

Antidiarrhoeal and Antiulcer Activities of *Mammea Africana*

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ABSTRACT

The stem bark of *Mammea africana* is used traditionally for the treatment of stomach pains. The present study was designed to evaluate the effects of ethanolic stem bark 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 stem bark 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 stem bark is also used traditionally to treat stomach pains, rheumatic pains, scabies, cough and hypertension [2,3]. The chloroformic and ether stem bark extract are reported to possess cytotoxic activity on cell culture [4]. Ouahouo *et al.* [5], reported cytotoxic coumarins with antimicrobial activity against *Staphylococcus aureus* from the plant stem bark. The stem bark has been reported to possess antiplasmodial [6], cardioprotective [7], antidiabetic and hypoglycaemic [8], vasorelaxant [9], antihypertensive [10] effects. The stem bark 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 stem bark 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 stem bark 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 stem bark 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 stem bark (2 kg) of the plant were washed 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°C. The yield was 2.08% w/w. The extract was stored in a refrigerator at 4°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 °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 unanaesthetized 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% aqueous 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% Na₂CO₃); 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	-
<i>M. africana</i> 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
<i>M. africana</i> +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	-
<i>M. africana</i> 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
<i>M. africana</i> +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	-
<i>M. africana</i> 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
<i>M. africana</i> + 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 stem bark 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 stem bark 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 stem bark 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	-
<i>M. africana</i> 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
	100	4.16±1.51 ^a	66.2
Cimetidine + <i>M.africana</i>	100+60	3.83±0.47 ^b	68.7

Data were expressed as mean ± SEM. significant at $p < ^a0.001, ^b0.01, ^c0.05$ 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	-
<i>M. africana</i> extract p.o	30	2.33±0.43*	59.5
	60	2.04±0.02*	64.6
	90	1.32±0.12*	77.1
	40	3.00±0.01*	47.9
Propranolol + <i>M.africana</i>	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 antidysentery properties of medicinal plants were found to be due to the presence of tannins, alkaloids, saponins, flavonoids, steroids and or terpenoids [26]. Coumarins, flavonoids and xanthenes have been reported to be present in the stem bark extract of this plant [11,12,13,27]. Coumarins, flavonoids and xanthenes 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* stem bark extract.

Mammea africana stem bark 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 cyclooxygenase 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 lipooxygenase activity [20]. Okokon *et al.* [6], reported that the stem bark 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 stem bark extract of *M. africana* possess anti-diarrhoeal and antiulcer activities and this confirms the ethnomedical usage of the stem bark extract in the treatment of stomach pains.

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