EVALUATION OF ANTI CONVULSANT ACTIVITY OF FLOWER EXTRACT OF IXORA COCCINEA ON RATS

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ABSTRACT: In the present study Preclinical evaluation of antiepileptic effect of ethanolic extract of flowers of *Ixora coccinea*. The results of the study have demonstrated that EEIC possessed potent anti convulsant action in the animal's model investigates as well as these provide a rationale in favor of its uses inside traditionally drug in favor of organization of convulsion. The present results suggested that EEIC containing marketed formulation is also being useful or the management of epilepsy. Further study is to establish the exact molecular level mechanism of action of *Ixora coccinea*.

Key words: *Ixora coccinea,* EEIC, convulsion etc.

INTRODUCTION

The disorders of Central nervous systems (CNSs), the huge values inside now a current day's in the world which is due to rising in the stress and changing in living situation. CNS disorders are typical diseases which represent the major challenge for contemporary drug. Because convulsion is single the majority common C.N.S. diseases, plus numeral of adverse property are linked by means of the here anti-epileptic medicine treatment[1].

Convulsion

Convulsion, an ordinary neurological disease moving an predictable 40.00-50.00 millions populace world wide frequently unidentified, it is recognized that manifold factor such as imperfection in heredity or epigenetic, environmental as wealthy as the inequity in neurotransmission receptors system be everyone at engage n recreation in formative individuals' vulnerability to sickness[2]. Prevalence of chronic epilepsy is in the range of 4-10 per 1000 people. The incidence of epilepsy is uppermost in the middle of children's below 7 existences of period and n individuals of above 55 years. The reported prevalence of epilepsy in India is about .5 to 7.9 per 1000 people, which is about 1/18th of the world population.

Importance of herbal plants in convulsions

Botanical and herbals contain a century - elderly custom of make use of via people by means of convulsion, in a lot of culture approximately the planet. At there, herbs therapy is trying through patient within rising because healthy since urbanized country future intended for manage of seizure otherwise unfavorable belongings as of anti epileptic drug (AED), otherwise intended for universal physical condition preservation, more often than not with no the information of physician who lay down their AEDs. Elegant medical trial of herbals therapies in patient by means of convulsion are inadequate and practical issue averts several conclusion of their effectiveness or security in this inhabitants. In addition, a few botanicals and herb might be convulsion producer or might amend AEDs metabolisms[39].

Herbs therapy is in the middle of the large quantity more often than not used form of balancing and option checkup (CAM) therapy by patients. Patients by means of diversity constant illness, counting epilepsy, take herbal therapy for a lot of reason. Intended for instance, patients in urbanized country might sight herbs therapy as usual and time - experienced and so secure compare by means of what being professed because false medicines — an approach support by new information of security concern connected by extensively set FDA - accepted medicines. Inside mounting country, there can be admission to herbs therapy except not to pharmaceutical, since of edifying plus financial factor. Herbs civilization comprise conventional Chinese drug, Ayurveda, and additional ethnically exact practice in which fix resources, process or not, be swallowed by people by means of the meaning of plummeting symptom or curative sickness.

This appraisal focus on the degree and pattern of make use of herbs therapy through patients by means of convulsion, narrow considerations on behalf of nutritional supplement (which comprise herbs therapy during the joint states), protection issue, explicit herbs therapy that encompass be old and evaluate on behalf of convulsion, plus a worktable to bedside move toward to herbs treatment investigate on behalf of convulsion[26].

Preclinical evaluation of antiepileptic effect of ethanolic extract of flowers of *Ixora coccinea* through the following objectives: Collection of Flowers of *Ixora coccinea,* Identification and Authentification of plant material, Standardization, extraction and phytochemical evaluation of plant material, Study of the acute toxicity of ethanolic extract of Flowers of *Ixora coccinea,* Study of the antiepileptic effect of aqueous extract of *Ixora coccinea* gum resin using:

a. Pentylene tetrazole induced convulsions test

b. Maximal electroshock induced convulsions test.

c. Thiopental induced sleeping time method

Ixora coccinea is a species of flowering plant in the Rubiaceae family. It is a common flowering shrub native to Southern India, Bangladesh, and Sri Lanka. It has become one of the most popular flowering shrubs in South Florida gardens and landscapes. It is the national flower of Suriname.

Fifty-four components have been identified in the essential oil of *I. coccinea* flower, representing 99.97% of the total components detected. The oil is composed mainly of triterpenes 62.60%, monoterpenes 31.73%, sesquiterpenes 3.35% and an ester 2.29%. The major constituents of triterpenes were ursolic acid (27.34%), oleanolic (20.16%) and lupeol (15.10%). *Ixora coccinea* flower is of ursolic acid chemotype. Geranyl Acetate (8.74%) is the major monoterpenes, followed by Linalyl acetate (6.79%), Neryl acetate (6.49%), Terpineol acetate (4.91%), and Borneol acetate (4.77%); Ethyl cinnamate (2.29%) an ester while the sesquiterpenes are Cyperene (2.72%) and α–Copaene (0.63%) [10].

A new triterpene, ixorene with dammarane skeleton was isolated from the leaves of *I. coccinea*, along with the three known constituents β-sitosterol, lupeol and D-mannitol. The structure was elucidated on the basis of extensive 1D and 2D-NMR studies and mass spectrometry as 17β-dammara-12, 20-diene-3β-ol [11].

The air-dried flowers of *I. coccinea* afforded two new cycloartenol esters, lupeol fatty ester, lupeol, ursolic acid, oleanolic acid and sitosterol. The structures were elucidated by extensive 1D and 2D NMR spectroscopy and MS [12].

EXPERIMENTAL METHODOLOGY

Determination of extractive values for Crude drug[16 17]

Detection for extract value helps for decides quantity of soluble constituent inside a known quantity of therapeutic plants materials, at what time extract with solvents. The extractions of some basic medicine by means of a meticulous in the black give way answer contain dissimilar phytoconstituents. A work of art of these phytoconstituents within exacting in the black depend upon the natural world of medicine plus in the black second-hand. Single in the black can also be second-hand intended for as long as beginning in order of excellence of an exacting medicine example.

a) Determination of alcohol soluble extractives: set regarding 4.00 gm roughly crushed air dried fabric, precisely weigh, inside a glass- stopper tapering flasks. Macerate by means of 100.00 ml alcohols in favor of 6.00 hrs. trembling often, and then allow standing used for 18.00 hrs. Filter fast captivating mind not to misplace any in the black, move 25.00 mls of remains to a tared flat bottomed plate and fade away upto a redness on top of a water bath. Dehydrated for 105.00 °C for 6.0hrs, chill inside desiccators in favor of 30.00 notes and consider with no delays. Calculate happy of extractable substance inside mgs per gm of air-dried materials.

b) Detection for water soluble extractives: Water soluble extractives values were obtained by following same process as describe in favor of alcohol soluble extractives using chloroform water (0.25 % chloroform in water) instead of alcohol.

c) Detection of chloroform soluble extractives: Chloroform soluble extractives worth's were obtained by following the same procedure as describe in favor of alcohol soluble extract using Chloroform in its place of alcohols.

d) Detection of petroleum ether soluble extractives: Petroleum ether soluble extractives worth's were obtained by following the same procedure as describe in favor of alcohol soluble extract using Chloroform in its place of alcohols.

Determination of Ash values for Crude drug[22]

a) Determination of Total Ash:

Accurately weigh 2 gms for crushed medicine was in use in a taken in silicas plate and it was incinerate at a hotness not more than 450.00°C waiting gratis as of carbons. Samples were refrigerated and weigh. Stipulation carbons gratis pallid cannot exist obtain inside like way; the overcooked accumulation was tired by means of hot irrigate. The remains was composed on residue fewer sift papers were incinerated; relics was evaporate to aridness, as well as ignite on a hotness not more than 450.00 °C. Proportion of residue was designed by means of orientation to atmosphere dehydrated medicine[18].

b) Detection of Acid-insoluble Ashes:

Ashes obtain as describe in the strength of mind of sum residue was boil in favor of 5.00 mint by 25.00 mls of thin hydro chloric acids. The inexplicable substances was collected in Goochs crucibles or on top of an ash less sieve document and wash by means of hot irrigates and ignite to steady heaviness. The proportion of acid insoluble residue was designed through position to the space dehydrated medicine.

c) Detection of Water soluble Ashes:

Ashes obtain as describe in the strength of mind of sum ashes was boil for 5 mins by 25 ml of waters and in-soluble substance was composed in a Goochs crucibles, otherwise on top of an residue fewer sift document, wash by means of burning irrigate and ignite for 15 minutes at a hotness not more than 450.00^0C. Heaviness of inexplicable substance was subtracted as of heaviness of residue. Disparity within heaviness represents the water - soluble residue. Percentages of water soluble ashes are intended by orientation in the direction of the atmosphere dehydrated medicines.

d) Determination of Sulphated Ash

The residue obtained in total ash determination is refrigerated and moisten with 1.00 ml of sulphuric acids. Gentle heating is done waiting pallid vapors be no longer evolve. Ignition is carried out at a temperature of 800^0C until all the black particles disappear and is done in a put secluded as of air current. The crucibles are cooled and a small number of drop of sulphuric acids are additional and animated. Ignition is carried out as before. Cooling is allowed and crucible weighed. The operation is repeated till constant weight.

Extraction and Phytochemical Investigations of Crude drug

Successive extraction of Flowers of *Ixora coccinea* [13]

The shade dried Flowers of *Ixora coccinea* L were reduced to coarse powder (# 10 size mesh) and around 200 gm of fine particles subjects to consecutive hot continuous extractions (soxhlet) by means of petroleum ethers (40.00° - 60.00 °C), chloroforms as well as alcohol. Lastly medicine macerate by means of chloroforms irrigate. Every occasion previous to extract by means of the then in the black the crushed cloth was atmosphere dehydrated. Following the effectual removal, the solvents were distilling rotten plus the take out was after that intense on water bathtub dehydrated up to steady heaviness and the take out obtain by means of each in the black was weigh. Proportion of extract was intended in conditions of atmosphere dehydrated heaviness of plants fabric. The colour and consistency of the extract was notes. The obtained extract was subject for phytochemical investigation.

Qualitative chemical investigation of extracts[23]

Qualitatively chemically test was conduct intended for ethanolic extract of Flowers of *Ixora coccinea* L for recognize variety of phytoconstituents likes alkaloid, glycoside, carbohydrate, phenolic and tannin, phytosterol, fixed oil and fat, protein and amino acid, flavonoid, saponin, etc. using following methods.

Toxicological evaluation. (OECD 423)

Determination of LD50 value by acute oral toxicity study in rats

Acute toxicity is involved in estimation of LD_{50} (the dose which has proved to be lethal (causing death) to 50% of the tested group of animals). In screening drugs, determination of LD50 (the dose which has proved to be lethal (causing death) to 50% of the tested group of animals) is usually an initial step in the assessment and evaluation of the toxic characteristics of a substance. It is an initial assessment of toxic manifestations (provides information on health hazards likely to arise from short-term exposure to drugs) and is one of the initial screening experiments performed with all compounds.

In the present study, LD_{50} value of the EEIC was determined by the **'**Acute oral Toxicity Test**'.**

The procedure was followed by using OECD-423 (Acute Toxic Class Method) (OECD Guide lines 423,1996). The acute toxic class method is a step wise procedure with three animals of a single sex per step. Depending on the mortality or moribund status of the animals and the average two to three steps may be necessary to allow judgment on the acute toxicity of the test substance. This procedure results in the use number of animals while allowing for acceptable data based scientific conclusion. The method used to defined doses (5, 50, 500, 2000 mg/kg body weight) the results allow a substance to be ranked and classified according to the Globally Harmonized System (GHS) for the classification of chemicals which cause acute toxicity.

Preparation of Animals

All animals used for the Limit Test were fasted over-night. Food but not water was withheld from 5:00 p.m. on the day preceding dosing.

In order to minimize stress caused by fasting, animals were offered a 10% w/v aqueous solution of glucose during this period.

Preparation of doses

The extract was prepared as a suspension by triturating with 1% SCMC.

Experimental procedure

Two groups (Group 1-2), each of three female rats, were treated with vehicle and EEIC by oral gavage administration at starting dose level of the plant drug was 2000 mg/kg body weight as most of the crude extracts posses LD_{50} value more than 200mg/kg p.o. Dose volume was administered 0.2ml per 100gm body weight to overnight fasted rats with were *ad libidum*.

Food was withheld for a further 3-4 hours after administration of extract. Animals are observed individually after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 4 hours, and daily thereafter, for a total of 14 days, Except where they need to be removed from the study and humanely killed for animal welfare reasons or are found dead. However, the duration of observation should not be fixed rigidly. It should be determined by the toxic reactions, time of onset and length of recovery period, and may thus be extended when considered necessary.

The body weight of the rats before and after administration were to be noted and the changes in skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system and motor activity and behavior pattern were observed and sign of tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma were also noted.

Evaluation of anticonvulsant Activity

Drugs and chemicals

Diazepam (D.Z.) & Pentylenetetrazole (P.T.Z.) acquired as of Sigmas (St. LouisMO-USA). Phenytoin sodium (PS) & Picrotoxin (PCT) were conventional like contribution example as of PiramalHealth Care limited, H.P, India. Thiopental sodium was acquired as of market.

Each experiment consists of five group of flora and fauna of ten in every collection. Groups I (vehicle control, vehicle treated); Group II (standard control), Groups III (test drug, EEIC] 250mg/kg), Group IV (test drug, EEIC 500mg/kg) and Group V (test drug, EEIC 1000mg/kg). Every one drug solution was newly ready through dissolve/ suspend in usual saline intended in intra peritoneal (ip) administered.

Convulsant induction models

Maximally Electro shock Seizures (M.E.S.) examination:

Maximal electroshock seizure pattern induced in animals through using convulsiometer (Techno, India) to give an irregular existing of 150.00 mA for 0.200 sec. After 45 minutes of position dose, mice was subjects to M.E.S. of 150 mA of irregular existing as of a convulsion meters for 0.200 secs from side to side a couple of electrode emotionally involved to every ear. The period of the boost back members extensors stage, chronics stage and the figure of flora and fauna secluded from convulsion was renowned. Phenytoin in doses of 10 mg/kg PO was be used as standard control. Pentylene tetrazole (P.T.Z.) induce seizure: This assay is second-hand to evaluate antiepileptic drugs. Pentylene tetrazole was second-hand inside an amount 40.00 mg / kg, intraperitoneally. This is dosage that produces chronically seizure inside every one the animal with no humanity. The test drug is administered 45 minutes previous to pentylene tetrazole management. Latencies for first convulsion and the no. of mice which exhibited seizure were experiential right away following test medicine inoculation in favor of era of 30.00 minutes.

Statistical analysis:

Values reported are means ± SEM (number of animals). The significance of difference with respect to controls was evaluated using the Mann Whitney U tests. Its probability (p value) level, which is lower than 0.050, were careful as significant. All analyses were conducted using SPSS 17.00 for Windows.

RESULTS & DISCUSSION

Evaluation physicochemical parameters

Table 1. Physical parameters

S no	Physical parameters	Value obtained in % w/w
1	Total ash	8
2	Acid-insoluble ash	0.2
3	Water soluble ash	3.45
4	Sulfated ash	8.14
5	Alcohol soluble extractive	20.0
6	Water soluble extractive	36.45
7	Petroleum ether soluble extractive	6.82
8	Chloroform soluble extractive	5.9

In this study *Ixora coccinea* showed total ash (7%), acid insoluble ash (0.2%) and water soluble ash (3.75%) and sulfated ash (8.14%).

Extraction of Flowers of *Ixora coccinea*

The coarse powder of *Ixora coccinea* was sequentially extracted through petroleum ether, chloroform as well as alcohol by Soxhlet apparatus and macerate by water. The result is described in table 3. The petroleum ether *Ixora coccinea* extract was oily viscous, brown and the yield was 5.58% w/w, alcohol extract was semi-solid, dark brownish and the yield was 13.84 %w/w. Chloroform extract was semi-solid, dark brown and the yield was 2.11% w/w and water soluble extract was brown and the yield was 7.73% w/w.

Table 2 Extraction of Flowers of *Ixora coccinea* using different solvents

S.No	Extract	Colour & consistency	Weight in gm	Yeild (%)
1	Petroleum ether	Oily viscous brown	11.6	5.58
2	Chloroform	Semi solid dark brown	4.22	2.11
3	Ethanol	Semi solid brown	27.69	13.84
4	Water	Semi sloid brown	15.46	7.73

Preliminary phytochemical analysis of ethanolic extract of leaf of *Ixora coccinea.*

The result of preliminary phytochemical analysis of leaf extract of *Ixora coccinea*L is shown in **Table 2**

Table 3 Phytochemical Screening of Ethanolic extract of leaf of *Ixora coccinea*

S.No.	Constituents	Test	Ethanolic Extract
1.	Alkaloids	a) Mayer's reagent b) Dragendorff's reagent c) Hagner's reagent d) Wagner's reagent	Absent Absent Absent Absent
2.	Carbohydrates	a) Molisch's reagent b) Fehling's solution A and B c) Benedict's reagent d) Barfoed's reagent	Present Present Present Present
3.	Protein	a) Biuret test b) Millon's reagent	Absent Absent
4.	Steroids	a) Libermann's burchard test b) 5% potassium hydroxide	Present Present
5.	Phenols	a) Ferric chloride b) 10% Sodium chloride	Absent Absent
6.	Tannins	a) 10% Lead acetate solution b) 10% Sodium chloride c) Aqueous bromine solution	Present Present Present
7.	Flavanoids	a) Con. H_2SO_4 b) Magnesium turning test	Present Present
8.	Gums and Mucilage	Swelling test	Absent
9.	Glycosides	Glacial acetic acid + Ferric chloride + Con. Sulphuric acid	Present
10.	Sterols	5 % Potassium Hydroxide	Present
11.	Saponins	Foam test	Present
12.	Terpenes	Tin + Thionyl chloride	Present

Acute oral toxicity study

The acute oral toxicity study was done according to OECD 423 guide lines (Acute toxicity class method). A single administration of a starting dose of 2000 mg/kg bw/p.o, of EEIC was administered to 3 female rats and observed for 14 days. There was no considerable change in body weight before and after treatment of the experiment and no signs of toxicity were observed. The results are shown in **Table 4.**

Table 4 Sign of toxicity, mortality and mean body weight results of acute oral toxicity observations of EECS in rats

Treated group	**Dose**	**Sign of toxicity (ST/NB)[a]**	**Mortality (D/S)[a]**	**Mean body weight (g)[a]**		
				Day 0	**Day 7**	**Day 14**
Group-I: vehicle	10ml/kg b.w	0/3	0/3	218 ± 2.6	230 ±4.3	276 ± 2.6
Group-II: EEIC	2000 mg/kg b.w	0/3	0/3	220 ± 2.2	232 ± 3.6	278 ± 3.2

[a] Values are expressed as animal numbers; **ST**, Sign of toxicity; **NB,** Normal behavior; **D,** Died; **S,** Survived

MES-induced seizures the anticonvulsant activity of EEIC was determined using electrically induced (MES) convulsion in rats.

Table 5 Effect of EEIC on MES induced seizures in rats

Group	Dose(mg/kg,i.p)	Latency of HLTE(s)	Duration of HLTE(s)	Duration of conclusion(s)
Control	Vehicle	1.17±0.17	14.83±0.65	333.83±8.19
PS	25	00.00±0.00***	00.00±0.00***	127.17±8.57***
EEIC	50	2.67±0.21**	7.50±0.43**	151.67±1.45**
EEIC	100	2.67±0.21**	7.50±0.43**	147.50±5.79**

Significance (Value) expresses by mean plus or minus S.E.M.., n=6.00,

Oneway Analysis of Variances(A.N.O.V.A)follow through multiples compare Dunnet's tests,**p<0.01,***p<0.001 vs.Control.

PCT-induced seizures The EEIC at any doses did not show a significant effect against seizures induced by PCT (Table 6).

Table 6 Effect of EEIC on PCT-induced seizures

Group	Dose(mg/kg,i.p)	Onset Of Convulsion(min)	Onset of HLTE(min)
Control	Vehicle	3.67±0.46	16.57±1.46
DZ	4	6.51±0.33**	0.0±0.0
EEIC	50	3.82±0.19	17.90±2.88
EEIC	100	3.90±0.16	18.48±1.20
EEIC	200	4.36±0.19	21.78±0.99

Significance (Value) expresses by mean plus or minus S.E.M., n=6.00, Oneway Analysis of variances (A.N.O.V.A) follow through multiples compare Dunnet's tests, **p<0.01 vs. Control.

PTZ-induced seizures

In PTZ-induced seizures, the administration of BAs, in a dose of 200 mg/kg, 30 min. prior to the injection of PTZ, significantly (p<0.001) delayed the onset of EEIC. DZ in a dose 4 mg/kg totally abolished the episodes of convulsions (p<0.001). There was less significant effect of the BA at dose of 100 mg/kg on onset of EEIC (p<0.01) as compared to control (Table 7). There was no significant effect of EEIC at dose of 50 mg/kg on onset of EEIC (Fig. 5) (Table 7).

Table 7 Effect of EEIC on PTZ-induced seizures

Group	Dose(mg/kg,i.p)	Onset of HLTE (min)	Convulsion (%)	Protection(%)
Control	Vehicle	3.59±0.28	100.00	00.00
DZ	4	00.00±0.00***	0.00	100.00
EEIC	50	4.25±0.35	100.00	0.00
EEIC	100	5.52±0.34**	83.33	33.33
EEIC	200	10.08±0.50***	50.00	50.00

Significance (Value) expresses by mean plus or minus S.E.M., n=6.00, One way Analysis of Variances (A.N.O.V.A) follow through multiples compare Dunnet's tests,**p<0.01,***p<0.001 vs. Control.

Thiopental sodium-induced sleeping time

Complete values for sleep latencies (onset of sleep) as well as sleep time are obtainable in Table 8. No alteration was observed on onset of sleeping at any doses of EEIC as compared to control. However, the duration of sleeping was significantly increased (p<0.001) in EEIC (200 mg/kg) as compared to control. Similarly, animals treated with DZ (4 mg/kg, i.p.), as expected, an increase in duration of sleeping (p<0.001) and did show significant effects onset of sleeping (p<0.001). There was no significant effect observed on EEIC in doses 50 & 100 mg/kg, on onset of sleeping as well as on duration of sleeping (Table 8)

Table 8 Effect of EEIC on thiopental sodium induced sleeping time

Group	Dose(mg/kg,i.p)	Onset of sleep (min)	Duration of Sleep(min)
Control	Vehicle	3.14±0.11	8.32±0.47
DZ	4	1.97±0.20***	40.42±1.86***
EEIC	50	3.17±0.10	8.60±0.59
EEIC	100	3.59±0.18	9.892±0.34
EEIC	200	2.53±0.23	29.57±1.56***

Significance (Value) expresses by mean plus or minus S.E.M., n=6.00, One way Analysis of Variances (A.N.O.V.A) follow through multiples compare Dunnet's tests, ***p<0.001 vs. Control.

SUMMARY & CONCLUSION

The CNS depression action of EEIC was established through reduce inside latency to sleeping as well as tendency to considerably increasing thiopental sodium- induce sleeping times which may be credited to a reserve of thiopental sodium metabolisms otherwise to an act in the rule of sleeping. The sleeping time was increased significantly at higher dose of EEIC, as compared to control. Animals treated with DZ (4 mg/kg, i.p.), as expected, prolong the sleeping time & reduces the latency of sleep. There was no significant effect on latency as well as sleeping time at lower doses of EEIC.

The results of the study have demonstrated that EEIC possessed potent anti convulsant action in the animal's model investigates as well a s these provide a rationale in favor of its uses inside traditionally drug in favor of organization of convulsion. The present results suggested that EEIC containing marketed formulation is also being useful for the management of epilepsy.

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