Metabolic Brain Disease (2019) 34:537–544
https://doi.org/10.1007/s11011-019-0390-z

ORIGINAL ARTICLE

Evaluation of some neuropharmacological effects of *Caladium bicolor* aiton (araceae) leaf extracts in mice

Abigail M. Akhigbemen[1] · Raymond I. Ozolua[1] · Enitome E. Bafor[1] · Emmanuel O. Okwuofu[1]

Received: 26 February 2018 / Accepted: 27 January 2019 / Published online: 7 February 2019

Abstract

Caladium bicolor Aiton (Araceae) is used in ethnomedicine for the treatment of boils, wound ulcers and convulsion. This study investigated the effects of the leaf extracts on some neuropharmacological parameters. The leaves were collected, dried, powdered and then extracted by maceration in methanol to yield the whole extract (WE). Extraction was also done using n-hexane, ethyl acetate and methanol in a Soxhlet apparatus to obtain n-hexane (HE), ethyl acetate (EA) and methanol (ME) extracts. Preliminary phytochemical screening was done using the whole extract. Some neuropharmacological evaluations were carried out using standard methods. Phytochemical screening revealed the presence of carbohydrates, proteins, alkaloids and flavonoids. WE showed varying levels of protection against strychnine-induced convulsion. Each of HE, EA and ME increased latency ($P < 0.01$) to pentylenetetrazole-induced convulsion and offered varying levels of protection against maximal electroshock-induced seizure. Each of WE, HE and ME significantly increased the duration of stay on the open arm of the elevated plus maze. Both EA and ME at doses of 100 and 200 mg/kg, and HE at a dose of 400 mg/kg significantly reduced the duration of immobility in forced swim test. It is concluded that the leaf extracts possess anticonvulsant, anxiolytic and antidepressant properties.

Keywords *Caladium bicolor* leaf extracts · Anti-convulsant · Anxiolytic · Antidepressant

Introduction

The word 'epilepsy' is derived from the Greek word "epilambanein", which means "to seize upon" or "to attack" (Paramdeep et al. 2014). Epilepsy is the second most common neurological disorder that affects about 70 million people worldwide, out of which 80% are in developing countries (Yemadje et al. 2011). Studies show that up to 50% of patients with epilepsy develop psychiatric disorders, the most common being depression, anxiety and psychotic disturbances (Marsh and Rao 2012).

The adverse effects of antiepileptic drugs (AEDs) often result in patient non-compliance and reduction in drug effectiveness. Although the newer AEDs may have better adverse effect profile when compared to the older generation, they still have significant CNS-related effects such as decreased cognitive abilities and psychiatric complications (Schmidt 2009). This suggests the need for safer but efficacious drugs. The World Health Organization (2008) has reported that 80% of the emerging world's population depends on traditional medicine. Herbal remedies remain a major aspect of traditional medicine and are widely used because of the common belief that they are cheaper, safer and more culturally acceptable to people.

Caladium bicolor (CB) Aiton of family Araceae is an ornamental foliage plant grown from tubers. It is indigenous to South and Central America. In Nigeria, it is found most commonly in Calabar and Akwa Ibom States by the roadside, in school premises and in farmlands. The aqueous extract of *Caladium bicolor* has been shown to possess antidiarrhoeal effect (Salako et al. 2015). The tubers are used as emetic and purgative in Brazil (Clay and Hubbard 1987). In Nigeria, the leaves and tubers are used topically for boils, wounds and ulcers (Odugbemi 2006). The antiangiogenic, antitoxic and antioxidant properties of the methanol leaf extracts of *C. bicolor* have also been studied (Tosoc 2016). Akhigbemen et al. (2018) have also studied the acute and sub acute effect of methanol leaf extract of *C. bicolor*. There seems to be no scientific report evaluating the use of the leaf extract for the treatment of

✉ Abigail M. Akhigbemen
abigail.omo-isibor@uniben.edu

[1] Department of Pharmacology & Toxicology, Faculty of Pharmacy, University of Benin, Benin City 300001, Nigeria

convulsion-related disorders by herbalists in Nigeria. In this study, we evaluated some of the neuropharmacological effects of the leaf extracts in mice.

Materials and methods

Plant material and extraction

Fresh leaves of CB were collected from the horticultural garden of the University of Benin, Benin City, Nigeria in July 2015. The plant was identified and authenticated by Mallam I. Muazzam of the Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria where a voucher specimen (NIPRD.H.7035) has been deposited. The leaves were shade-dried to constant weight and powdered. A quantity (500 g) was macerated in 2 L of methanol for 72 h with intermittent shaking and stirring. The mixture was then filtered and the filtrate concentrated to dryness under reduced pressure in an oven at 50 °C. The dried whole extract (WE) was stored at 4 °C until use. A fresh batch (1.5 g) of the leaves was subjected to successive extraction in a Soxhlet apparatus with 1 L of solvent starting with the solvent of least polarity to highest (i.e., n-hexane, ethyl acetate, and methanol). The temperature was kept at the boiling point for each solvent (69, 76.5 and 64.7 °C) respectively. The extracts were concentrated using a rotary evaporator, dried in an oven at 50 °C and kept in a refrigerator till further use.

Mice

Experiments were performed using Swiss albino mice (20–33 g). They were in-bred in the Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria. The mice were housed in plastic cages under natural lighting and temperature conditions. They were fed with standard chow (Top Feeds, Nigeria Plc) and water ad libitum. All experiments were carried out in accordance with the Institute for Laboratory Mouse Research Guidelines for the Care and Use of laboratory Mice (NRC 2011). Ethical approval (Reference number: EC/FP/017/03) was obtained from the institutional Animal Ethics Committee. Food was withdrawn before and during the experiment.

Drugs and chemicals

Drugs used include strychnine and pentylenetetrazole (Sigma-Aldrich, USA), diazepam (Roche, Switzerland), phenobarbitone (BDH Chemicals, UK), and imipramine (Teva, Israel). They were all prepared fresh in distilled water before administration. WE and ME were reconstituted in 5% Tween-80 while HE and EA were reconstituted in olive oil.

Phytochemical screening

The whole extract was screened for the presence of carbohydrate, tannins, proteins, alkaloids, flavonoids, steroidal nucleus, cardiac glycosides and phenolic compounds using conventional methods (Sofowora 1993; Evans 2004).

Strychnine-induced convulsion

Mice were randomly allotted to five groups ($n = 5$ each). Group I (negative control) was treated orally with 0.2 ml of the vehicle (5% Tween 80) while groups II, III, IV and V were given oral doses of 100, 200 and 400 mg/kg of WE and 2 mg/kg of diazepam respectively. One hour later, 1 mg/kg of strychnine was administered i.p. to all the mice. Each mouse was observed for onset of convulsion or death for a period of 30 min (Porter et al. 1984). The test was repeated for HE,ME and EA.

Pentylenetetrazole-induced convulsion

Mice were randomly allotted to five groups ($n = 5$ each). Group I (negative control) was treated orally with 0.2 ml of the vehicle while groups II, III, IV and V were orally administered 100, 200 and 400 mg/kg of WE and 2 mg/kg diazepam, respectively. One hour later, 70 mg/kg of pentylenetetrazole was administered i.p. to mice in all the groups. The animals were observed for onset of tonic-clonic convulsion or death for a period of 30 min (Vogel and Vogel 1997). The test was repeated for HE, ME and EA.

Maximal electroshock-induced convulsion

The method described by (Swinyard et al. 1952) was used. Mice were randomly allotted to five groups ($n = 5$ each). Group I served as negative control and was treated orally with 0.2 ml of the vehicle. Groups II, III, and IV were given 100, 200, and 400 mg/kg of WE orally and Group V received 30 mg/kg of phenobarbitone (p.o.). One hour later, all mice were subjected to electroshock using a current of 50 mA for 0.2 s through a pair of ear clip electrodes (Ugo Basile model 16,182). The onset of tonic-hind limb extension as well as protection was noted. The test was repeated for HE, ME and EA.

Elevated plus maze test

Mice were randomly allotted to 5 groups of 5 mice each. Group I (negative control) received 0.2 ml of the vehicle orally while groups II, III and V received 100, 200 and 400 mg/kg of WE orally, and group IV received 2 mg/kg of diazepam orally. An hour later, each mouse was placed at the center of the maze, facing one of the open arms. The time spent in closed

and open arms within 5 min was recorded using a stop watch. The test was repeated for HE, ME and EA (Sen et al. 2007).

Forced swim test

Mice were randomly allotted to 5 groups of 5 mice each. Group I received 0.2 ml of the vehicle orally and served as negative control while groups II, III, IV, and V received 100, 200 and 400 mg/kg of WE orally, and 25 mg/kg of imipramine respectively. An hour later, each mouse was forced to swim in an open square tank (25 cm × 25 cm), filled with 15 cm of water (Porsolt et al. 1977). Total immobility time was recorded for the last 4 min out of a 6-min duration test. Water in the tank was changed with each group. In this test, mice were isolated from exposure to sound. The test was repeated for HE, ME and EA.

Statistical analysis

Data are expressed as Mean ± S.E.M (standard error of mean) and were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test (GraphPrism® version 6, San Diego, USA). $P < 0.05$ indicates significant difference between compared data.

Results

Phytochemical constituents of whole extract

Preliminary phytochemical screening of WE showed that it tested positive for carbohydrate, protein, alkaloid and flavonoid, but negative for tannins, compounds with steroidal nucleus, cardiac glycosides and phenolic compounds.

Strychnine-induced convulsion

The whole extract (WE) offered 20% protection at a dose of 100 mg/kg with no significant difference in latency to tonic convulsion when compared to the control. At doses of 200 and 400 mg/kg, WE produced 100% protection against strychnine-induced convulsion (Fig. 1). None of HE, EA and ME protected against strychnine-induced convulsion at doses of 100, 200, and 400 mg/kg (Figs. 2, 3 and 4). In Fig. 2 doses of 200 and 400 mg/kg HE significantly shortened the latency to tonic convulsion when compared to the control ($P < 0.05$; $P < 0.01$ respectively). As shown in Fig. 3, this effect was not dose-dependent in the case of EA which was significant at 100 and 400 mg/kg ($P < 0.01$, $P < 0.05$ respectively).

Pentylenetetrazole -induced convulsion

Single dose of PTZ produced hind-limb tonic seizures in all the mice administered 100, 200 and 400 mg/kg of WE, HE, EA and ME. With respect to latency to convulsion, there was no significant difference between WE and control group (Fig. 5) but HE increased the latency to tonic convulsion at doses of 100 mg/kg ($P < 0.0001$), 200 mg/kg ($P < 0.001$) and

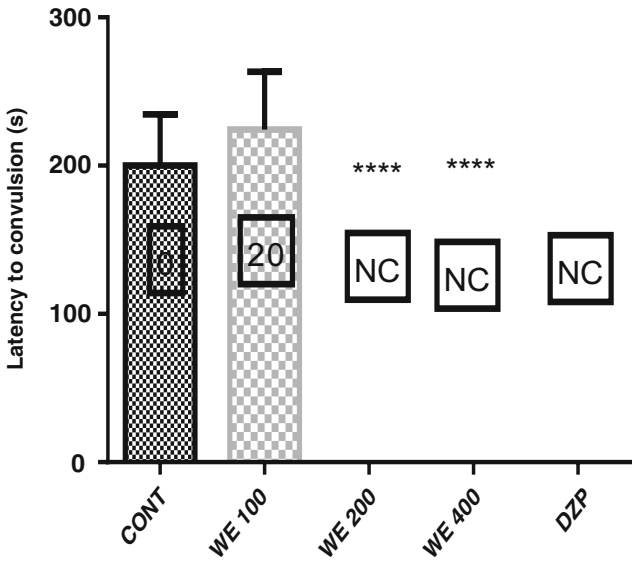

Fig. 1 Effect of whole extract (WE) of *C. bicolor* on strychnine induced convulsion. **** $P < 0.0001$ when compared to control group. CONT: control, DZP: diazepam. Values after abbreviation are doses in mg/kg. Values in the boxes represent percentage protection from convulsion. NC: no convulsion. $n = 5$ per group

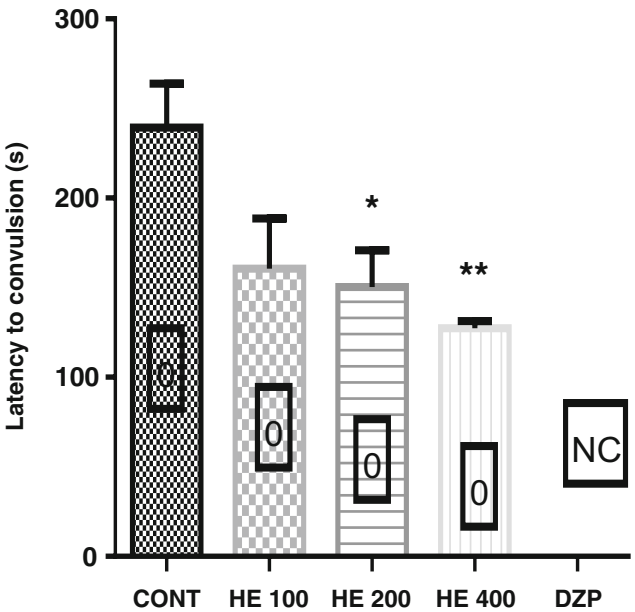

Fig. 2 Effect of n-hexane extract (HE) of *C. bicolor* on strychnine induced convulsion. *$P < 0.05$; **$P < 0.01$ when compared with control group. CONT: control, DZP;diazepam. Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection of mice from strychnine induced convulsion. NC: no convulsion. $n = 5$

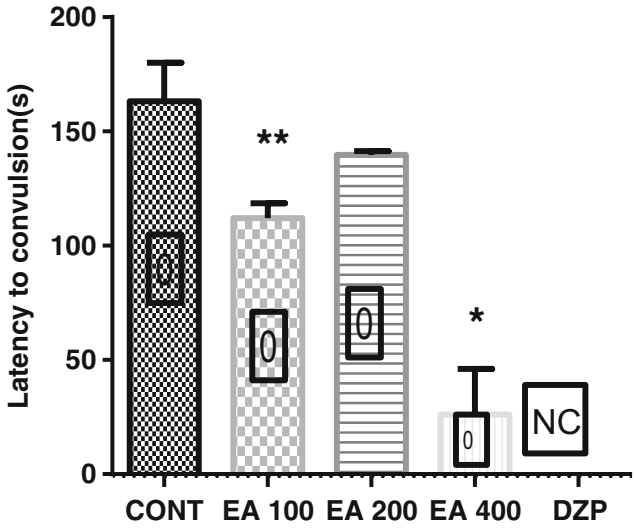

Fig. 3 Effect of Ethyl acetate extract (EA) of *C bicolor* on strychnine induced convulsion. $*P < 0.05$; $**P < 0.01$ when compared with control group. CONT: control, DZP: diazepam. Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection of mice from strychnine induced convulsion. NC: no convulsion. Data represent mean ± SEM; $n = 5$ mice

400 mg/kg (P < 0.001) (Fig. 6). ME and EA also increased the latency to tonic convulsion at doses of 200 mg/kg (P < 0.001) and 400 mg/kg ($P < 0.01$) respectively when compared to the control (Figs. 7 and 8).

Effect of extracts on maximal electroshock induced convulsions

Table 1 show that there was no protection against hind limb extension seizure (HLES) at doses of 100, 200 and 400 mg/kg

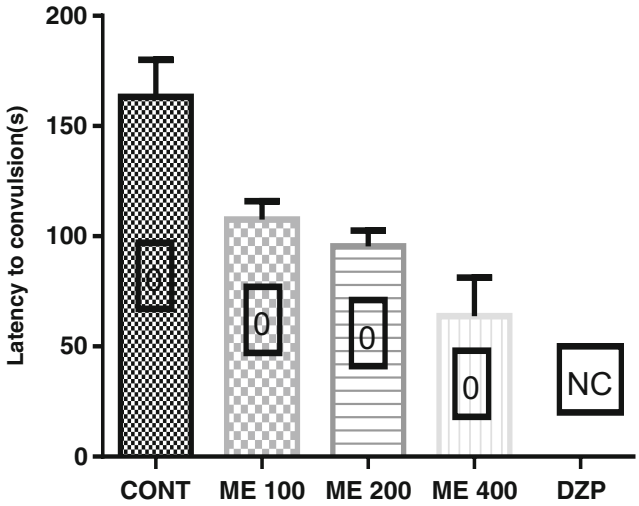

Fig. 4 Effect of methanol extract (ME) of *C bicolor* on strychnine induced convulsion. Values are not significantly different from control. CONT: control, DZP: diazepam. Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection from strychnine induced convulsion. $n = 5$ per group

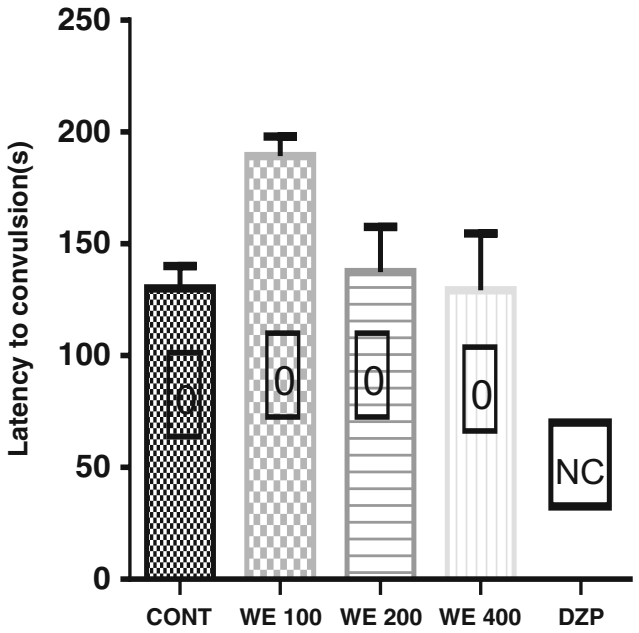

Fig. 5 Effect of Whole extract (WE) of *C bicolor* on PTZ induced convulsion. Values are not significantly different from control. CONT: control, DZP: diazepam. Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection from PTZ induced convulsion. n = 5 per group

of WE. However, HE exhibited 60% protection against HLES at 100 mg/kg and 100% protection at 200 and 400 mg/kg

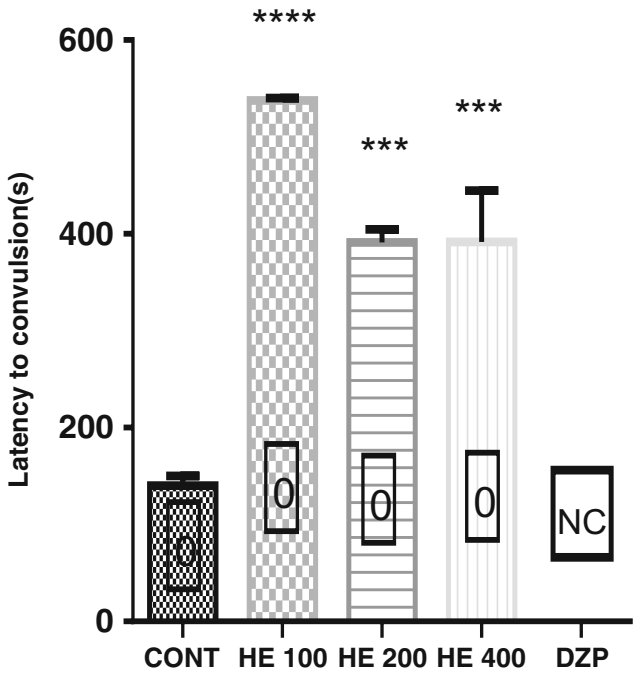

Fig. 6 Effect of n-hexane extract (HE) of *C bicolor* on latency to PTZ induced convulsion. $***P < 0.001$; $****P < 0.0001$ when compared with control group. CONT: control, DZP; diazepam . Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection of mice from PTZ induced convulsion. n = 5 per gro

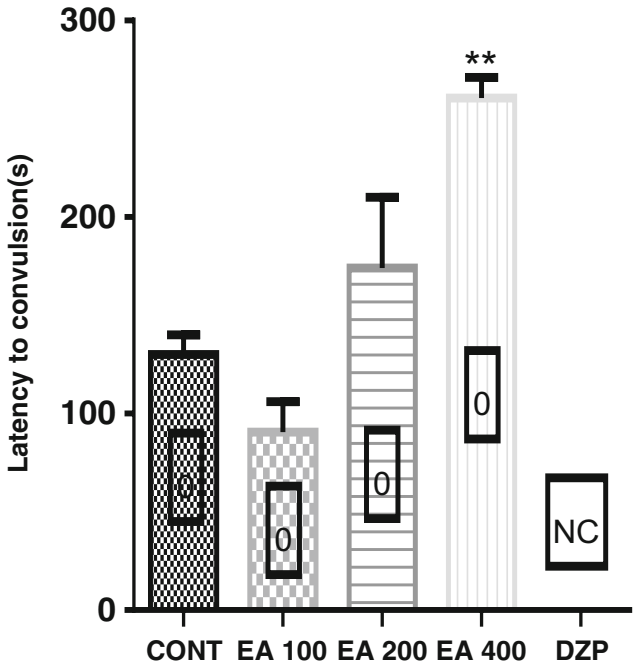

Fig. 7 Effect of Ethyl acetate extract (EA) of *C. bicolor* on PTZ induced convulsion. $^{**}P < 0.01$ when compared with control group. CONT: control, DZP: diazepam, NC: no convulsion. Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection of mice from PTZ induced convulsion. n = 5 per group

respectively. EA protected all mice at 100 and 400 mg/kg but offered 60% protection at 200 mg/kg. ME offered 40%

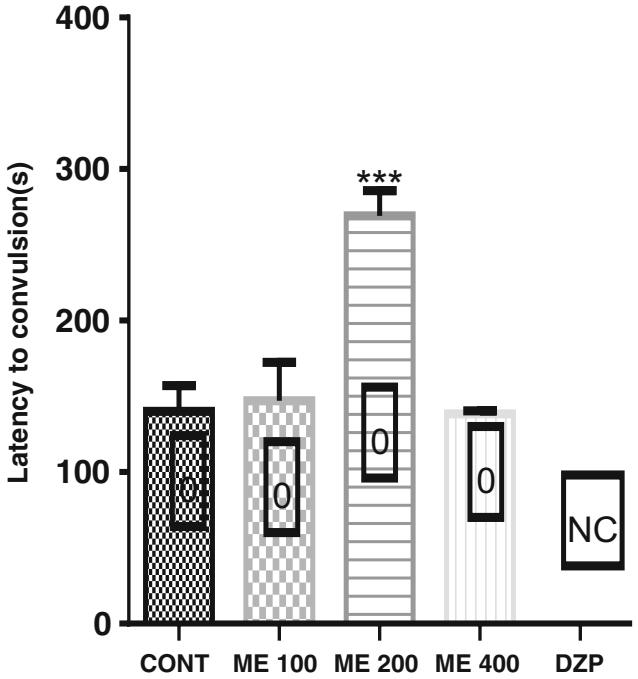

Fig. 8 Effect of Methanol extract (ME) of *C. bicolor* PTZ induced convulsion. ***P < 0.001 when compared with control group. CONT: control, DZP: diazepam. Values after abbreviation are doses in mg/kg. Values in the box represent percentage protection of mice from strychnine induced convulsion. Data represent mean ± SEM; n = 5 mic

Table 1 Percentage protection of mice from maximal electroshock induced convulsion by extracts of *C. bicolor*

	WE	HE	EA	ME
Control	0	0	0	0
100 mg/kg	0	60	100	40
200 mg/kg	0	100	60	20
400 mg/kg	0	100	100	40
Phenobarbitone	100	100	100	100

WE whole extract, *HE* n-hexane extract, *EA* ethyl acetate extract, *ME* methanol extract. *n* = 5 per group

protection at 100 and 400 mg/kg and 20% protection at 200 mg/kg.

Effect of extracts on time spent by mice in the open arm of the elevated plus maze apparatus

Figure 9 shows the time spent by mice on the arms of the elevated plus maze. The duration of time spent in the open arm decreased significantly ($P < 0.05$) at the dose of 100 mg/kg but increased significantly ($P < 0.0001$) at 200 mg/kg of WE. The n-hexane extract (HE) also significantly decreased the time spent in the open arm at a dose of 200 mg/kg ($P < 0.0001$) but significantly ($P < 0.05$) increased the time at 400 mg/kg. The ethyl acetate extract (EA) on the other hand, significantly ($P < 0.01$) decreased the time spent in the open arm at a dose of 200 mg/kg. The methanol extract (ME) significantly ($P < 0.0001$)decreased the time spent in the open arm at the dose of 100 mg/kg but significantly ($P < 0.0001$) increased the time at 400 mg/kg.

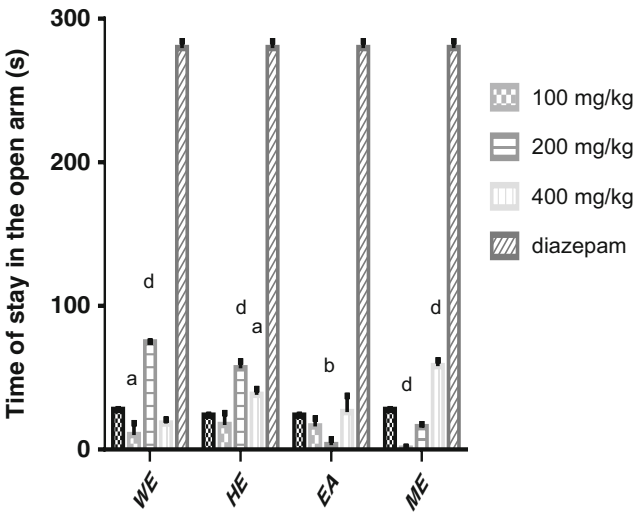

Fig. 9 Effect of extracts on the time of stay by mice in the open arm of the elevated plus maze apparatus. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{d}P < 0.0001$ when compared to control group. WE: whole extract, HE: n hexane, EA: ethyl acetate, and ME: methanol extract. n = 5 mice per group

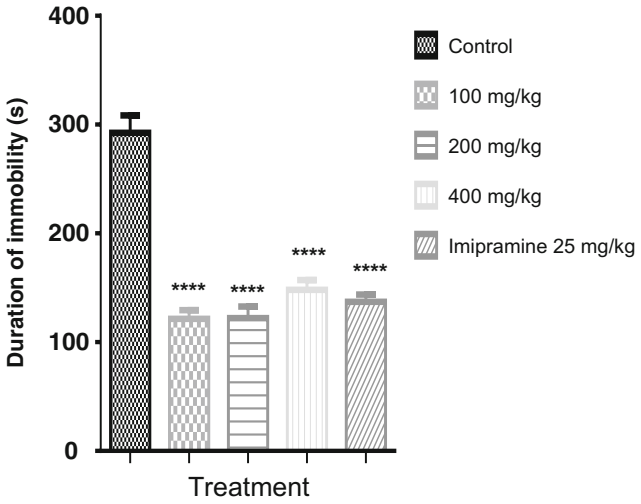

Fig. 10 Effect of Whole extract (WE) on the duration of immobility in forced swim test. ****P < 0.0001 compared to control group. n = 5 mice

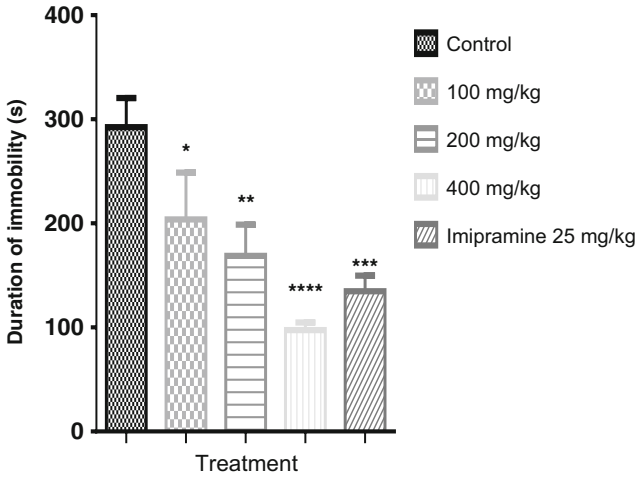

Fig. 12 Effect of Ethyl acetate extract (EA) on the duration of immobility in forced swim test.*P < 0.05; **P < 0.01;***P < 0.001;***P < 0.0001 compared to control group. n = 5 per group

Effect of extracts on the duration of immobility in model of depression

In Figs. 10, 11, 12 and 13 the effects of extracts on forced swimming test model of depression are shown. At doses of 100, 200 and 400 mg/kg, WE significantly (P < 0.0001) decreased the duration of immobility in comparison with the control (Fig. 10). With HE, a significant ($P < 0.001$) decrease was noted at the doses of 100 and 400 mg/kg but there was a significant ($P < 0.01$) increase at 200 mg/kg (Fig. 11). Figure 12 shows that EA also significantly reduced the duration of immobility at doses of 100, 200 and 400 mg/kg (P < 0.05, P < 0.01, P < 0.0001 respectively). Similarly, ME significantly reduced the duration of immobility (P < 0.05) at 100 mg/kg and (P < 0.01) at 200 and 400 mg/kg (Fig. 13).

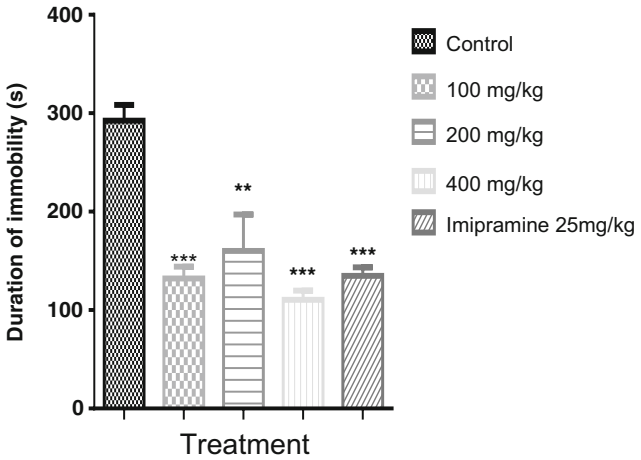

Fig. 11 Effect of n-hexane extract (HE) on the duration of immobility in forced swim test. ** P < 0.01;***P < 0.001 compared to control group. n = 5 per group

Discussion

The extracts demonstrated anticonvulsant activities to varying degrees. In the strychnine model the whole extract offered protection comparable to diazepam possibly via potentiation of the inhibitory neurotransmitter glycine. Strychnine produces its convulsant effect as a non-competitive blocker of the inhibitory neurotransmitter glycine (Adeyemi et al. 2010). Diazepam on the other hand potentiates GABAergic neurotransmission (Chindo et al. 2014).

Pentylenetetrazol (PTZ) induces convulsion by binding to picrotoxin sites of the $GABA_A$ receptor complex thus, inhibiting chloride conductance (Macdonald and Kelly 1995). Drugs that are effective against PTZ-induced convulsions are effective against myoclonic and absence seizures (Wolfgang 2010). The various extracts of *C. bicolor* increased the latency to PTZ-induced convulsion. Phytochemicals such as flavonoids inhibit seizure generation via direct activation of

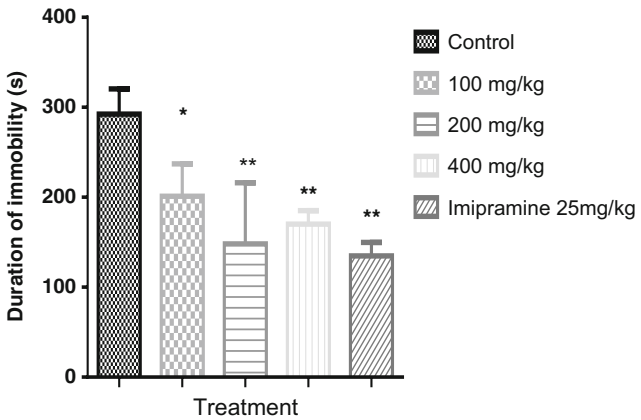

Fig. 13 Effect of methanol extract (ME) on the duration of immobility in forced swim test. * P < 0.05;**P < 0.01 compared to control group. n = 5 per group

inhibitory GABAergic receptors or through the benzodiazepine receptor resulting in increased chloride ion influx that cause neuronal hyperpolarisation (Singh et al. 2014). Flavonoids being non-polar phtochemical constituent are more likely to be present in the n-hexane extract thus accounting for increased latency to convulsion even at a low dose.

Drugs such as phenytoin, carbamazepine and phenobarbitone abolish MES-induced convulsions by inhibiting Na^+ channels. The MES test is effective against generalised tonic-clonic seizures (Kasthuri 2013). Flavonoids have also been found to modulate neuronal channels via inhibition of voltage gated Na^+ channels resulting in decrease Na^+ influx into the cell (Paramdeep et al. 2014). The flavonoid constituent of the plant extracts may be acting through this mechanism to protect against MES-induced seizures.

Increases in the time spent in the open arms of the maze indicate anxiolytic effects. It is known that anxiolytic agents such as diazepam increase the frequency of entries and the time spent in open arms of the elevated plus maze (Pellow et al. 1985). Most anxiolytic agents exert their action by opening of activated GABA-chloride channel (Sampath et al. 2011). The extracts significantly increased the time of stay in the open arm of the maze thereby indicating an axiolytic-like effect. The mechanism seems to be related to the enhancement GABAergic neurotransmission by constituents of the extracts, most likely the flavonoids.

The forced swim test is used to evaluate antidepressant effect of drugs. Different studies have shown that swimming is perculiar to serotonergic agents such as fluoxetine (a serotonin reuptake inhibitor), whereas climbing is perculiar to tricyclic antidepressant agents, and drugs with selective effects on noradrenergic transmission (Detke et al. 1995; Page et al. 1999). Imipramine a tricyclic antidepressant acts by inhibiting the reuptake of neurotransmitters such as norepinephrine, serotonin, and dopamine. All extracts reduced the duration of immobility in the forced swim test indicative of antidepressant-like effect that may be associated with serotonergic mechanisms. It is not immediately clear if this effect involves prevention of reuptake or other mechanisms that improve synaptic availability of the monoamines as has been reported for some flavonoids (Zheng et al. 2013; Guan and Liu 2016).

In conclusion, the leaf extracts of *C. bicolor* possess anticonvulsant, anxiolytic and antidepressant-like neuropharmacological properties that underscore their use in ethnomedicine. The efficacy of the extracts however, require further evaluations.

Acknowledgements The authors are grateful to Mr. Philip Obarisiagbon and Mr. Collins Osaigbovo for their technical support. The study was part of the M.Sc thesis by AMA in the University of Benin, Benin City, Nigeria.

Compliance with ethical standards

Conflict of interest No conflict of interest is associated with this study.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Adeyemi OO, Akindele AJ, Yemitan OK, Fagbo FI (2010) Anticonvulsant, anxiolytic and sedative activities of the aqueous root extract of Securidaca longependuncula fresen. J Ethnopharmacol 130:191–195

Akhigbemen AM, Ozolua RI, Bafor EE, Okwuofu EO (2018) Subacute toxicological profile of *Caladium bicolor* Aiton (*Araceae*) methanolic leaf extract in rat. J Pharm Pharmacogn 6(6):503–516

Chindo BA, Amos S, Odutola AA, Vongtau HO, Abbah J, Wambebe C, Gamaniel KS (2014) Central nervous system activity of the methanol extract of *Ficus platyphylla* stem bark. J Ethnopharmacol 85: 131–137

Clay HF, Hubbard JC (1987) The Hawai'I Graden. Tropicla exotics University of Hawaii. Press Honolulu, p 38

Detke MJ, Rickels M, Lucki I (1995) Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psycho- pharmacology 121(1):66–72

Evans WC (2004) Pharmacopoeial and related drugs of biological origin. *Trease and Evans Pharmacognosy*. UK: Elsevier Ltd. Pp 186–187

Guan LP, Liu BY (2016) Antidepressant-like effects and mechanisms of flavonoids and related analogues. Eur J Med Chem 121:47–57

Kasthuri S (2013) A review : animal models used in the screening of antiepileptic drugs neuropsy. International research journal of pharmaceutical and. Appl Sci 3(3):18–23

Macdonald RL, Kelly KM (1995) Antiepileptic drug mechanisms of action. Epilepsia 36:S2–S12

Marsh L, Rao V (2012) Psychiatric complications in patients with epilepsy: a review. Epilepsy Res 49:11–33

NRC - National Research Council (2011) Guide for the care and use of laboratory animals. 8th edition. USA. In: pp 1–246

Odugbemi T (2006) Outlines and pictures of medicinal plants of Nigeria. University of Lagos Press Pp 112

Page ME, Detke MJ, Dalvi A, Kirby JG, Lucki I (1999) Serotoninergic mediation of the effects of fluoxetine, but not desipramine, in the rat forced swimming test. Psychopharmacology 147:162–167

Paramdeep S, Damanpreet S, Rajesh KG (2014) Phytoflavonoids: Antiepileptics for the future. Int J Pharma Sci 6(8):51–66

Pellow S, Chopin P, File SE, Briley M (1985) Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Method 14:149–167

Porsolt RD, Bertin A, Jalfre M (1977) Behavioural despair in mice: a primary screening test for antidepressants. Archive Int Pharmacodynamic Therapeutics 229:327–336

Porter RJ, Cereghino JJ, Gladding GD (1984) Antiepileptic drug development program. Cleve Clin 51:293–305

Salako O, Akindele A, Shitta O (2015) Antidiarhoeal activity of aqueous leaf extract of *Caldium bicolor* (araceae) and its possible mechanisms of action. J Ethnopharmacol 176:225–231

Sampath TS, Santosh PL, Mangala AP, Pavan KS, Lingesh A (2011) Anxiolytic effect of ethanolic extract of *Oxalis corniculata .l* in mice. Int J Pharm Bio Sci 3(2):281–290

Schmidt D (2009) Drug treatment of epilepsy: options and limitations. Epilepsy Behav 15:56–65

Sen S, Jaiswal AK, Yanpallewar S, Acharya SB (2007) Anxiogenic potential of ciprofloxacin and norfloxacin in rats. Singap Med J 48(11): 1028–1032

Singh P, Singh D, Goel RK (2014) Phytoflavonoids: Antiepileptics for the future. Int J Pharm Pharm Sci 6(8):51–66

Sofowora LA (1993) *Medicinal plants and traditional Medicine in Africa*. Ibadan: Spectrum Books Ltd. Pp 55–71

Swinyard EA, Brown WC, Goodman LS (1952) Comparative assay of antiepileptic drugs in mice and rats. J Pharmacol Exp Ther 106:319–330

Tosoc JPS (2016) Antiangiogenic, antitoxic and antioxidant properties of methanolic extracts of Caladium bicolor (Aiton) Venten. Hum Vet Med 8(1):10–16

Vogel HG, Vogel WH (1997) Drug discovery and evaluation, pharmacological springer. Berlin:260–261

WHO (2008) Traditional medicine. Available from "http://www.who.int/mediaCentre/factsheets/. Accessed 22nd July, 2016

Wolfgang L (2010) Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. Seizure 20:359–368

Yemadje LP, Houinato D, Quet F, Druet-Cabanac M, Preux PP (2011) Understanding the differences in prevalence of epilepsy in tropical regions. J Epilepsia 52:1376–1381

Zheng M, Fan Y, Shi D, Liu C (2013) Antidepressant-like effect of flavonoids extracted from Apocynum venetum leaves on brain monoamine levels and dopaminergic system. J Ethnopharmacol 147(1): 108–113