



The potential anticonvulsant activity of the ethanolic extracts of *Achillea nobilis* and *Momordica charantia* in rats

[Actividad anticonvulsivante de extractos etanólicos de *Achillea nobilis* y *Momordica charantia* en ratas]

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Abstract

Context: Currently available antiepileptic drugs have debilitating adverse effects. Natural products and plants already used in traditional medicine can be a good place to start in the search for safer and more effective options.

Aims: To investigate the anticonvulsant potential of *Achillea nobilis* and *Momordica charantia* extracts in maximal electroshock (MES), as well as pentylentetrazole (PTZ)- and strychnine nitrate (STN)- induced seizure models in rats.

Methods: For each model, eight groups of 21-day-old male Albino rats were used. The 1st group was kept as control, 2nd as standard (diazepam, 7.5 mg/kg); 3rd - 5th treated with *A. nobilis* (100, 200 and 300 mg/kg); and 6th - 8th administered *M. charantia* (100, 200 and 300 mg/kg). After 30 min, rats were exposed to a shock of 150 mA by a convulsimeter, via ear electrodes for 2 s (in MES test) or sc injection of PTZ (85 mg/kg) or STN (2.5 mg/kg).

Results: *A. nobilis* and *M. charantia* extracts (200 and 300 mg/kg) demonstrated dose-dependent anticonvulsant effect against MES-induced seizures. In the PTZ induced convulsion, *A. nobilis* and *M. charantia* (200 and 300 mg/kg) significantly slowed the commencement of convulsions and minimized the duration of seizures. *A. nobilis* (300 mg/kg) showed 60% protection in rats against STN induced seizures. In contrast, *A. nobilis* (100 and 200 mg/kg) and *M. charantia* (100, 200 and 300 mg/kg) showed no significant protection against STN-induced seizures in rats.

Conclusions: The results of the present study suggest that both extracts exhibited marked anticonvulsant activities.

Keywords: *Achillea nobilis*; anticonvulsant; *Momordica charantia*; pentylentetrazole; seizures.

Resumen

Contexto: En la actualidad los fármacos antiepilépticos disponibles presentan numerosos efectos adversos. Los productos naturales y las plantas, utilizados en la medicina tradicional, pueden ser un buen punto de partida en la búsqueda de opciones más seguras y eficaces.

Objetivos: Investigar el potencial anticonvulsivo de extractos de *Achillea nobilis* y *Momordica charantia* en electroshock máximo (MES), así como en modelos de convulsiones inducidas por pentilentetrazol (PTZ) y nitrato de estriquina (STN) en ratas.

Métodos: Para cada modelo, se utilizaron ocho grupos de ratas albinas macho de 21 días de edad. El primer grupo se mantuvo como control, el segundo como referencia (diazepam, 7,5 mg/kg); del tercero-quinto tratados con *A. nobilis* (100, 200 y 300 mg/kg); y del sexto-octavo administrados con *M. charantia* (100, 200 y 300 mg/kg). Después de 30 min, las ratas se expusieron a un choque de 150 mA de un convulsiómetro por 2 s, a través de electrodos para los oídos (en la prueba MES) o inyección sc de PTZ (85 mg/kg) o STN (2,5 mg/kg).

Resultados: Los extractos de *A. nobilis* y *M. charantia* (200 y 300 mg/kg) demostraron efecto anticonvulsivo dependiente de la dosis contra las convulsiones inducidas por MES. En la convulsión inducida por PTZ, *A. nobilis* y *M. charantia* (200 y 300 mg/kg) disminuyeron significativamente el comienzo de las convulsiones y redujeron al mínimo la duración de éstas. *A. nobilis* (300 mg/kg) mostró una protección del 60% contra las convulsiones inducidas por STZ. En contraste, *A. nobilis* (100 y 200 mg/kg) y *M. charantia* (100, 200 y 300 mg/kg) no mostraron una protección significativa frente a ataques inducidos por STN.

Conclusiones: Los resultados del presente estudio sugieren que los dos extractos mostraron una marcada actividad anticonvulsivante.

Palabras Clave: *Achillea nobilis*; anticonvulsivante; convulsiones; *Momordica charantia*; pentilentetrazol.

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INTRODUCTION

Epilepsy, being one of the very prevalent and grave neurological disorders. It is characterized by frequent unrestrained convulsions (Adkar et al., 2014). Current antiepileptic drugs (AEDs) are non-favorable, as they provide only symptomatic satisfaction. About one-third of patients do not respond well to currently available treatment (Schmidt and Löscher, 2005). Furthermore, many AEDs have debilitating adverse effects, and lifelong medication may be required (Belcastro et al., 2010). Thus, the continued seeking for reliable and more effective AEDs is needful. The plants are considered as the main target in the investigation of new drugs of natural origin (Ojewole, 2008).

Achillea that relates to the family Compositae (Asteraceae) is a genus with around 130 species (Amjad et al., 2011). These plants are native to Europe and Western Asia, although they are also found in Australia, New Zealand and North America (Chevalier, 1996). Some plants of *Achillea* are widely used in folk medicine as anti-inflammatory, spasmolytic, antihemorrhoidal, stomachic and antiseptic (Falk et al., 1975, Afsharypuor et al., 1996 and Goldberg et al., 2006). Some *Achillea* species have shown antidiabetic (Yazdanparast et al., 2007) and antimicrobial activities (Maggi et al., 2009). The antispasmodic activity of a total extract of *A. nobilis* on rat duodenum was observed (Karamenderes and Apaydin, 2003). The genus *Achillea* is chemically characterized by an accumulation of sesquiterpene lactones and flavonoids (Abdel-Rahman et al., 2015a). From a phytochemical point of view, *Achillea* species contain terpenoids, lignans, flavonoids and amino acid derivatives (Si et al., 2006).

Momordica charantia, also known as bitter melon, is one of the most important species of the family, Cucurbitaceae (Bakare et al., 2010). The plant has been reported to possess anti-hyperglycemic (Singh et al., 2008), anti-tumor (Lee-Huang et al., 1995), anti-HIV (Jiratchariyakul et al., 2001), anti-ulcerogenic (Gürbüz et al., 2000) and hypotriglyceridemic activities (Ahmed et al., 2001). A tea prepared from the leaf is used to expel intestinal gas, to promote menstruation, and as an antiviral agent against measles and hepatitis (Sofowora, 2006). The bioactive compounds

of the plant include triterpens, saponins, alkaloids, flavonoids and acids (Gupta et al., 2011).

Some species of *Achillea* (Hosseini et al., 2014) and *Momordica* (Vangoori et al., 2013) are reported as anti-convulsants; however, no data are available concerning the anticonvulsant activity of *A. nobilis* and *M. charantia*. The present work was undertaken to investigate the potential anticonvulsant activities of *A. nobilis* and *M. charantia* extracts using MES, PTZ, and STN-induced seizure tests.

MATERIAL AND METHODS

Plant material

Fresh flowering aerial parts of *A. nobilis* and fruits and seeds of *M. charantia* were collected at summer 2011, from the A4 Ankara: Hasanoglan, surrounding Yeşildere villa, taxonomic identification was determined by Prof. Dr. Galip Akaydin and a voucher specimen from each plant (Akaydin 13450) were deposited at the Herbarium of Faculty of Education (HEF), Hacettepe University, Ankara, Turkey. The mature *M. charantia* fruits were collected in July, 2011 from a garden in Kuşadası, İzmir, Turkey. The fruits were identified and cultivated by Prof. Dr. İrem Tatlı Çankaya from Department of Pharmaceutical Botany, Faculty of Pharmacy, Hacettepe University, Ankara, Turkey.

Preparation of plant extract

The collected plants were shade dried and then grinded to fine powders. The air-dried powdered roots (100 g) were extracted with 3 L of ethanol-water (80:20) under reflux for 4 h each and filtered. The filtrates were combined and subjected to rotary evaporation (Büchi rotavapor R-215, vacuum pump V-700) ($70 \pm 2^\circ\text{C}$) to concentrate. The procedure was repeated twice. The thick solution was lyophilized using freeze drier give the total extracts of *A. nobilis* (15 g) and *M. charantia* (33.5 g). Both extracts were stored in the refrigerator and an aliquot of the concentrations was prepared immediately before use.

Animals

Twenty one-day-old male Albino rats (50-55 g body weight) bred in the Lab Animal Care Unit, Pharmacy College, Prince Sattam bin Abdulaziz University, Al-Kharj, KSA, were used for the experiment. Rats were preserved under standard situations of temperature ($23 \pm 1.0^\circ\text{C}$) and 12 h light/12 h dark cycle. The animals were kept in groups of ten in standard polypropylene cages and fed with a standard diet with water ad libitum. They were allowed to adapt to the laboratory environment for one week before experimentation. Each rat was used for only one experiment. Experimental procedures were carried out in accordance with international regulations on animal protection, and/or the Guide for the Care and Use of Laboratory Animals. The study protocol was approved by the Institutional Animal Ethics Committee.

Acute toxicity test

Acute toxicity study of the ethanol extracts of *A. nobilis* and *M. charantia* was carried in adult male albino rats according to OECD-423 guidelines (OECD, 2001). Rats were divided into 3 groups ($n = 6$) and fasted overnight. Rats of the 1st and 2nd groups received *A. nobilis* and *M. charantia* extracts, respectively at a dose of 3000 mg/kg (5 mL/kg) by the oral route. Rats of the 3rd group (control) treated with the vehicle (3% v/v Tween 80 in distilled water) and kept under the same conditions. Each animal was observed for symptoms of toxicity and/or mortalities during the first 30 min and periodically during 24 h, with special attention given during the first 4 h and daily thereafter, for a total of 14 days.

Selection of doses

Doses up to 3000 mg/kg of *A. nobilis* and *M. charantia* extracts were nontoxic. Therefore, doses of 100, 200 and 300 mg/kg that are equal to 1/30, 1/15 and 1/10 of the maximal possible dose tolerated by rats were selected for the study.

The anticonvulsant activity

The anticonvulsant activity of *A. nobilis* and *M. charantia* extracts was investigated in rats using

the electrically (MES) and chemically (scPTZ and scSTN) induced seizure models.

Electrically induced seizure model (MES test)

This test was implemented in rats according to the method of Garg et al. (2010). Twenty-one day-old male Albino rats (50-55 g body weight) were separated into 8 groups ($n = 10$). The 1st group was medicated with the vehicle, orally and the 2nd one received diazepam intraperitoneally (7.5 mg/kg). Rats of the 3rd, 4th and 5th groups received *A. nobilis* aerial part extract by oral route at doses of 100, 200 and 300 mg/kg, respectively. Rats of the 6th, 7th and 8th groups received *M. charantia* seed extract orally (100, 200 and 300 mg/kg, respectively). Medications with the vehicle, diazepam and extracts were continued for 10 days. On the 10th day, 30 min after administration of the last dose of the vehicle, diazepam, and extracts, animals were exposed to a shock of 150 mA by convulsimeter, through ear electrodes for 2 s as described by Swinyard (1969). The number of rats showed HLTE and the percentage of animals protected against HLTE were recorded. Rats in which HLTE response was abolished within 10 sec after transmission of the electroshock were taken as protected animals. The HLTE was considered abolished if the extension of the hind limb did not exceed a 90° angle with the plane of the body (Swinyard and Woodhead, 1982).

Chemically induced seizure models (PTZ and STN-induced seizure tests)

Eight groups of rats ($n=10$) were used for each seizure model. Rats were treated for ten days like those stated with MES test. On the 10th day, 30 min after administration of the last dose, convulsions were induced in rats by subcutaneous injection of 85 mg/kg of PTZ or 2.5 mg/kg of STN (in PTZ and STN-induced seizure test, respectively). Number of animals showing seizures, latency (s), duration of seizures (s), percentage protection against seizures and percentage protection against lethality were recorded for the duration of 30 min (Abdel-Rahman et al., 2015b).

Statistical analysis

Results were expressed as mean \pm SEM and percentage protection. Data were analyzed by one-way ANOVA followed by Dunnett's test for multiple comparisons using the SPSS version 10. Results were considered significant at $p < 0.05$.

RESULTS

Acute toxicity test

No visible signs of toxicity were reported in the rats exposed to different doses of *A. nobilis* and *M. charantia* extracts indicating their safety. Both extracts did not provoke any gross behavioral changes such as abnormal motor activity, tremors, muscle spasm, sedation and hypnosis over a period of 24 h. The ethanolic extracts of *A. nobilis* and *M. charantia* were non-lethal even at the maximum single oral dose of 3000 mg/kg. Accordingly, the oral LD₅₀ values of both extracts were determined to be higher than 3000 mg/kg b.w, which is the highest tested dose.

The anticonvulsant activity

Electrically induced seizure model (MES test)

The results of the MES seizure model were presented in Table 1. The controlled animals manifested tonic flexion of fore and hind limb and fore and hind limb tonic extension (HLTE). The reference drug; diazepam completely protected rats against MES-induced seizures. *A. nobilis* extract demonstrated dose-dependent anticonvulsant activity against electroshock-induced HLTE. There was a complete abolishment of hind limb tonic extension (HLTE) in 60% and 80% of the rats treated with 200 and 300 mg/kg, respectively of *A. nobilis*. Also, they protected rats against lethality (70 and 90%, respectively). *A. nobilis* extract at 100 mg/kg did not protect rats against maximal electroshock seizures (20%) and lethality (20%). The ethanolic extract of *M. charantia* at a dose of 300 mg/kg protected rats against MES-induced seizures (60%) and against lethality (70%). *M. charantia* extract at 100 and 200 mg/kg did not protect rats against maximal electroshock seizures (0 and 30%, respectively) and lethality (0 and 30%, respectively).

Chemically induced seizure models (PTZ and STN-induced seizure tests)

The anticonvulsant activity of the *A. nobilis* and *M. charantia* extracts was further determined after administration of pentylenetetrazol (PTZ) and strychnine (STN). Subcutaneous injection of PTZ at 85 mg/kg elicited clonic seizure in 100% of the animals used in vehicle treated control with 57.8 ± 2.36 s latency of seizure and 184.7 ± 7.35 s duration of seizures (Table 2). The standard anti-epileptic drug, diazepam (7.5 mg/kg) completely antagonized seizures and lethality of rats produced by PTZ. Prior administration of *A. nobilis*, dose-dependently protected rats against PTZ-induced seizures with peak effect at 300 mg/kg. Doses of 200 and 300 mg/kg protected 60% and 80%, respectively of the rats against PTZ-induced seizures. Both doses of *A. nobilis* extract significantly delayed the onset of seizures (98.2 ± 5.38 and 137.5 ± 5.52 s, respectively) and reduced duration of seizures (128.7 ± 4.22 and 90.3 ± 3.63 s, respectively) in non-protected rats. Rats pre-treated with *M. charantia* extract at doses of 200 and 300 mg/kg showed a significant delay in the onset of PTZ induced seizures (89.4 ± 5.71 and 117.2 ± 5.45 s, respectively). Both doses reduced the duration of convulsions (133.7 ± 5.85 and 109.5 ± 4.38 s, respectively) and protected against lethality to 50% and 70%, respectively. At a dose of 100 mg/kg, *M. charantia* extract showed 0% protection against seizures and lethality.

In the STN model, subcutaneous injection of STN produced seizure duration of 39.5 ± 2.18 s in vehicle control treated (Table 3). The standard anticonvulsant drug, diazepam totally abolished the effects of STN induced convulsion in rats. *A. nobilis* extract protected 60% of the rats against STN-induced seizures at a dose of 300 mg/kg, and significantly delayed the onset of tonic seizures in non-protected rats (164.6 ± 7.50 s) compared with the control group (122.5 ± 5.27 s). It decreased the duration of seizure (23.8 ± 1.82 s) compared with the control group (39.5 ± 2.18 s). In contrast, the ethanol extracts of *A. nobilis* (100 and 200 mg/kg) and *M. charantia* (100, 200 and 300 mg/kg) showed no significant protection against STN-induced convulsions in rats.

DISCUSSION

Evaluation of the potential toxicity of natural products is usually an initial step in screening for their pharmacological activities. In our investigation, *A. nobilis* and *M. charantia* extracts at oral doses up to 3000 mg/kg did not induce any sign of acute toxicity, and none of the animals died during 48 h of observation. The oral LD₅₀ values for the tested extracts were indeterminable being more

than 3000 mg/kg b.w. In general, the higher the LD₅₀ value, the lower toxic the compound. Therefore, *A. nobilis* and *M. charantia* extracts can be classified as slightly toxic or practically non-toxic as materials possessing LD₅₀ between 500 - 5000 and 5000 - 15 000 mg/kg body weight are categorized as slightly toxic and practically non-toxic respectively (Loomis and Hayes, 1996).

Table 1. The anticonvulsant effect of *A. nobilis* and *M. charantia* extracts using MES-induced seizure in rats.

Treatment	Dose (mg/kg)	Number of animals showing seizures	Protection against seizures (%)	Protection against lethality (%)
Control (Vehicle)	5 mL/kg	10/10	0	0
Diazepam	7.5	0/10	100	100
<i>A. nobilis</i>	100	8/10	20	20
	200	4/10	60	70
	300	2/10	80	90
<i>M. charantia</i>	100	10/10	0	0
	200	7/10	30	30
	300	4/10	60	70

The results are expressed as ratio and percentage, n =10 rats/group.

Table 2. The anticonvulsant effect of *A. nobilis* and *M. charantia* extracts using PTZ-induced seizure in rats.

Treatment	Dose (mg/kg)	Number of animals showing seizures	Latency (s)	Duration of seizures (s)	Protection against seizures (%)	Protection against lethality (%)
Control (Vehicle)	5 mL/kg	10/10	57.8 ± 2.36	184.7 ± 7.35	0	0
Diazepam	7.5	0/10	0	0	100	100
<i>A. nobilis</i>	100	8/10	63.5 ± 3.25	180.5 ± 6.50	20	20
	200	4/10	98.2 ± 5.38*	128.7 ± 4.22*	60	70
	300	2/10	137.5 ± 5.52*	90.3 ± 3.63*	80	100
<i>M. charantia</i>	100	10/10	60.3 ± 2.53	185.8 ± 6.40	0	0
	200	5/10	89.4 ± 5.71*	133.7 ± 5.85*	50	60
	300	3/10	117.2 ± 5.45*	109.5 ± 4.38*	70	80

The results are expressed as ratio, mean ± SEM and %, n = 10 rats/group.

* indicate significance compared to control group at p < 0.05.

Table 3. The anticonvulsant effect of *A. nobilis* and *M. charantia* extracts using STN-induced seizure in rats.

Treatment	Dose (mg/kg)	Number of animals showing seizures	Latency (s)	Duration of seizures (s)	Protection against seizures (%)	Protection against lethality (%)
Control (Vehicle)	5 mL/kg	10/10	122.5 ± 5.27	39.5 ± 2.18	0	0
Diazepam	7.5	0/10	0	0	100	100
<i>A. nobilis</i>	100	9/10	128.5 ± 6.23	36.3 ± 2.41	10	0
	200	6/10	141.5 ± 7.92	32.7 ± 2.26	40	40
	300	4/10	164.6 ± 7.50*	23.8 ± 1.82*	60	60
<i>M. charantia</i>	100	10/10	125.7 ± 6.25	37.9 ± 2.50	0	0
	200	9/10	129.2 ± 6.83	34.3 ± 2.42	10	0
	300	8/10	140.6 ± 7.17	32.6 ± 2.47	20	10

The results are expressed as ratio, mean ± SEM and %, n = 10 rats/group.

* indicate significance compared to control group at p < 0.05.

Convulsive attacks are common problems of medical practice. The management of most epilepsies is fairly satisfactory with the range of drugs available. However, a certain percentage of epilepsies do not respond to even polypharmaceutical therapy (Garbhapu et al., 2011). Also, the available range of drugs for use in epilepsy itself indicates that there is no single satisfactory drug to meet the needs of therapy (Brodie et al., 2010). Hence, the necessity exists for exploring newer drugs, for either greater anti-seizure activity, or lesser side effects. Plant sources remain a huge untapped resource for exploring for such new agents. Hence this trial was initiated.

The emergence of new materials for the control of convulsions are based mainly on the use of predictable animal models. The MES and PTZ induced seizure tests are the primary assays in the conventionally accepted anticonvulsant screening procedure (Kamiński et al., 2015). In our investigation, the anticonvulsant effect of *A. nobilis* and *M. charantia* extracts was estimated by electroshock (MES) and chemoshock (scPTZ and scSTN) methods.

The MES-induced seizure in animals represents the grandmal type of convulsion. The tonic extensor stage of convulsion is selectively eliminated by the compounds that are effective against generalized tonic-clonic seizure. In the MES test, *A. nobilis* extract totally abolished the HLTE herewith providing 60 and 80% seizure protection in the rats

treated with 200 and 300 mg/kg, respectively. *M. charantia* (300 mg/kg) extract also protected 60% of rats against MES-induced seizures. Protection against MES-induced seizures in rats indicated that *A. nobilis* and *M. charantia* extracts have anticonvulsant activity. In this respect, MES-induced HLTE can be antagonized by compounds that block voltage-dependent Na⁺ channels (Ambavadea et al., 2009). Also, GABA (γ -aminobutyric acid) is the major inhibitory neurotransmitter in the brain, and is excessively involved in convulsions. Substances that elevate the brain level of GABA have showed an anticonvulsant effect against seizures induced by MES (Manigauha et al., 2009). At this phase, we suppose that the attenuation of HLTE by *A. nobilis* and *M. charantia* extracts may be due to their sodium channel blocking action, or as a result of the elevated level of brain γ -aminobutyric acid. Furthermore, diverse classes of active compounds such as flavonoids and terpenes have been reported to possess anticonvulsant activity (Ali and Chaudhary, 2011). Accordingly, the anticonvulsant activities of *A. nobilis* and *M. charantia* extracts may be due to the presence of many phytochemicals such as flavonoids (Abdel-Rahman et al., 2015a and Gupta et al., 2011, respectively).

PTZ is a GABA antagonist and is specifically used in seizure assays. PTZ has been stated to induce convulsions by blocking γ -aminobutyric acid neurotransmission (Pérez-Saad and Buznego, 2008). In

this investigation, the protection of rats against PTZ-induced seizures by the standard anticonvulsant drug; diazepam is expected. Diazepam is thought to induce its effect by enhancing of the GABAergic neurotransmission in the brain (MacDonald and Kelly, 1995). Similarly, *A. nobilis* (200 and 300 mg/kg) and *M. charantia* (200 and 300 mg/kg) significantly slowed the commencement of convulsion, decreased the duration of seizures and increased the percentage of protection against lethality in rats exposed to PTZ-induced convulsions. As PTZ has been shown to interact with γ -aminobutyric acid, the antagonism of PTZ-induced convulsions suggests that *A. nobilis* and *M. charantia* might have an effect on GABAergic neurotransmission. Convulsions induced by PTZ can also be minimized by decreasing T-type Ca^{2+} currents (Meldrum, 1996). Inducement of the NMDA (N-methyl-d-aspartate) receptors is also implicated in the initiation and expansion of PTZ-induced convulsions (Yudkoff et al., 2006). In this consideration, materials that block glutamatergic stimulation mediated by NMDA receptors have showed an anticonvulsant effect against PTZ-induced seizures (MacDonald and Kelly, 1995). Thus, it is possible that the anticonvulsant activities shown in this investigation by *A. nobilis* (200 and 300 mg/kg) and *M. charantia* (200 and 300 mg/kg) against convulsions produced by PTZ might be due to suppression of T-type Ca^{2+} currents or blockade of glutamatergic neurotransmission mediated by NMDA receptor.

In addition, *A. nobilis* extract protected animals against STN-induced convulsions. The convulsive effect of STN is due to intervention with postsynaptic inhibition mediated by glycine, a significant inhibitory transmitter to motor neurons in the spinal cord. STN acts as a selective, competitive antagonist to antagonize the depressant actions of glycine at all glycine receptors (Kuno and Weakly, 1972). The protective effect of the aerial part of *A. nobilis* extract against STN-induced convulsions, proposes that it possesses anticonvulsant activity and that glycine neurotransmission is involved. In this present study, we have found that the *M. charantia* seed extract was not showing any protection against STN-induced convulsion. Depending on these evidences, it was presumed that the anticonvulsant effect of *M. charantia* may not be due to its

effect on glycine neurotransmission but may be due to γ -aminobutyric acid mediated mechanism.

CONCLUSIONS

The ethanolic extracts of aerial parts of *A. nobilis* and seeds of *M. charantia* demonstrated marked protective activities against MES and PTZ seizures. Also, *A. nobilis* was found to have anticonvulsant activity against seizures induced by STN. More, it is postulated that the anticonvulsant effect of *A. nobilis* and *M. charantia* may be attributed to their phytochemical constituents. Further phytochemical studies will be required to isolate the active constituents of both plants responsible for their anticonvulsant activities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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