IJPT
1735-2657/10/92-96-101
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 9: 96-101, 2010

RIDR

RESEARCH ARTICLE

Antidiarrhoeal and Antiulcer Activities of Mammea Africana

J. E. OKOKON, E. E. UMOH, U. F. UMOH and E. I. ETIM

For author affiliations, see end of text.

Received June 14, 2009; Revised April 10, 2010; Accepted May 30, 2010

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

The stembark of *Mammea africana* is used traditionally for the treatment of stomach pains. The present study was designed to evaluate the effects of ethanolic stembark extract of *Mammea africana* on experimentally induced diarrhoea and ulcer. The extract (30 – 90mg/kg) was administered orally in rats 30 minutes to one hour before the induction of diarrhoeal and ulcer using different experimental models. Castor oil (2ml) was used to induce diarrhoea, while indomethacin (60mg/kg) and ethanol (2.5ml/kg) were used to induce ulcers in rats. Frequency of defecation, inhibition of intestinal propulsion and fluid accumulation were measured in the case of diarrhoea and ulcer index were calculated to examine ulcer preventive ratio of the extract.The extract (30 – 90mg/kg) significantly inhibited castor oil induced diarrhoea, small intestine transit time and castor oil induced fluid accumulation as well as indomethacin and ethanol induced ulcer models. The effect of the extract in these models was uncomparable to the various standard drugs used.These findings justify the use of this stembark traditionally in the treatment of stomach pains and disorders.

Keywords: *M. African, Stomach pains, Diarrhoea*

Mammea africana sabine (Guttiferae) (syn. *Ochrocarpus africana* Oliv.) is a large forest tree of 50 to 100 feet high with bark often yellow with pale scales and resinous yellow sap [1]. The plant is widely distributed in tropical Africa. The stem bark of the plant is used traditionally by the Ibibios of Niger Delta region of Nigeria in the treatment of malaria related fever, diabetes, and microbial infections. The stembark is also used traditionally to treat stomach pains, rheumatic pains, scabies, cough and hypertension[2,3]. The chloroformic and ether stembark extract are reported to posses cytotoxic activity on cell culture [4]. Ouahouo *et al.* [5], reported cytotoxic coumarins with antimicrobial activity against *Staphylococcus aureus* from the plant stembark. The stembark has been reported to posses antiplasmodial [6], cardioprotective [7], antidiabetic and hypoglycaemic [8],vasorelaxant [9], antihypertensive [10] effects. The stembark has been reported to contain 5,-7-dihydroxy-8-(12-methyl-butryl) –4- N - Pentyl coumarins [11,12,13], Mesuxanthone B [11]. Alkaloids have been reported to be absent in the entire plant parts [14]. Although reports of scientific studies on *Mammea africana* have been widely published, there is no information regarding the antidiarrhoeal and antiulcer activities of the stembark extract of the plant in rats eventhough it is used traditionally in the treatment of gastrointestinal tract disorders.

The present study, therefore, was to establish if the stembark of *M. africana* has any antiulcer and antidiarrhoeal activities to confirm its ethnomedical uses in the treatment of stomach disorders.

MATERIALS AND METHODS

Plant materials

Fresh stembark of *M. africana* were collected in November, 2007 at Anwa forest in Uruan, Akwa Ibom State, Nigeria. The plant was identified and authenticated by Dr. Margaret Bassey, a taxonomist in the Department of Botany, University of Uyo, Uyo. Nigeria. Herbarium specimen was deposited at Faculty of Pharmacy Herbarium (voucher no. FPHUU. 381). The fresh stembark (2 kg) of the plant were was on laboratory table for 2 weeks and reduced to powder. The powder 100g was macerated in 95% ethanol (300ml) for 72 hours [6]. The liquid filtrate obtained was concentrated in vacuo at 40^{o}C. The yield was 2.08% w/w. The extract was stored in a refrigerator at 4^{o}C until used for experiment reported in this study.

Animals

Albino wistar rats (105 – 165g) of either sex used for the experiments were obtained from the University of Uyo animal house. They were housed in standardized environmental conditions (22 ± 2.5 ^{o}C, relative humidity 80 – 85%, 12h light/ 12h dark cycle) and maintained on standard animal pellets and water ad libitum. Permission and approval for animal studies were obtained from the College of Health Sciences Animal Ethics committee, University of Uyo.

Castor oil induced diarrhoea

Diarrhoea was induced in adult albino male rats using a modified method developed by Sunil *et al*. [15, 16]. Animals were fasted for 24h but allowed free access to water. They were randomized into five groups of six rats each. Group 1(control) received 10% Tween 80 (5ml/kg) orally, Group 2- 4 were treated with *M. africana* extract (30, 60 and 90mg/kg, p.o. respectively); Group 5 was treated with atropine (0.1mg/kg, i.p) and Group 6 treated with extract, 60mg/kg, ten minutes later atropine 0.1mg/kg, i.p). After 1h, each rat received 2ml of castor oil (p.o) and was then observed for consistency of faecal matter and frequency of defecation for 3h.

Small intestinal propulsion

The effects of the extract on intestinal propulsion in unanaesthesized adult albino male rats were tested using charcoal method of Nwafor and Okwuasaba, [17]. Adult albino male rats were fasted for 24h but allowed free access to water only and were further randomized into six groups of six rats each. Group 1(control) received 10% Tween 80 (5ml/kg) by orogastric gavage; group 2-4 were treated with *M. africana* extract (30, 60 or 90mg/kg, p.o. respectively); Group 5 received atropine (0.1mg/kg, i.p) and Group 6 treated with extract, 60mg/kg, ten minutes later atropine 0.1mg/kg, i.p). After 1h, each rat was administered 1ml charcoal meal (5% activated charcoal suspended in 10% acqueous tragacanth), orally. The animals were killed 30min later by cervical dislocation and bled, and the small intestine was rapidly dissected out and placed on a clean surface. The small intestine was carefully inspected and the distance traversed by the charcoal meal from the pylorus was measured. The length of the whole small intestine was also measured using a metre rule [16, 17]. The distance traversed by the charcoal meal from the pylorus was expressed as a percentage of the distance from the pylorus to the ileocaecal junction.

Castor oil induced fluid accumulation.

Fluid accumulation was induced in adult albino male rats according to the method of DiCarlo *et al.*, [18]. Animals were deprived of food for 24h but allowed free access to water. They were randomized into 6 groups of six rats each. Group 1(control) received castor oil (2ml/rat), Group 2 – 4 were administered with *M. africana* (30, 60 or 90 mg/kg, p.o), Group 5 received atropine (0.1mg/kg, i.p), Group 6 received atropine (0.1mg/kg,i.p), 10min later, *M. africana* extract (60mg/kg, p.o.). After 1h, each rat received 2ml castor oil (p.o.), 30 minutes later, the rats were killed by cervical dislocation and exsanguinated, the small intestine was ligated at both pyloric sphincter and at the ileocaecal junctions. The entire small intestine was dissected out, its content was expelled into a graduated measuring cylinder and the volume of the contents recorded.

Indomethacin induced ulcer

Male adult albino rats were used for the experiment. They were randomized into six groups of six rats each. Food was withdrawn 24 hours and water 2h before the commencement of experiment [19]. Group 1(control) received only indomethacin (Sigma, 60mg/kg p.o. dissolved in 5% Na_2Co_3); Groups 2- 4 were pretreated with *Mammea africana* extract (30,60 and 90 mg/kg p.o. respectively);Group 5 received cimetidine (100mg/kg p.o. dissolved in 50% Tween 80), while Group 6 received cimetidine (100mg/kg. p.o) and 10 minutes later, extract (60mg/kg. p.o) was given. One hour later, groups 2 - 6 were administered with indomethacin. Four hour 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 [20]. Ulcer index (UI) and preventive ratio (PR) of each of the groups pretreated with extract was calculated using standard methods [21, 22].

Ethanol induced gastric ulceration

The procedure was similar to that used in indomethacin induced ulceration. Adult albino male rats were randomly assigned into six groups of six rats each. Food was withdrawn 24 hours and water 2h before the commencement of experiment [19]. Group 1(control) received only ethanol (2.5 ml/kg p.o),Groups 2- 4 were pretreated with *Mammea africana* extract (30,60,and 90mg/kg p.o. respectively); Group 5 received propranolol (40mg/kg p.o. dissolved in distilled water), while Group 6 received propranolol (40mg/kg. p.o dissolved in distilled water) and 10 minutes later, extract (60mg/kg.p.o) was given. One hour later, groups 2 - 6 were administered with ethanol. Four hour after ethanol 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 [22].

Table 1. Effect of *Mammea africana* extract on castor oil induced diarrhea in rats

Treatment	Dose(mg/kg)	Mean faecal matter	%inhibition
Control(10%Tween 80)	-	8.76±0.91	-
M. africana extract	30	4.66±0.75*	46.80
	60	5.00±0.77*	42.92
	90	5.00±1.09**	42.92
Atropine	0.1	0.66±0.42***	92.46
M. africana+atropine	60+0.1	1.33±0.55***	84.81

Data were expressed as mean ± SEM. significant at *p<0.01, **p<0.05, ***p < 0.001 when compared to control n = 6.

Table 2. Effect of *Mammea africana* extract on small intestinal propulsion in rats

Treatment	Dose(mg/kg)	Intestinal transit%	%inhibition
Control(10%Tween80)	-	67.2±0.21	-
M. africana extract	30	64.6±0.90	3.86
	60	63.6±0.24	5.36
	90	56.3±0.84**	16.22
Atropine	0.1	41.8±0.91**	37.79
M. africana+atropine	60+0.1	60.66±2.60*	9.73

Data were expressed as mean ± SEM. significant at *p<0.01, **p < 0.001, when compared to control n = 6.

Table 3. Effect of *Mammea africana* extract on castor oil induced fluid accumulation in rats

Treatment	Dose(mg/kg)	Mean volume of intestinal fluid(ml)	% reduction
Control(10%Tween80)	-	2.40±0.19	-
M. africana extract	30	1.80±0.26	25.00
	60	1.90±0.14	20.83
	90	1.40±0.17*	41.66
Atropine	0.1	0.80±0.10**	66.66
M. africana+ atropine	60+ 0.1	0.80±0.14**	66.66

Data were expressed as mean ± SEM. significant at *p<0.01, **p < 0.001, when compared to control n = 6.

Statistical analysis

Data obtained from this study were statistically analysed with one –way ANOVA, followed by Tukey–Kramer multiple comparison post test. Values of p<0.01 were considered significant.

RESULTS

Castor oil-induced diarrhoea

Mammea africana extract (30 – 90mg/kg) reduced the castor oil-induced diarrhoea significantly (p<0.01). However, the effect of the median dose (60mg/kg) was similar to that of the highest dose (90mg/kg). The effect of the extract was lower than that of the standard drug, atropine, but was enhanced in the presence of the standard drug, atropine (Table1).

Castor oil induced intestinal propulsion

Table 1 shows the effect of *M. africana* stem bark extract on intestinal propulsion of rats. The extract inhibited the intestinal propulsion in a dose-dependent manner. However, the effect was only significant (p<0.001) at the highest dose of the extract (90mg/kg)

The effect of the extract was enhanced in the presence of atropine, a muscarinic antagonist (Table2).

Castor oil induced intestinal fluid accumulation

The stembark extract (30 – 90mg/kg) demonstrated a significant reduction in intestinal fluid accumulation due to castor oil administration relative to control. The reduction, though dose dependent was significant (p<0.01) only at the highest dose of the extract (90mg/kg) when compared to control but lower than that of the standard drug, atropine, used in the study. The effect of the extract was enhanced in the presence of atropine, a muscarinic antagonist (Table 3).

Indomethacin induced gastric ulceration

The extract pretreatment on indomethacin – induced gastric ulceration exerted a statistically significant and dose dependent decrease (p<0.01) in ulcer indices relative to control. The effect of the extract was comparable to that of the standard drug, cimetidine (Table4).

Ethanol induced gastric ulceration

The stembark extract pretreatment significantly (p<0.001) reduced the ulcer indices of ethanol induced ulceration relative to control. The effect of the extract was more than that of the standard drug, propranolol (40mg/kg) (Table5).

DISCUSSION

In this study, ethanolic stembark extract of *M. africana* exhibited significant antidiarrhoeal and antiulcer activities in the models tested. Castor oil induces diarrhea due to active ingredient, ricinoleic acid, which is liberated as a result of action of lipases on castor oil. This stimulates peristaltic activity in the small intestine, leading to changes in the electrolyte

Table 4. Effect of *M. africana* extract on indomethacin induced ulcer

TREATMENT	DOSE (mg/kg)	ULCER INDICES	PREVENTIVE RATIO
Control (indomethacin)	60	12.30±1.14	-
M. africana extract p.o.	30	7.83±0.33[a]	36.3
	60	7.50±2.21[c]	39.0
	90	4.00±0.49[b]	67.5
Cimetidine	100	4.16±1.51[a]	66.2
Cimetidine +*M.africana*	100+60	3.83±0.47[b]	68.7

Data were expressed as mean ± SEM. significant at $p <$ [a]0.001, [b]0.01, [c]0.05 when compared to control n = 6.

Table5. Effect of *Mammea africana* extract on ethanol induced ulcer

Treatment	Dose (mg/kg)	Ulcer indices	Preventive ratio
Control (ethanol)	-	5.76±0.47	-
M. africana extract p.o	30	2.33±0.43*	59.5
	60	2.04±0.02*	64.6
	90	1.32±0.12*	77.1
Propranolol	40	3.00±0.01*	47.9
Propranolol + *M.africana*	40 + 60	0.50±0.22*	91.3

Data were expressed as mean ± SEM. significant at *$p < 0.001$ when compared to control n = 6.

permeability of the intestinal mucosa. It also stimulates the release of endogenous prostaglandins [23, 24]. Castor oil elicits secretory and motility diarrhoea [25]. Inhibitors of prostaglandin synthesis are known to delay diarrhoea induced with castor oil [15]. The observations suggest that the antidiarrhoeal effect of the extract may be due to inhibition of prostaglandin synthesis. Also since the effect was enhanced in the presence of atropine, the extract may have acted also through antimuscarinic activity to reduce castor oil induced diarrhea. The extract also exhibited a significant inhibition of the small intestine propulsive movement, but the effect was not comparable to that of the standard drug, atropine, used in the study. More so, when the extract was given with atropine, an anticholinergic, enhanced activity was observed pointing to a possible involvement of anticholinergic activity. Conversely, the extract may be inhibiting the small intestinal movement through some other mechanism such as antagonism of α_2-adrenoceptor stimulation. This extract also inhibited significantly (p<0.001) castor oil induced intestinal fluid accumulation (enteropooling). This effect was not comparable to that of the standard drug, atropine, which also exerts antisecretory activity. The effect of the extract, however, was enhanced in the presence of atropine, supporting earlier suggestion that the extract may be acting through an anticholinergic mechanism. Antidiarrhoeal and antidysentric properties of medicinal plants were found to be due to the presence of tannins, alkaloids, saponnins, flavonoids, steroids and or terpenoids [26]. Coumarins, flavonoids and xanthones have been reported to be present in the stembark extract of this plant [11,12,13,27]. Coumarins , flavonoids and xanthones have been reported to cause relaxation of vascular smooth muscles [28,29], though acting through different mechanisms. These constituents which have been reported to be present in the extract of the *M. africana* maybe responsible for the in vivo antidiarrhoeal activity of *M. africana* stembark extract.

Mammea africana stembark extract was also evaluated for antiulcer activity using indomethacin and ethanol – induced ulcer models. Indomethacin, a known ulcerogen especially on an empty stomach [30] causes ulcer mostly on the glandular (mucosal) part of the stomach [20, 31], by inhibiting prostaglandin synthetase through the cycloxygenase pathway [32]. 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 [33, 34]. Suppression of prostaglandin synthesis by indomethacin results in increased susceptibility stomach to mucosal injury and gastro duodenal 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 [35]. This is attributed to the release of superoxide anion and hydroperoxy free radicals during metabolism of ethanol as oxygen derived free radicals have been found to be involved in the mechanism of acute and chronic ulceration in the gastric mucosa [36]. 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) [37]. The gastroprotective effect of the extract may in part be due to the suppression, by the extract of lipoxygenase activity [20]. Okokon *et al.* [6], reported that the stembark extract contains flavonoids, terpenes, saponins, alkaloids and cardiac glycosides among others. Flavonoids such as quercetin have been reported to prevent gastric mucosal lesions in various experimental models [38, 39] by increasing the

amount of neutral glycoproteins [38]. Flavonoids have been reported to protect the gastric mucosa from damage by increasing the mucosal prostaglandin content and by inhibiting histamine secretion from mast cells by inhibition of histidine decarboxylase. Free radical scavenging ability of flavonoids has been reported to protect the gastrointestinal tract from ulcerative and erosion lesion [39]. 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 [40, 41].

In conclusion, the results of this study have shown that the stembark extract of *M. africana* possess antidiarrhoeal and antiulcer activities and this confirms the ethnomedical usage of the stembark extract in the treatment of stomach pains.

ACKNOWLEDGEMENT

The authors are grateful to Ms. Sifon Akpan, Pharmacology and Toxicology Department, University of Uyo, Uyo, Nigeria, for her technical assistance.

REFERENCES

1. Hutchinson LJ, Daziel JM. Flora of West Tropical Africa, revised by R. W. J. Keay.Vol.1, part 2, 2nd edition. White Press, London. 1958.
2. Raponda- Walker A, Sillans R, Les plantes utiles du Gabon. Paul Leechevalier, Paris, 1961.
3. Adjanohoun JE, Aboubakar N, Dramane K, et al. Traditional medicine and Pharmacopeia-Contribution to ethnobotanical and floristic studies in Cameroun.CNPMS, Porto – Novo, Benin, 1996,p15.
4. Chapius JC, Sordat B, Hostettman K. Screening for cytotoxic activities of Plants used in traditional Medicine. *J Ethnopharmacol*. 1988; 2322 (2/3): 273 - 284.
5. Ouahouo BMW, Asebaze AGB, Meyer M, Bodo B, Fomum ZT, Ngengfack AE, Cytotoxic and antimicrobial coumarins from *Mammea africana*. Ann Trop Med Parasitol 2004; 98: 737 – 739.
6. Okokon JE, Udokpoh AE, Essiet GA. Antimalarial Activity of *Mammea africana*. Afr J Trad Com Alt Med 2006; 3:43 – 49.
7. Okokon JE, Antia BS. Hypolipidaemic and Cardioprotective Activity of *Mammea africana. Res J Med Plants.* 2007; 1(4):154 – 157.
8. Okokon JE, Antia BS, Osuji L, Udia PM. Antidiabetic and Hypolipidaemic activity of ethanolic stembark extract of *Mammea africana. J Pharmacol Toxicol* 2007; 2: 278 - 283.
9. Dongmo AB, Azebaze AGB, Nguelefack TB,et al. Vasodilator effect of the extracts and some coumarins from the stem bark of *Mammea africana* (Guttiferae). *J Ethnopharmacol* 2007;111:329 – 334.
10. Nguelefack-Mbuyo PE, Nguelefack TB, Dongmo AB, et al. Anti- hypertensive effects of the methanol/methylene chloride stem bark extract of *Mammea africana* in L-NAME- induced hypertensive rats. *J Ethnopharmacol* 2008;117: 446 – 450.
11. Carpenter I, Mc Garry EJ, Scheimann F. Extractives from Guttiferae. Part XXI. The isolation and structure of nine coumarins from the bark of *Mammea africana* G. Don. *J Chem Soc* 1971; 22: 3783 - 3789.
12. Crichton EG, Waterman PG. Dihydromammea c/ob: A New Coumarin from the seed of *Mammea africana. Phytochemistry* 1978; 17: 1783-1786.
13. Carpenter I, Mc Garry EJ., Scheimann F. The neoflavonoids and 4-alkylcoumarins from *Mammea africana* G. Don. Tetrahedron Lett 1970; 46: 3983 - 3986.
14. Gartlans JS, Key DB, Waterman PG, Mbi CN, Struhsaker TT. Comparative study of the Phytochemistry of two African rain forests. *Biochem Syst. Ecol* 1980; 8: 401- 422.
15. Sunil B, Bedi K, Singla A, Johri R. Antidiarrhoeal activity of piperine in mice. *Planta Medica* 2001; 67: 284 – 287.
16. Nwafor PA, Jacks TW, Ekanem AU, Ching FP. Antiulcerogenic and antidiarrhoeal potentials of *Pausinystalia macroceras* stem-bark in rats. *Nig J Nat Prod Med* 2005; 9: 66 – 70.
17. Nwafor PA, Okwuasaba FK. Effect of methanolic extract of *Cassia nigricans* leaves on gastrointestinal tract. *Fitoterapia* 2001; 72: 206 – 214.
18. Dicarlo GD, Mascolo N, Izzo AA, Capasso F, Autore G. Effects of Quercetin on gastrointestinal tract in rats and mice. *Phytotherapy Res* 1994; 8: 42- 45.
19. Alphin RS, Ward JW, Action of hexopyrronium bromide on gastric secretion in dogs and on gastric secretion and ulceration in rats. *Arch Intern Pharmacodynam Therap* 1967; 270: 128 - 140.
20. Nwafor PA, Effraim KD, Jacks TW. Gastroprotective effects of aqueous extracts of *Khaya senegalensis* bark on indomethacin – induced ulceration in rats. *West Afr J Pharmacol Drug Res.* 1996; 12:46 – 50.
21. Zaidi SH, Mukerji B, Experimental peptic ulceration. Part1. The significance of mucus barrier. *Indian J Med Res* 1958;46:27 – 37.
22. Nwafor PA, Okwuasaba FK, Binda l. G., Antidiarrhoeal and antiulcerogenic effects of methanolic extracts of *Asparagus pubescens* root in rats. *J Ethnopharmacol.* 2000; 72: 421 – 427
23. Galvez J, Zarzuelo A, Crespo ME, et al. Antidiarrhoeic activity of *Euphorbia hirta* extract and isolation of an active flavonoid constituent. *Planta Medica* 1993; 59: 333 – 336.
24. Yoshio K, Kazuko S, Bunsyo M, et al. Relationship between antidiarrhoeal effects of Hange-shashin-To and active components. *Phytotherapy Res* 1999; 13: 468 – 473.
25. Rouf AS, Islam MS, Rahman MT. Evaluation of antidiarrhoeal activity of *Rumex maritimus* roots. *J Ethnopharmacol* 2003; 84: 307 – 310.
26. Havagiray R, Ramesh C, Sadhna K. Study of antidiarrhoeal activity of *Calotropis gigantea* r.b.r. in experimental animals. *J Pharmacol Pharmaceut Sci* 2004; 7: 70 – 75.
27. Games DE. Identification of 4-phenyl and 4-alkylcoumarins in *Mammea americana, Mammea africana* and *Calophyllum ionophyllum* by gas chromatography – mass spectrometry. *Tetrahedron* 1972; 31: 3187 – 3190.
28. Beretz A, Stoclet J, Anton R. Inhibition of isolated rat aorta contraction by flavonoids. Possible correlation with cAMP-phosphodiesterase inhibition. *Planta Medica.* 1980; 39: 236 – 241.
29. Bhargava KP, Gupta MB, Tangri KK. Mechanism of ulcero-genic activity of indomethacin and oxyphenbutazone. *Euro J Pharmacol* 1973; 22:191 – 195.
30. Evbuonwa MT, Bolarinwa AF. Effect of diet on indomethacin-induced peptic ulceration in pregnant rats. *Nig J Physiol Sci.*1990; 6: 189 – 191.
31. Rainsford KD.The effects of 5- lipoxygenase inhibitors and leukotriene antagonists on the development of gastric lesions induced by nonsteroidal anti-inflammatory drugs in mice. *Agents Action.* 1987; 21: 316 – 319.
32. Hiruma-Lima CA, Calvo TR, Rodriguez BCM, et al. Antiulcerogenic activity of *Alchornea castaneaefolia* effects on somatostatin, gastrin and prostaglandin. *J Ethnopharmacol* 2006; 104: 215 – 224.
33. Hayllar J, Bjarnason I, NSAIDS, COX-2 inhibitor and the gut. *Lancet* 1995; 346 - 522

34. Salim AS. Removing oxygen derived free radicals stimulates healing of ethanol induced erosive gastritis in the rats. *Digestion.* 1990; 47:24 – 28.
35. Pihan G, Regillo C, Szabo S. Free radicals and lipid peroxidation in ethanol or aspirin – induced gastric mucosa injury. *Digest Dis Sci* 1987; 32:1395 – 1401.
36. Whittle BJR, Oren-Wolman N, Guth PH Gastric vasoconstrictor actions of leukotriene C_4 and $PGF_{2\alpha}$ and thromboxane mimetic (U-4669) on rats sub mucosal microcirculation in vivo. *American J Physiol* 1985; 248: G580 – G586.
37. Di Carlo G, Mascolo N, Izzo AA, Capasso F. Flavonoids: old and new aspects of a class of a natural therapeutic drug. *Life sci* 1999; 64: 337 – 353.
38. Zayachkivska OS, Konturek SJ, Drozdowicz D, et al. Gastroprotective effects of flavonoids in plants extracts. *J Physiol Pharmacol* 2005; 56: 216 231.
39. Borrelli F, Izzo AA. The plant kingdom as source of anti ulcer remedies. *Phytotherapy Res* 2000; 14: 581 – 591.
40. Agwu CN, Okunji CO. Gastrointestinal studies of *Pyrenacantha staudii* leaf extracts. *J Ethnopharmacol*. 1986; 15:45 – 55.
41. Lewis DA, Hanson D. Anti-ulcer drugs of plants origin. *Prog Med Chem* 1991; 28: 208 – 210.

CURRENT AUTHOR ADDRESSES

J. E. Okokon, Dept of Pharmacology and Toxicology,Faculty of Pharmacy,University Of Uyo, Uyo,Nigeria. E-mail: judeefiom@yahoo.com (Corresponding author)

E. E. Umoh, Dept of Pharmacology and Toxicology,Faculty of Pharmacy,University of Uyo, Uyo,Nigeria.

U. F. Umoh, Dept of Pharmacognosy and Traditional Medicine,Faculty of Pharmacy, University of Uyo, Uyo,Nigeria.

E. I. Etim, Dept of Pharmaceutical and Medicinal Chemistryt, Faculty of Pharmacy, University of Uyo,Uyo, Nigeria.