Dose Selection:

Dose was selected from a previous research work which is 100mg/kg and 200mg/kg respectively^[8].

Experimental Animals:

The Swiss Albino mice (20-25 g) of either sex was used for this study. The animals were housed in colony cages and maintained under the standard environmental condition's temperature $25 \pm 2^\circ\text{C}$, 12h light: 12 h dark cycle, and $50 \pm 5\%$ relative humidity. They were fed with food and water *ad libitum*. The Institutional Animal Ethics Committee reviewed and approved the experimental protocol (Approval no: **SCP/IAEC/F150/P217/2023**). All the procedures were performed in accordance with Institutional Animal Ethics Committee considered as per the direction of the Committee for Control and



Supervision of Experiments on Animals (CCSEA).

Experimental Design:

Hole Board Test:

The four groups of six mice each were randomly assigned to the following conditions Group I (Normal control: Vehicle), Group II (Diazepam: 3mg/kg, p.o.), Group III (*Plumeria obtusa*: 100 mg/kg, p.o.), Group IV (*Plumeria obtusa*: 200 mg/kg, p.o.). The mice were of both sexes and weighed (20-25g). Except for the vehicle-treated control group, all treatments were given orally for ten days. The animals were given medications 30 minutes before the sedative activity was evaluated on day 11th. A flat platform (60 x 30 cm) with 16 uniformly spaced holes was used to measure sedative activity. Each animal was given five minutes to investigate the platform, and the number of head dips into the holes was noted. During this time, the head dip counts were used to assess the sedative effects of treatments [9].

Potentiation of Pentobarbital-induced sleeping time test:

The mice of either sex weighing 20-25g were randomly assigned to four groups of six animals each including Group I (Normal control: Vehicle + Pentobarbital 30 mg/kg i.p.), Group II (Diazepam 3 mg/kg p.o. + Pentobarbital 30 mg/kg i.p.), Group III (*Plumeria obtusa* extract: 100 mg/kg p.o. + Pentobarbital 30 mg/kg i.p.), Group IV (*Plumeria obtusa* extract: 200 mg/kg p.o. + Pentobarbital 30 mg/kg i.p.). Except for the vehicle group, all treatments were given orally for ten days. Each animal was treated for 30 minutes before inducing hypnosis with pentobarbital on

day 11th. Pentobarbital was injected intraperitoneally to induce hypnosis and the animals were placed in a supine position on a pad that had been warmed to 37°C for 30 minutes after the injection. The time it took for the animals to lose the righting reflex was measured. This was verified by the fact that the animals could right themselves in less than a minute if they were placed on their backs. The hypnotic effect was assessed via loss of righting reflex [10].

Statistical Analysis:

The data were expressed as mean $\pm$ SEM and were analyzed by the one-way ANOVA (Analysis of variance) followed by Dunnett's multiple-comparison test.

RESULTS:

The preliminary phytochemical screening of ethanolic extract of *Plumeria obtusa* (POEE) flowers showed the presence of flavonoids, tannins, alkaloids, phenolics, and glycosides. Because of these substances' antioxidant qualities, result in possible pharmaceutical uses.

Hole Board Test: The Hole Board Test assesses sedative activity by measuring reduced exploratory behavior, such as decreased head-dipping, indicating CNS depression. It can also reflect anxiolytic effects if exploratory behavior increases. The diazepam showed a significant decrease in head-dip response. Treatment with *Plumeria obtusa* ethanolic extract (POEE) showed a dose-dependent reduction in head-dip response in comparison to control animals, suggesting that the extract possesses sedative activity rather than anxiolytic potentials as shown in Table No.1 and Fig No. 1,2 respectively.

Table No. 1: Effect of POEE on hole board test in mice

Group	Treatment	Dose (mg/kg)	Number of head dips	% Inhibition
I	Control	Vehicle	80.33 $\pm$ 2.89	0
II	Diazepam	3	23.16 $\pm$ 1.9***	71.23
III	POEE (low dose)	100	44.66 $\pm$ 2.01*	44.45
IV	POEE (high dose)	200	38.33 $\pm$ 2.06**	52.3
Values are expressed Mean $\pm$ SEM, (n=6). *p<0.05 ** p<0.01 *** p<0.001 compared to control group. (ANOVA followed by Dunnett's multiple comparison test).				



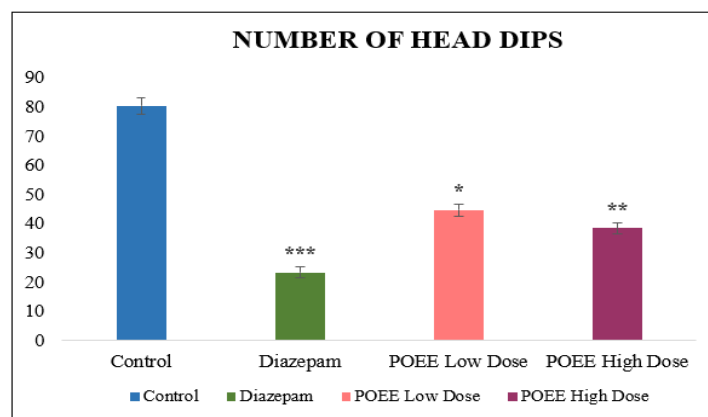


Fig.No.1: Effect of POEE on Number of Head Dips in mice

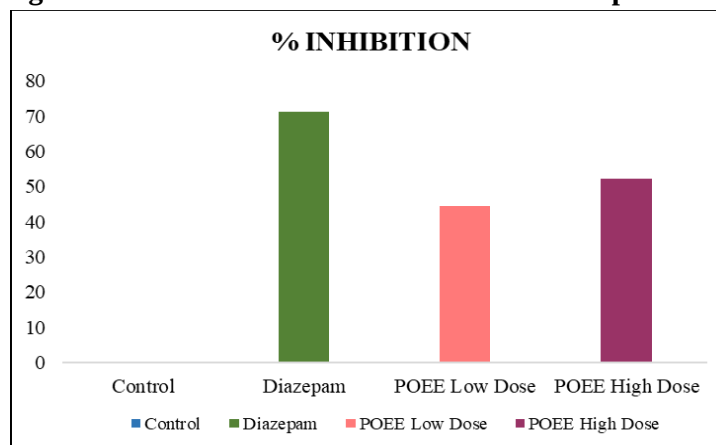


Fig.No.2: Effect of POEE on % Inhibition in mice

Potentiation of Pentobarbital-induced sleeping time test

The pentobarbital-induced sleeping time test evaluates hypnotic activity by examining compound effects on pentobarbital-induced sleep duration. Mice treated with the POEE showed a marked reduction in the onset of sleep and a dose-

dependent prolongation of sleep duration compared to control animals, indicating enhanced sedative effects. The extract potentiated pentobarbital's hypnotic action, when compared to control group animals as shown in Table No. 2 and Fig No. 3,4 respectively.

Table. No.2: Effect of POEE on the potentiation of pentobarbital-induced sleep time test in mice.

Group	Treatment	Onset of sleep	Duration of sleep
I	Control (Vehicle) + Pentobarbital (30 mg/kg)	8.93±0.82	37.33±2.52
II	Diazepam (3 mg/kg) + Pentobarbital (30 mg/kg)	3.13±0.73***	81.5±2.12***
III	POEE low dose (100 mg/kg) + Pentobarbital (30 mg/kg)	4.83±0.96**	49±1.52*
IV	POEE high dose (200 mg/kg) + Pentobarbital (30mg/kg)	3.45±0.8***	66.33±1.7**
Values are expressed Mean ± SEM, (n=6). *p<0.05 ** p<0.01 *** p<0.001 compared to control group. (ANOVA followed by Dunnett's multiple comparison test).			

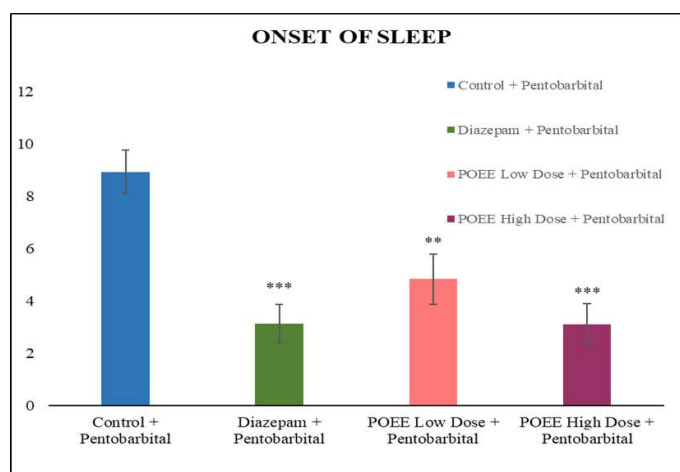


Fig.No.3: Effect of POEE on onset of sleep-in mice

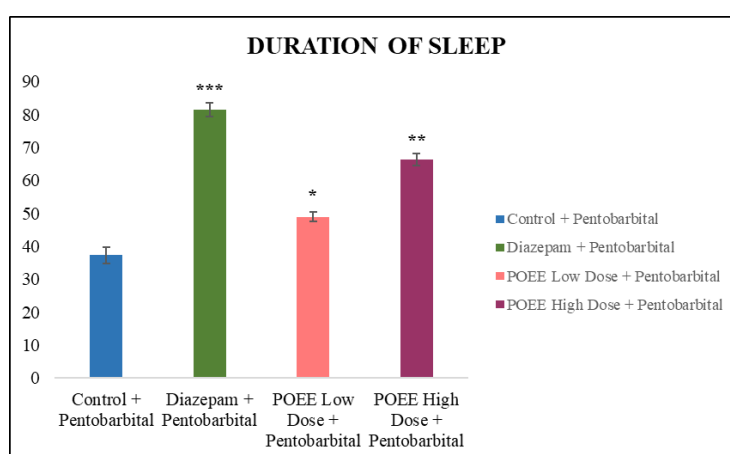


Fig.No.4: Effect of POEE on duration of sleep-in mice

DISCUSSION:

Humans have long used plant-based remedies to alleviate mental health issues. In many cultures, these herbal treatments have been fundamental components of traditional medicine. Even though medicinal plants are still useful for psychiatric and neurological conditions, where they frequently have fewer adverse effects, their usage in mainstream medicine has decreased with the development of modern pharmacology. As patients continue to face difficulties with traditional pharmaceuticals, such as side effects, limited efficacy, and eventual tolerance, the growing interest in herbal remedies today emphasizes their significance [11,12].

Since herbal medicines have fewer side effects than synthetic pharmaceuticals, they have

historically been used extensively to treat neurological and mental problems. *Plumeria obtusa* has developed popularity as an herbal remedy because of its sedative and hypnotic qualities, particularly among Indian tribal populations. Flavonoids such as apigenin, quercetin, and rutin, which are abundant in this plant, interact with the GABA_A- benzodiazepine receptor complex to affect GABAergic pathways [5]. *Plumeria obtusa* ethanolic extract (POEE) was examined using two models, the Hole board test found less exploratory behavior which was consistent with a sedative condition, and the Potentiation of pentobarbital-induced sleeping time test, to evaluate hypnotic effects, as indicated by increased sleep duration, which suggested central nervous system depression. *Plumeria*

obtusa's capacity to produce a sedative-hypnotic effect was validated by both experiments ^[5].

The ethanolic extract of *Plumeria obtusa* flowers (POEE) showed dose-dependent sedative and hypnotic effects in this study, decreasing exploratory behavior and increasing test animal sleep duration. The effectiveness of POEE was confirmed by comparisons with the common sedative diazepam, which also increased the length of pentobarbital-induced sleep ^[13,14].

The current study provides a strong foundation for POEE's sedative-hypnotic potential, further research is necessary to fully understand its mechanism of action and bioactive compounds. The presence of flavonoids indicates GABAergic involvement, but other compounds, such as alkaloids and phenolics, may also play a role. Isolating and characterizing these components would enable a better understanding of POEE's pharmacodynamic and safety profile, essential steps for advancing it as a therapeutic option.

CONCLUSION:

In conclusion, the ethanolic extract of *Plumeria obtusa* flowers exhibited significant sedative and hypnotic activity, supporting its traditional use. Nevertheless, additional research is necessary to isolate, identify, and characterize the specific phytochemicals responsible for the observed biological activities in this study, as well as to elucidate their precise mechanisms of action.

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