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Dhanapal Venkatachalam
Department of Pharmacognosy, Sanjo College of Pharmaceutical Studies, Velappara, Palakkad, Kerala – 678 702, India

Samuel Thavamani B
Department of Pharmacognosy, Sanjo College of Pharmaceutical Studies, Velappara, Palakkad, Kerala – 678 702, India

Sampath Kumar
Department of Pharmaceutics, Coimbatore Medical College, Coimbatore, Tamil Nadu, India

Correspondence:
Dhanapal Venkatachalam
Department of Pharmacognosy, Sanjo College of Pharmaceutical Studies, Velappara, Palakkad, Kerala – 678 702, India
Email: vddpaul[at]gmail.com

Sedative activity of ethanolic and aqueous extracts of *Euphorbia hirta*

Dhanapal Venkatachalam, Samuel Thavamani B, Sampath Kumar

ABSTRACT

Insomnia is persistent difficulty in falling asleep that affects regular day time activities. It can induce significant psychological and physical disorder. Insomnia is treated pharmacologically and non-pharmacologically or by a combination of both. Relaxation, sleep restriction, stimulus control and sleep hygiene are known behavioural therapies for insomnia. Modern studies have shown that herbal drugs exert good sedative and hypnotic effect on the central nervous system. One such medicinal plants is *Euphorbia hirta*.. *E. hirta* belongs to the plant family *Euphorbiaceae* and genus Euphorbia. The leaf of *Euphorbia hirta* have several therapeutic applications in folk medicine in curing or managing wide range of diseases including insomnia. In the present study ethanol and aqueous extract of leaf *Euphorbia ssssshirta* was evaluated for sedative activity using phenobarbiton–induced sleep model in rat. Aqueous and ethanolic extracts (100mg/kg and 200 mg/kg) produced significant onset of sleep and duration of sleep ($p<0.01$). These results suggest that the fractions of aqueous and ethanolic extracts obtained from the leaf of *Euphorbia hirta* possess sedative activity.

Keywords: Insomnia, Phenoborbitone, *Euphorbia hirta*, sedative.

INTRODUCTION

Insomnia is the inability to fall asleep. It is a prevalent and potentially serious condition that affects the well-being of individuals. There is enough evidence that insomnia is under-recognized, under diagnosed and under-treated. Insomnia can be triggered by psychological (such as stress, anxiety and depression), environmental (excess cold, heat, etc), dietary, medical (such as cough, chronic pain, apnea, circadian rhythm disorders, neural diseases, etc) and drug related causes [1]. Insomnia is cured either pharmacologically or non-pharmacologically otherwise a combination of both [2]. Relaxation, sleep restriction, stimulus control and sleep hygiene are known behavioural therapies for insomnia [3]. People who suffer from insomnia take prescription drugs such as benzodiazepines, Zolpidem, Zopiclone and zaleplon to sleep [4]. These drugs help to calm the nerves, reduce anxiety and decrease awareness of one's surroundings. Drugs containing H1 antagonist diphenyl hydramine are also used for the treatment of occasional insomnia [5]. These drugs can easily lead to dependency and addiction. Apart from these negative factors, there could also be side effects such as drowsiness, dizziness, depression, nausea, etc. In order to eliminate these negative factors and the expected side effects researchers have resorted to nature for alternative ways of alleviating insomnia. The occurrence of natural products with medicinal properties has led to the widespread use of herbal remedies across the world. This is as a result of the development of several drugs and chemotherapeutics from medicinal plants [6]. According to clinical questionnaire, around 44% patients treated insomnia with the long-term use of benzodiazepines drugs. But certain drugs in this class have limited benefits which shorten slow wave sleep (SWS) and rapid eye-movement sleep (REM sleep) resulting in producing residual sedative effects, such as impaired cognitive function, memory and general daytime performance [7]. Recent studies have shown that herbal drugs have very good sedative and hypnotic effect [8].

Medicinal plant like Euphorbia *hirta* also has such an activity. *E. hirta* belongs to the plant family *Euphorbiaceae* and genus Euphorbia. It is a slender-stemmed, annual hairy plant with many branches from the base to top, spreading up to 40 cm in height, reddish or purplish in colour. Leaves are opposite, elliptic - oblong to oblong- lanceolate, acute or subacute, dark green above, pale beneath, 1-2.5 cm long, blotched with purple in the middle, and toothed at the edge. The fruits are yellow, three-celled, hairy, keeled capsules, 1-2 mm in diameter, containing three brown, four-sided, angular, wrinkled seeds [9-12].

The present study describes the screening of the sedative activity of ethanolic and aqueous extracts of the leaves of *Euphorbia hirta*. in albino rat.

MATERIALS AND METHODS

Plant material

The leaves of *Euphorbia hirta* was collected from Palakkad, Kerala, India and it was authenticated by a taxonomist. The plant material was made free from soil and other adulterants and vegetative debris. The dried plant material was grinded to coarse powder with the help of a special herbal grinder and passed through 60 mesh sieve to get the powder of desired coarseness. Powdered material was preserved in an air tight container.

Extraction of Plant material

For preliminary phytochemical analysis, the extract was prepared by weighing 500 grams of the dried powdered leaves and was subjected to hot successive continuous extraction using Soxhlet apparatus with different solvents as per polarity, petroleum ether, benzene, chloroform, ethanol and finally with aqueous. The extracts were filtered in each step using Whatman filter paper. The filtrate was concentrated using a rotary evaporator at low temperature (40-45ºC) and pressure. The presence or absence of the primary and secondary phytoconstituents was detected by usual prescribed method [13].

Chemicals and Drugs

Phenobarbitone and Tween 80 were purchased from Sigma Co. (Sigma St. Louis, MO). Absolute ethanol was of analytical grade and was purchased from Merck (Germany). The other reagents were of analytical grade.

Animals

Swiss albino rats weighing 90-170gms and maintained in the Animal house Facility of the Department of Pharmacology, Sanjo College of Pharmaceutical Studies, were used in these experiments. The animals were maintained on standard small animal feeds (Excel feed, Ilorin) and water *ad libitum*. This research was carried out in accordance with the rules governing the use of laboratory animals, as accepted internationally. The experiment was conducted between the hours 09.00 h and 16.00 h. The experimental groups consisted of six animals. They were maintained at constant room temperature (22° ± 1 °C) and subjected to12 h light/dark cycle with free access to food and water.

Experimental procedure

Acute oral toxicity study

Acute oral toxicity was conducted as per OECD guidelines (Organisation of Economic Cooperation and Development) 423 (Acute toxic class method). The acute toxic class method is a step wise procedure of three animal of a single sex per step. Depending on the mortality and / or moribidity status of animals, on an average, 2-4 steps may be necessary to allow judgment on the acute toxicity of the test substance. This procedure results in the use of a minimal number of animals while allowing for acceptable data based on scientific conclusion. The method uses defined doses, (5, 50, 300, 2000 mg/kg body weight) and the results allow a substance to be ranked and classified according to the globally harmonized system (GHS) for the classification of chemicals which causes acute toxicity. The method previously described by Lorke [14] was adopted.

Phenobarbitone – induced sleeping time test in rats

Albino rats of either sex weighing 90-170 gms were divided into five groups of five animals in each group for the study. The first group served as control and was treated with normal saline through intra peritoneal route. 30 min after treatment with normal saline or the fractions, all the rats were treated with phenobarbitone at a dose of 5mg/kg. The onset and duration of sleep was recorded for each rat. The loss of righting reflex was regarded as the onset of sleep while the time difference between the disappearing and the recovery of righting reflex was taken as the duration of sleep (sleeping time) [15].

Group I (n=6) – Control, received normal saline, i.p
Group II (n=6) – EEEH 100 mg/kg, i.p
Group III (n=6) – EEEH 200 mg/kg, i.p
Group IV (n=6) – AEEH 100 mg/kg, i.p
Group V (n=6) – AEEH 200 mg/kg, i.p

Statistical analysis

The results were statistically analyzed by using One way ANOVA followed by Dunnet's test. The results with **p <0.01 were considered as significant. The data are expressed as mean ± SD.

RESULTS

Acute toxicity

Acute toxicity test of the extract produced no death or signs of toxicity after 24 hours even at the dose of 2000 mg/kg which shows that the extract was well tolerated.

Phenobarbitone induced sleep in rat:

Aqueous and ethanolic extracts produced a significant ($p<0.01$) on dose dependant reduction in the onset of sleep and duration of sleep. Aqueous extract of 100mg/kg and 200mg/kg are highly significant in the onset of sleep when compared to ethanolic extracts and control. The ethanolic extract of 200mg/kg is more significant in duration of sleep when compared to aqueous extracts and control. (Table.1, Figure.1)

Table 1: Effects of fractions obtained from *Euphorbia hirta* on phenobarbitone - induced sleeping

Group no.	Drug treatment	Dose Mg/kg	Mean Onset of sleep (in seconds)	Mean duration of sleep (in seconds)
1	Control	Nacl 5ml/kg	17.2±0.847	21±1.1024
2	EEEH	100	12.8±0.799***	18±1.118*
3	EEEH	200	6.8±0.582***	14±1.341***
4	AEEH	100	10±0.707***	17±1.182**
5	AEEH	200	5.2±0.509***	15±1.414***

One way ANOVA followed by Dunnet's test. Values are mean ± S.E.M. n=5, in each group **p <0.01 is significant.
AEEH – Aqueous extract of *Euphorbia hirta*
EEEH - Ethanolic extracts of *Euphorbia hirta*

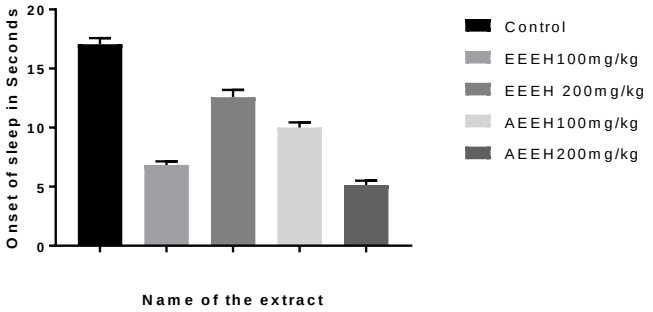

Figure 1: Sedative activity of Ethanol and Aqueous extract of leaf of *Euphorbia hirta* (Onset of sleep in seconds)

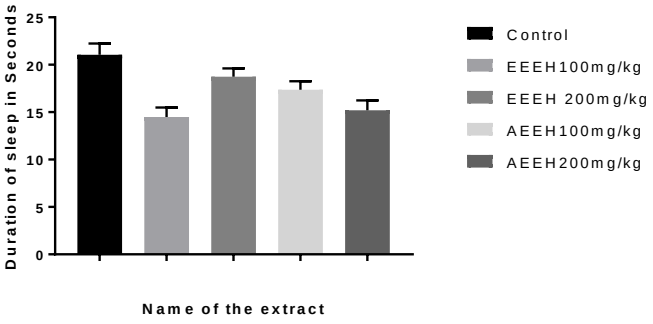

Figure 2: Sedative activity of Ethanol and Aqueous extract of leaf of *Euphorbia hirta* (Duration of sleep in seconds)

Sedative activity of Ethanol and Aqueous Extracts

The data presented in this study showed that the Aqueous extracts produced a dose dependent reduction in the onset of sleep which is highly significant when compared with the ethanolic extracts and control. Reduction in onset of sleep in aqueous extracts of *Euphorbia hirta* in 100mg/kg and 200mg/kg are 10 seconds and 5.2 seconds respectively when compared with ethanolic extracts and control as ethanolic extract shows 12.2 seconds in 100 mg/kg and 6.8 seconds in 200 mg/kg, which is significant in p<0.01 value and control shows 17.2 seconds. Ethanolic extracts of *Euphorbia hirta* at 200mg/kg shows more significance in duration of sleep when compared to aqueous extract and control. Duration of sleep of ethanolic extract 200mg/kg is 14 seconds and as ethanolic extract 100mg/kg shows 18 seconds and aqueous extracts 100mg/kg shows 17 seconds and 200mg/kg shows 15 seconds and control shows 21 seconds.

DISCUSSION

These results indicate that there is a significant correlation between the onset of sleep and the duration of sleep. This may be due to the similar chemical compositions of the crude extract and their timing to bind with GABA. It is generally believed that locomotors activity results from brain activation, which is manifested as an excitation of central neurons involving different neurochemical mechanism and an increase in cerebral metabolism. It is possible that the sedative activity of aqueous and ethanolic extract of *Euphorbia hirta* is mediated by GABAergic pathway, since GABAergic transmission can produce profound sedation in mice [16]. The inhibitory action of GABA consists in the opening of chloride channels to allow hyperpolarizing the membrane, leading to CNS depression and resulting in sedative and hypnosis activity. Glutamate and GABA are quantitatively the most important excitatory and inhibitory neurotransmitters, respectively, in the mammalian brain [17]. Thus, receptors for these two neurotransmitters are regarded as important targets for psychotropic drugs. In the test of thiopental-induced sleep in mice, the potentiated effect of lavender extract in mice was represented. It not only prolonged the sleeping time but also decreased the latency of falling asleep and increased the rate of sleep onset. *Euphorbia* extract has produced hypnosis at high doses that is, 200 mg/kg, since the effect of phenobarbitone on the CNS involves the activation of the inhibition GABAergic system [18, 19]. This finding suggests that some constituents in *Euphorbia* extract produce facilitation of this inhibitory system. Further chemical and pharmacological analysis of the extracts will be conducted to isolate and characterize the active principles responsible for the sedative and hypnotic effect. In conclusion, p.o. administration of aqueous and ethanolic extract of *Euphorbia* induces similar sedative effects, supporting its use in folk medicine. Given that the LD_{50} value for these extracts was beyond 5000 mg/kg for oral administration, as determined by Litchfield and Wilcoxon [20], the results suggest a remote risk of acute toxicity and good tolerance of these extracts in traditional medicine. To sum up, this work represents that the aqueous and ethanolic extracts have obvious sedative and hypnotic activity and these data provide pharmacological basis for its therapeutic efficacy on insomnia.

Research on herbs with sedative or antidepressant actions such as *Hypericum perforatum* (St. John's Wort) has recently centered on the BDZ receptor complex, but in general, herbal extracts have shown to have multiple pharmacodynamic and pharmacokinetic actions across a range of neurotransmitters and receptors [21]. Attempts to characterize sedative herb action as single active constituent effects paralleling orthodox drug action at single receptors have now been recognized as fruitless by most researchers. Further work has to be carried out to purify and isolate the sedative compound in order to use without much side effects.

CONCLUSSION

In conclusion, the present findings in our study indicate that *Euphorbia hirta* possesses strong sedative and hypnotic activities.

The effect is rapid, long-lasting, and statistically significant at all the experimental doses tested. However, further studies are needed to isolate bioactive compound(s) and elucidate the precise molecular mechanisms responsible for the pharmacological activities of the plant.

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