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Research Article

Anticonvulsant profile of nardostachys jatamansi roots in albino rats

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ABSTRACT

Background: Epilepsy is a common neurological disorder. Despite the massive scale of the problem and much research, epilepsy remains poorly understood. Most of the currently used antiepileptic drugs have some neurotoxic effects, cognitive deficits and teratogenic effects, which decrease their clinical utility and up to 30% of patients are still refractory to treatment. The present study is undertaken to evaluate the anticonvulsant activity of ethanolic extract of nardostachys jatamansi root in albino rats.
Methods: Albino rats (150-200 gms) of male sex were randomly selected, from central animal facility. They were divided into 5groups(per model) of 6 rats each, control group-propylene glycol 0.5 ml, standard group-sodium valproate (300 mg/kg), dose 1-ethanolic extract of nardostachys jatamansi roots (100 mg/kg), dose 2-ethanolic extract of nardostachys jatamansi roots (200 mg/kg) and dose 3-ethanolic extract of nardostachys jatamansi roots (400 mg/kg). The anti-convulsant activity was screened using maximal electroshock seizure model and pentylenetetrazole model. Results were analysed by ANOVA followed by post hoc Fisher's LSD test.
Results: The ethanolic extract of nardostachys jatamansi roots at the dose of 400 mg/kg has shown significant anticonvulsant activity in maximal electroshock seizure (MES) model. Whereas, in pentylenetetrazole induced seizure model, the ethanolic extract of nardostachys jatamansi roots has shown significant anticonvulsant activity at the dose of 200 mg/kg and 400 mg/kg body weight.
Conclusions: The anticonvulsant activity of ethanolic extract of nardostachys jatamansi roots was less when compared to Sodium Valproate in Maximal Electro Shock model. Whereas, in Pentylenetetrazole induced seizure model, anticonvulsant activity of ethanolic extract of nardostachys jatamansi roots was comparable to sodium valproate.

Keywords: Epilepsy, MES model, Nardostachys jatamansi, Pentylenetetrazole, Sodium valproate.

INTRODUCTION

Epilepsy is one of the most frequent neurodegenerative diseases.[1] Epilepsy is a condition in which a person has recurrent seizures. Seizure can defined as an abnormal, disorderly discharging of nerve cells of brain; resulting in a temporary disturbance of motor, sensory, or mental function.[2] Epilepsy is a major neurological disorder and up to 5% of the world population develops epilepsy in their lifetime.[3] Annual incidence of epilepsy in India is approximately 2.7/100,000 per year.[4] Epilepsy is not curable, but can be controlled with anticonvulsant which prevent the seizures or lessen their intensity. 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.[5,6]

There is still a need for an ideal antiepileptic agent with properties like broad spectrum activity, rapid onset of action, least side effects, good oral bioavailability and low costs. The discovery of novel antiepileptic drugs relies upon the preclinical employment of animal models to establish efficacy and safety prior to the introduction

of the antiepileptic drugs in human volunteers.[7] Over the last few years, researches have aimed at identifying and validating plant derived substances for the treatment of various diseases. Interestingly, it is estimated that more than 25% of modern medicines are directly or indirectly derived from plants.[8] Therefore there is growing interest in alternative approach for the treatment of seizures and the use of medicinal plants has gained popularity around the world. Hypericum perforatum, piper methysticum, actaea racemosa and erythrophleum ivorense are among plants that have been used to treat seizures.[9]

The advantages of indigenous medicinal treatment would include its complementary nature to the conventional treatment making latter safer, well tolerated and economical remedy for epilepsy. Nardostachys jatamansi DC (valerianaceae) is widely used in ayurvedic medicine. The essential oil obtained from the roots of jatamansi showed fungi toxic activity, antimicrobial, antifungal, hypotensive, antiarrhythmic and anticonvulsant activity.[10] The information regarding the studies on jatamansi root are fewer and the studies on ethanolic extract of root on different anti-convulsant models are sparse, hence the present study has attempted to fill in the lacunae of this invaluable drug. Hence the present study was done to compare the anti-epileptic activity of jatamansi in comparison with the standard drug sodium valproate in electrically and chemically induced epileptic animal models.

METHODS

This study was conducted at a medical college in South India. Adult healthy male wistar rats weighing 150-200 g bodyweight, obtained from the central animal house facility were group housed in polyacrylic cages with each cage containing not more than four rats. The animals were maintained under standard laboratory conditions with natural dark and light conditions (12:12 hours) and ambient room temperature. They were allowed free access to standard pellet feed and tap water ad libitum. All procedures of the study were reviewed and approved by the institutional animal ethics committee. The care of animals was taken as per the guidelines of the committee for the purpose of control and supervision of experiments on animals (CPCSEA).

Collection and authentication of plant material - The plant was obtained from Gadgil Vanoushadhi Sangrah, Belgaum, which was identified and authenticated by a botanist.

Preparation of ethanolic extract of nardostachys jatamansi- The dried roots of nardostachys jatamansi was coarsely powered. 50 grams of the powder was wrapped in a filter paper and put into a thimble with 500 ml of 95% ethanol in a round bottom flask and subjected to soxhlation for 6-8 hours. Dark brown solution of extract with alcohol was collected. Dark brown paste like extract was obtained after evaporation of alcohol.

Drugs and chemicals-pentylenetetrazol and propylene glycol were obtained from sigma chemicals, Mumbai, Maharashtra, India. Sodium valproate was obtained from local pharmacy.

Selection of the dose of toxicity

Acute oral toxicity study was carried out as per OECD-423 guidelines.[13] A group of six wistar rats of either sex selected by randomly and were used for acute toxicity study. The extracts were administered orally at the dose level of 5 mg/kg body weight by gastric intubation to overnight fasted animals and observed for 14 days. If mortality was observed in 2 out of 3 animals, then the dose administered was assigned as toxic dose, but if mortality was observed in one animal, then the same dose was repeated again to verify the toxic dose. If mortality was not observed, the procedure was repeated for further higher doses such as 50, 300 and 2000 mg/kg body weight.

Selection of dose of the extract

The ethanolic extract of nardostachys jatamansi (EENJ) root was found to be non-toxic up to the dose of 2000 mg/kg and did not cause any death, therefore it is considered as safe. The biological evaluation was carried out at100 mg/kg, 200 mg/kg and 400 mg/kg dose levels. A total of 60 rats were used, which were equally divided for MES induced seizure and PTZ induced seizure model. Each model comprised of 5 groups with 6 rats each (n=6). After over-night fasting, group I received 0.5 ml/100g of propylene glycol (control) and group II received sodium valproate 300 mg/kg (standard). Group III, group IV and group V received 100 mg/kg, 200 mg/kg and 400 mg/kg of ethanolic extract of nardostachys jatamansi root, respectively. The route of administration was intraperitoneal.

Maximal electro shock (MES) induced seizure model

On the day of experimentation, 60 minutes after administration of drug/vehicle, seizures were induced by delivering an electroshock (50 mA at 50 Hz for 0.2 sec) by means of an electro convulsiometer (techno India) through a pair of ear clip electrodes.[14] The animals were observed individually for 30 minutes from the time of electric shock applied for different phases of epileptic seizures. The various parameters recorded were tonic flexion of fore and hind limb, tonic extension of hind limb, clonus, stupor and post-ictal depression. The abolition of the hind limb tonic extension is taken as an index of anticonvulsant activity.

Pentylenetetrazole induced seizure model

Sixty minutes after administration of drug/vehicle, animals were challenged with a convulsive dose of pentylenetetrazole (80 mg/kg i.p) dissolved in distilled water.[14] The time taken for the onset of convulsion (seizure latency), duration of convulsion and the mortality were noted (James JEP, et. Abolition of seizure onset was taken as an index of anticonvulsant activity.

Statistical analysis

The summary statistics was done by measuring range, mean and standard deviation. The test of significance was done using two way repeated measures, analysis of variance (ANOVA) at appropriate places. Analysis of variance was do ne to compare more than two groups at a time. Following ANOVA, fisher's least significant difference (LSD) test was done to compare mean of one group with mean of another group. P-value: P is the probability rate at 0.05 level of significance for the corresponding degree of freedom (P< 0.05 is considered statistically significant).

RESULTS

The Effect of ethanolic extract of nardostachys jatamansi root on MES-induced seizures in wistar albino rats (Table 1).

Table 1: Effect of ethanolic extract of nardostachys jatamansi root on MES-induced seizures in wistar albino rats.

Group	Treatment	Tonic hind limb flexion	Tonic hind limb extension	Clonus	Stupor	Post-ictal depression
I	Control (propylene glycol i.p)	3.80±0.28	7.22±0.97	10.83±2.80	277.50±42.80	255.00±53.89
II	Standard (sodium valproate 300 mg/kg i.p)	8.60±1.09	0.00±0.00	12.60±0.87	286.33±47.62	303.00±25.84
III	EENJ (100 mg/kg i.p)	4.40±0.50	7.15±0.60	19.94±0.51	112.33±5.50	254.00±10.75
IV	EENJ(200 mg/kg i.p)	4.53±0.52	6.10±0.40	15.95±0.91	105.83±3.91	208.50±30.84
V	EENJ(400 mg/kg i.p)	5.02±1.10	3.67±0.62	11.50±0.36	92.83±3.80	114.16±9.13

Table 2: Effect of ethanolic extract of nardostachys jatamansi root on PTZ-induced seizure.

Group	Treatment	Seizure latency or onset (second)	Duration of myoclonic jerks (second)
I	Control (propylene glycol i.p)	222.17±16.23	797.67±49.04
II	Standard (sodium valproate 300 mg/kg i.p)	377.00±28.89	442.50±18.71
III	EENJ (100 mg/kg i.p)	239.00±27.14	773.17±69.70
IV	EENJ(200 mg/kg i.p)	334.67±20.70	524.00±56.05
V	EENJ(400 mg/kg i.p)	372.50±25.09	430.83±32.76

The tonic hind limb extension (THLE) phase was abolished in group II (standard group).When group I is compared with group III, the difference between mean of THLE is statistically not significant (t=0.051, p>0.1). When group I is compared with group IV, the difference between mean of THLE is statistically not significant (t=1.069, p>0.2). When group I is compared with group V, the difference between mean of THLE is statistically significant (t=3.03, p<0.02). This shows that only group V (400 mg/kg) is having a statistically significant reduction in mean duration of THLE when compared to control group.

The effect of ethanolic extract of nardostachys jatamansi root on PTZ-induced seizure (Table 2).

When group I was compared with group II, there was a statistically significant prolongation in mean duration of seizure latency (t=4.673, p<0.01). When group I was compared with group III, the prolongation in mean duration of seizure latency (t=4.673, p<0.01) was statistically not significant (t=0.53, p>0.6). When group I was compared with group IV, there was a statistically significant prolongation in mean duration of seizure latency (t=4.25, p<0.01). When group I was compared with group V, there was a statistically significant prolongation in mean duration of seizure latency (t=5.01, p<0.01).This shows that at doses of 200 mg/kg and 400 mg/kg of EENJ root, there were statistically significant prolongation in mean duration of seizure latency.

DISCUSSION

In the present study, the EENJ root at a dose of 400 mg/kg reduced the duration of tonic hind limb extension phase in MES induced seizure, which was statistically significant. On the other hand, when the convulsive challenge was made with PTZ, there was a statistically significant prolongation of seizure latency at doses of 200 mg/kg and 400 mg/kg. The findings are in contradiction

to previously published reports on the antiepileptic effect of this plant. A study anticonvulsant and neurotoxicity profile of nardostachys jatamansi in rats by Rao VS suggested that the ethanolic extract of nardostachys jatamansi root, to be effective only in MES induced seizure model whereas ineffective in PTZ induced seizure model.[15]

The present study indicated effectiveness in both MES induced and PTZ induced seizure model. However, the standard drug and assessment parameters were different in both these studies. Other studies have found EENJ root to inhibit electroshock convulsions, increase in the levels of central monoamines and inhibitory amino acids, including a change in the levels of serotonin, 5-hydroxyindole acetic acid, gamma-amino butyric acid, and taurine in rat brain.[16,17] MES-induced seizure is employed as a model for grand-mal epilepsy MES induced seizures can be prevented either by drugs that inhibit voltage dependant Na^+ channels such as phenytoin, valproate, felbamate and lamotrigine. Phenobarbitone antagonizes PTZ-induced seizure by enhancing GABA neurotransmission diazepam and phenobarbitone antagonizes PTZ-induced seizure by enhancing GABA neurotransmission.

Hence ethanolic extract of nardostachys jatamansi roots i.e. test compound may act in any of the following manner;

- Phenytoin like effect on voltage dependent sodium channels
- May block NMDA type excitatory amino acid receptors or increase synaptic norepinephrine levels.
- Can affect GABAergic neurotransmission, either by enhancing brain GABA levels or by altering the sensitivity of post synaptic GABA receptors
- By blocking T-type voltage dependent calcium channels.

By and large, the traditional system of medicine is slow-acting as compared to the modern synthetic drugs because they are administered as crude preparations. A previous study has clearly shown that nardostachys jatamansi has an influence on the excitatory and inhibitory neurotransmission, of special interest being the increase in the gamma amino butyric acid (GABA) levels.[17] Further study is required to confirm and isolate the active principle/principles that contributes to the anticonvulsant activity. The active principle/principles when isolated may prove to be a prospective broad spectrum anticonvulsant agent, either alone or in combination with already available anticonvulsant drugs. However, its long term effects have to be evaluated as convulsive disorders generally need prolonged therapy.

CONCLUSION

In conclusion, the result obtained from the present study suggests that the ethanolic extract of nardostachys jatamansi roots has anticonvulsant property which may be mediated by multiple mechanisms. The anticonvulsant activity of ethanolic extract of nardostachys jatamansi roots was less when compared to sodium valproate in maximal electro shock model. Whereas, in pentylenetetrazole induced seizure model, anticonvulsant activity of ethanolic extract of nardostachys jatamansi roots was comparable to sodium valproate.

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