ANTIULCER AND ANTICONVULSANT ACTIVITY OF CROTON ZAMBESICUS

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ABSTRACT
The ethanolic root extract of *Croton zambesicus* was investigated for its potential to protect gastric mucosa against ulcers induced by indomethacin, ethanol and reserpine. The anticonvulsant activity of the root extract against pentylene tetrazol(PTZ)- and picrotoxin-induced convulsion in mice was also studied. The extract (27-81mg/kg) produced a significant (P<0.005-0.001) dose-dependent effects against the ulcerogenic effect of differents agents used; indomethacin, ethanol and reserpine. The effect of the extract was lower than that of the standard drug, cimetidine (100mg/kg) in the indomethacin and reserpine-induced ulcer models and higher than that of propranolol (40mg/kg) in ethanol- induced ulcer model. The extract (27-81mg/kg) could not protect mice from convulsion in both PTZ – and picrotoxin- induced convulsion. The root extract significantly (P<0.01-0.001) delayed the onset and latency of convulsion caused by PTZ and picrotoxin. The root extract possesses antiulcer and anticonvulsant properties.

Keywords: *Croton zambesicus,* antiulcer, anticonvulsant.

INTRODUCTION

Croton zambesicus Muell Arg. (Euphorbiaceace) (syn *C. amabilis* Muell. Arg. *C. gratissimus* Burch) is an ornamental tree grown in villages and towns in Nigeria. It is a Guineo – Congolese species widely spread in tropical Africa. Ethnobotanically, the leaf decoction is used in Benin as anti hypertensive and anti- microbial (urinary infections) (Adjanohoun *et al*,1989) and in parts of Nigeria as antidiabetic and malarial remedy (Okokon *et al.,* 2005a, 2006). The roots are used as antimalarial and antidiabetic by the Ibibios of Niger Delta region of Nigeria. The root is also used in Sudan for menstrual pain (El-Hamidi, 1970) and as aperients (Ngadjui *et al.,* 1999). Boyom *et al.* (2002) studied the composition of essential oils from the leaves, stem and roots of *Croton zambesicus* and found the three types of oils to be similar in composition, with those from the leaves and stem rich in monoterpenes, while that of the root bark contains sesquiterpenes. The root and stem bark oils were found to be rich in oxygen-containing compounds, with spathulenol and linalool as major components. Studies have reported on the antimicrobial properties of the leaf and stem (Abo *et a.l*, 1999). The ethanolic leaf extract has been reported to possess antiplasmodial (Okokon *et al.*, 2005a), antidiabetic (Okokon *et al*., 2006), anti-inflammatory, analgesic and antipyretic activities (Okokon *et al.,* 2005b). Okokon and Nwafor (2008) reported that the root extract whose LD_{50} is 273.86 mg/kg contains alkaloids, saponins, terpenes, tannins, phlobatannins, anthraquinones and cardiac glycosides, while flavonoids were reported to be absent. Information on biological activity of the root is scarce. We therefore investigated the antiulcer and anticonvulsant activities of the root extract of the plant to ascertain the folkloric claim of its activities.

MATERIALS AND METHODS

Plant materials

The plant part (roots) was identified by a taxonomist in the Department of Botany, University of Uyo, Uyo. The roots were collected from compounds in Uyo metropolis and were authenticated. A voucher specimen (DPNM.31c) of the plant was deposited in the hebarium of Department of Pharmacognosy and Natural medicine, University of Uyo, Uyo, Nigeria

Extraction

The roots were shade dried for 2 weeks. The dried roots were further chopped into small pieces and reduced to powder. The powdered roots were divided into two parts, one parts was macerated in 97% ethanol for 72 hours to give the crude ethanolic extract while the other part was successively and gradiently macerated for 72 hours in each of these solvents; n-hexane, chloroform, ethyl acetate and methanol to give the corresponding gradient fractions of these solvents. The liquid filtrates were concentrated and evaporated to dryness in vacuo 40°C using rotary evaporator. The yield of each extract was calculated. The dry extracts were stored in a refrigerator at 4°C until use for the proposal experiment.

Animals

The animals (Swiss albino male rats and mice of either sex) that were used for these experiments were obtained from University of Uyo animal house. The animals were housed in standard cages and were maintained on a standard pelleted feed (Guinea feed) and water *ad libitum*. Permission and approval for animal studies were obtained from College of Health Sciences Animal Ethics committee, University of Uyo.

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Evaluation of antiulcer activity of the extract

Indomethacin-induced gastric ulceration

Male adult rats were used for the experiment .They were randomized into six groups of six animals each. Food was withdrawn 24h and water 2h before the commencement of the experiment (Alphin and Ward, 1967). Group I (control) received only indomethacin (Sigma, 60 mg/kg p.o dissolved in 5% $NaCo_3$, groups 2 – 4 were pretreated with *Croton zambesicus* extract (27, 54 and 81 mg/kg p.o. respectively. Group 5 received cimetidine (100mg/kg dissolved in 5% Tween 80), while group 6 received cimetidine (100mg/kg p.o.), 10 minutes later, extract (54 mg/kg p.o) was given. One hour later, groups 2- 6 were administered with indomethacin. The drugs were administered intragastrically via the aid of an orogastric cannula. Four hours after indomethacin administration, animals were killed by cervical dislocation. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10% formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored (Nwafor *et al*., 1996). Ulcer index (UI), Preventive ratio (PR) and degree of ulceration (DU) of each of the groups pretreated with the extract were calculated using standard methods (Zaidi and Mukerji, 1958; Nwafor *et al.,* 2000).

Ulcer Scoring System criteria

0.0 Normal
0.5 Punctuate or pinpoint haemorrhagic ulcer.
1.0 Two or more small haemorrhagic ulcer less than 3mm in diameter.
2.0 Ulcers greater than 3mm in diameter.
3.0 Several Ulcers.

Ethanol induced gastric ulceration

The procedure used was similar to that used in indomethacin induced ulceration. The rats were randomly assigned to six groups of six animals each. Food was withdrawn 24h and water 2h before the commencement of the experiment. Group I (control) received only ethanol (2.5 ml/kg p.o.), Groups 2-4 were pretreated with *Croton zambesicus* root extract (27, 54 and 81mg/kg p.o. respectively). Group 5 received propranolol (40 mg/kg p.o dissolved in distilled water), while group 6 received propranolol, Ten minutes later, extract (54 mg/kg p.o.) was given. One hour later, groups 2 – 6 were administered with ethanol. The drugs were administered intragastrically via the aid of an orogastric cannula. Four hours after indomethacin administration, animals were killed by cervical dislocation. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10% formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored using standard methods (Nwafor *et al.,* 2000).

Ulcer scores Scoring System criteria

5 Multiple ulcers along the entire length of the gastric fold.
4 Lesions which followed approximately 80% of the fold.
3 Ulcer 1 – 4mm in length of 80% of the fold.
2 At least 2 ulcer of approximately 2mm in length.
1 The presence of 1 ulcer and generalized erythema.
0 No visible.

Table 1: Effect of *Croton zambesicus* on indomethacin induced ulceration in rats

Treatment/route of admin	Dose (mg/kg)	Ulcer index	Preventive ratio
Control (indomethacin)	60	14.91 ± 4.01	-
Croton zambesicus (p.o)	27	10.41 ± 2.99[a]	30.18
	54	8.58 ± 0.67[b]	42.45
	81	4.50 ± 1.73[b]	69.82
Cimetidine	100	2.66 ± 0.47[b]	82.15
Cimetidine + *C. zambesicus*	100 + 54.0	1.00 ± 0.70[b]	93.29

Data are represented as mean ± SEM .significant at [a]P < 0.05, [b]P< 0.001when compared to control (n=6).

Table 2: Effect of *Croton zambesicus* root extract on ethanol induced ulceration in rats

Treatment/route of admin	Dose (mg/kg)	Ulcer index	Preventive ratio
Control (ethanol)	-	5.00 ± 1.00	-
Croton zambesicus (p.o)	27	4.00 ± 0.81	20.0
	54	2.00 ± 1.00[a]	60.0
	82	1.83 ± 0.68[a]	63.4
Propranolol	40	2.00 ± 1.00[a]	60.0
propranolol + *C. zambesicus*	40 + 54.0	0.50 ± 0.50[a]	90.0

Data are represented as mean ± SEM .significant at [a]P < 0.001 when compared to control (n=6).

Effect of the extract on Reserpine-induced gastric ulceration in rats

Adult albino male rats (120-170 g) were used for the experiment. They were randomized into six groups of six rats each. Food was withdrawn 24 hours and water 2 h before the commencement of experiment (Alphin and Ward, 1967). Group 1 (control) received only reserpine (Sigma, 8 mg/kg, i.p dissolved in 10% Tween 80); Groups 2-4 were pretreated with *Croton zambesicus root* extract (27, 54 and 81 mg/kg p.o. respectively); Group 5 received cimetidine (100 mg/kg p.o. dissolved in 10% Tween 80), 1 hour prior to reserpine administration, while Group 6 were pretreated with cimetidine (100 mg/kg.p.o), 10 minutes later, extract (54 mg/kg.p.o) was given. One hour later, groups 2-6 were were administered with reserpine, 8 mg/kg i.p. dissolved in 10% Tween 80 (Maity *et al*., 1995). 18 hours animals were killed by cervical dislocation. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10% formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored (Nwafor *et al*., 1996). Ulcer index (UI), preventive ratio (PR) and degree of ulceration (DU) of each of the groups pretreated with extract were calculated using standard methods (Zaidi and Mukerji, 1958; Nwafor *et al.,* 2000) as shown above.

Anticonvulsant activity

Anticonvulsant effect of the extract was assessed using a modified method of Vellucci and Webster (1984) on overnight fasted mice. The mice were divided into six groups of six animals each and treated with 27, 54 and 82mg/kg of the extract, phenytoin, 40mg/kg, phenytoin + extract (40 + 54mg/kg) one hour before induction of convulsion. Seizure was induced in each set of mice with PTZ (70mg/kg i.p.) and picrotoxin (4mg/kg). Control

Table 3: Effect of *Croton zambesicus* on reserpine- induced ulceration in rats

Treatment/route of admin	Dose (mg/kg)	Ulcer index	Preventive ratio
Control (reserpine)	8 mg/kg i.p	16.08 ± 0.78	-
Croton zambesicus (p.o)	27	11.0 ± 0.57[a]	31.59
	54	7.0 ± 0.46[a]	56.46
	81	5.16 ± 0.86[a]	67.91
Cimetidine	100	2.41 ± 0.30[a]	85.01
Cimetidine + *C. zambesicus*	100 + 54.0	1.08 ±0.23[a]	93.23

Data are represented as mean ± SEM. Significant at [a]p< 0.001. when compared to control (n=6).

Table 4: Anticonvulsant activity *Croton zambesicus* root extract on Picrotoxin-induced convulsion

Drug Extract	Dose (mg/kg)	Latency of clonic convulsion (s)	Latency of Tonic convulsion (s)	Convulsion %	Mortality %
Control (normal saline)	0.2ml	3.20 ± 0.26	6.95 ± 0.19	100	100
C. zambesicus root extract	27	5.34 ± 1.08[b]	9.54 ± 2.61	100	100
	54	7.98 ± 0.25[,b]	13.99 ± 2.96[b]	100	100
	81	8.76 ± 1.67 [b]	13.58 ± 1.69 [b]	100	100
Phenytoin	40	7.40 ± 1.47 [a]	12.92 ± 1.67 [b]	100	100
Phenytoin (40mg) + *C.zambesicus* (54)	40 + 54	4.71 ± 0.88[a]	7.73 ± 0.39	100	100

Data are represented as mean ± SEM. Significant at [a]P < 0.01, [b]P<0.001 when compared to control. (n=6)

Table 5: Anticonvulsant activity of *Croton zambesicus* root extract on PTZ-induced convulsion

Drug Extract	Dose (mg/kg)	Latency of clonic convulsion (s)	Latency of tonic convulsion (s)	Convulsion %	Mortality %
Control (normal saline)	0.2ml	1.35 ± 0.08	4.77 ± 0.48	100	100
C. zambesicus root extract	27	4.94 ± 0.48[a]	6.97 ± 0.73 [a]	100	100
	54	6.09 ± 0.30[a]	11.70 ± 0.92[a]	100	100
	81	6.73 ± 0.41[a]	11.73 ± 0.73[a]	100	100
Phenytoin	40	3.18 ± 0.27[a]	7.28± 0.68 [a]	100	100
Phenytoin + *C.zambesicus*	40 + 54	3.42 ± 0.33[a]	6.83 ± 2.49	100	100

Data are represented as mean ± SEM. Significant at [a]P < 0.01 when compared to control (n=6).

group received normal saline. The onset of Clonic/tonic convulsion and the mortality rate was recorded and compared with the respective control group. The ability of the plant extract to prevent or delay the onset of the hind limb extension exhibited by the animals was taken as an indication of anticonvulsant activity (Vellucci and Webster, 1984; Amabeoku and Chikuni, 1993).

RESULTS

Antiulcer activity

Indomethacin-induced ulcer

The results of antiulcer activity of the root extract on indomethacin- induced ulceration in rats is shown in table 1. There was a progressive decline in ulcer index of the rats pretreated with the extract. The decline was dose-dependent and significant (P<0.05-0.001) compared to control. However, the reduction of ulcer index caused by the the standard drug, cimetidine (100mg/kg) was higher than that of the extract.

Ethanol-induced ulcer

Table 2 shows the results of antiulcer activity of the root extract against ethanol- induced ulceration in rats. Pretreatment of rats with the root extract result in a dose-dependent decrease in the ulcer index. The decrease in ulcer index of the extract treated groups was significant (P<0.001) compared to control and higher than that caused by the standard drug, propranolol (40mg/kg).

Effect of the root extract of *C. zambesicus* on Reserpine- induced ulcer in rats

The results of the effect of extract pretreatment on reserpine- induced gastric ulceration in rats is as shown in table 3. The extract significantly (P<0.001) reduced the ulcer indices relative to control in a dose-dependent manner. The extract demonstrated a progressive increase in preventive ratio of ulcer induced by reserpine. However, the decrease was lower than that of the standard drug, cimetidine (100mg/kg).

Anticonvulsant activity

Pentylene tetrazole-induced convulsion

The results of the effect of ethanolic root extract of *C. zambesicus* on pentylene tetrazole (PTZ)-induced convulsion in mice is shown on table 4. The root extract significantly (P<0.01-0.001) delayed the onset of clonic and tonic convulsion caused by PTZ when compared to control. The delay caused by the extract was higher than that of the standard, phenytoin(40mg/kg). However, the extract could not prevent convulsion and mortality due to PTZ-induced seizure. Phenytoin also could not protect the animals.

Picrotoxin-induced convulsion

The results of the effect of ethanolic root extract of *C. zambesicus* on picrotoxin-induced convulsion in mice is shown on table 5. The root extract exerted significant (P<0.01) delay in the onset of clonic and tonic convulsion caused by picrotoxin when compared to control. The activity of the extract was comparable to that of the standard, phenytoin (40mg/kg). The extract as well as phenytoin could not prevent convulsion due to picrotoxin in the mice.

DISCUSSION

Antiulcer activity

The antiulcer activity of the root extract was evaluated using indomethacin, ethanol, reserpine-induced ulcer models. Indomethacin is known to cause ulcer especially in an empty stomach (Bhargava *et al*., 1973) and mostly on the glandular (mucosal) part of the stomach (Evbuonwa and Bolarinwa, 1990; Nwafor *et al*., 1996) by inhibiting prostaglandin synthetase through the cycloxygenase pathway (Rainsford, 1987). Prostaglandins function to protect the stomach from injury by stimulating the secretion of bicarbonate and mucus, maintaining mucosal blood flow and regulating mucosal turn over and repair (Hayllar and Bjarnason, 1995; Hiruma-Lima *et al*., 2006). Suppression of prostaglandins synthesis by indomethacin results in increase susceptibility of the stomach to mucosal injury and gastroduodenal ulceration. The extract was observed to significantly reduce mucosal damage in the indomethacin–induced ulcer model, suggesting the possible extract mobilization and involvement of prostaglandin in the anti ulcer effect of the extract. Administration of ethanol has been reported to cause disturbances in gastric secretion, damage to the mucosa, alterations in the permeability, gastric mucus depletion and free radical production (Salim, 1990). This is attributed to the release of superoxide anion and hydroperoxy free radicals during metabolism of ethanol as oxygen derived free radicals has been found to be involved in the mechanism of acute and chronic ulceration in the gastric mucosa (Pihan *et al.*,1987). It was observed in this study that the extract significantly reduced ethanol-induced ulcer. This may be due to cytoprotective effect of the extract via antioxidant effects. Ethanol is also reported to cause gastric mucosal damage by stimulating the formation of leukotriene C4 (LTC4) (Whittle *et al*., 1985). The gastroprotective effect of the extract may in part be due to the suppression, by the extract of lipoxygenase activity (Nwafor *et al*., 1996).

The mechanism at which reserpine produces ulceration is not completely understood. Some mechanisms have been suggested to be responsible for this action. Reserpine-induced gastric ulceration has been attributed to vagotonic hypermotility and degranulation of gastric mast cells with consequent increased in gastric acid secretion which is believed to be cholinergically mediated (Cho *et al*., 1985; Kagoshima and Suguro, 1982). Besides, mobilization of super oxide and hydroxyl radicals (oxygen-derived free

radicals) as described for ethanol above (Salim, 1989; 1990), inhibition of mucus release and stimulation of surface mucus breakdown via β-adrenoceptor stimulation (Yusuf *et al.,* 2008) have also been attributed to the ulcerative potentials of reserpine. Accordingly, the antiulcer activity of the extract against reserpine-induced ulceration could in part be due to its inhibition of histamine, anticholinergic and antisecretory effects. It may have also resulted from the extract's ability to inhibit oxygen-derived free radicals formation in rat gastric mucosa and stimulate endogenous prostaglandin synthesis as earlier suggested. Saponins, especially triterpenes type have been implicated in antiulcer activity mediated by formation of protective mucus on the gastric mucosa and also protect the mucosa from acid effects by selectively inhibiting PGF2α (Agwu and Okunji, 1986; Lewis and Hanson, 1991). However, the root extract has been reported above to contain sesquiterpenes (Boyom *et al.,* 2002). Several sesquiterpene lactones have been reported as the anti-ulcerogenic constituents of folk remedies; e.g dihydroleucodine, a guaianolide, from *Artemisia douglasiiang* (Giordano *et al*., 1990), parthenolide, a germacranolide from *Tainacetum parthenium* (Tournier *et al*.,1999), and 13-acetyl soltitialin A and soltitialin A from *Centaurea solstitialis* (Gurbuz and Yesilada, 2007). α, β-unsaturated carbonyl and α-methylene-χ-lactone moieties are suggested as specific requirements for anti-ulcerogenic activity in sesquiterpene lactones (Giordano *et al.,* 1992). These moieties would serve as the Michael acceptors to induce a Michael addition reaction between the sulfhydryl containing peptides of the mucosa. According to Begley *et al*. (1989), the α-methylene-χ-butyrolactone moiety was shown to possess chemical reactivity toward biological nucleophiles, e.g thiol and amines. The antiulcerogenic activity of this root extract may in part be due to the sesquiterpenes present in the extract. Moreso, since gastric damage induced by non-steroidal antiinflammatory drugs (indomethacin) is due to a decrease in endogenous prostaglandin synthesis and an increase in acid secretion (Robert *et al.,* 1979). Sesquiterpene lactones bearing Michael acceptors offer cytoprotection also through stimulation of the endogenous synthesis of prostaglandins (Giordano *et al*., 1992). This has been suggested by Maria *et al*. (1995), to be due to increased biosynthesis of glutathione which in turn leads to increased biosynthesis of PGE_2. The antiulcerogenic activity observed in this study with the root extract may in part be exerted through the above mechanism.

Anticonvulsant activity

Results of this study shows that the extract significantly delayed the onset of clonic/tonic convulsion produced by PTZ and picrotoxin. This was observed also for phenytoin the standard drug used.According to De Sarro *et al.* (1999), PTZ may be exerting its anticonvulsant effect by inhibiting the activity of gamma aminobutyric acid (GABA) at $GABA_A$ receptors. Gamma aminobutyric acid is the major inhibitory neurotransmitter which is implicated in epilepsy. The enhancement and inhibition of the neurotransmission of GABA will attenuate and enhance convulsion respectively (Gale, 1992; Westmoreland *et al.,* 1994). Phenobarbitone and diazepam, standard epileptic drugs, have been shown to exert their antiepileptic effects by enhancing GABA-mediated inhibition in the brain(Porter and Meldrum,2001; Rang *et al*., 2003). These drugs are reported to antagonise PTZ-induced convulsion (Amabeoku *et al*., 2007) by enhancing GABA neurotransmission. Phenytoin was unable to prevent PTZ-induced seizure because it is thought to exert its antiepileptic effect by blocking sodium ions into brain cells thus inhibiting generation of repitative action potential (Porter and Meldrum, 2001). Since the root extract was able to delay PTZ-induced convulsion it is probable that it may be interfering with gabaergic mechanism(s) to exert its effect. The leaf extract of *C. zambesicus* has been reported to increased significantly the onset of PTZ-induced convulsion and maximum electroshock seizure test and at some doses offered protection against the experimental seizure models (Ayanniyi, 2008). These report collaborate the findings of this investigation although a far more higher dose was used for the leaf extract.

According to Rang *et al*. (2003), picrotoxin exerts its convulsant effect by blocking the $GABA_A$ receptor-linked chloride ion channel which normally opens to allow increased chloride ion conductance into brain cells following the activation of $GABA_A$ receptor by GABA. The root extract of *C. zambesicus* delayed picrotoxin-induced convulsion by enhancing GABA neurotransmission.

From the results above, the root extract has a significant antiulcer activity as well as a considerable anticonvulsant activity. It will be interesting to isolate and characterised the active ingredient in this extract.

REFERENCES

Abo KA, Ogunleye VO and Ashidi JS (1999). Antimicrobial potential of *Spondias mombin, Croton zambesicus,* and *Zygotritonia crocea. Phytotherapy Research,* **13**(6): 494-497.

Adjanohoun EJ, AdjakideV and deSouza S (1989). Contribution to ethnobotanical and floristic studies in Republic of Benin.Vol.1.Agency for Cultural and Technical Cooperation, p.245.

Agwu CN and Okunji CO (1986). Gastrointestinal studies of *Pyrenacantha staudii* leaf extracts. *Journal of Ethnopharmacology,* **15**: 45-55.

Alphin RS and Ward JW (1967). Action of hexopyrronium bromide on gastric secretion in dogs and on gastric secretion and ulceration in rats. *Archives*

Internationals de pharmacodynamie et al therapies, **270**: 128-140.

Amabeoku GJ and Chikuni O (1993). Cimetidine-induced seizures in mice: antagonism by some gabaergic agents. *Biochemical Pharmacology,* **46**: 2171-2175.

Ayanniyi RO and Wannang NW (2008). Anticonvulsant activity of the aqueous leaf extract of *Croton zambesicus* (Euphorbiaceae) in mice and rats. *Iranian Journal of Pharmacology and Therapeutics* (In press).

Baccelli C, Block S, Van Holle B, Schancke A, Chapon D, Tinant B, Van Meervelt L, Morel N and Quertin-Leclkercq J (2005). Diterpenes isolated from *Croton zambesicus* inhibit KCl-induced contraction.*Planta Medica,* **71**: 1036-1039.

Begley MJ, Hewlett MJ and Knight DW (1989). Revised structures for guaianolide α-methyl-en butyrolactones from feverfew. *Phytochemistry,* **28**: 940-943.

Bhargava KP, Gupta MB and Tangri KK (1973). Mechanism of ulcerogenic activity of indomethacin and oxyphenbutazone. *European Journal of Pharmacology,* **22**: 191-195.

Boyom FF, Keumdjio F, Dongmo PM, Ngadjui BT, Amvam-Zollo PH, Menut C and Bessiere JM (2002). Essential oil from *Croton zambesicus* Muell. Arg. growing in Cameroun. *Flavour and Fragrance Journal,* **17**: 215-217.

Block S, Baccelli C, Tinat B, Meervelt L, Rozenberg R, Jiwan J, Llabres G, DePauw-Gillet M and Quetin-Leclercq J (2004). Diterpenes from the leaves of *Croton zambesicus*. *Phytochemistry,* 1165-1171.

Block S, Stevigny C, Llabres G, deHoffman E, Adjakide V, DePauw-Gillet M and Quetin-Leclercq J (2002). Ent-Trachyloban-3β-ol,a new cytotoxic diterpene from *Croton zambesicus. Planta Medica,* **68**: 647-648.

Cho CH, Ogle CW and Dai S (1985). A study on the etiology of reserpine ulceration and the antiulcer action of solcoseryl in rat stomach. *Journal of Pharmacy and Pharmacology,* **37**: 823-825.

DeSarro A, Cecchetti V, Fravlini V, Naccari F, Tabararrini O and DeSarro G (1999). Effect of novel 6-desfluoroquinolones and classic quinolones on pentylene tetrazole induced seizures in mice. *Antimicrobial Agents and Chemotherapy,* **43**: 1729-1736.

El-Hamidi A (1970). Drug plants of the Sudan Republic in native medicine. *Plantae Medica,* **18**: 278-280.

Evbuonwa MT and Bolarinwa AF (1990). Effect of diet on indomethacin-induced peptic ulceration in pregnant rats. *Nigerian Journal of Physiological Sciences,* **6**: 189-191.

Gale K (1992). GABA and epilepsy:basic concepts from preclinical research. *Epilepsia,* **33**: S3-S12.

Giordano OS, Guerreiro E, Pestchanker MJ, Guzman J, Pastor D and Guardia T (1990). The gastric protective effect of several sesquiterpene lactones. *Journal of Natural Products,* **53**: 803-809.

Giordano OS, Pestchanker MJ, Guerreiro E, Saad JR, Enriz RD, Rodriguez AM, Jauregui EA, Guzman J, Maria OMA and Wendel GH (1992). Structure-activity relationship in the gastric cytoprotective effect of several sesquiterpene lactones. *Journal of Medicinal Chemistry,* **35**: 2452-2458.

Gurbuz I and Yesilada E (2007). Evaluation of the anti-ulcerogenic effect of sesquiterpene lactones from *Centaura solstitialis L. Ssp. Solstitialis* by using various *in vivo* and biochemical techniques. *Journal of Ethnopharmacology,* **112**: 284-291.

Kagoshima M and Suguro N (1982). Gastric movements of the rat in reserpine- induced ulcers. *Folia Pharmacological Japanica,* **80**: 231-238.

Lewis, D.A.,Hanson, D.(1991). Anti-ulcer drugs of plants origin. *Progress in Medicinal Chemistry*.28:208 – 210.

Maity S,Vedasiromoni JR and Ganguly DK (1995). Anti-ulcer effect of the hot water extract of black tea (Camellia sinensis). *Journal of Ethnopharmacology,* **46**: 167-174.

Maria AO, Wender GH, Guardia J, Guzman JA, Pestchanker MJ, Guerreiro E and Giordano OS (1995). Gastric activity of 2-cyclopenten -1- one and related compounds. *Biological and Pharmaceutical Bulletin,* **18**: 1784-1786.

Nwafor PA, Okwuasaba FK and Binda LG (2000). Antidiarrhoeal and antiulcerogenic effect of methanolic extracts of *Asparagus pubescens* root in rats. *Journal of Ethnopharmacolgy,* **72**: 421-427.

Nwafor PA, Effraim KD and Jacks TW (1996). Gastroprotective effects of acqeous extracts of *Khaya senegalensis* bark on indomethacin-induced ulceration in rats. *West African Journal of Pharmacology and Drug Research,* **12**: 46-50.

Okokon JE and Nwafor PA (2008). Antiplasmodial activity of root extract and fractions of *Croton zambesicus. Journal of Ethnopharmacology,* **121**(1): 74-78 .

Okokon JE, Nwajuakwu N and Udokpoh A (2005b). Ppreliminary study of analgesic, anti inflammatory and anti pyretic activities of ethanolic leaf extract of *Croton zambesicus*. *Journal of Pharmacy and Bioresources,* **2**(2): 75-79.

Okokon JE, Bassey AL and Obot J (2006). Antidiabetic activity of ethanolic leaf extract of *Croton zambesicus* on alloxan diabetic rats. *African Journal of Traditional, Commplementary and Alternative Medicine,* **3**(2): 21-26.

Okokon JE, Ofodum KC, Ajibesin KK, Danladi B and Gamaniel KS (2005a). Pharmacological screening and antiplasmodial activity of *Croton zambesicus* against *Plasmodium berghei berghei* infection in mice.*Indian Journal of Pharmacology,* **37**(4): 243-246.

Pihan G, Regillo C and Szabo S (1987). Free radicals and lipid peroxidation in ethanol or aspirin-induced gastric mucosa injury. *Digestive Diseases and Sciences,* **32**: 1395-1401.

Porter RJ and Meldrum BS (2001). Antiseizure drugs. *In*: Katzung BG (Ed.), Basic and Clinical Pharmacology. 8th ed. Lange Medical Books/McGraw-Hill, New York, pp.403-417.

Rang HP, Dale MM, Ritter JM and Moore PK (2003). Pharmacology, 5th ed. Churchill Livingstone. Edinburg, pp.557-587.

Robert A, Nezamis JE, Lancester C and Hanchar AJ (1979). Cytoprotection by prostaglandins in rats. *Gastroenterology,* **77**: 433-443.

Salim AS (1989). Role of oxygen derived free radicals in the mechanism of chronic gastric ulcers in rats: implication for cytoprotective. *Digestion,* **1-2**: 113-119.

Salim AS (1990). Removing oxygen derived free radicals stimulates healing of ethanol induced erosive gastritis in the rats. *Digestion,* **47**: 24-28.

Tournier H, Schinella G, DeBalsa EM, Buschiazzo H, Manez S and Buschiazzo PM (1999). Effect of chloroform extract of *Tanacetum vulgare* and one of its active principles, parthenolide, on experimental gastric ulcer in rats. *Journal of Pharmacy and Pharmacology,* **51**: 215-219.

Westmoreland BF, Benarroch EE, Dube JR, Regan TJ and Sandok BA (1994). Medical Neurosciences. Mayo Foundation, Rochester, pp.307-312.

Yusuf S, Adelaiye AB, Nok AJ, Ameh DA and Balogun EO (2008). Effect of acute bilateral adrenalectomy and reserpine on gastric mucus secretion and mucosal injury in pyloric ligated rats. *African Journal of Biotechnology,* **7**(17): 3143-3148.