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ANTI CONVULSANT POTENTIAL OF LEAVES OF *PSIDIUM GUAJAVA* LINN. IN MES AND PTZ INDUCED CONVULSION IN EXPERIMENTAL ANIMALS

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ABSTRACT: Objectives: To study the anti-convulsant potential of leaves of *Psidium guajava* Linn. in MES and PTZ induced convulsion in experimental animals. **Materials and methods**: The anticonvulsant potential of the ethanolic extracts of *Psidium guajava* Linn. (EEPG) were tested in the mice model of Maximal electroshock (MES) and Pentylenetetrazole (PTZ). In the MES model, seizures were induced by delivering electroshock of 50 mA for 0.2 seconds via a pair of transauricular electrodes using an electro-convulsiometer. In the PTZ model, seizures were induced by injecting 80 mg/kg i.p Pentylenetetrazole (PTZ). For MES model, parameters measured were - duration of hind limb tonic extension, total recovery time and percentage protection. For the PTZ model, parameters measured were –duration of onset of clonic convulsions, duration of clonic convulsions, percentage reduction of clonic phase, mortality percentage and seizure score. **Results and Observation:** The EEPG (200 mg/kg and 400 mg/kg) produced dose dependent anticonvulsant effect on MES induced seizures in albino mice, as suggested by reduction in the HLTE and total recovery time, and increase in the percentage protection from MES induced convulsions. EEPG also prolonged the latency of clonic convulsion and reduced the duration of convulsion in a dose dependent manner, as well as reduce the seizure score, thus suggesting the anticonvulsant effect of the extract on PTZ induced seizures. **Conclusion:** The present study concludes that the ethanolic extract of the leaves of Psidium guajava Linn. have anticonvulsant effect on PTZ and MES induced convulsion in albino mice.

INTRODUCTION: *Psidium guajava* Linn. commonly known as guava, is a fruit-bearing tree belonging to the family, Myrtaceae. It is a medium sized tree growing up to 15 meters in height in the tropical and semitropical regions.[1]

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Guava contains broad spectrum of phytochemicals including polysaccharides, vitamins, essential oils, minerals, enzymes, proteins, sesquiterpenoid alcohols and triterpenoid acids, alkaloids, glycosides, steroids flavanoids, quercetin, tannins, oxalates and saponins.[2, 3] Guava leaves contain essential oil rich in cineols, tannins, triterpenes, flavanoids, resin, tannin, eugenols, mallic acid, fat, cellulose, chlorophyll, mineral salts and a number of other fixed substances. Chief among the terpenes are limonene, β sitosterol, guayavolic acid, guajavolide, guavenoic acid and others.[4] It is very

rich in antioxidants and vitamins and also high in lutein, zeaxanthine and lycopene. [2] The roots, bark, leaves and immature fruits, because of their astringency, are commonly employed to halt gastroenteritis, diarrhoea and dysentery, throughout the tropics.[5, 6] A decoction of the new shoots is taken as a febrifuge.

The leaf infusion is prescribed in India in cerebral ailments, nephritis and cachexia. An extract is given in epilepsy and chorea and a tincture is rubbed on the spine of children in convulsions. A combined decoction of leaves and bark is given to expel the placenta after childbirth.[6] Phytochemicals like triterpenoids, saponins, flavonoids, coumarin, essential oils, tannins, steroids, alkaloids, sterols, isolated from other plants have been reported to have anticonvulsant property in various animal models of epilepsy like PTZ, MES, electrical kindling, etc.[7, 8] In view of its traditional use by the people in this part of the world in the treatment of convulsion and epilepsy; and also due to the presence of phytochemicals (having anticonvulsant property), the present study has been undertaken to carry out Pharmacological investigations of *Psidium guajava* (guava) for its anticonvulsant potential in mice models *in-vivo*.

MATERIALS AND METHOD:

The present study has been carried out in the Department of Pharmacology, Gauhati Medical College and Hospital, Guwahati, Assam to study the anticonvulsant potential of leaves of *Psidium guajava* Linn. (Guava) in Pentylenetetrazole (PTZ) and Maximum electroshock seizure (MES) induced convulsion in albino mice after obtaining due approval from Institutional Animal Ethics Committee (IAEC) No.MCI 32/2012/1. The study was performed according to the CPCSEA guidelines.

Extraction of Plant material:

The leaves of *Psidium guajava* Linn. were collected from in and around Guwahati during April-June 2011 and were used in the study. The collected leaves were shade dried and finely powdered in an electric grinder and 300 grams of the powdered leaves were extracted with 99.9% ethanol using Soxhlet apparatus at a temperature of 60°C for 24 hours.[9] The solvent was taken in glass petri dishes and evaporated in a controlled water bath (temperature 40-50°C) which gave semisolid mass.[10, 11] A final yield of 48 grams i.e. 16% w/w with respect to the original air dried powder was obtained. The extract was finally stored in air tight containers in a refrigerator at 2-8°C for further use in the experiment.

Experimental animals:

Healthy albino mice of either sex weighing between 25-30 gm were procured from the Institute`s Central animal house, Gauhati Medical College & Hospital, Guwahati. The animals were acclimatized to the laboratory conditions for at least seven days prior to the experiments. The animals were housed in animal room in groups, in polypropylene cages as per the standard laboratory conditions at 25^{o}C with 12:12 hours light & dark cycle, with alternating light-dark cycle of 12 hours each. The animals were maintained on a standard animal diet with water ad libitum, but fasted prior to dosing (food but not water was withheld for 3-4 hours).

Induction of convulsion:

The anticonvulsant effects of the ethanolic extracts of *Psidium guajava* Linn. (EEPG) were tested in the animal models of Maximal electroshock (MES) and Pentylenetetrazole (PTZ). In the MES model, seizures were induced by delivering electroshock of 50 mA for 0.2 seconds by means of an electro-convulsiometer through a pair of transauricular (ear clip) electrodes.[7] In the other model i.e., Pentylenetetrazole (PTZ) model, seizures were induced by injecting 80 mg/kg i.p Pentylenetetrazole (PTZ) to the mice. This is the convulsive dose in 97% of the mice.[12] Experimental animals were grouped and administered the study drugs and standard drug for both the models as shown in the **Table 1** and **Table 2**

TABLE 1: GROUPING OF ANIMALS FOR MES MODEL[13]

Serial No.	Groups	Drugs
1.	Group IA: Control group	10 ml/kg of 0.1% gum acacia in saline p.o.
2.	Group IIA: Standard group	Phenytoin 25 mg/kg p.o
3.	Group IIIA	EEPG 200 mg/kg p.o
4.	Group IVA	EEPG 400 mg/kg p.o

TABLE 2: GROUPING OF ANIMALS FOR PTZ MODEL[12]

Serial No.	Groups	Drugs
1.	Group IB: Control group	10 ml/kg of 0.1% gum acacia in saline p.o.
2.	Group IIB: Standard group	Phenytoin 25 mg/kg p.o
3.	Group IIIB	EEPG 200 mg/kg p.o
4.	Group IVB	EEPG 400 mg/kg p.o

Maximal electroshock (MES) model:

The mice were pretested with a current of 50 mA for 0.2 seconds via a pair of transauricular (ear clip) electrodes, using an electro-covulsiometer. Only those mice which produced hind limb tonic extension (HLTE) component of MES were selected for the main study. A recovery period of 3-4 days was given before repeating the experiment. The mice were allowed free access to food and water except during the short time they were removed from their cages for testing.[14] The mice were taken out randomly from the cages and weighed in an electronic weighing machine and marked according to groups.

Normal saline, standard drug (phenytoin) and test extracts were suspended in 1% gum acacia and administered orally to the control, standard and test groups mice respectively. One hour (60 minutes) after administration of the test extracts/ drugs/ vehicle the animals were subjected to maximal electroshock seizure (MES) by convulsiometer with a current of 50mA for 0.2 seconds via a pair of transauricular (ear clip) electrodes. MES produced various phases of convulsions i.e. tonic flexion of the forelimbs and hindlimbs, hind limb tonic extension, clonus and stupor followed by recovery.[14, 15] Parameters measured were (a) duration of hind limb tonic extension (HLTE), (b) total recovery time and (c) percentage protection.

The percentage protection was calculated as:

$$\frac{\text{Duration of HLTE in Control} - \text{Duration of HLTE in Test/Standard}}{\text{Duration of HLTE in Control}} \times 100$$

The duration of tonic extension of hind limb was used as end point i.e. prevention or decrease in the duration of hind limb extension was considered as a protective action.[16]

Pentylenetetrazole (PTZ) seizure model:

The animals were allowed free access to food and water except during the short time they were removed from their cages for testing.[17, 18] The mice were taken out randomly from the cages and weighed in an electronic weighing machine and marked according to groups. The standard drug (phenytoin) and test extracts were suspended in 1% gum acacia and administered orally to the respective groups as given in **Table 2**. One hour (60 minutes) after administration of the test extracts/ drugs/ vehicle the animals were given Pentylenetetrazole (PTZ) at a dose of 80 mg/kg intraperitoneally after dissolving in distilled water.[8] Each animal was placed into an individual plastic cage for observation lasting 1 hour. The onset of a general clonus was used as the endpoint. The general clonus was characterized by forelimb clonus followed by full clonus of the body. The time taken for the onset of clonic convulsions (latency period), the duration of clonic convulsions, the percentage reduction of clonic phase and the percentage mortality were recorded.[18]

The percentage reduction of clonic convulsion was calculated as:

$$\frac{\text{Duration of Clonus in Control} - \text{Duration of Clonus inTest/Standard}}{\text{Duration of Clonus in Control}} \times 100$$

PTZ *seizure scoring* was done as per the scale described by Velisek et al. (1992) as described in **Table 3**.[20]

TABLE 3: SEIZURE SCORING, THE SCALE DESCRIBED BY VELISEK ET AL. (1992):

Serial No.	Scoring	Changes
1.	0	No change in behaviour
2.	0.5	Atypical behavior (e.g., intensive grooming, sniffing, moving arrests)
3.	1	Isolated myoclonic jerks and ear and facial twitching
4.	2	Atypical minimal seizures and convulsive waves throughout the body
5.	3	Fully developed minimal seizures, clonus of the head muscles and forelimbs, and the presence of the righting reflex
6.	4	Major seizures (i.e., generalized, without the tonic phase
7.	5	Generalized tonic-clonic seizures beginning with running followed by lost righting ability and a short tonic phase (i.e., flexion or extension of forelimbs and hind limbs) progresses to the clonus.

Statistical analysis:
All the data were entered into the statistical software, SPSS 16.0. Data were expressed as mean ± SEM. Results were analysed by one way analysis of variance (ANOVA), followed by Dunnett multiple comparison test. P value<0.05 was considered as statistically significant.

RESULTS AND OBSERVATION:

Acute Toxicity Study:
NOAEL of ethanolic extract of *Psidium guajava* Linn. leaves was found to be 2000 mg/kg/day. Hence, $1/10^{th}$ (200 mg/kg) and $1/5^{th}$ (400 mg/kg) doses were taken for further study.

Anticonvulsant Study:
The results obtained from the study have been summarized in the following tables (**Table 4, Table 5** and **Table 6**) and the values are expressed in specific units for each of the parameters as mentioned in the tables. All the data were entered into the statistical software, SPSS 16.0. Data were expressed as mean ± standard error of mean (Mean ± SEM). The statistical significance were analyzed by using one way analysis of variance (ANOVA), followed by Dunnett multiple comparison test using SPSS version 16. The significance in both the tests was expressed by F ratio and p values, as mentioned in the tables. p value of < 0.05 was considered to be statistically significant.

Maximal Electroshock (MES) Induced Seizure Study:
The results of the MES induced seizures study are tabulated in the **Table 4**. The results of one way ANOVA for maximal electroshock induced seizures are statistically significant (p < 0.05).

TABLE 4: MAXIMAL ELECTROSHOCK (MES) INDUCED SEIZURES IN MICE:

Group	Treatment	Duration of HLTE (in sec) Mean ±SEM	Total Recovery Time (in sec) Mean ±SEM	% Protection
IA	Control	19.17 ± 0.749	183.33 ± 9.804	-
IIA	Phenytoin 25 mg/kg p.o	02.67 ± 0.333#	22.50 ± 0.619#	86.07
IIIA	EEPG 200 mg/kg p.o	14.00 ± 0.577#	122 ± 1.461#	26.97
IVA	EEPG 400 mg/kg p.o.	06.50 ± 0.764#	50.00 ± 1.033#	66.09
One way ANOVA		df 3, 20 F 138.205 p< 0.05	df 3, 20 F 211.471 p< 0.05	

# p<0.05 when compared with the Control group (Group IA)

The mean duration of the hind limb tonic extension (HLTE) in the control group (Group IA) was 19.17 ± 0.749 seconds. The mean duration of hind limb tonic extension (HLTE) were 2.67 ± 0.333, 14 ± 0.577 and 6.50 ± 0.764 seconds for groups IIA, IIIA and IVA respectively (**Table 4**). Analysis of variance followed by Dunnett's t test showed that the reduction in the hind limb tonic extension (HLTE) were statistically significant (p<0.05) when compared with the control group. The extracts of EEPG showed dose dependent reduction in the HLTE.

The mean duration of total recovery time in the control group (Group I) was 183.33 ± 9.804 seconds. The mean duration of total recovery time were 22.5 ± 0.619, 122 ± 1.461 and 50 ± 1.033 seconds for groups IIA, IIIA and IVA respectively (**Table 4**). Analysis of variance followed by Dunnett's t test showed that the reduction in total recovery time were statistically significant (p < 0.05) when compared with the control group. The extracts of EEPG also showed dose dependent reduction in total recovery time. The percentage protection in the Phenytoin treated group was 86.07%, whereas the groups treated with EEPG 200 mg/kg and EEPG 400 mg/kg, showed percentage protection of 26.97% and 66.09% respectively. Graphical representation of the duration of hind limb tonic extension (HLTE) and total recovery time after oral administration of the standard drug phenytoin, EEPG (200 mg/kg and 400 mg/kg) and the control group are shown in the **Fig.1**.

PTZ Induced Seizures Study:
The results of the PTZ Induced seizures study are tabulated in the **Table 5**. The results of one way ANOVA for PTZ induced seizures are statistically significant (p < 0.05).

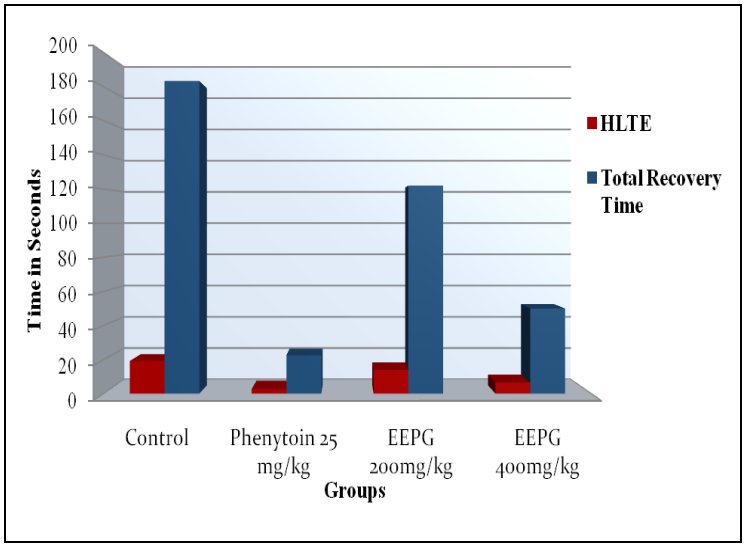

FIG.1: BAR DIAGRAM SHOWING MES INDUCED SEIZURES IN MICE

TABLE 5: PTZ INDUCED SEIZURES IN MICE

Group	Treatment	Onset of Clonus (s) Mean ± SEM	Duration of Convulsion (s) Mean ± SEM	% Reduction	% Mortality
IB	Control	129.50±6.820	77.17±4.086	_	100
IIB	Phenytoin 25 mg/kg p.o	419.67±8.876*	8.83±0.307*	88.56	16.67
IIIB	EEPG 200 mg/kg p.o	176.50±5.548*	49.00±3.044*	36.50	66.67
IVB	EEPG 400 mg/kg p.o.	300.00±6.890*	19.83±1.276*	74.30	33.33
One way ANOVA		df 3, 20 F 334.371 p< 0.05	df 3, 20 F 136.484 p < 0.05		

*p<0.05 when compared with the Control group (Group IB)

The mean duration of the onset of clonic convulsion (latency) in the control group (Group IB) was 129.50 ± 6.820 seconds. The mean durations of the onset of convulsion were 419.67 ± 8.876, 176.50 ± 5.548 and 300 ± 6.890 seconds for groups IIB, IIIB and IVB respectively (**Table 5**). Analysis of variance followed by Dunnett's t-test showed that prolongation of the onset of convulsion were statistically significant ($p < 0.05$) when compared with the control group (Group IB). The extract of EEPG also showed dose dependent prolongation of the latency of clonus.

The mean duration of convulsion in Group IB, IIB, IIIB and IVB were 77.17 ± 4.086, 8.83 ± 0.307, 49 ± 3.044 and 19.83 ± 1.276 seconds respectively. Analysis of variance followed by Dunnett's t-test showed that reduction of the duration of convulsion were statistically significant ($p<0.05$) when compared with the control group (Group IB). The extract EEPG showed dose dependent reduction of the duration of convulsion. The percentage reduction of convulsion in the phenytoin treated group was 88.56%, whereas the percentage reduction of convulsion in the groups treated with EEPG at doses of 200 mg/kg and EEPG 400 mg/kg were 36.5% and 74.3% respectively.

The control group showed 100% mortality. The mortality of the mice in Phenytoin treated group was 16.67%, whereas the groups treated with EEPG at the doses 200 mg/kg and 400 mg/kg, showed mortality percentage of 66.67 and 33.33 respectively. Graphical representation of the onset of clonic convulsion (latency) and duration of convulsion after oral administration of the standard drug phenytoin, EEPG (200 mg/kg and 400 mg/kg) and the control group (Group 1B) are shown in the **Fig.2**.

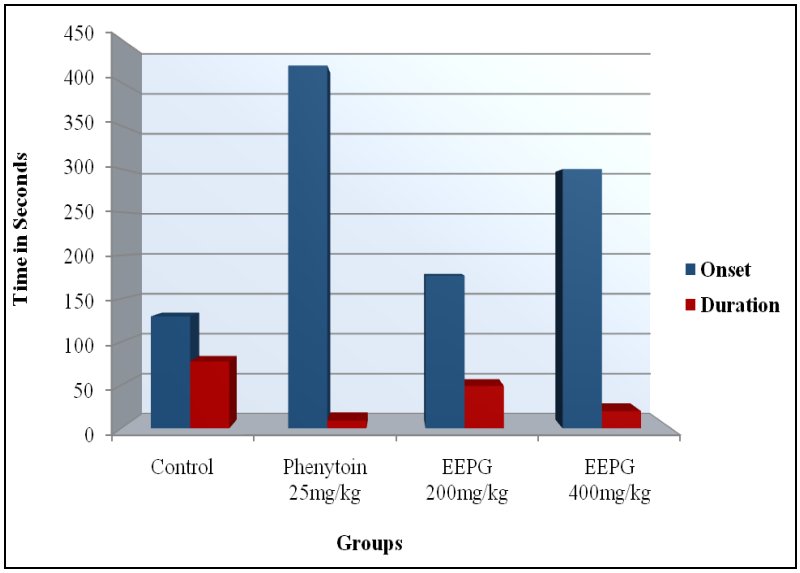

FIG.2: BAR DIAGRAM SHOWING PTZ INDUCED SEIZURES IN MICE

PTZ Induced Seizure Score:

Phenytoin induced a significant decline in the seizure score (2.50±0.224) as compared to the control group (5 ± 0). $p < 0.05$ was considered statistically significant (**Table 6**). While the 200 mg/kg doses of EEPG showed a decline in seizure score (4.50 ± 0.224); the 400 mg/kg dose showed a significant reduction in the seizure scores (3.50 ± 0.224), p value being < 0.05 when compared to the control group. Graphical representation of the seizure score after oral administration of the standard drug phenytoin, EEPG (200 mg/kg and 400 mg/kg) and the control group (Group 1B) are shown in the **Fig. 3.**

TABLE 6: PTZ INDUCED SEIZURE SCORE

Group	Treatment	Seizure Score (Mean ± SEM)
IB	Control	5 ± 0
IIB	Phenytoin 25mg/kg p.o	2.50 ± 0.224**
IIIB	EEPG 200 mg/kg p.o	4.50 ± 0.224
IVB	EEPG 400mg/kg p.o.	3.50 ± 0.224**
One way ANOVA		df 3, 20 F 32.778 p < 0.05

** p<0.05 when compared with the Control group (Group IB)

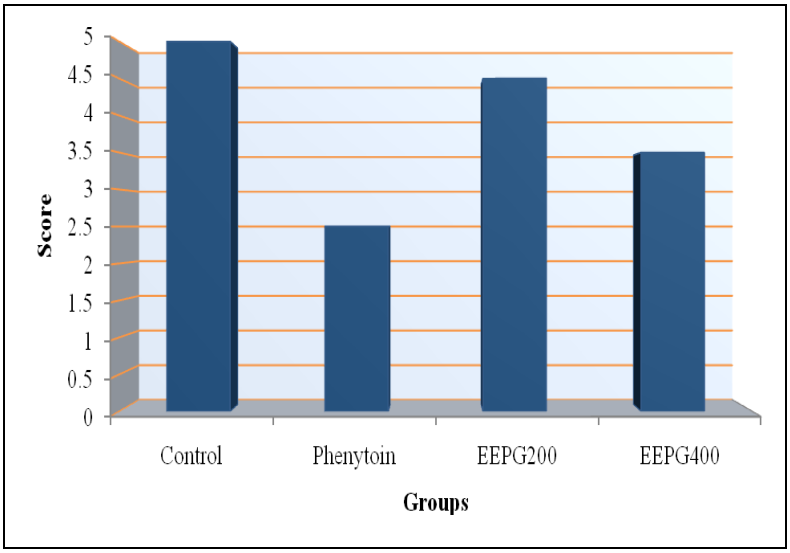

FIG.3: BAR DIAGRAM SHOWING PTZ INDUCED SEIZURE SCORE

DISCUSSION: The maximal electroshock seizure test induced by bilateral corneal or transauricular electrical stimulation, is thought to be predictive of anticonvulsant drugs effective against generalized tonic-clonic seizures, while the pentylenetetrazole test, in which seizures are induced by systemic administration of convulsant doses of PTZ, is thought to represent a valid model for generalized absence and/or myoclonic seizures in humans.[21] Meckes *et al.* (1996) found that sesquiterpenes isolated from hexane extract of *Psidium guajava* leaves had depressant activities on the CNS. The extract potentiated the latency of convulsions induced by leptazol in mice.[22] Sushma *et al.* (2012) reported that the hydro ethanolic extract of the *P. guajava* leaves had protective effect on PTZ induced seizure at 100 mg/kg, 200 mg/kg and 400 mg/kg doses whereas it showed anticonvulsant effect at 200 mg/kg and 400 mg/kg doses in MES induced convulsion.[23] PTZ is an antagonist of GABA at GABA-A receptor which has been widely implicated in epilepsy.

Furthermore, drugs which protect animals against the seizure induced by PTZ act by elevating the seizure threshold and are effective in myoclonic and absence seizures. The antiepileptic drugs that block the MES induced tonic extension act by blocking seizure spread and are effective in the management of and/or protecting against grand mal epilepsy. [7]

CONCLUSION: Modern researchers are increasingly taking interest in studying guava for its beneficial effects considering its long history of use in traditional medicines for various ailments. Its traditional use for diarrhoea, gastroenteritis and other digestive complaints has been validated in numerous clinical studies. A plant drug has even been developed from guava leaves (standardized to its quercetin content) for the treatment of acute diarrhoea. In India the leaf extract of guava is used for epilepsy and chorea and the tincture has been employed by rubbing it into the spine of children suffering from convulsions.

Besides its use in India, it is also used traditionally in the treatment of epilepsy in many other parts of the world like Haiti and Malaya. Very few studies are available on its antiepileptic effects. From our study it's evident that the guava, known as the poor man's apple of the tropics, has the potential antiepileptic effects. The probable mechanisms of anticonvulsant action of *Psidium guajava* L. may be due to potentiation of GABA-ergic inhibition or it may be due to blocking the seizure spread by inhibiting either voltage gated Na^+ channels and/or glutamatergic excitation through NMDA receptors. However, the components of the extract responsible for this effect were not investigated in this study. Further investigations are needed for identification of the active compounds and their exact molecular mechanism of action, responsible for the anticonvulsant activity of this plant. The results from the present study provide scientific evidence to the ethno- medicinal use of guava in treating convulsion and epilepsy.

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COMPETING INTERESTS: There are no competing interests to declare.

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