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ANTICONVULSANT EFFECT OF ISOLATED COMPOUNDS FROM THE LEAVES OF GLOBIMETULA BRAUNII ENGLER VAN TIEGH (LORANTHACEAE) IN MICE AND CHICKS

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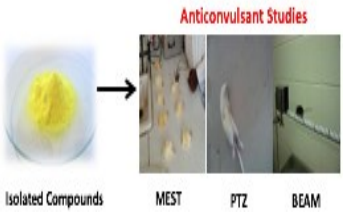
Graphical abstract



Abstract

The anticonvulsant evaluation of globrauneine A (1), globrauneine C (2) globrauneine D (3), globrauneine F (4), lupeol (5), β-sitosterol (6), (1R,5S,7S)-7-[2-(4-hydroxyphenyl) ethyl]-2,6-dioxabi-cyclo [3. 3.1]-nonan-3-one (7), dodoneine (8), quercetin (9) and rutin (10) from *Globimetula braunii* leaves were analyzed with the aid of pentylenetetrazole-induced seizure test in mice (PTZ) and maximal electroshock seizure test in chicks (MEST), while the neurotoxicity was evaluated using the beam walking assay in mice. 50% of the tested mice were protected by globrauneine A (1) and dodoneine (8) against PTZ-induced mortality. The mean onset of clonic spasm of the unprotected animals was increased by quercetin (9) and also the mice were differentially protected against mortality. The tested compounds also produced significant ($p<0.05$) increase in the mean onset of seizure against pentylenetetrazole-induced seizure. The chicks were not protected by the tested compounds against MEST and the recovery time was not significantly reduced. In the beam assay, with the exception of dodoneine (8), the number of foot slips and the time taken to complete the task was not significantly changed by the tested isolated compounds, suggesting that the observed activities are not due to general CNS depression. The results suggest mild protective effects of these isolated compounds against seizure which might be useful in the control of petit mal epilepsy.

Keywords: *Globimetula braunii*, compounds, anticonvulsant, MEST, PTZ, Beam walking assay

Abstrak

Penilaian antikonvulsan bagi konstituen kimia daripada daun Globimetula braunii dianalisis dengan bantuan ujian sawan yang disebabkan oleh pentylenetetrazol pada tikus (PTZ) dan ujian sawan kejutan elektrik maksimum pada anak ayam (MEST), manakala neurotoksisiti dinilai menggunakan ujian berjalan rasuk pada tikus. 50% daripada tikus yang diuji telah dilindungi oleh globrauneine A (1) dan dodoneine (8) terhadap kematian akibat PTZ. Purata permulaan kekejangan klonik haiwan yang tidak dilindungi telah meningkat oleh kuarsetin (9) dan juga tikus dilindungi secara berbeza daripada kematian. Sebatian yang diuji juga menghasilkan peningkatan yang ketara ($p<0.05$) dalam purata permulaan sawan terhadap sawan akibat pentylenetetrazol. Anak ayam tidak dilindungi oleh sebatian yang diuji terhadap MEST dan masa pemulihan tidak berkurangan dengan ketara. Dalam ujian rasuk, dengan pengecualian dodoneine (8), bilangan gelinciran kaki dan masa yang diambil untuk menyelesaikan tugas tidak banyak berubah oleh sebatian terpencil yang diuji, menunjukkan bahawa aktiviti yang diperhatikan bukan disebabkan oleh kemurungan CNS umum. Hasilnya mencadangkan kesan perlindungan ringan sebatian terpencil ini terhadap sawan yang mungkin berguna dalam kawalan epilepsi petit mal.

Kata kunci: *Globimetula braunii*, sebatian, antikonvulsan, MEST, PTZ, kaedah berjalan rasuk

1.0 INTRODUCTION

A considerable interruption of electrical interaction between neurons in the brain results into a transient discharge of excessive energy in a coordinated form by discharging electrical compulsions [1]. These compulsions move from the neuron near the axon and then arouse the firing of neurotransmitters which runs within the synaptic cleft. The consequence could be an unexpected muscle jerk, an unexpected fall and distorted vision [1]. Pharmacological analyses reveal that antagonists of the GABA receptor or agonists of different glutamate-receptor subtypes [Kainic acid, a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) or N-methyl-D-aspatate (NMDA)] cause seizures in experimental animals in vivo. Glutamate-receptor antagonists also prevent seizures in distinctive models, comprising seizures produced by electroshock and chemical convulsants such as pentylenetetrazole (PTZ) [2]. Presently, all the available antiepileptic drugs are synthetic or semi-synthetic molecules. However, there is still a huge unmet need in the management of epilepsy making the search into medicinal plants with proven efficacy and safety a veritable. Medicinal plant such as *Globimetula braunii* used for the management of convulsion in conventional medicine has displayed an encouraging anticonvulsant action in animal models of anticonvulsant screening [3]. This species is a parasitic shrub of the Loranthaceae family and is widely found in some African countries including Nigeria. The plant contains several medicinally active compounds including lactones and flavonoids [4] and triterpenoids [5]. Previously, the extract of ethyl acetate has been reported to be very effective against pentylenetetrazole-induced seizure at dose of 150 mg/kg [3]. This prompted the need for further research targeted towards the isolation of compound(s) liable for the observed biological effect.

In this study, the anticonvulsant study of ten isolated compounds of *G. braunii* was carried out using the maximal electroshock seizure test in chicks (MEST), pentylenetetrazole-induced seizure test (PTZ) and the neurotoxicity was evaluated with the aid of the beam walking assay.

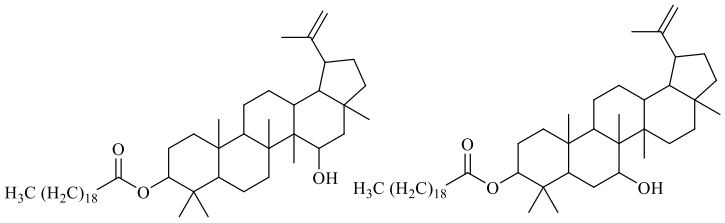
2.0 METHODOLOGY

2.1 Plant Material

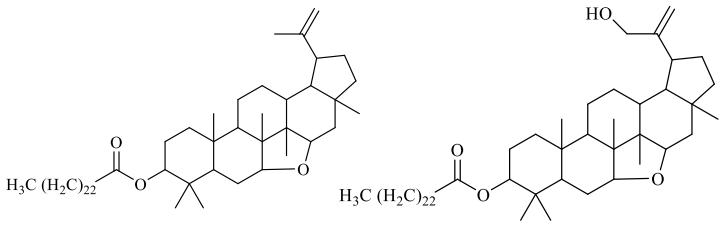
The leaves of *G. braunii* were collected in October, 2014, at Sheda Science and Technology complex (SHESTCO), Abuja, Nigeria. This was confirmed and authenticated at the Department of Biological Sciences, Ahmadu Bello University, Zaria-Nigeria with a voucher specimen (No 9016).

2.2 Structural Details of Isolated Compounds

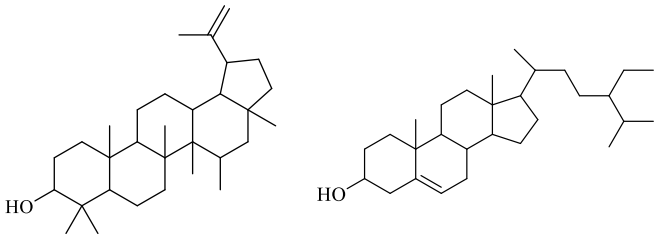
The isolation and characterization of ten isolated compounds were obtained by chromatographic methods and identified spectroscopically and also by direct comparison with literature data. About 3.0 kg of powdered *G. braunii* was extracted using cold extraction technique in order of increasing polarity starting with n-hexane, EtOAc and MeOH at room temperature. The solvents were evaporated in vacuo to give black gummy residues. Subsequent separation with silica gel vacuum liquid chromatography (VLC) and column chromatography (CC) afforded globrauneine A **(1)**, globrauneine C **(2)**, globrauneine D **(3)** globrauneine F **(4)**, lupeol **(5)**, β-sitosterol **(6)**, (1R,5S,7S)-7-[2-(4-hydroxyphenyl) ethyl]-2,6-dioxabi-cyclo [3. 3.1]-nonan-3-one **(7)**, dodoneine **(8)**, quercetin **(9)** and further purification with Sephadex LH-20 afforded rutin **(10)** (Figure 1). The complete experimental procedures were previously reported by Ja'afar *et al*. 2017 [4] and Muhammad *et al*. 2020 [5].



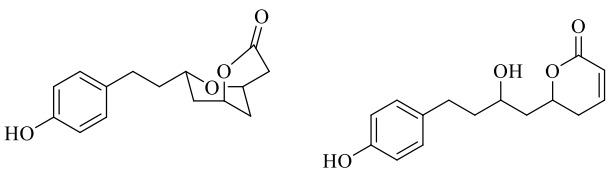
(1) **(2)**



(3) **(4)**



(5) **(6)**



(7) **(8)**

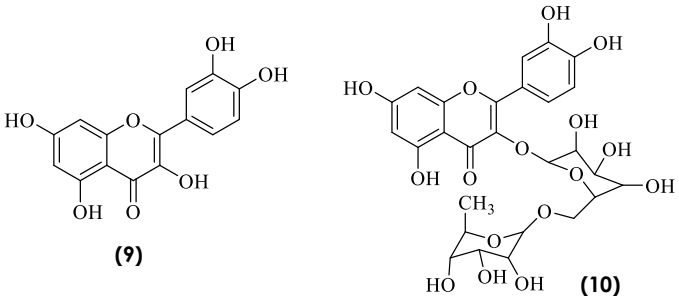


Figure 1 Isolated Compounds from *Globimetula braunii* leaves

2.3 Experimental Animals

The experiment was carried out using either sex of Adult Swiss Albino mice (18-24 g) and day old Rangers cockerels. The mice and chicks were acquired from the Animal House Facility of the Department of Pharmacology and Therapeutics, ABU, Zaria and National Animal Production Institute (NAPRI), Shika, Kaduna, Nigeria respectively. They were preserved at 23.0 ± 2.0 °C, 12 hrs light and dark circle, fed with standard rodent feed and water was provided *ad libitum*. Investigational techniques were conducted in agreement with the National institute of Health Guide for the Care and Use of Laboratory Animals (Publication No 5-23, revised 1985). Ethical approval for the conduct of the study was obtained (Approval Number DAC/W-OT/301-27).

2.4 Maximal Electroshock Seizures Test in Chicks (MEST)

Swinyard *et al.* [6] and White *et al*. [7] method was used to conduct the maximal electroshock test. Day old chicks were randomly divided into 32 (I and XXXII) groups and each group containing 10 chicks. Groups I and II received normal saline (10 ml/kg) and phenyltoin (20 mg/kg), respectively. Groups III-XXXII received three graded doses (30, 100 and 300 mg/kg) for each tested compound under investigation (IP) for 30 minutes before the administration of shock. The seizure was induced by applying a Ugobasile electroconvulsive machine (Model 7801) with corneal electrodes on the upper eyelids of the chicks. A shocking parameter comprising of a current of 75 mA, 0.8 s shock duration, 100 pulses/sec frequencies and 0.8 m/s pulse width, was used. Seizures were established as tonic extension of the hind limbs, while absence of tonic extension of the hind limbs was considered as protection. The mean recovery time from seizure was recorded for each unprotected chick.

2.5 Pentylenetetrazole Induced Seizure in Mice (PTZ)

Swinyard *et al*, [6] method was used in this study. Mice were randomly divided into 32 groups (I-XXXII). Groups I and II received normal saline (10 ml/kg) and sodium valproate (200 mg/kg), respectively. Groups III-XXXII received three graded doses (30, 100 and 300 mg/kg) for each tested compound. All treatments were by intraperitoneal routes. 30 minutes after treatment, the CD97 of PTZ (85 mg/kg) was administered subcutaneously to each Mouse and then observed for starts and spans of convulsions for 30 minutes. Absence of this episode was considered an index of protection against seizure. The onset of seizure was also recorded for unprotected mice.

2.6 Beam Walking Assay (Neuro Toxicity)

This procedure was based on method by Stanley *et al*. and Magaji *et al*. [8-9]. Mice were trained to walk on a cylindrical plank of 100 cm long and 3 cm broad raised 30 cm over the stall with the support of two stainless iron rods. Each mouse was trained three times to be mindful of a task at the end of the plank (identification of a goal box). 20 groups of six mice each were randomly formed from the trained mice. The mice in cluster I and XX were administered with normal saline (10 ml/kg, i.p) and diazepam (2 mg/kg, i.p). The remaining clusters were administered with graded dosages (30, 100 and 300 mg/kg) of the isolates. After 30 minutes of administration, the mice were positioned at one end of a tubular plank (lengthy of 80 cm and diameter of 0.8 cm). The number of foot slips and period taken to finish the mission with a maximum spell of 60 seconds set on the plank were recorded.

2.7 Statistical Analysis

The data were presented as mean ± standard deviation of three replicates for each tested sample. SPSS for windows (version 21) was used to determine the statistical analysis and the biological analysis data were analysed with one-way ANOVA followed by Dunnet post hoc t-test for multiple comparison.

3.0 RESULTS AND DISCUSSION

Plants of the Loranthaceae family have been claimed to be used ethnomedicinally for the treatment of many diseases including rheumatism, coughs, malaria, chest conditions, epilepsy, infertility and as laxative [10–12]. The vast diversity of medicinal plant species is bestowed with a rich source of potentially therapeutic compounds with new structures. Many drugs in the markets today have their origin in pure chemical substances isolated from higher plants. Thus, the anticonvulsant activity of ten isolated compounds globrauneine A **(1)**, globrauneine C **(2)**, globrauneine D **(3)**, globrauneine F **(4)**, lupeol **(5)**, β-sitosterol **(6)**, (1R,5S,7S)-7-[2-(4-hydroxyphenyl) ethyl]-2,6-dioxabicyclo [3. 3.1]-nonan-3-one **(7)**, dodoneine **(8)**, quercetin **(9)** and rutin **(10)** were evaluated for their potential anticonvulsant activities which could act as lead compound in the discovery of novel therapeutic molecules.

The MEST test is arguably the best validated preclinical examination that identifies drugs with activity against generalized tonic-clonic seizures and further reveals the capability of the testing material to inhibit seizure spread through neural tissue [21, 22]. Protection against hind-limbs tonic extension (HLTE) predicts the ability of the test compound to stop the advancement of seizure from an epileptic emphasis in the brain. In MEST, all the tested compounds produced a very weak inhibition as they failed to protect against tonic hind limbs extension (Table 1). Currently obtainable anticonvulsants such as carbamazepine, lamotrigine and phenytoin (sodium channel blockers) or intermediaries that obstruct glutamatergic neurotransmission umpired by NMDA receptors are clinically effective compounds that suppress tonic hind limbs extension in MEST [10, 23]. This result suggests that the tested isolated compounds might not be suitable in managing of grand mal seizures or partial seizures since there is no obliteration of the tonic extension unit of the electroshock seizures. Though, no mortality was recorded in the tested chicks after treatment with the isolates [24].

Table 1 Effect of Compounds obtained from Scurrula parasitica against maximal electroshock in mice

Samples	Treatment mg/kg	Quantal protection	Mean time of recovery (Min)
Normal saline	10 ml/kg	0/10	3.72±0.58
(1)	300	0/10	5.80 ± 0.37
	100	0/10	4.59 ± 0.51
	30	0/10	4.78 ± 0.43
(2)	300	0/10	4.78 ± 0.43
	100	0/10	2.85 ± 0.55
	30	0/10	5.24 ± 0.62
(3)	300	0/10	5.23 ± 1.33
	100	0/10	6.73 ± 0.81
	30	0/10	5.80 ± 0.37
(4)	300	0/10	4.57 ± 0.52
	100	0/10	3.44 ± 0.72
	30	0/10	4.53 ± 0.55
(5)	300	0/10	5.97 ± 0.80
	100	0/10	5.89 ± 1.06
	30	0/10	6.12 ± 1.24
(6)	300	0/10	5.83 ± 0.99
	100	0/10	5.65 ± 0.93
	30	0/10	5.89 ± 0.52
(7)	300	0/10	4.71±1.06
	100	0/10	4.82±0.58
	30	0/10	4.92±1.17
(8)	300	0/10	6.67±0.44
	100	0/10	6.39±0.36
	30	0/10	5.57±0.83
(9)	300	1/10	5.43±0.91
	100	0/10	5.37±0.36
	30	0/10	6.36±1.41
(10)	300	0/10	6.28±0.87
	100	0/10	6.61±0.67
	30	0/10	5.67±0.48
Phenytoin 20	20	9/10	7.14±0.00

Percentages expresses Protection against seizure, mean ± SD expresses mean onset of seizure, $p < 0.05$ (compared with normal saline treated control), n=10. Globrauneine A **(1)**, globrauneine C-D **(2-3)**, globrauneine F **(4)**, lupeol **(5)**, β-sitosterol **(6)**, (1R,5S,7S)-7-[2-(4-hydroxyphenyl) ethyl]-2,6-dioxabicyclo [3. 3.1]-nonan-3-one **(7)**, dodoneine **(8)**, quercetin **(9)** and rutin **(10)**

Pentylenetetrazole-induced seizure test represents an acceptable model for detecting isolated compounds that elevates the convulsion threshold in brain. Pharmacological profile of the scPTZ convulsion standard is coherent with individual generalized absence and myoclonic seizures [11]. PTZ activates seizure by blocking the main GABAergic inhibitory pathways and induces convulsion by constraining the GABAA receptor complex [25, 26]. Standard anticonvulsant drugs such as benzodiazepine, barbiturates and phenobarbitone demonstrated their effect through augmentation of GABA receptor chloride channel complex which is a GABA benzodiazepine umpired inhibition pathway in the central nervous system. Their pharmacological actions are exhibited through the decrease of muscle tone, calmness and introduction of sleep by antagonizing the GABA receptor chloride channel complex [27]. The subcutaneous PTZ administration of the tested isolated compounds at the dosage of 300 mg/kg, 100 mg/kg, 30 mg/kg significantly delayed the spasm, jerking, seizure onset and the mortality time of the unprotected mice. Globrauneine A **(1)** (30 mg/kg) and dodoneine **(8)** (300 mg/kg) body weight protected 50% of the tested animals against seizure in mice induced by pentylenetetrazole (Table 2).

These compounds protection effect against pentylenetetrazole induced seizure indicated that they might have potential anticonvulsant activity that may plausibly involve interaction with the GABA receptor complex and/or enhance GABA umpired inhibition in the brain from side to side inspiration of the CNS inhibitory passageway. The mild anticonvulsant activity may also involve reduction of the t-type calcium current or augmentation of the GABAA – BZD receptor mediated neurotransmission by activation of NMDA receptor in the induction and generalization of the PTZ induced seizure [28]. The slight protective effect of all the isolates studied which delayed the start of spasm, myoclonic jerking and mortality time may also, probably be through dopaminergic mechanism or suppression of t-type calcium currents [29]. Evaluation of the performance of the animals on the beam balance was designed initially to identify deficits of motor coordination caused by motor cortex mutilation and to enable the identification of motor shortfalls due to age, hereditary, pharmacological influences and central nervous system injuries in both rats and mice [30, 31]. The separate performances of the beam walking assay are being allowed to be observed more thoroughly, achievement of how the task was made is measured and also allows several actions to be noted. Approximately, only 30% GABAA receptor occupancy of diazepam is needed to detect significant coordination deficit on the beam walking assay related to 70% receptor tenancy coordination deficit on the rotarod, and is therefore more sensitive [8]. Six isolated compounds were selected to be evaluated for the beam walking assay. The time spent to complete the task was decreased by these

compounds compared to diazapem 1 mg/kg (Table 3). However, the the time taken to finish the task and the number of foot slips were not significantly changed by these compounds, suggesting that the observed activities may not be due to general CNS depression. Nevertheless, the number of foot slips upsurge produced by dodoneine **(8)** at highest dose tested (300 mg/kg) may be indicative of sedative potential and may suggest possible mechanistic similarity with agents that interact with the GABAA-BDZ reception complex [29]. GABA-mediated synaptic inhibition are increase by the action of sedative-hypnotic agents either by straight triggering GABA receptors or augmenting the performances of GABA on GABAn receptors [9]. Dodoneine appears to have a sedative constituent by increasing the number of foot slips made by the mice, [8].

Table 2 Effect of Compounds against Pentylenetetrazole Induced Seizure in Mice

Samples	Treatment (mg/kg)	Quantal protection against seizure	Mean onset of myoclonic jerk	Mean onset of Seizure
Normal saline		0/6	2.46±0.46	5.92±1.05
(1)	300	1/6	5.71 ± 2.20*	12.14 ±2.10
	100	3/6	6.40 ± 1.54*	12.53 ±1.27
	30	1/6	5.01 ± 0.20*	11.09 ±3.12
(2)	300	1/6	3.01 ± 0.20	6.33 ±1.31
	100	0/6	3.56 ± 0.34	5.59 ± 2.98
	30	0/6	3.85 ± 0.36	6.00 ± 2.10
(3)	300	0/6	2.82 ± 0.58	2.95 ± 0.83
	100	0/6	3.42 ± 1.86	4.21 ± 3.30
	30	0/6	2.97 ± 0.30	5.57 ± 1.30
(4)	300	2/6	3.52 ± 1.32	5.41 ±1.57
	100	1/6	3.36 ± 0.96	6.50 ± 2.88
	30	2/6	2.84 ± 0.89	5.22 ± 2.65
(5)	300	0/6	4.09 ± 1.29*	9.34 ± 1.30
	100	0/6	4.28 ± 0.99*	7.59 ± 1.93
	30	0/6	3.97 ± 0.61*	8.37 ± 1.06
(6)	300	1/6	5.44 ± 0.93	4.55 ± 2.50
	100	2/6	3.94±0.87	5.97 ±1.69
	30	1/6	4.00± 0.87	5.70 ± 0.89
(7)	300	1/6	4.08±0.28*	10.62±1.77
	100	0/6	3.96±0.69*	11.35±1.59
	30	0/6	4.57±0.85*	8.88±0.72
(8)	300	3/6	4.87±0.39*	13.98±1.11
	100	1/6	5.19±0.34*	11.97±1.34
	30	0/6	4.62±0.88*	10. 52±1.94
(9)	300	0/6	4.15±0.55	9.66±2.20
	100	2/6	4.79±0.89	8.94±1.26
	30	0/6	4.14±1.34	9.69±1.79
(10)	300	2/6	4.17±0.20	8.37±1.28
	100	1/6	4.51±1.41	9.35±1.02
	30	1/6	4.02±1.83	10.85±2.83
Sodium valproate	200	6/6	5.45±0.00	20.45±0.00

Data presented as Mean ± SD; $p < 0.05$ (Dunnet post hoc test for multiple comparison); n = 6. Globrauneine A **(1)**, globrauneine C-D **(2-3)**, globrauneine F **(4)**, lupeol **(5)**, β-sitosterol **(6)**, (1R,5S,7S)-7-[2-(4-hydroxyphenyl) ethyl]-2,6-dioxabicyclo [3. 3.1]-nonan-3-one **(7)**, dodoneine **(8)**, quercetin **(9)** and rutin **(10)**

Table 3 Effect of Compounds on Beam Walking Assay

Samples	Treatment mg/kg	Number of foot slips	Time taken to complete the tasks (Secs)
Normal saline		0.33 ± 0.21	36.01
(1)	300	1.33 ± 0.88	19.17 ± 10.25
	100	0.83 ±0.65	28.17 ± 8.32
	30	0.33 ± 0.33	29.00 ± 4.77
(5)	300	0.33 ± 0.33	33.33 ± 4.36
	100	0.33 ± 0.21	17.33 ± 6.12
	30	0.33 ± 0.33	18.67 ± 6.23
(7)	300	3.08±0.28	18.17 ± 3.98
	100	3.96±0.69	8.83± 0.23
	30	4.57±0.85	11.67±0.22
(8)	300	4.17±0.39*	46.23±0.87*
	100	3.99±0.34	11.02±0.67
	30	4.62±0.88	15.34±0.56
(9)	300	4.15±0.55	18.6±0.34
	100	3.43±0.89	17.16±0.78
	30	3.14±1.34	18.01±2.87
(10)	300	4.17±0.20	11.51±1.29
	100	4.21±1.41	15.17±2.33
	30	4.02±1.83	12.33±0.43
Diazepam	2	4.23 ± 1.09*	69.33±5.79*

Data presented as Mean ± SD; $p < 0.05$ (Dunnet post hoc test for multiple comparison); n = 6. Globrauneine A **(1)**, lupeol **(5)**, (1R,5S,7S)-7-[2-(4-hydroxyphenyl) ethyl]-2,6-dioxabicyclo [3. 3.1]-nonan-3-one **(7)**, dodoneine **(8)**, quercetin **(9)** and rutin **(10)**

It has been established that flavonoids, lactones and triterpenoids exert various pharmacological activities including anticonvulsant effects [9, 32–35]. Previously, investigation of lactones effect in animal models of convulsions and their anticonvulsant properties were established both in mice and rats. Tolardo *et al*, [34] reported a sesquiterpene lactone called Podoandin and its antidepressant effect. The immobility time of the mice was significantly reduced by the compound. Ascomycin, a macrolide lactone also showed a tremendous anticonvulsant action when infused into the rat hippocampus through microdialysis investigations, it similarly prevented PTZ induced chemical kidling in mice [34]. The distinct GABAA – receptor related actions and antidepresant activities of triterpenoids lupane such as betulinic acid, betulin, lupeol and α/β-amyrin isolated from Protium heptaphyllum has been reported to reduce the stillness time in the behavioral hopelessness test in mice [37]. In addition, tonic inhibition action on depression was observed with β-amyrin palmitate [38]. Another pentacycyclic triterpenoid compound urs-12-en-27α,30-dioicacid-3-0-α-L-rhamno- pyranosyl (1→2)- α-L-arabinopyranoside has also displayed significant ($p<0.05$) obliteration of seizure induced by maximal electro shock (MES) and PTZ seizures [24]. Chaturvedi et al, [39] has reported a 10 – 40% range of protection against the convulsion produced by pentylenetetrazol on the triterpenoids tested. Different animal models of seizures have reported the anticonvulsant effects of rutin and quercetin and were in conformity with our research findings which

shows a weak and short term anticonvulsant potential of the studied flavonoids [32, 40–46].

4.0 CONCLUSION

The result of these study showed that globrauneine A **(1)** and dodoneine **(8)** offered remarkable protection of the mice against pentylenetetrazole-induced seizure. Quercetin **(9)** also significantly ($p<0.05$) augmented the mean onset of spasm in the unprotected animals and differentially protected the mice against mortality. These corroborated the anticonvulsant potential of *G. braunii* previously reported and thus provide some rational in supporting the conventional use of the plant by different ethnic groups in Africa for alleviating seizure disorders. Further anticonvulsant tests will be necessary to establish the possible mechanism of anticonvulsant action of these compounds.

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Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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