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EVALUATION OF ANTICONVULSANT AND ANTIDEPRESSANT ACTIVITY OF EPIC-Q TAB: AN AYURVEDIC POLYHERBAL FORMULATION

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ABSTRACT
In Ayurveda classical texts administration of potent psycho-physical rejuvenator formulation comes under Rasayana chikitsa which frees one of diseases and improves quality of life. This study was designed to evaluate the anti-convulsant and antidepressant activity of polyherbal formulation Epic-Q in experimental animal models. The study was conducted by administering high dose (500 mg/kg) and low dose (100 mg/kg) of formulation. The animal models selected wereMaximum Electroshock-induced Seizuresand Isoniazid induced for anticonvulsant activity and forced swim and tail suspension test for antidepressant tests. The study entails that the Epic-Q at a high dose (500 mg/kg) have anticonvulsant activity and it shows a significant decrease in duration of extension phase in comparison with standard drug phenytoinin INH method, it delayed the latency of convulsions in rats in a dose-dependent manner but failed to protect the rats against mortality and it has potent antidepressant action and it shows moderately significant action. Whereas, the low dose (100 mg/kg) have a weak antidepressant action. From the observations of the present study, we found out that the polyherbal formulation Epic-Q has anticonvulsant and antidepressant activity.
Keywords: Epic-Q, Anticonvulsant, Anti-depressant, EPHF, Neurodegenerative disorders.

INTRODUCTION

Central Nervous System controls important aspects of body function and maintains homeostasis and the pathological condition associated with this leads to some of the severe condition such asepilepsy, depressive disorders, anxiety, Parkinson's disease, Alzheimer's disease, insomniawhich statistically increasing the mortality and morbidity ratio all around the globe[1]. Epilepsy is a brain disorder characterized by convulsive seizures or loss of consciousness or both. Epilepsy affects an estimated 7 million people in India, and 50 million worldwide. As per WHO the prevalence of epilepsy is 0.7 % in India, and approximately 80 % people with epilepsy live in developing countries[2]. Depression is a condition characterized by altered mood, where individual's become disruptive to function socially and complete the daily activities of life and there is a loss of interest in all usually pleasurable outlets such as food, sex, work, friends, hobbies or entertainment. An estimated 3-5 % of the world's population experiences depression[3]. Drug therapies for epilepsy and depression is often associated with several undesirable side effects and it is effective only in a certain portion of the patients is often associated with side-effects, dose-related and chronic toxicity that involves virtually every organ system. Moreover, all the currently available drugs have potential for adverse effects on cognition and behavior. This made man to search for alternative medicine from natural source[4,5]. Herbal remedies which were used traditionally now significantly documented for the safety profile and as a therapy for some of the pathological conditions. By observing the synergistic activity of phytochemicals, recently it has been advocated to use polyherbal formulation and in recent trend to achieve the maximum benefit of herbal therapy researcher combining a set of herbs in the form of specific formulation which is expected to deliver maximum potency compared to a single herb[6]. "Epic-Q" Polyherbal Formulation (EPHF), each 500 mg tablet contains the extract of medicinal plants like Ashwaghanda (*Withania somnifera*) -150 mg, Vacha (*Acorus calamus*) – 3 mg, Shankapushpi (*Evolvulus alsinoides*) – 150 mg, *Nardostachys jatamansi* – 100 mg, Mandukaparani (*Centella asciatica*) – Juice and Yastimadhu (*Glycyrrhiza glabra*) – 100 mg. The use of Poly herbal Formulation finds the way for curing certain neurodegenerative disease. Ayurveda claims that several plants, the so-called 'medhya' plants, which are present in this formulation, possess such neuroprotective properties[7]. Ashwaghanda used to treat epilepsy, stress and neurodegenerative diseases such as Parkinson's and Alzheimer's disorders[8]. *Acorus calamus* is known as brain tonic and possesses neuroprotective and antiepileptic activity[9]. Shankhapushpi has been suggested for neuropsychiatric states such as epilepsy, psychosis, fatigue, low energy levels, memory loss, anxiety, stress, neuroticism and nervous debility and known as rejuvenator[10]. *Centella asciatica* shows anticonvulsant activity[11]. The poly herbal formulation claiming to possess anticonvulsant and antidepressant and memory enhancing properties. But till there is no scientific data has been documented. Hence, the present study is therefore, focused on the evaluation of the anticonvulsant and antidepressant activity of EPHF in experimental animals.

MATERIALS AND METHODS

Experimental Animals

Swiss albino mice (25-30 g) and albino wistar rats (160-220 g) of either sex, were procured from animal house of Shree Devi College of Pharmacy, Mangalore, India were used for the study after the clearance from Institutional Animal Ethical Committee. Animals were acclimatized for one week to laboratory conditions before starting the experiment; they had free access to water and standard rat feed. The experimental protocol was approved by Institutional Animal Ethical Committee as per the guidance of committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Materials

The poly herbal formulation "Epic- Q" was manufactured and supplied by Swadeshi Ayurvedic Bhandar Pvt. Ltd., India. And chemicals used were of analytical grade and procured locally.

Preparation of EPHF suspension and dose selection

"Epic- Q" is a polyherbal formulation available in the form of tablets. The dose selection of EPHF was based on acute toxicity studies carried out according to OPPTS (Office of Prevention, Pesticide and Toxic Substance) guidelines following the limit test procedure. The animals were fasted overnight prior to the experiment. Test dose of 2 g/kg body weight and 5 g/kg body weight were given orally to either groups of rats and mice. Both the animals were observed for 72 hours for mortality. Both the doses were found to be safe. Hence $1/10^{th}$ and $1/50^{th}$ of the maximum safe dose corresponding to 500 and 100 mg/kg body weight were selected as high and low doses respectively[12].

Methods

The animal models selected were potentiation test for anticonvulsant activity and antidepressant tests.

Experimental Design

Anti-convulsant activity

Maximum Electroshock-induced Seizures (MES)

Rats will be divided into 4 groups (n = 6).

- Group I - Control (vehicle only).
- Group II – Standard -Phenytoin (25 mg/kg i.p).
- Group III - EPHF low dose.
- Group IV – EPHF high dose[13].

The animals will receive a current of 45 mA for 0.2 sec duration through electro convulsion meter using corneal electrodes, after 60 min of oral administration of EPHF, vehicle or phenytoin. The incidence and duration of extensor tonus will be noted. A complete abolition of hind limb tonic extension will be considered as 100 % protection.

Isoniazid (INH) induced seizure

Albino wister mice of either sex were divided into 4 groups of 6 mice in each was fasted overnight prior to the test but water was supplied *ad libitum*. Group I was maintained as control which was given with 3 % Tween 80 (10 ml/kg p.o.) once daily for 7 days on 7^{th} day 60 minutes after administration (3 % Tween 80) INH (300 mg/kg i.p) was administered. Group II was administered with diazepam (5 mg/kg i.p.) alone on 1st day only; 30 minutes after administration (diazepam), INH was administered. Groups III and IV were treated with EPHF (100 and 500 mg/kg po) respectively once daily for 7 days on 7^{th} day 60 minutes after extract administration the INH were administered[5]. The following parameters were recorded;

- Latency (onset) of clonus
- Latency of death.

Antidepressant activity

Forced swim test

Mice will be divided into 4 groups (n = 6).

- Group I - Control (vehicle only)
- Group II - Standard–Imipramine (10 mg/kg i.p).
- Group III –EPHF low dose.
- Group IV - EPHF high dose[14].

FST will be performed in glass jar. This test consists of two parts, an initial training period of 15 minutes followed by actual test for 5 minutes duration 24 h later. Mice will be individually forced to swim inside a vertical borosilicate glass cylinder (height: 40 cm; diameter: 15 cm; containing 15 cm height of water maintained at 25^{o} C. The mice from each group II, III, IV will be placed in the cylinder 24 h later after two doses of EPHF and imipramine (20 mg/kg) respectively and their activity will be recorded. The recordings will be analyzed to find the duration of immobility and swimming behavior. Water in the chamber was changed after subjecting each animal to FST because "used water" has been shown to alter the behavior. Each animal showed vigorous movement during initial 2 minutes period of the test. The duration of immobility was manually recorded during the next 4 minutes of the total 6 minutes testing period. Mice were considered to be immobile when they ceased struggling and remained floating motionless in water, making only those movements necessary to keep their head above water. Following swimming session, mice were towel dried and returned to their housing conditions.

Tail Suspension Test (TST)

The grouping of animals will be similar to that of FST. The total duration of immobility induced by tail suspension will be measured according to the described method as a facile means of evaluating potential antidepressants. Mice will be suspended on the edge of a table 50 cm above the floor by the adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time will be recorded during a 6 minutes period. Animal will be considered to be immobile when it did not show any movement of body and hanged passively[15].

Statistical analysis

Results are expressed as mean +/- SEM. Statistical significance was assessed by using One-way Analysis of variance (ANOVA) followed by Tukey-Karmer multiple comparison tests. $P < 0.05$ was considered significant.

RESULTS

Maximal Electro-shock induced seizures

EPHF (Epic-Q Poly Herbal Formulation) showed significant anticonvulsant activity by lowering the duration of extension phase when compared to control group. The duration of clonus in mice was 6.84 ± 0.29 at a high dose of 500 mg/kg ($P < 0.05$). The activity of EPHF was comparable to that produced by phenytoin.

Table 1: Effect of EPHF on MES induced convulsion

Groups	Flexion	Extension	Clonus	Stupor	Recovery/ Death
Control	8.48 ± 0.18	16.03 ± 0.65	3.16 ± 0.62	10.40 ± 0.85	Recovery
Phenytoin (25 mg/kg)	3.15 ± 0.35	-	9.53 ± 0.49**	3.21 ± 0.81	Recovery
EPHF (100 mg/kg)	5.98 ± 0.43	5.49 ± 0.49	4.06 ± 0.49	20.14 ± 0.88	Recovery
EPHF (500 mg/kg)	5.34 ± 0.29	3.15 ± 0.30	6.84 ± 0.29*	20.79 ± 1.60	Recovery

Values are expressed as mean ± SEM (n = 6) *p<0.05, **p<0.01 when compared to control

Isoniazid (INH) induced seizures

The animals treated with low dose of EPHF (100 mg/kg) exhibited a no significant delay in onset of clonic as well as tonic convulsion. However those treated with EPHF (500 mg/kg) exhibited a significant ($P < 0.05$) delay in onset of clonic convulsion and a moderately significant delay of tonic phase as compared to the control. The animals treated with Diazepam (4 mg/kg) showed an extremely significant delay in the onset of clonic as well as tonic convulsion.

Table 2: Effect of EPHF and Diazepam on INH induced convulsion in mice

Group	Duration of seizure(min)		Mortality
	Onset of clonic phase (min)	Onset of tonic phase (min)	
Normal control	39.63 ± 0.91	49.51 ± 0.56	6
Standard (Diazepam)	63.43 ± 1.53***	71.42 ± 0.65***	2
EPHF (100 mg/kg)	37.85 ± 0.83^{ns}	50.86 ± 0.94^{ns}	6
EPHF (500 mg/kg)	45.52 ± 0.96*	56.12 ± 1.19**	5

Values are expressed as mean ± SEM (n = 6) *p < 0.05, **p < 0.01, ***p< 0.001when compared to control

Anti-depressant activity

Tail suspension test

In this test, animals treated with low dose of EPHF (100 mg/kg) showed a significant decrease in their immobility time and those treated with high dose of EPHF (500 mg/kg) showed a moderately significant decrease in immobility time compare to control. Animals treated with imipramine (10 mg/kg) showed extremely significant reduction in the immobility time.

Table 3: Effect of EPHF on Tail suspension test in mice

Groups	Time of immobility
Control	241.5 ± 0.763
Standard (Imipramine 10 mg/kg)	129.83 ± 0.833***
EPHF (100 mg/kg)	237 ± 0.730*
EPHF (500 mg/kg)	235.16 ± 1.493**

Values are expressed as mean ± SEM (n = 6) *p < 0.05, **p < 0.01, ***p < 0.001when compared to control

Forced swim test

In this test, animals treated with low dose of EPHF (100 mg/kg) showed a significant decrease in their immobility time and those treated with high dose of EPHF (500 mg/kg) showed a moderately significant decrease in immobility time compare to control. Animals treated with imipramine (10 mg/kg) showed extremely significant reduction in the immobility time.

Table 4: Effect of EPHF on Forced swim test in mice

Groups	Time of immobility
Control	243.29 ± 1.78
Standard (Imipramine 10 mg/kg)	127.73 ± 1.54***
EPHF (100 mg/kg)	235.02 ± 0.91*
EPHF (500 mg/kg)	231.11 ± 1.51**

Values are expressed as mean ± SEM (n = 6) *p < 0.05, **p <0.01, ***p < 0.001 when compared to control

DISCUSSION

The aim of the present study was to elucidate the role of polyherbal formulation Epic-Q tablets for its anticonvulsant activity induced by MES and INH induced convulsion and antidepressant activity by tail suspension and forced swim test. The EPHF at a dose of (500 mg/kg) have demonstrated anticonvulsant activity on MES induced convulsion and INH induced convulsion by increased onset time for clonic as well as tonic phases and decreased mortality. The duration of tonic and hind limb extension in rates was 6.84 ± 0.29 at a dose 500 mg/kg. The activity of EPHF was comparable to that produced by phenytoin sodium, a standard antiepileptic drug. Epileptic seizures which occur as a result of an imbalance between excitatory and inhibitory neurotransmitters, standard Diazepam is usually used which provides protection by stimulation of GABA. The INH, convulsive agent, is act by inhibiting GABA synthesis in the CNS. EPHF treated groups were protected from seizures either by enhanced GABA synthesis by the stimulation of L-glutamate or by the prevention of GABA degradation by GABA transaminase. The anticonvulsant activity is due to the interaction of isoflavonoids and other organic mixtures (chemical constituents present in drugs of formulation) with the GABA receptor complex in the brain. In both tail immersion and forced swim test, animals treated with low dose of EPHF (100 mg/kg) showed a significant decrease in their immobility time and those treated with high dose of EPHF (500 mg/kg) showed a moderately significant decrease in immobility time compare to control. Animals treated with imipramine (10 mg/kg) showed extremely significant reduction in the immobility time. Imipramine acts by inhibiting NE reuptake and has been used as a standard drug in majority studies. The beneficial effect of imipramine in the FST model seems to be due to increased availability of these neurotransmitters nor epinephrine (NE) and serotonin (5HT) at the post synaptic site following reuptake inhibition[16]. The presence of potential phytocontituents such as mixtures of organic chemicals, which may include fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins, tannins, terpenes and so forth produces anticonvulsive and anti depressive actions.

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