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## Anticonvulsant Activities of Crude Flavonoid Fraction of the Stem Bark of *Ficus sycomorus* (Moraceae)

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**Abstract:** The anticonvulsant effects of the crude flavonoid fraction of the stem bark of *Ficus sycomorus* were studied using the subcutaneous Pentylentetrazole (PTZ) and Maximal Electroshock Test (MEST) models in mice and chicks respectively. The crude flavonoid fraction exhibited a significant ( $p < 0.05$ ) latency in mean onset and mean time of death of convulsed animal with a 20% protection at a dose of  $10 \text{ mg kg}^{-1}$  body weight i.p. (comparable to Valproic acid at  $200 \text{ mg kg}^{-1}$ ) while it showed a significant ( $p < 0.05$ ) and dose dependent maximal protection (83.3%) in the Maximal Electroshock Test (MEST) at an optimal dose of  $20 \text{ mg kg}^{-1}$  body weight i.p. (comparable to Phenytoin at  $20 \text{ mg kg}^{-1}$ ). The results obtained supported the claim in the traditional use of the stem bark of the plant in the management of epilepsy.

**Key words:** Anticonvulsant, crude flavonoids, pentylentetrazole-induced seizure, maximal electroshock test, *Ficus sycomorus*, Moraceae

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### INTRODUCTION

A number of plants have been used in traditional medicine for many years. Some do seem to work although there may not be sufficient data to confirm their efficacy (for example double blind trials) (Sofowora, 1993).

*Ficus sycomorus* is found in the Arabian Peninsula, tropical Africa to the east, very extended to all Africa. It is also found abundantly in Nigeria (Dalziel, 1956). It is commonly called *Sycamore* or *Sicomoro*. In Northern Nigeria the plant is called *Baure* or *Bore* by the Hausa-Fulani tribes.

The plant is characterized by a milky juice, the prominent stipules that leave a scar on falling and the minute unisexual flowers often arranged on variously shaped receptacle. *F. sycomorus* is a large evergreen tree (10-25 m) but also reported to grow up to 45 m with spreading crown and a pale yellowish trunk that is usually buttressed (Sofowora, 1993).

Ethno-medically the plant is widely used in the management of some ailments. Humans, birds and mammals use the fruits as foods. The infusion when taken orally is used to treat tuberculosis. The dried root extracts and leaf infusion are used for diarrhea. The stem bark is used to increase lactation (Umar *et al.*, 2003).

The powdered stem bark is soaked in water for about 6 h and the resulting aqueous solution is administered to the patient orally three times daily for several days for the treatment of a variety of ailments such as mental illness, epilepsy, insomnia, diarrhea and to relieve pain (Quinn-Beattie, 2003).

The crude ethanol extract of the stem bark was found to have a median lethal dose ( $LD_{50}$ ) of  $471.2 \text{ mg kg}^{-1}$  in mice (i.p.). Phytochemical screening of ethanol extract of the stem bark showed the presence of carbohydrates, flavonoids, saponins, tannins, steroids and triterpenes but alkaloids and anthraquinones were absent (Victor, 2006).

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The crude ethanol extract of the plant was found to have anticonvulsant and sedative effects (Umar *et al.*, 2003); antidiarrhoeal activity (Victor, 2006).

Epilepsy is one of the most common neurological problems worldwide with the incidence of 3% in the general population (Annerger, 2001). In many tropical countries the incidence of epilepsy was estimated to be greater than 0.5% of a given population and is higher in male than female with a majority having their first attack before the age of twenty (Aguwa and Ochei, 1998).

The currently available synthetic antiepileptic drugs (AEDS) provide seizure control in up to 70% patient with epilepsy, the remaining patient have refractory epilepsy. Moreover these drugs are associated with many side effects including teratogenicity, sedation, fatigue and behavioral disturbances (Avanzini and Franchetti, 2003). Thus there is need to develop new drugs with greater efficacy, minimal side effects and devoid of unfavorable drug interactions.

The present study was aimed at screening the crude flavonoids of *F. sycomorus* for its possible anticonvulsant activity.

## MATERIALS AND METHODS

### Plant Collection and Identification

The stem bark of *F. sycomorus* was collected in July, 2006 at Samaru Zaria, Kaduna state, Nigeria. The plant material was identified and authenticated at the Herbarium section of the Department of Biological Sciences, A.B.U. Zaria. Its voucher specimen number was 1466 and a sample was deposited there for future reference.

### Preparation of the Plant Material

The stem bark pieces of the plant were air dried at ambient room temperature. The air-dried stem bark was then comminuted using mortar and pestle to obtain a fine powder. The dried stem bark of the plant, after comminution, gave a pale reddish brown powder.

### Extraction of the Plant Material

Two hundred and thirty gram of the powdered stem bark was macerated in ethanol (96% v/v) using a one-liter beaker. After the maceration process, the supernatant was decanted. The residual marc was strained with a clean and dry net sieve with fine mesh to free more supernatant. This was added to the already decanted supernatant and filtered. The filtrate thus obtained was concentrated to dryness on water bath and labelled as Ethanol Extract (EE). 15.5 g of the dried ethanol extract were obtained with a percentage yield of 6.7%.

### Fractionation of Plant Extract

Fifteen gram of the dried Ethanol Extract (EE) was dissolved in hot water and filtered. Then the method employed by Woo *et al.* (1980) was adopted to partition the flavonoid portion from the filtrate. The crude flavonoid fraction was then evaporated to dryness on water bath to obtain 47.6 mg mass with percentage yield of 0.31%. The scheme is shown as Fig. 1.

### Test for Flavonoids on the Crude Fraction

These tests were carried out as reported by Sofowora (1993) and Trease and Evans (1983).

### Anticonvulsant Screening

#### Experimental Animals

Twenty five locally bred adult albino mice of either sex weighing between 13-27 g were used.

They were housed in cages at room temperature. The animals were allowed free access to food and water *ad libitum*. Day old white ranger cockerels (30 in number) weighing 25-38 g were obtained from Palladan, Zaria for the experiments.

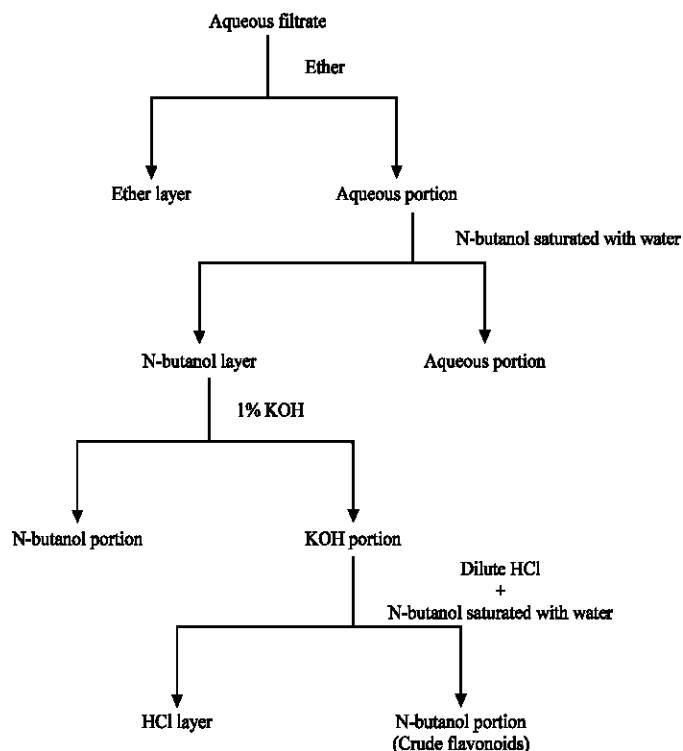


Fig. 1: Scheme for the fractionation of crude flavonoids from ethanol extract of the stem bark of *F. sycomorus*

#### **Pentylentetrazole (PTZ) Induced Seizure Test**

The method of Swinyard (1969) was employed. Twenty five mice were divided into five groups of five mice each. Group I (Negative Control) was given 1.0 mL kg<sup>-1</sup> body weight of 2% gum acacia intraperitoneally (i.p). Group II (Positive Control) was given Valproic acid 200 mg kg<sup>-1</sup> body weight i.p. The Third (III), Fourth (IV) and Last (V) groups were given 20, 10 and 5 mg kg<sup>-1</sup> body weight i.p. of the crude flavonoid fraction respectively. After 30 min post treatment, all the groups (I-V) were administered 85 mg kg<sup>-1</sup> body weight freshly prepared PTZ subcutaneously. All mice in each group were observed for a period of 30 min after scPTZ administration for the presence or absence of threshold seizures (i.e., an episode of clonic spasm of at least 5 sec duration). The percentages of protection were observed and recorded.

#### **Maximal Electroshock Induced Seizures in Chicks**

The modified methods of Swinyard and Kupterberg (1985) and Browning (1992) were employed. Thirty day old white Ranger cockerels were randomly divided in 5 groups of 6 chicks each. Group I received Normal Saline i.p., while groups II, III and IV were treated with the crude flavonoid fraction at doses of 20, 10 and 5 mg kg<sup>-1</sup> body weight i.p., respectively. The last group (Group V), the positive control group was administered Phenytoin 20 mg kg<sup>-1</sup> body weight i.p. Thirty minutes later, maximal electroshock was conferred to induce seizure in all groups using Ugo-basile electroconvulsive machine (Model 7801) with corneal electrodes placed in the upper eyelids of the chicks. The current, shock duration, frequency and pulse width were set and maintained at 90 mA 1 sec, 150 pulses per second and 0.6 ms, respectively. Hind Limb Tonic Extension (HLTE) was selected as the endpoint of the

experiment and the abolition of the HLTE was considered as protection from electroshock induced convulsion (Swinyard and Kupferberg, 1985).

### Statistical Analysis

The mean onset of seizure, mean time of death and mean recovery time were presented as Mean±Standard Error of Mean (SEM). The mean values of the control group were compared with the mean values of the groups treated with the crude flavonoid fraction using student t-test. Results were considered significant at  $p < 0.05$  (Crossland, 1980).

## RESULTS AND DISCUSSION

The crude flavonoid fraction from the ethanol extract of the plant exhibited a weak anticonvulsant activity against pentylenetetrazole (PTZ) induced seizure in mice. Highest anticonvulsant activity (20% protection) was observed at a dose of 10 mg kg<sup>-1</sup> with a significant ( $p < 0.05$ ) increase in latency in both mean time of onset of the seizure, mean time of death and different seizure patter (Table 1, 2).

The control chicks (Negative Control) exhibited seizure with tonic hind limb extension after the delivery of electroshock. The crude flavonoid fraction showed a significant ( $p < 0.05$ ) and a dose dependent protection (83.3%) in the maximal electroshock (MEST) test with a maximum protection at dose of 20 mg kg<sup>-1</sup> body weight i.p. which is comparable to Phenytoin 20 mg kg<sup>-1</sup> body weight i.p. (Table 3).

Table 1: Effects of crude flavonoid fraction from the ethanol stem bark extract of *F. sycamoros* and valproic acid on pentylenetetrazole-induced seizure in mice

Treatments (mg kg <sup>-1</sup> )	Mean onset of seizures (sec)	Mean time of death (sec)	Quantal protection	Protection (%)	Mortality (%)
Negative control (2% Acacia solution)	384.40±0.50	997.70±3.77	0/5	-	60
Valproic acid (200)	0.00	0.00	5/5	100	-
CFF (20)	197.05±0.56	709.00±4.39	0/5	0	100
CFF (10)	336.50±0.50*	575.00±3.29*	1/5	20	20
CFF (5)	531.60±0.66	839.00±3.59	0/5	0	60

CFF = Crude Flavonoid Fraction, \*Significant at  $p < 0.05$ ; n = 5, Data presented as Mean±SEM (Standard Error of Mean)

Table 2: Illustration of the anticonvulsant effect of crude flavonoid fraction of the ethanol extract of stem bark *F. sycamoros* on different seizure pattern in sc PTZ test in mice

Dose	Generalized myoclonic body twitches	Generalized body seizure with loss of right reflex	Loss of right reflex with tonic fore limbs extension	Loss of right reflex with tonic fore and hind limbs extension
scPTZ 85 mg kg <sup>-1</sup>	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
Valproic acid 200 mg kg <sup>-1</sup>	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)
CFF 20 mg kg <sup>-1</sup>	0/5 (0%)	1/5 (20%)	0/5 (0%)	0/5 (0%)
CFF 10 mg kg <sup>-1</sup>	1/5 (20%)	1/5 (20%)	2/5 (40%)	1/5 (20%)
CFF 5 mg kg <sup>-1</sup>	0/5 (0%)	1/5 (20%)	0/5 (0%)	0/5 (0%)

Table 3: Effect of crude flavonoid fraction from ethanolic stem bark extract of *F. sycamoros* and phenytoin on maximal electroshock induced seizures in chicks

Treatments (mg kg <sup>-1</sup> )	Mean onset of seizures (sec)	Mean time of recovery (min)	Quantal protection	Protection (%)	Mortality (%)
Normal saline	6.00±1.00	5.50±1.5	0/6	0.0	0.00
Phenytoin (20)	0.00	0.00	6/6	100.0	0.00
CFF(20)	10.00	5.00	5/6	83.3*	0.00
CFF (10)	4.50±0.50	7.50±2.5	4/6	66.3*	0.00
CFF (5)	3.50±0.29	8.50±3.0	2/6	33.3*	0.00

CFF = Crude Flavonoid Fraction, \*Significant at  $p < 0.05$ ; n = 6, Data presented as Mean±SEM (Standard Error of Mean)

The crude flavonoid fraction of the plant exhibited a weak anticonvulsant activity against scPTZ-induced seizures. The fraction was found to protect 20% of the mice against threshold seizure at a dose of 10 mg kg<sup>-1</sup>, with a maximum protection (20%) found against loss of right reflex with tonic fore and hind limbs extension at this dose. This effect of the fraction was found to be independent of dose (Table 1, 2).

The maximal electroshock test (MEST) is a standard procedure that evaluates the testing materials ability to protect against Hind Limb Tonic Extension (HLTE) in MEST (Giuliano and Silvana, 2003). Toman *et al.* (1914) reported that the seizure pattern in MEST for all laboratory animals and man are similar except for time scale. The crude flavonoid fraction exhibited a significant ( $p < 0.05$ ) anticonvulsant activity in maximal electroshock-induced seizures in a dose dependent manner in chicks. The fraction exhibited maximum protection of 83.3% at 20 mg kg<sup>-1</sup> i.p. comparable to that produced by Phenytoin (20 mg kg<sup>-1</sup> i.p.). Phenytoin, a standard AED that suppresses HLTE is effective in the therapy of generalized tonic-clonic and partial seizures (Loscher, 1983). It limits the repetitive firing of action potentials and this effect is mediated by a slowing of the voltage activated sodium ion channels from recovering from inactivation (Goodman and Gilman, 2001).

Protection against HLTE in the maximal electroshock test predicts anticonvulsant activity of anti-epileptic drugs that prevent the spread of the epileptic seizure from an epileptic focus during seizure activity (Loscher, 1983). Also protection against HLTE indicates the ability of the testing material to inhibit or prevent seizure discharge within the brain stem substrate. Since the crude flavonoid fraction of the plant showed anticonvulsant activity in the MES test, it may or may not act through any of the above-mentioned mechanisms.

Furthermore, the behavioral and electrographic seizure generated in this model is consistent with the human disorder (Swinyard and Kupterberg, 1985). The inhibitory effect of the fraction (83.3% at 20 mg kg<sup>-1</sup> i.p.) suggests that the plant possesses anticonvulsant activity for the treatment of generalized tonic-clonic and partial seizures in humans. However the usefulness of the fraction in absence seizures (PTZ induced seizures) cannot be guaranteed. In view of these, the crude flavonoid fraction of the ethanol extract of stem bark of *F. sycomorus* can be of importance in the management of Grand mal epilepsy seizures. This was supported by Umar *et al.* (2003) that the aqueous extract of the stem bark of *F. sycomorus*, which contains various phytochemical including flavonoids, possesses anticonvulsant activity in rats. Therefore, the characterization and identification of such crude flavonoids and knowledge of their presence in other medicinal plants can provide a rich store of potential medicines for the effective management of epileptic seizures.

## CONCLUSION

The anticonvulsant screening of the crude flavonoid fraction of the ethanolic extract of *F. sycomorus* revealed a significant and dose-dependent anticonvulsant activity in the maximal electroshock test and also a weak anticonvulsant activity in the subcutaneous PTZ test. The results therefore supported the claim for the traditional use of the stem bark of the plant in the management of epilepsy.

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