ORIGINAL ARTICLE

Evaluation of antiepileptic activities of *Ficus religiosa* bark and *Aegle marmelos* leaves using Swiss albino mice

Subha Bikram Sapkota[1], Aviskar Khanal[1], Neeta Neupane[1], Prashamsha Karki[1], V. K. Sharan[1], Dharma Raj Marasini[1], Chandra Bahadur Budha[2], Himal Barakoti[3], Rabindra Kumar Rokaya[4], Jitendra Pandey[1], Atul Adhikari[5], Ravin Bhandari[1]

[1]Department of Pharmacy, Crimson College of Technology, Butwal, Rupandehi, Nepal, [2]Department of Education, Bheri Gyanodaya Multiple Campus, Affiliated to Midwestern University, Jajarkot, Nepal, [3]Department of Pharmacy, Purbanchal University, Biratnagar, Nepal, [4]Department of Pharmacology, Karnali Academy of Health Science, Jumla, Nepal, [5]Department of Pharmacy, Kantipur Academy of Health Science, Tinkune, Kathmandu, Nepal

ABSTRACT

Introduction: Epilepsy is defined as the infrequent, unexpected, excessive, quick, and abnormal coordinated electrical depolarization in the gray matter of the central nervous system. The main objective of this study, involving *Ficus religiosa* and *Aegle marmelos* was to evaluate their antiepileptic activity. **Materials and Methods:** The plants were selected based on their ethnomedicinal values and literature reviews. Thirty-six Swiss albino mice were divided into six groups, each group comprised of six mice (25–30 g) were used for the experiment. Antiepileptic effect of ethanolic extract of *F. religiosa* (EEFR) at oral doses 200 and 400 mg/kg and cow urine extract of *A. marmelos* (CUEAM) at oral doses 200 and 400 mg/kg was studied using standard convulsive agent isoniazid (INH). The latency of the first epilepsy, duration of epilepsy, percentage mortality, and protection were observed after the administration of INH. **Results:** EEFR 200 and 400 mg/kg significantly delayed the onset of convulsion and reduced the duration of convulsion and showed the protection against convulsion. Similarly, CUEAM 200 and 400 mg/kg significantly delayed the latency of the first convulsion and significantly reduced the duration of action of convulsion. CUEAM 200 and 400 mg/kg showed 33.33% and 100% protection against INH-induced convulsion in mice, respectively. **Discussion:** Dose-dependent antiepileptic action of *F. religiosa* and *A. marmelos*. *F. religiosa* was found and the protection offered by *A. marmelos* may suggest the presence of compounds potentiating GABAergic action. **Conclusion:** It was concluded that *F. religiosa* and *A. marmelos* possess significant antiepileptic activity. Hence, it may be beneficial and an alternative in the treatment of epilepsy like disorders.

Key words: *Aegle marmelos,* diazepam, epilepsy, *Ficus religiosa,* isoniazid

INTRODUCTION

People tend to rely on traditional and other forms of complementary and alternative medicine for chronic conditions such as diabetes, anxiety, pain, urolithiasis, and epilepsy, as modern medicines do not respond well or may produce numbers of adverse effects.[1-4] Epilepsy is defined as the infrequent, unexpected, excessive, quick, and abnormal coordinated electrical depolarization (local discharge) in the gray matter of the central nervous system.[5] About 1% of the world's population has epilepsy.[6] Epilepsy is the most common chronic neurological disorder. It imposes the highest-burden on health care systems. Epilepsy is a symptom of a variety of conditions, and the mortality may be different for each condition. Deaths are likely to be caused by the background etiology of epilepsy such as

Address for correspondence:
Ravin Bhandari, Department of Pharmacy,
Crimson College of Technology, Rupandehi, Nepal.
E-mail:ravinbhandari2000@gmail.com

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tumors, trauma, degenerative conditions, or cerebrovascular diseases.[7]

Literature review reveals that several plants such as *Acorus calamus, Crocus sativus, Emblica officinalis, Ginkgo biloba, Hypericum perforatum, Matricaria recutita, Panax ginseng*, and Passiflora incarnata have been reported to demonstrate antiseizure activity.[8] Several classes of phytoconstituents such as alkaloids, lipids, terpenes, triterpenoids, flavonoids, and coumarins have been reported to acquire anticonvulsant activity.[9-12] Anticonvulsant is the diverse group of natural product or pharmaceutical which are used to control or prevent the epileptic seizure or any convulsion of known or unknown origin. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder since many seem to act as mood stabilizers and for the treatment of neuropathic pain. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure.[13] Isoniazid INH-induced seizure bear asemblance to petit mal Epilepsy. Evidence indicates that an imbalance between excitatory and inhibitory neurotransmission in the brain is the main cause, contributing to seizure development in both, experimental and clinical conditions.[14]

Ficus religiosa (L.) is a large perennial deciduous tree found throughout the plains of India up to 170 m altitude in the Himalayas.[15,16] In the traditional medicinal system, the bark of this plant is used for stomatitis and clean ulcers, the powder of the bark stem is used to promote granulations and has strong anti-inflammatory and analgesic properties.[17] The anticonvulsant activity of the aqueous aerial root extract of *F. religiosa* was investigated in strychnine, pentylenetetrazole, picrotoxin, and INH-induced seizures in mice. The extract showed no toxicity and protected the animals in the strychnine, pentylenetetrazole tests in a dose-dependent manner. Their effects in the picrotoxin and INH tests were less potent.[16]

Aegle marmelos is a slow-growing, medium-sized tree and has its origin from Eastern Ghats and Central India.[18] In traditional medicine, its leaves are used for peptic ulcers. Alcoholic extracts of fruit of this plant have shown cardioprotective, antiprotozoal, antidiabetic, and blood lipid-lowering activities.[16]

Cow urine has a unique place in Ayurveda and has been described in ancient Hindu literature "Sushruta Samhita" and "Ashtanga Sangraha" to be the most effective substance/secretion of animal origin with innumerable therapeutic values.[19] This kind of alternative treatment, termed as "Panchagavya Therapy" or "Cowpathy," has been reported to be beneficial even for dreaded diseases such as cancer, AIDS, and diabetes.[20] Bioactive substances and hormones such as urokinase, urea, uric acid, minerals, epithelial growth factors, growth hormones, erythropoietin, gonadotrophins, trypsin inhibitor, allantoin, antineoplaston, and H-11 beta-iodole-acetic acid were reported in cow urine.[21]

F. religiosa and *A. marmelos* have tremendous medicinal activities. Different researches have revealed that the extract of leaves, fruits, and flowers has antiepileptic activity. Along those parts of this plant, bark may also possess antiepileptic activity. The cow urine together with the leaves of *A. marmelos* has been used as ethnomedicine for the treatment of epilepsy in Palpa district, Nepal and it has no scientific evidence. Therefore, this research was carried out to provide scientific evidence to acclaim ethanolic extract of bark of *F. religiosa* (EEFR) and cow urine (*Bos indicus*) extract of the leaves of *A. marmelos* for antiepileptic activity.

MATERIALS AND METHODS

Chemicals

Diazepam was used as standard drug and obtained from Asian Pharmaceuticals, Rupandehi, Nepal. INH (Macleods Pharmaceuticals Pvt. Ltd., Mumbai Batch no.HIA8011A), ethanol (Changshu Hongsheng Fine Chemical Co. Ltd.; Lot No. 20161021), distilled water (prepared in laboratory), normal saline (Axa Parenterals Ltd.; Batch No. AH71078), sterile water (Thermo Fisher Scientific India Pvt. Ltd.; Lot No. 3263 7209-3), and cow urine (obtained from Ramdi, Nepal) were used for this study.

Plant Material

The plant materials of *F. religiosa* (bark) and *A. marmelos* (leaves) were collected from Palpa district Nepal (1350 m above the sea level) in March 2018. The plant materials were identified by Botanist Hom Nath Pathak from Prithvi Narayan Campus, Pokhara, and pharmacists Ravin Bhandari and Pramod Aryal from Crimson College of Technology, Butwal, Nepal. The voucher specimen of the authenticated plants was preserved in Crimson College of Technology, Pharmacognosy lab (Voucher specimen number: CCT-HRB-2018/175).

Plant Material Preparation

Collected plant materials were cleaned with tap water and rinsed with distilled water. They were then air-dried at room temperature in a well-ventilated room. The drying was carried out for 20 days with proper checking at regular intervals. After the plant parts were dried, they were ground to a coarse powder using a grinder. The coarse powder was then sifted through the sieve (40 mesh size), kept in an airtight container, and stored in a cool, dark, and dry place until it was used.

Experimental Animals

Young Swiss albino mice of either sex weighing between 25 and 30 g were selected for the experiment, which were bred in the Natural Product and Research Laboratory, Thapathali,

Kathmandu, Nepal. They were housed in well ventilated clean plastic cages in a group of six with a metal frame lid on top. The animals were maintained in standard environmental conditions of 25°C temperature and light/dark cycles, that is, 12/12 h. They were fed with rodent food and water *ad libitum*. They were acclimatized for 15 days before performing the experiments. Animal care, handling, and experimental steps were all carried out under the official ethical guidelines.[22,23] All animals were submitted to 35% CO_2 euthanasia after completion of the study. The experimental protocol was registered to the Nepal Health Research Council (Reg. no.454/2018).

Preparation of Plant Extract

The plant parts were collected, washed, and subjected to shade drying followed by grinding into fine powder. The triple cold maceration technique was chosen. For the *F. religiosa* bark methanol was used as menstruum whereas cow urine was used for the *A. marmelos* leaves. About 200 g of crude sample was immersed in 1000 mL of menstruum in conical flasks with frequent shaking for 72 h. Liquids were strained filtered. The process was repeated up to triple maceration and the filtrates were mixed.

Evaporation of Extracts

The extraction filtrate was evaporated using a rotatory evaporator at temperature 40–45°C for methanolic extract and 60–65°C for cow urine extract, followed by the use of vacuum desiccator to remove trace of solvents. Thus, obtained concentrate was kept in vials and was stored in a refrigerator at temperature 4°C until it was used.

Lethal Dose (LD_{50})

Adult albino mice of either sex were subjected to LD_{50} which were studies as per guideline (425) suggested by the Organization for Economic Co-operation and Development. The mice were observed for 24 h for behavioral and autonomic profiles and any lethality during the next 48 h. Three groups of three mice each were administered orally with the *F. religiosa* and *A. marmelos* extract at doses of 250, 500, and 1000 mg/kg body weight and observed for signs of toxicity and death within 24 h.[22]

Phytochemical Screening

Phytochemical screening for alkaloids, saponin, flavonoid, phytosterol, phenol, and terpenoids were performed using standard procedure.[24-26]

Antiepileptic Activity

Thirty-six Swiss albino mice weighing 25–30 g were included in the study. Animals were evaluated for antiepileptic activity of extracts after inducing INH-induced seizures in them. Six groups of mice with six mice in each group received normal saline (control), diazepam 4 mg/kg I.P (standard), EEFR 200 mg/kg, EEFR 400 mg/kg, cow urine extract of *A. marmelos* (CUEAM) 200 mg/kg, and CUEAM 400 mg/kg (test groups), respectively, by the oral route.

INH-induced Convulsions

One hour after administration of normal (10 mL/kg), diazepam (4 mg/kg, I.P), EEFR 200, and 400 mg/kg, CUEAM 200, and 400 mg/kg body weight, animals were administered orally with standard convulsive agent INH (250 mg/kg, I.P) and placed in isolated cages. Animals that did not convulse within the 3 h of observation were qualified as protected. In unprotected animals, the latency to first epilepsy, duration of epilepsy, percentage protection, and mortality were recorded.[27]

Data Analysis

The mean latency of onset of epilepsy and duration of action for the antiepileptic activity was calculated by observing the total activity of animals and expressed in minutes as mean ± SEM. The mean between the control group and test groups was compared using a two-tailed Student's *t*-test. $P < 0.005$, $P < 0.0005$, and $P < 0.00005$ were considered statistically significant when compared to the control group.

RESULTS

The extractive values for extracts of bark of *F. religiosa* and the leaves of *Aegle marmelos* were found to be 17.26% and 9.06%, respectively.

Phytochemical Screening

Preliminary phytochemical screening of ethanolic extracts of both *F. religiosa* and *A. marmelos* was found positive for presence of alkaloids, saponin, flavonoid, phenols, and terpenoids. Phytosterol was absent in both extract samples.

LD_{50}

Three groups of three mice each were administered orally with the *F. religiosa* and *A. marmelos* extracts at doses of 250, 500, and 1000 mg/kg body weight and observed for signs of toxicity and death within 24 h. None of the groups reported mortality. Symptoms of toxicity such as corner sitting and paw licking were precipitated only at a dose of 1000 mg/kg body weight.

Antiepileptic Effect of Extracts

Oral INH dose of 250 mg/kg body weight produced tonic-clonic seizures in all the animals used. Both the EEFR and

Table 1: Effects of EEFR and CUEAM on isoniazid-induced convulsion in mice

Treatment group	Latency of first convulsion (min)	Convulsion duration (min)
INH+Saline (10 mL/kg)	30±6.09	24±9.79
INH+EEFR (200 mg/kg)	42±8.53*	20±7.16
INH+EEFR (400 mg/kg)	66±6.7***	17±5.10***
INH+CUEAM (200 mg/kg)	49±6.36**	18±7.41
INH+CUEAM (400 mg/kg)	79±7.0629***	11.5±3.12***
INH+Diazepam (4 mg/kg)	0	0

Data are analyzed using student *t*-test, two tail distribution, two sample equal variances. Values are mean±SEM, n=6 *P<0.005, **P<0.0005, ***P<0.00005 are considered statistically significant with compare to control group. INH: Isoniazid, EEFR: *Ficus religiosa* ethanolic extract, CUEAM: *Aegle marmelos* cow urine extract

CUEAM groups were compared with the control group. An oral dose of 200 mg/kg of EEFR significantly delayed the latency of first convulsion and significantly reduced duration of convulsion ($P < 0.005$) in mice against INH-induced convulsion. An oral dose of 400 mg/kg of EEFR significantly delayed the latency of first convulsion ($P < 0.0005$) and significantly reduced the duration of action of convulsion ($P < 0.0005$) induced by INH [Table 1]. Oral doses of 200 mg/kg and 400 mg/kg of EEFR showed 0% protection against INH-induced convulsion in mice [Table 2].

An oral dose of 200 mg/kg of CUEAM significantly delayed the latency of the first convulsion ($P < 0.005$) and significantly reduced the duration of convulsion in mice against INH-induced convulsion. An oral dose of 400 mg/kg of CUEAM significantly delayed the latency of the first convulsion ($P < 0.0005$) and significantly reduced the duration of action of convulsion ($P < 0.0005$) induced by INH [Table 1]. Oral doses of 200 mg/kg and 400 mg/kg of CUEAM showed 33.33% and 100% protection against INH-induced convulsion in mice, respectively [Table 2].

The standard anticonvulsant drug, diazepam when given orally at a dose of 4 mg/kg body weight, totally abolished the effects of INH-induced convulsion in mice [Tables 1 and 2].

DISCUSSION

Gamma-aminobutyric acid (GABA) is the predominant inhibitory neurotransmitter in the CNS. Impairment of GABA function is widely recognized to provoke seizures, whereas facilitation has an anticonvulsant effect.[26] Epilepsy in the INH method is due to the disturbed activity of GABA in the brain, which involves the disruption of GABAergic neurotransmission in the central nervous system. It has been reported that INH inhibits glutamic acid decarboxylase, an enzyme that catalyzes the synthesis of GABA from glutamic acid. Several antiepileptic drugs for example diazepam (standard drug) in current clinical use facilitate GABA neurotransmission by different mechanisms: Barbiturates, benzodiazepines, and other anti-epilepsy modulate the action of GABA by enhancing chloride currents in channels linked

Table 2: Protection and mortality of EEFR and CUEAM on isoniazid-induced convulsion in mice

Treatment group	Protection (%)	Mortality (%)
INH+Saline (10 ml/kg)	0	100
INH+EEFR (200 mg/kg)	0	100
INH+EEFR (400 mg/kg)	0	100
INH+CUEAM (200 mg/kg)	33.33	66.66
INH+CUEAM (400 mg/kg)	100	0
INH+Diazepam	100	0

INH: Isoniazid, EEFR: *Ficus religiosa* ethanolic extract, CUEAM: *Aegle marmelos* cow urine extract

to different receptor sites; other anticonvulsant reduce the degradation of GABA by blocking GABA transaminase or by inhibiting reuptake of GABA into the presynaptic terminals.[28,29]

In the present investigation, we have found dose-dependent antiepileptic action of *F. religiosa* and *A. marmelos*. The EEFR showed an increase in onset of time, a decrease in duration of epilepsy and *A. marmelos* in combination with cow urine at 400 mg/kg showed maximum protection, that is, 100% against epilepsy in higher dose phase. Therefore, the protection offered by *A. marmelos* (at both dose) by increasing the latency time may suggest the presence of compounds potentiating GABAergic action.

The possible mechanism for the anticonvulsant effect of *F. religiosa* bark extract might be due the presence of high saponin content. Saponin can exert anticonvulsant effect by blocking the voltage dependent Na+ channels and NMDA receptors. Methanolic extract *F. religiosa* fruit extract has shown anticonvulsant effect by modulating the GABAergic functions.[30,31] Previous study has reported that serotonin is abundantly present in the *F religiosa* plant and plant extract has exhibited carbamazepine like potent anticonvulsant effect probably by serotonergic mechanism.[32] Many scientific research have been conducted to describe the possible mechanism of anticonvulsant effect by *A. marmelos*. It has been reported that ethanolic extract of this plant can inhibit

the pentylenetetrazole and maximal electroshock-induced convulsions by protecting the peroxisome proliferator-activated receptors through the inhibition of nitric oxide expression in the brain.[33] Furthermore, interference of GABAergic neurotransmission might also be the another possible mechanism.[34]

CONCLUSION

This preclinical study substantiated the traditional antiepileptic use of plant *F. religiosa* and *A. marmelos* where further study can be utilized to identify certain trace of antiepileptic molecule or compound which can be potent option for significant anti-epileptic activity and hence may prove to be beneficial and an alternative in the treatment of epilepsy like disorders.

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