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Anticonvulsant Activity of *Emilia sonchifolia* Leaf Extracts

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Abstract. Anticonvulsant effect of the leaf extracts of *Emilia sonchifolia* is reported for the first time. The ethanol, chloroform and aqueous extracts, especially the aqueous extract, showed marked anticonvulsant effect (ED_{50} of 4 mg/kg and 8 mg/kg in chicks and mice, respectively). This research finding gives scientific justification to the traditional healers in Nigeria for the use of aqueous leaf extract of the plant for treating infantile convulsion. The extracts of *E. sonchifolia* showed concentration-dependant protective effect against maximal electroshock (MES) and strychnine-induced seizures (SIS). The potent anticonvulsant effect exhibited by the extracts of *E. sonchifolia* (especially the aqueous extract) is an indication of its promising anticonvulsant application as a possible new clinical drug. Further studies on the principal anticonvulsant compounds of the aqueous extract are in progress.

Keywords: *Emilia sonchifolia*, anticonvulsant drug, epilepsy, maximal electroshock seizure (MES), strychnine induced seizure (SIS)

Introduction

Epilepsy is a central nervous system disorder which is characterized by repeated occurrence or sudden and transitory episodes known as seizures. Approximately 20 - 40 million (~1-2 %) people worldwide are epileptic (McNamara, 1999; Saxena and Saxena, 1995). For many epileptic patients, the development of a new anticonvulsant drug offers the hope of achieving control of their seizures with lesser side-effects, which they usually tolerate to gain control of seizures (Anderson *et al.,* 1997; Krall *et al.,* 1978). Epilepsy impacts society at multiple levels; at the top most among these is its social impact particularly in Nigeria where some ethnic groups strongly believe that it is due to the aftermath of evil spells. Hence, it is a dreaded disease to be prevailing in a family. Although advances have been made in the development of anticonvulsant drugs, only about 60-70% of the epileptic patients are reported to respond to the available chemotherapy (Hauser and Hesdorffer, 1990). Also, despite the large therapeutic range of old and new antiepileptic drugs (AEDs), approximately 30% of the patients with epilepsy are still not seizure-free and, consequently, there is a substantial need to develop new AEDs (Bialer, 2006). The development of novel anticonvulsant agents from herbs remains a scientific challenge, which provides the necessary rationale for the present study. Anticonvulsant activity of *Emilia sonchifolia* is being reported for the first time in the present communication.

Emilia sonchifolia (L.), family Compositae, is an erect annual herb (Adams, 1980; Harold,1966), which is quite abundant in Nigeria having a long history of ethnomedicinal use. The roots and leaves are employed in ethnomedicine for the treatment of sore throat, fever, rashes, measles, inflammatory diseases, eye and ear ailments and vertigo (Kohler *et al.,* 2002; Gill, 1992; Hutchinson and Dalziel, 1985). The roots are listed among the recipes used in the traditional Chinese medicine for regenerating bath therapy (Cai, 2003). There are also reports on its cytotoxic, antitumor, antioxidant, antidiabetic and antiinflammatory properties (Muko and Ohiri, 2000; Shylesh and Padikkala, 2000; 1999). This plant is documented in the Nigerian folk medicinal plants for epilepsy treatment (Gill *et al.,* 1993; Adesina, 1982a). Our literature survey revealed no anticonvulsant report on this plant till date.

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Materials and Methods

Collection and preparation of plant material. Fresh leaves of *Emilia sonchifolia* were collected at the Ugbowo campus of the University of Benin, Nigeria. The Taxonomist at the Department of Pharmacognosy, University of Benin, Nigeria, where voucher specimens are kept, authenticated the plant. The leaves were oven dried at 40 °C for two days after which they were pulverized to fine powder. About 300 g of the powder was macerated with 500 ml distilled water for 24 h and filtered. The filtrate was dried under reduced pressure and the resultant powder was stored for further study. Likewise, two additional 300 g samples of the leaf powder were exhaustively extracted separately with ethanol and chloroform. These two extracts were likewise dried under reduced pressure and the resultant powders were stored for further study.

Phytochemical screening. The powdered plant materials were screened for the following classes of secondary metabolites: alkaloids, glycosides, anthraquinones, saponins, flavonoids and tannins by standard phytochemical test methods (Sofowora, 1989; Harborne, 1983; Adesina, 1982b; Stahl, 1973).

Acute toxicity. Thirty six rats were randomly divided into six groups of six rats each (three males + three females), each group having average rat weight of 130 g. Groups 1-5 were injected intraperitoneally (i.p.) with the crude extracts (ethanol, chloroform and aqueous), at doses between 100-900 mg/kg. The sixth group serving as the control received no more than 1 ml/kg of normal saline by the same route. The animals were observed for mortality and gross effects over a period of 24 h. Deaths within this period were recorded and the LD_{50} value was determined using a standard method (Miller and Tainter, 1944).

Animals for seizure studies. Male mice and chicks were used for the study on chemical and electrical seizures, while male rats were used for the toxicity test.

Anticonvulsant test. The anticonvulsant potency of the leaf extracts of *E. sonchifolia* was determined on both male albino mice (average weight of 30 g) and on Cockerel chicks (four-day old; average weight of 42.72 g). The animals were divided into 12 groups of five animals each; keeping the weight of animals in each group as close as possible. There were three control groups, those treated with saline-distilled water, those treated with dimethylsufoxide (DMSO), and those treated with phenobarbitone or sodium valproate as the reference anticonvulsant drug (Burnham, 1989). A pre-test on a concentrated solution of the crude extracts was carried out on mice and chicks to ascertain their respective anticonvulsant properties. A similar test was carried out with the vehicle (DMSO) to ensure that it was devoid of anticonvulsant property. A dose response study was carried out on different extracts.

Maximal electroshock (MES) induced seizures. This study was conducted on albino mice, which were divided into eighteen groups (three sets of six groups) for the three extracts studied (ethanol, chloroform and aqueous extracts). The crude drug extracts were administered intraperitoneally (i.p.) in graded doses of 100, 70, 30 and 8 mg/kg. If a test extract at 30 mg/kg protected 50% of animals, then a further test was performed at 8 mg/kg. The vehicle and the reference drugs were also administered by i.p. route, based on the body weight of the animals. Convulsion was induced via corneal electrodes (60 Hz alternating current of 50 mA, 220 v for 0.2 sec at 100 pulse/second) after the application of normal saline to the eyes of all animals. A higher stimulus was used during this experiment, as it had been demonstrated that the level of protection of an anticonvulsant agent was dependent on the intensity of the stimulus (Barton *et al.,* 2001). The seizure parameters being stun, a clonic/tonic flexion (i.e., a tonic limb flexion up to 12 sec), followed by a tonic limb extension of up to 10-12 sec and a generalised clonic movement of 12 sec were followed. An abolition of hind limb tonic extension spasm was considered as a protection. The animals were challenged at intervals of ½, 1½, 2½, 3½ and 4½ h post-treatment time. The experiment was conducted three times and the number of protected animals per group was recorded and expressed as its mean percentage.

Strychnine-induced seizures. Seizure of the midbrain/spinal cord origin was assessed using strychnine. The anticonvulsant potency of *E. sonchifolia* leaf extracts was investigated on four-day old chicks in graded doses of 100, 70, 30, 8 and 4 mg/kg by the i.p. route. Chicks were divided into eight groups of five animals each per extract. After single dose administration, animals were challenged with 7.0 mg/kg solution of strychnine in distilled water at different time intervals and closely observed for convulsive signs. The control group received 8 mg/kg solution of phenobarbitone prepared in distilled water. All experiments were performed in the absence of noise to eliminate seizures triggered by sensory stimuli in treated animals. This was done, as it was observed that following strychnine treatment, picking up the chicks at the end of the test period frequently resulted in triggering of a fatal tonic seizure. The experimental time was reduced by an hour for chicks because of their low tolerance to repeated strychnine applications. Strychnine was used as it has been reported to have a good index for absence seizures (Rang *et al.,* 1995).

Results and Discussion

Our experiment model involved repeated application of stimuli to animals to investigate whether these would affect the degree and duration of protection of *E. sonchifolia* extracts, and to observe their effect on the level of tolerance of non-protected animals. The animals were first challenged with the convulsive stimuli, 30 min after the extract or reference drug administration, as phenobarbitone (reference drug) is known to reach its CNS peak level 20 min after the injection (Stirling *et al.,* 1999). The results so obtained showed that the degree or duration of protection was dependent on the extract and with the animal model. Only unprotected chicks showed low tolerance to the repeated application of strychnine.

Table 1 shows the anticonvulsant activity of *E. sonchifolia* leaf extracts on mice induced with maximum electroshock

(50 mA). The results showed that *E. sonchifolia* leaf extracts effectively inhibited MES seizures in the brainstem and midbrain. At higher doses (70 and 100 mg/kg), the extracts of *E. sonchifolia* leaves showed good protection against MES seizure within the first 30 min after administration for all the extracts. The chloroform extract gave the least protection to seizure in mice induced with strychnine. The anti-convulsive effect of *E. sonchifolia* leaf extracts was relatively dose-dependent with the least assayed dose giving the least protection to mice. The observed negative protection of chloroform and equeous extract after 4½ h may be due to high serum level of some MES seizure potentiating substances in these extracts, otherwise absent or in low amount in the ethanolic extract. This may also be due to the bioavailability of the active comound(s) from the various extracts at the site of action.

Table 2 shows the anticonvulsant activity of *E. sonchifolia* leaf extract in chicks against strychnine-induced seizure. All the extracts effectively blocked the effect of strychnine on the convulsions of midbrain/spinal cord origin and the effect was found to be dose-dependent. There was no significant statistical difference ($p = 0.05$) between the observed antistrychnine effect of *E. sonchifolia* aqueous extracts at the doses of 70 and 100 mg/kg.

Table 3 shows the percentage protection elicited by the leaf extracts of *E. sonchifolia* on mice corresponding to the studied doses. The aqueous extract at 100 mg/kg gave the maximal protection of 100% to all mice within the study period of 4½ h while 70 mg/kg protected 100% of the mice within the first 3 h after its administration. The dose response study of the aqueous extract to effectively protect 50% of mice was 8 mg/kg (ED_{50}). However, at a higher dose, the active compound in both the ethanol and chloroform extracts tended to reach its plasma peak within the first 3½ h to protect more than 50% of the mice. The active compound responsible for the observed anticonvulsant effect of the extracts of *E. sonchifolia* studied is believed to have attained its CNS peak after 2 h post-extract administration as reflected in the groups treated with 8 mg/kg within the first 3½ h (Table 3).

The preliminary phytochemical screening of *E. sonchifolia* leaves showed the presence of the following classes of secondary metabolites: alkaloids, steroidal saponins, condensed tannins, flavonoids, anthraquinones and cyanogenic glycosides. The presence of alkaloids in our sample extracts confirms the isolation of pyrrolizidine alkaloid from the leaves of *E. sonchifolia* (Cheng and Roeder, 1986). However, this is the first report of anthraquinone and cyanogenic glycosides in the leaves of *E. sonchifolia*. Saponins and glycosides have

Table 1. Anticonvulsant effect of *Emilia sonchifolia* leaf extracts in mice challenged with maximal electroshock (50 mA, 220 v for 0.2 sec at 100 pulse per sec) induced seizure

Treatment	Dose given	Challenged time (h)				
	(mg/kg)	½	1½	2½	3½	4½
Normal saline (control)*		-ve	-ve	-ve	-ve	-ve
DMSO (control)*		-ve	-ve	-ve	-ve	-ve
Phenobarbitone (control)	8 mg	+ve	+ve	+ve	+ve	+ve
Aqueous extract	100 mg	+ve	+ve	+ve	+ve	+ve
	70 mg	+ve	+ve	+ve	+ve	+ve
	30 mg	-ve	+ve	+ve	+ve	-ve
	8 mg	-ve	-ve	+ve	+ve	-ve
Ethanol extract	100 mg	+ve	+ve	+ve	+ve	+ve
	70 mg	-ve	+ve	+ve	+ve	+ve
	30 mg	-ve	-ve	+ve	+ve	+ve
	8 mg	-ve	-ve	-ve	+ve	+ve
Chloroform extract	100 mg	+ve	+ve	+ve	+ve	+ve
	70 mg	+ve	+ve	+ve	+ve	-ve
	30 mg	-ve	-ve	+ve	+ve	-ve
	8 mg	-ve	-ve	-ve	+ve	-ve

-ve = not protected; + ve = protected; DMSO = dimethylsulfoxide; controls = did not contain any leaf extract; * = 1 ml/kg body weight of (test animal) normal saline and DMSO (controls)

been reported in literature to elicit anticonvulsant properties (Adesina, 1982b; Srinivasan and Subramanian, 1980; Adesina and Sofowora, 1979).

The value of the degree of protection of *E. sonchifolia* leaf extracts in chicks is well evident from Fig. 1. The result was quite similar with those obtained for the MES test on mice with the aqueous extract eliciting the maximum protection of 100% to chicks, even at the lowest administered dose and the chloroform affording the least protection. The ED_{50} for chicks was 4 mg/kg for all the extracts. There was equally no statistical difference between the activity of phenobarbitone and the aqueous extract. This result corresponds with the report of Krall *et. al.* (1978) that there was no qualitative difference between the antiepileptic drugs response in mouse and rats. It is observed that after 2½ h of administering the lowest dose of the extracts, there was a sharp decrease in the protection of animals, which may be due to the half-life of the active compound (Table 3; Fig. 1). This finding suggests its use as a prophylactic treatment of infantile convulsions.

The duration of protection to both mice and chicks by the extracts of *E. sonchifolia* is shown in Fig. 2. The duration of activity of the extracts in the respective dose in chicks was between 2-3 h for all the assayed doses. It was more dose-dependent in mice, with the highest dose giving protection for up to 2 h following the extract administration. Generally, the different extracts of *E. sonchifolia* were active between 30 min to 2 h for both chicks and mice.

The latency time of onset of convulsion of *E. sonchifolia* leaf extract was statistically significant ($p = 0.05$) in comparison with the control at all the doses studied (Fig. 3). Each bar corresponds with the total response for the total assay period for mice and chicks. However, the latency time was higher for the aqueous extract with a correspondingly high anticonvulsant activity. This was followed by the ethanol extract and the

Table 2. Anticonvulsant activity of different doses of *Emilia sonchifolia* leaf extracts in chicks challenged with strychnine

Treatment	Dose given (mg/kg)	Challenged time (h) ½	1½	2½
Normal saline (control)*		-ve	-ve	-ve
Phenobarbitone (control)	8 mg	+ve	+ve	+ve
Aqueous extract	100 mg	+ve	+ve	+ve
	70 mg	+ve	+ve	+ve
	30 mg	+ve	+ve	+ve
	8 mg	+ve	+ve	+ve
	4 mg	+ve	+ve	+ve
Ethanol extract	100 mg	+ve	+ve	+ve
	70 mg	+ve	+ve	+ve
	30 mg	+ve	+ve	+ve
	8 mg	+ve	+ve	+ve
	4 mg	+ve	-ve	+ve
Chloroform extract	100 mg	+ve	+ve	+ve
	70 mg	+ve	+ve	+ve
	30 mg	+ve	+ve	+ve
	8 mg	+ve	+ve	+ve
	4 mg	+ve	+ve	+ve

-ve = not protected; + ve = protected; control = did not contain any leaf extract; * = 1 ml/kg body weight (test animal) of saline (control)

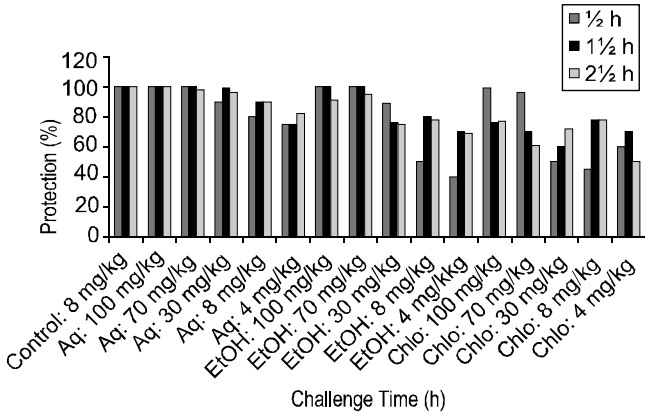

Fig. 1. Degree of protection of chicks by *Emilia sonchifolia* leaf extracts (aqueous, ethanol, chloroform) after strychnine induced seizure; the dose levels (mg/kg animal body weight); Aq = aqueous extract, EtOH = ethanol extract; Chlo = chloroform extract; control = 8 mg/kg phenobarbitone.

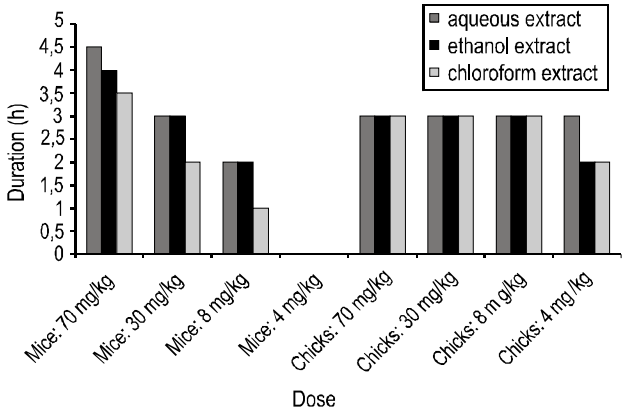

Fig. 2. The effect of *Emilia sonchifolia* leaf extracts (aqueous, ethanol, chloroform) on animals (mice, chicks) subjected to either maximal electroshock seizure (MES) or strychnine-induced seizure (SIZ).

chloroform extract being the least. There was no statistically significant difference in the latency time between mice and chicks.

The MES test is a routine procedure included in the experimental models of epileptiform seizures as the conventional approach to the study of potentially active drugs, as well as plant extracts and their isolates (Navarro-Ruiz *et al.,* 1996; Garzón *et al.,* 1990). Strychnine was used in this study as a convulsant and any extract or compound which can retard its action may be termed as anticonvulsant. All the leaf extracts of *E. sonchifolia* exhibited anticonvulsant activities by blocking MES induced seizures in mice. The ethanol extract gave the maximal protection of 100% at all doses (8, 30, 70 and 100 mg/kg) up to 4½ h after extract administration. This was followed by the ethanol extract while the chloroform extract gave the least protection. There was no statistical difference ($p = 0.05$) between the observed protection elicited by the aqueous extract and those of the reference drug phenobarbitone. A similar result was obtained from chicks induced with strychnine, where the aqueous extract gave up to 100% protection to chicks at all the doses studied within the assay period. The extracts of *E. sonchifolia* protected mice for a longer period than chicks. This observed preferential sensitivity, especially the aqueous extract, to both animal models may be explained on the basis of high potency of strychnine, the higher dose used to induce the stimuli, and the different level of tolerance to stress by mice and chicks.

Phenobarbitone is a well known anticonvulsant drug for the management of all forms of epilepsy (especially status epilepsy at 10-20 mg/kg) except absence seizure in humans. We postulate that the aqueous extract of *E. sonchifolia* may act in a similar mechanism as phenobarbitone. It was observed that there was no qualitative difference in the anticonvulsant activity of the extracts of *E. sonchifolia* on both mice and chicks. However, there was a significant qualitative difference in the activity (between the administered doses) for the tested extracts within the assayed period in both mice and chicks. The highest administered dose to both chicks and mice was 100 mg/kg for all extracts. This dose protected 100% of the mice and 95% of chicks against maximal electroshock and strychnine induced convulsion, respectively. There were no observed toxicity symptoms in both mice and chicks at the studied doses, however, the LD_{50} of extracts was found to be greater than 400 mg/kg from preliminary toxicity tests. There was no observed physical neurological disorder induced by the leaf extract of *E. sonchifolia* when 250 mg/kg (single oral dose) was administered to rats even after seven days. The ED_{50} for chicks was 4 mg/kg for all the extracts while it was 8 mg/kg for mice. However, the present finding is consistent with those of Akah *et al.* (1997), who reported differences in the ED_{50} for pentylenetetrazole and

Table 3. Dose response in mice to electroshock seizure pretreated with *Emilia sonchifolia* leaf extracts

Treatment	Dose given (mg/kg)	Challenged time (h)				
		½	1½	2½	3½	4½
Normal saline (control)*		0	0	0	0	0
DMSO (control)*		0	0	0	0	0
Phenobarbitone (control)	8 mg	100	100	100	100	100
Aqueous extract	100 mg	100	100	100	100	100
	70 mg	100	100	100	98	89
	30 mg	20	40	70	89	42
	8 mg	10	18	94	65	30
Ethanol extract	100 mg	89	100	100	93	82
	70 mg	43	89	97	100	70
	30 mg	30	30	100	75	30
	8 mg	6	20	58	55	10
Chloroform extract	100 mg	81	85	100	100	50
	70 mg	63	100	100	60	41
	30 mg	25	45	100	100	24
	8 mg	0	22	50	60	10

control = did not contain any leaf extract; * = 1 ml/kg body weight (test animal) of normal saline and DMSO (dimethylsulfoxide) in the controls

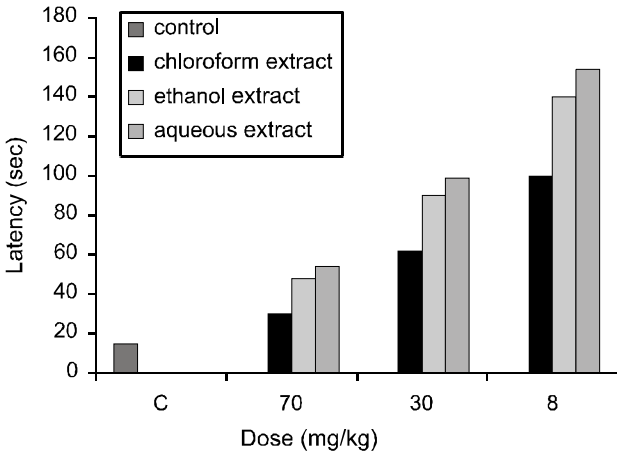

Fig. 3. Effect of *Emilia sonchifolia* leaf extracts (equeous, ethanol, chloroform) on latency to maximal electroshock seizure (MES) or strychnine induced seizure (SIZ).

MES of some Nigerian plants in two animal models (ED_{50} for pentylenetetrazole and MES being 38 ± 12 and 45 ± 9, respectively, for *Tetrapleura tetraptera*).

Wang *et al*. (2000) also reported the ED_{50} for MES of *Scutellariae radix* in mice at the lower doses to be between 0.5-3.0 g/kg. The findings obtained during the present investigation show high potency of the extracts of *E. sonchifolia,* when compared with the reports of Wang *et al.* (2000) and Akah *et al.* (1997) on the plant extracts that these authors studied. The active compound in the extracts of *E. sonchifolia* is believed to potentiate the receptor both in the midbrain and brainstem owing to its ability to antagonize the activity of strychnine and MES seizures. The high inhibition of inducible MES and strychnine seizures on both mice and chicks by the ethanol and aqueous extracts of *E. sonchifolia* partly justifies the traditional mode of using the aqueous decoction for the treatment of infantile convulsion. However, the alcoholic extract is recommended for use as an emergency first aid or of prophylactic treatment/management of epileptic patients; with generalized clonic tonic (grand mal/absence) seizures after a full pharmacological and toxicological evaluation of the leaf.

Though the active compound responsible for the anticonvulsant activity has not been isolated, it is speculated that the observed activity may be due to the presence of glycosides or steroids, which are known to exert anticonvulsant properties by blocking γ-aminobutyric acid (GABA), or interfere with the synaptic transmission. Research work is presently undergoing to isolate the active chemical constituent from this plant responsible for anticonvulsant activity.

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