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Evaluation of Anticonvulsant Activity of Ethanolic & Aqueous Extract of *Hemidesmus indicus* L. Stem & Leaves and *Lantana camara* L. Stem & Flowers on Experimental Animals

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ABSTRACT: Objective: The aim of present study was to investigate anticonvulsant activity of ethanolic & aqueous extract of stem & leaves of *Hemidesmus indicus* and ethanolic & aqueous extract of stem & flowers of *Lantana camara* in wistar rats. Anticonvulsant activity was studied against maximal electroshock seizure (MES) induced convulsions in rats. The extracts suppressed hind limb tonic extensions (HLTE) induced by MES induced seizures. Study includes ethanolic & aqueous extract of stem & leaves of *Hemidesmus indicus* (200 and 400 mg/kg, p.o.) and ethanolic & aqueous extract of stem & flowers of *Lantana camara* (200 and 400 mg/kg, p.o.). The latency of tonic convulsions and the number of animals protected from tonic convulsions were noted. The effects were compared to those of Phenobarbitone (30 mg/kg, *i.p*). The preliminary phytochemical analysis identified alkaloids, flavonoids, saponins and large amounts of cardiac glycosides, triterpenoids, phenolic compounds and tannins in extracts. The extracts of *H. indicus* & *L. camara* significantly reduced the duration of seizures induced by maximal electroshock (MES). The ethanolic extract & aqueous extract of *H. indicus* in doses of 200 and 400 mg/kg conferred protection in Wistar rats. The same extracts with same doses of stem & flowers of *L. camara* also protected animals from MES induced tonic-seizures. More than 75% seizures were protected by all extracts comparatively to standard Phenobarbitone.
The data suggest that the extracts of both plants produces its anticonvulsant effects via non-specific mechanisms since it reduced the duration of seizures produced by maximal electroshock.It has been showed that the aqueous extracts have better anticonvulsant effect than ethanolic extracts in both plants suggesting their possible depressant action in the central nervoussystem.
Nonetheless, the ethanolic & aqueous extracts of stem & leaves of *H. indicus* and similarly ethanolic & aqueous extracts of stem & flowers of *L. camara* has been beneficial in the management and treatment of anxiety and seizures.

Keywords: *Hemidesmus indicus, Lantana camara*, anti-convulsant activity, maximal electro shock, MES, GABA, hind limb tonic extension seizure (HLTE), *H. indicus, L. camara.*

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INTRODUCTION

Traditional systems of medicine becoming popular in developing countries. Nearly 80% population uses traditional medicines or herbal remedies for primary health care (Akerele, 1988, Karunakar *et al.,* 2009). Medicinal plants are vital source of new chemical substances that have potential therapeutic effects (Farnsworth, 1989). So many medicinal plants have been used for treating epilepsy in different systems of traditional medicines.

Lots of plants have showed activity when tested in modern bioassays as anticonvulsant and such plants are yet to be scientifically investigated (Raza *et al.,* 1999, K. Hegde *et al.,* 2009).

The past decade has been observed notably change in opinion for ethnopharmacological therapeutic applications of such plants (Nayak and Pereira 2006). The presence of life preserving chemical constituents in plants has develops desire in scientists or researchers to examine such plants with a view to determine potential antiepileptic properties.

Epilepsy is a neurological disorder, in which a person has two or more recurrentun provoked seizures. Seizure is a paroxysmal event, due to abnormal, excessive and hypersynchronous discharge from an aggregate of central nervous system neurons (Rao and Subbalakshmi 2010). This brain disorder is characterized by unpredictable and periodic occurrence of a transient alteration of behavior due to the disordered, synchronous and rhythmic firing of populations of brain neurons (Vipin and Sarvesh, 2011). It affects a wide range of people throughout the world. (Kaushik *et al.*, 2009). After stroke epilepsy is the second most common disorder of the CNS. Up to 5% of world's population develops epilepsy in their whole lifetime (Sander and Shorvon 1996). The current therapy of epilepsy with modern antiepileptic drugs is associated with side effects, dose-related and chronic toxicity, as well as teratogenic effects, and approximately 30% of the patients continue to have seizures with current antiepileptic drugs therapy (Smith and Bleck 1991, Mattson, 1995, SamrJn *et al.*, 1997).

Herbs may have antiepileptic effects in several ways. Some herbs may increase brain levels and / or the binding of nerve transmitter gamma aminobutyric acid (GABA), which quiets nerve activity (Visweswari *et al.*, 2010, Mansoor *et al.*, 2010).

Concurrently, phytochemicals identified from traditional medicinal plants are presenting an exciting opportunity for the development of new types of therapeutics. This has accelerated the global effort to harness and harvest those medicinal plants that bear substantial number of potential phytochemicals showing multiple beneficial effects in convulsion (Jiban *et al.*, 2010).

MATERIAL AND METHOD

A. Collection & Preparation of Plant Parts

H. indicus stem & leaves were procured from Elixer distributors, Kanpur (U.P.) although *L. camara* stem & flowers obtained locally from Indore. Identification of both plant samples were done by Botanist Dr. S. N. Dwivedi, Professor and Head, Department of Botany, Janta PG College, APS University, Rewa, M.P. (Voucher No. J/BOT/H-238) for *H. indicus* and (Voucher No.J/BOT/L-251) for *L. camara.* All parts of the plants were sun dried for several days. Then plant materials were oven dried for 24 hours at considerably low temperature for better grinding. The dried parts were ground in coarse powder using high capacity grinding machine.

B. Washing and Drying of Plant Parts

At first all parts were thoroughly washed with tap water to remove dust, soil, bird's droppings etc. within them. Then dried under sunlight for several days. Also dried in hot air oven at 50°C for 2 hours.

C. Grinding and Storage of Dried Samples

The dried parts were ground to coarse powder with the help of home blender machine. This process breaks the plant parts into smaller pieces thus exposing internal tissues and cells to solvents and facilitating their easy penetration into the cells to extract the constituents. Then the powdered sample was kept in clean closed glass containers till extraction. During grinding of sample, the grinder was thoroughly cleaned to avoid contamination with any remnant of previously ground material or other extraneous matters deposited on the grinder.

D. Extraction of the Dried Powdered Sample

The fine powder of all parts of both plants were dissolved separately in ethanol and thoroughly shaken to dissolve the powder into the solvent. Then it was kept in a closely covered glass jar for 7 days and shaken several times during the process for more interaction between the powdered particles and the solvents. This process is termed as maceration. The cover of the jar was closed properly to resist the entrance of air in the jar.

E. Filtration of the extracts

After the extraction process the plant extracts was filtered with sterilized cotton filter and filter paper. The filtrate was collected in a beaker. The filtration process was repeated three times by using cotton and filter paper. Then the filtrate was taken into a volumetric flask and covered with aluminum foil paper was prepared for rotary evaporation.

F. Evaporation and Condensation of extracts

The extracts were transferred to the round bottle flask of rotary evaporator. Then excess amount of solvents in the extracts were removed by rotary evaporator, with reduced pressure which was done by using a vacuum pump. The temperature of the rotary evaporator was set 50ºC. It run for 1 hours 10 minutes and the RPM was set 80 for evaporation process. After evaporation extracts were transferred in a beaker. Rest of the extracts were removed from the round bottle flask. Then extracts have been kept in hot air oven to get more dried extract. All beakers were covered with aluminum foil. Then extracts were collected and stored in a cool (4˚C) dry place for further experimental model.

G. Experimental Protocols

All experimental protocols were reviewed and accepted by the Institutional Animal Ethical Committee (IAEC) prior to the initiation of the experiment. Protocol approval reference number (PBRI/IAEC/PN-17047a)

Wistar adult rats, weighing between 120-150 gram was taken for pharmacological activity and females of the same strain for LD_{50} calculation.

The rats werekept in animal house at a standard environmental condition (temperature-22 ± 1°C relative humidity-55 ± 5% and 12h light/12 h dark cycle). Animals were fed *ad libitum* with standard food and water except when fasting was required in the course of study. The animals were acquired from the local market. Animals were kept in standard environmental conditions and had free access to feed and water. All the animals were acclimatized to laboratory condition for a week before commencement of experiment.

H. Method for Identification of Animals

Each group consists of 06 Wistar rats. It is quite necessary to identify individual animal of groups during treatment. The animals were individualized by marking lines on tail.

Group	Category	Drug administered *H. indicus*	Drug administered *L. camara*
1.	Normal Control	Normal saline or no any drug	Normal saline or no any drug
2.	Positive control	standard drug as per activity	standard drug as per activity
3.	Test 1 200 mg/kg	5% W/V*H. indicus stem extract (ethanol)*	5% W/V *L. camara stem extract (ethanol)*
4.	Test 2 400 mg/kg	10% W/V*H. indicus stem extract (ethanol)*	10% W/V *L. camara stem extract (ethanol)*
5.	Test 3 200 mg/kg	5% W/V*H. indicus stem extract (Aqueous)*	5% W/V *L. camara stem extract (Aqueous)*
6.	Test 4 400 mg/kg	10% W/V*H. indicus stem extract (Aqueous)*	10% W/V *L. camara stem extract (Aqueous)*
7.	Test 5 200 mg/kg	5% W/V*H. indicus leaves extract (ethanol)*	5% W/V *L. camaraflower extract (ethanol)*
8.	Test 6 400 mg/kg	10% W/V*H. indicus leaves extract (ethanol)*	10% W/V *L. camaraflower extract (ethanol)*
9.	Test 7 200 mg/kg	5% W/V*H. indicus leaves extract (Aqueous)*	5% W/V *L. camaraflower extract (Aqueous)*
10.	Test 8 400 mg/kg	10% W/V*H. indicus leaves extract (Aqueous)*	10% W/V *L. camaraflower extract (Aqueous)*

I. Pharmacological Evaluations

The activity of ethanolic & aqueous extract from *H. indicus* stem & leaves and ethanolic & aqueous extract from *L. camara* stem & flowers on CNS was studied, using maximal electroshock seizure (MES). We analyzed the effect of different doses of the ethanolic and aqueous extracts (200mg/kg and 400 mg/kg, *p.o.*) of both plants for their anticonvulsant effect.

J. Chemical Agents used in activity

Normal saline (1 ml per rat) as negative control.

Standard drug: Phenobarbitone (30mg/kg, *i.p*) *as positive control.*

Doses in activity: Ethanolic & Aqueous extracts of *H. indicus* stem & leaves at a dose of 200 mg/kg & 400mg/kg were administered orally.

Ethanolic & Aqueous extracts of *L. camara* stem & flowers at a dose of 200 mg/kg & 400mg/kg were administered orally. Distilled water has been used as a vehicle extracts for preparing different doses.

K. Acute Toxicity Study

Acute oral toxicity studies have been conducted separately followed by using OECD guideline 423. The method used defined doses of 5, 50, 300, 2000 mg/kg *p.o.* body weight. Results were allowed substance rank and classify according to the Globally Harmonized System (GHS) for classification of chemicals which causes acute toxicity. From LD_{50} determination, $1/10^{th}$ of the dose was focused as the medial for pharmacological screening. Since all animals were alive; no mortality, no toxicity and no significant changes in the body weight between the control and treated group were observed at a dose of 2000 mg for duration of 72 hours. This finding probably suggests that the ethanol and aqueous extract are relatively safe or non-toxic in rats at the doses used for this study (OECD, 2000).

Maximal Electrical Shock (MES) - Induced seizures (Hegde et al., 2009). Malathi and Maharani, 2011). Adult Wistar male rats were randomly grouped in to respective designed groups (n=6). All groups received dose per orally (p.o). Group I served as vehicle control group. Group II as Standard group received Phenobarbitone (30mg/kg, i.p) prior to the induction of convulsion. Rest groups served as test groups (200 and 400 mg/kg, p.o., 60 min). To induce seizure current was given after 2 hours of drug administrations. Seizures were induced by electro convulsiometer delivering electrical shock of 150mA of AC current for 0.2ms through ear electrodes attached to the pinna. The phases of convulsion namely latent phase, tonic flexion of fore limbs, tonic extension of hind limbs & post ictal depression were observed in all groups. Decrease in the duration of hind limb extension & post ictal depression was considered as protective response & considered for statistical analysis. Percentage inhibition of tonic extension was calculated by considering the duration of tonic extension in control group as 100%. The number of animals protected from hind limb tonic extension seizure (HLTE) and the time spent in this position were determined for each dose group. All the experimental groups were compared with the control treated with vehicle.

RESULTS

A. Phytochemical screening

Phytochemical screening of all extracts showed that the crude extracts contained small quantities of alkaloids, flavonoids, saponins and large amounts of cardiac glycosides, triterpenoids, phenolic compounds and tannins (Table 1 & 2).

B. Statistical Analysis

All the results obtained from activities, are described over here, were analyzed statistically by using Student's t test and $p < 0.05$ were considered significant (Kulkarni, 2003). The results are summarized in the tables given below (Table 3 & 4).

Table 1: Phytochemical Screenings of *H. Indicus.*

S. No.	Chemical Constituents	Ethanolic (Stem)	Aqueous (Stem)	Ethanolic (Leaves)	Aqueous (Leaves)
1.	Alkaloids	+	+	+	+
2.	Carbohydrates	+	+	+	+
3.	Glycosides	+	+	+	+
4.	Steroids	+	+	+	+
5.	Flavonoids	+	+	+	+
6.	Saponins	-	-	-	-
7.	Fixed oils and fats	-	-	-	-
8.	Tannins	+	+	+	+
9.	Proteins and amino acids	+	+	-	-
10.	Terpenoids	+	+	-	-

Table 2: Phytochemical Screenings of *L. camara* L.

S. No.	Chemical Constituents	Ethanolic (Stem)	Aqueous (Stem)	Ethanolic (Flowers)	Aqueous (Flowers)
1.	Alkaloids	-	-	-	-
2.	Carbohydrates	+	+	+	+
3.	Glycosides	-	+	-	+
4.	Steroids	+	-	+	-
5.	Flavonoids	+	+	+	+
6.	Saponins	+	-	+	-
7.	Fixed oils and fats	+	-	+	-
8.	Tannins	+	-	+	-
9.	Proteins and amino acids	-	-	-	-
10.	Terpenoids	+	-	+	-

Table 3: Anticonvulsant effect of *H. indicus* on rats.

Group	Treatment (mg/kg), *p.o.*	Duration of tonic extensor (sec.)	Duration of post ictal depression (sec.)	% Inhibition of duration Tonic Extensor Phase
		2 HOURS	2 HOURS	2 HOURS
Normo Control	Saline	25.50 ± 0.50	250.50 ± 6.10	--
Positive Control	Phenobarbitone (30 mg/kg) *i.p.*	0.00 ± 0.00	105.20 ± 2.40	100.00
Test 1 200 mg/kg	5% W/VStem extract *(ethanol)*	8.65 ± 0.45	125.25 ± 2.10	66.07
Test 2 400 mg/kg	10% W/VStem extract *(ethanol)*	3.30 ± 0.45	110.10 ± 1.25	87.05
Test 3 200 mg/kg	5% W/VStem extract *(Aqueous)*	7.45 ± 0.35	118.15 ± 1.07	70.78
Test 4 400 mg/kg	10% W/VStem extract *(Aqueous)*	2.80 ± 0.40	105.10 ± 1.05	89.01
Test 5 200 mg/kg	5% W/VLeaves extract *(ethanol)*	9.38 ± 0.41	120.15 ± 1.30	63.21
Test 6 400 mg/kg	10% W/VLeaves extract *(ethanol)*	4.55 ± 0.35	140.15 ± 1.09	82.15
Test 7 200 mg/kg	5% W/VLeaves extract *(Aqueous)*	6.30 ± 0.79	111.10 ± 1.25	75.29
Test 8 400 mg/kg	10% W/V Leaves extract *(Aqueous)*	3.00 ± 0.10	121.10 ± 1.10	88.23

Table 4: Anticonvulsant effect of *L. camara* on rats.

Group	Treatment (mg/kg), *p.o.*	Duration of tonic extensor (sec.)	Duration of post ictal depression (sec.)	% Inhibition of duration Tonic Extensor Phase
		2 HOURS	2 HOURS	2 HOURS
Normo Control	Saline	25.50 ± 0.50	250.50 ± 6.10	--
Positive Control	Phenobarbitone (30 mg/kg) *i.p.*	0.00 ± 0.00	105.20 ± 2.40	100.00
Test 1 200 mg/kg	5% W/V Stem extract *(ethanol)*	9.54 ± 0.45	127.25 ± 2.10	62.58
Test 2 400 mg/kg	10% W/V Stem extract *(ethanol)*	4.40 ± 0.45	113.10 ± 1.25	83.00
Test 3 200 mg/kg	5% W/V Stem extract *(Aqueous)*	8.55 ± 0.35	120.15 ± 1.07	66.47
Test 4 400 mg/kg	10% W/V Stem extract *(Aqueous)*	3.30 ± 0.40	107.10 ± 1.05	87.00
Test 5 200 mg/kg	5% W/V Flower extract *(ethanol)*	10.28 ± 0.41	123.15 ± 1.30	60.00
Test 6 400 mg/kg	10% W/V Flower extract *(ethanol)*	5.55 ± 0.35	144.15 ± 1.09	78.23
Test 7 200 mg/kg	5% W/V Flower extract *(Aqueous)*	7.30 ± 0.79	114.10 ± 1.25	71.37
Test 8 400 mg/kg	10% W/V Flower extract *(Aqueous)*	4.00 ± 0.10	124.10 ± 1.10	84.31

DISCUSSION

The results of present study indicate that extracts of both plants possess anticonvulsant activity in rats, against seizures induced by MES in a dose dependent manner. Since inhibition of the MES test predicts activity against generalized tonic-clonic and cortical focal seizures (Kumaresan and Saravanan 2009). The study shows that the extracts of the plants protected some of the animals against seizures induced by maximal electroshock and also delayed the latency of the seizures.

In the present study maximal electroshock produced seizures in all the animals used. Antiepileptic drugs that block MES-induced tonic extension are known to act by blocking seizure spread (Karunakar *et al.,* 2009). Moreover, drugs that inhibit voltage-dependent Na+ channels, such as phenytoin can prevent MES-induced tonic extension (Rogawski and Porter 1990, MacDonald and Kelly 1995).

However, phenobarbitone is as effective against electrically-induced convulsion as it is against pentylenetetrazole - induced convulsions in mice and phenobarbitone is known to reduce the electrical activity of neurons within a chemically-induced epileptic focus in the cortex, while diazepam does not suppress the focal activity but prevents it from spreading (Levy *et al.,* 1995, Meldrum 1996).

Phenobarbitone (30 mg/kg) *i.p*is more potent in the prevention of MES-induced tonic seizures, so it has used as anticonvulsant drug for maximal electroshock-induced seizures (Krall *et al.,* 1978).

GABA appears to play an important role in the pathogenesis of several neuropsychiatric disorders. GABA is the major inhibitory neurotransmitter in the brain while glutamic acid is an excitatory neurotransmitter in the brain. The inhibition of GABA neurotransmitter and the enhancement of the action of glutamic acid have been shown to be the underlying factors in epilepsy (Westmoreland *et al.,* 1994, Rang *et al.,* 2005).

Furthermore, studies have proved that the agents which increase the brain GABA content and administration of centrally active GABA mimetic agents have been used as effective therapeutic approach for treatment of anxiety and epilepsy. Many of the traditional agents used to treat psychiatric disorders are known to act, at least in part, by enhancing GABA activity, while some of the newer agents may exert their therapeutic effects exclusively through GABA ergic actions.

In our present investigation, treatment with *H. indicus* & *L. camara* extracts at dose levels of 200 and 400 mg/kg showed significant increase in whole brain levels of GABA when compared to control. Flavonoids are known as positive modulators of $GABA_A$ receptors at low dose. Hence, presence of flavonoids in stem & leaves of *H. indicus* and stem & flowers of *L. camara* could be responsible partly for its anxiolytic and antiepileptic action through GABA modulation.

Nonetheless, at dose level of 200 and 400 mg/kg of *H. indicus* & *L. camara* extracts showed significant reduction in the duration of hind limb extensor phase in case of maximal electroshock induced convulsions.

CONCLUSION

The results obtained from the study suggested that stem & leaves extracts of *H. indicus* and stem & flowers extracts of *L. camara* have excellent anti-convulsant property which are possibly mediated partly via facilitation of GABA transmission and the results verify its traditional use in epilepsy.

It has been minutely observed that aqueous extracts of both plant parts exhibit better anticonvulsant property than that of ethanolic extracts of both plants.

Secondly it has been found that ethanolic extract & aqueous extract of *H.indicus* stem have 87.05% and 89.01% respectively and ethanolic extract & aqueous extract of same *H. indicus* leaves have 82.15% and 88.23% respectively.

Thirdly observed that ethanolic extract & aqueous extract of *L. camara* stem have 83.00% and 87.00% respectively and ethanolic extract & aqueous extract of same *L. camara* flowers have 78.00% and 84.31% respectively as compare to the standard drug. In totality finding clearly shows that aqueous extracts are better property than ethanolic extracts.

These results suggested that the ethanolic & aqueous extracts of stem & leaves of *H. indicus* and similarly ethanolic & aqueous extracts of stem & flowers of *L. camara* will be beneficial in the management of anxiety and seizures. Furthermore, there is still a way for isolation, characterization and identification of particular active compounds in these plant extracts responsible for the anti-convulsant activity. These results might be a revolutionary step for either homeopathy or ayurvedic field globally.

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CONFLICT OF INTERSEST: NIL

SOURCE OF SUPPORT: NIL

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