

Antipyretic Activity of Stembark Extract of *Mammea africana* in Rats

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Abstract

Mammea africana Sabine (Guttiferae), is a tree plant whose parts are variously used locally for the treatment of various diseases such as malaria and fever among others. The stembark extract of *M. africana* (30 -90 mg/kg) was investigated for antipyretic activity in rats using different experimental models; amphetamine, dinitrophenol and yeast-induced pyrexia. The extract exerted prominent inhibition of pyrexia on amphetamine, dinitrophenol and yeast -induced pyrexia. Inhibition was significant ($p < 0.05-0.001$) from 3 to 5 h post-administration of extract and in a dose-dependent fashion. The antipyretic effects of this plant may in part be mediated through the chemical constituents of the plant. The results of this investigation validate the ethnomedical uses of this plant in the treatment of febrile conditions.

Keywords: *Mammea Africana*; Medicinal plant; antipyretic; fever.

INTRODUCTION

Mammea africana Sabine (Guttiferae) (syn. *Ochrocarpus africana* Oliv.) (*M. africana*), widely distributed in tropical Africa, is a tall tree of 50 to 100 feet high whose bark is often yellow with pale scales and resinous yellow sap (Hutchison and Daziel, 1958). The stembark of the plant is traditionally used by the Ibibios, of Niger Delta region of Nigeria, in the treatment of a number of diseases such as malaria related fever, diabetes, microbial infections and mental disorders. Traditionally, the stembark is used also to treat stomach pains, rheumatism pains, scabies, cough and hypertension (Raponda-Walker and Silans, 1961; Adjanohoun *et al.*, 1996). The stembark extract which possesses cytotoxic activity, *in vitro* (Chapius *et al.*, 1988; Okokon *et al.*, 2012), has been reported to contain cytotoxic coumarins with antimicrobial activity against *Staphylococcus aureus* (Ouahouo *et al.*, 2004). Other pharmacological activities reported on the stembark include; anti-plasmodial (Okokon *et al.*, 2006), cardioprotective (Okokon and Antia, 2007), anti-diabetic, hypolipidaemic (Okokon *et al.*, 2007; Tchamadeu *et al.*, 2010), vasorelaxant (Dongmo *et al.*, 2007), anti-hypertensive (Nguelefack-Mbuyo *et al.*, 2008), anti inflammatory, analgesic (Okokon *et al.*, 2009), antioxidant (Nguelefack-Mbuyo *et al.*, 2010), anti-diarrheal, anti-ulcer (Okokon *et al.*, 2010), immunomodulatory, anti-lesihmanial (Okokon *et al.*, 2012), depressant and anti-convulsant (Okokon and

Davies, 2014), nephroprotective (Okokon and Bawo, 2014), hepatoprotective (Okokon *et al.*, 2016), genotoxic and cytotoxic (Ebong *et al.*, 2022) activities. Phytochemical study on the stembark reported the presence of 5,7-dihydroxy-8-(12-methyl-butyl) - 4 -N-pentylcoumarins and mesuxanthone B (Carpenter *et al.*, 1970;1971; Cricton and Waterman, 1978), 4-phenyl and 4-alkylcoumarins (Games, 1972). While alkaloids have been reported to be absent in the entire plant parts (Gartlans *et al.*, 1980). We report in this study the antipyretic activities of the stembark extract.

MATERIALS AND METHODS

Plants collection

The plant materials, *Mammea africana* (stembark), were collected in Anwa forest in Uruan area, Akwa Ibom State, Nigeria in January 2022. Identification and authentication of the plant was carried out by a taxonomist of Department of Botany and Ecological Studies, University of Uyo, Uyo, Nigeria.

Extraction

Pieces of the stembark were washed and shade-dried for two weeks. The dried plants' materials were further chopped into small pieces and reduced to powder using electric grinder. The powdered material (1.5 kg) was macerated for 72 h in 50% ethanol. This was thereafter

filtered and the liquid filtrate was concentrated and evaporated to dryness in *vacuo* 40°C using a rotary evaporator (BuchiLab, Switzerland). The extract was stored in a refrigerator at -4°C, until used for the proposed experiments.

Animals

Albino Wistar rats (122-1136 g) of either sex were obtained from the University of Uyo animal house. They were 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.

Evaluation of antipyretic activity of the *Mammea africana* stembark extract on D-amphetamine-induced pyrexia

The albino rats that were used in this experiment were fasted for 24 hours but allowed water *ad libitum* before the experiment commenced. They were randomized into groups of 5 rats each according to their weights. The initial basal temperatures of the rats were taken after which pyrexia was induced by intraperitoneal administration of amphetamine (5 mg/kg, i.p) to the animals. Pyrexia was allowed to develop within 30 min post administration of amphetamine. At the confirmation of temperature increase of at least 1°C by monitoring the rectal temperature, the leaf extract was respectively administered to the different groups of rats at 30, 60 and 90 mg/kg orally and aspirin (100 mg/kg) and distilled water (10 mL/kg, orally) were administered respectively to the positive and negative control groups of rats. Rectal temperatures of the animals were monitored at an hour interval for 5 h (Edem *et al.*, 2023).

Effect of *Mammea africana* stembark extract on 2,4-Dinitrophenol (DNP)-induced pyrexia

The albino rats that were used in this experiment were fasted for 24 hours but allowed water *ad libitum* before the experiment commenced. They were randomized into groups of 5 rats each according to their weights. The initial basal temperatures of the rats were taken after which pyrexia was induced by intraperitoneal administration of dinitrophenol (DNP) (10 mg/kg, i.p.) to the animals. Pyrexia was allowed to develop within 30 min post administration of dinitrophenol. At the confirmation of temperature increase of at least 1°C by monitoring the rectal temperature, the leaf extract was respectively administered to the different groups of rats at 30, 60 and 90 mg/kg orally and aspirin (100 mg/kg) and distilled water (10 mL/kg, orally) were administered respectively to the positive and negative control groups of rats. Rectal temperatures of the animals were monitored at an hour interval for 5 h (Edem *et al.*, 2023).

Effect of *Mammea africana* stembark extract on yeast-induced pyrexia

In this experiment, 24 hours fasted adult albino rats of both sexes allowed water *ad libitum* were randomized into groups of 5 rats each. At zero hour, the basal rectal temperature of the rats were taken using digital clinical thermometer. Thereafter, each animal was administered subcutaneously with 20% W/V aqueous suspension of yeast at a volume of 10 mL/kg (Okokon and Nwafor, 2010; Edem *et al.*, 2023). The temperatures of rats were monitored at one hour post yeast injection. Rats with temperature increase of 1°C were selected and grouped for the study. The extract under study was administered orally after the pyrogen at doses of 30, 60 and 90 mg/kg to respective groups of rats. The control group received distilled water (10 mL/kg) and the reference group was administered with ASA (100 mg/kg) both orally. The rectal temperatures of the groups were taken at 1h interval for 5 h.

Statistical analysis

Data collected were analyzed using one way analysis of variance (ANOVA) followed by Tukey's multiple comparison post-test (Graph pad prism software Inc. La Jolla, CA, USA). Values were expressed as mean $\pm$ SEM and significance relative to control were considered at $p < 0.05$.

RESULTS

Effect of stembark extract of *Mammea africana* on D-amphetamine induced pyrexia

The antipyretic effect of the stembark extract on amphetamine- induced pyrexia is shown in Table 1. The stembark extract (30-90 mg/kg), in the presence of amphetamine, demonstrated significant ($p < 0.05 - 0.001$) lowering of body temperatures of the extract- treated rats when compared with the control. These effects were pronounced and sustained from 2- 5 h post treatment with the extract. The body temperature lowering activity of the extract was not comparable to that of the standard drug, ASA, 100 mg/kg (Table 1).

Effect of ethanol stembark extract of *Mammea africana* on 2,4-dinitrophenol (DNP)-induced pyrexia in rats

The stembark extract of *M. africana* (30-90 mg/kg) demonstrated significant ($p < 0.05 - 0.001$) dose-dependent lowering of temperature in DNP-induced pyretic rats. The temperature lowering effect was, however, significant ($p < 0.05 - 0.001$) and sustained from 4 - 5 h in all the extract-treated groups. The effect of the highest dose (90 mg/kg) was strong but not comparable to that of the standard drug, ASA, 100 mg/kg (Table 2).

Effect of stembark extract of *M. africana* on yeast-induced pyrexia in rats

Treatment of rats with yeast-induced elevated body temperature with stembark extract of *M. africana* (30-90 mg/kg) caused significant ($p<0.05$ - 0.001) lowering of body temperature of rats elevated by the

administration of yeast. The standard drug, ASA, 100 mg/kg, lowered the temperature significantly ($p<0.05$) when relative to the control group (Table 3). The activity of the highest dose (90 mg/kg) of the extract was lower compared to that of the standard drug, ASA, 100 mg/kg (Table 3)

Table 1. Antipyretic effect of *Mammea africana* stembark extract on D-amphetamine-induced pyrexia.

Treatment/ Dose(mg/kg)	Time Intervals (hrs)							
	Basal Temp	0	0.5	1.0	2.0	3.0	4.0	5.0
Control	34.60±0.35	35.94±0.13	36.23±0.17	36.61±0.26	36.77±0.15	37.25±0.38	37.20±0.16	37.5±0.44
Extract 30	34.78±0.68	35.71±0.53	35.63±0.16	35.50±0.14	35.33±0.13 ^a	35.28±0.15 ^b	35.33±0.36 ^a	34.68±0.13 ^a
Extract 60	35.33±0.76	36.56±0.15	35.91±0.31	35.44±0.33	35.30±0.16 ^a	35.01±0.60 ^a	35.13±0.29 ^b	34.70±0.26 ^b
Extract 90	34.28±0.18	35.42±0.28	35.33±0.18	35.22±0.26	34.90±0.27 ^a	34.65±0.33 ^b	34.30±0.22 ^b	34.23±0.21 ^c
ASA 100	35.04±0.11	36.11±0.31	35.50±0.12	35.03±0.14	34.86±0.12 ^a	34.54±0.28 ^c	34.11±0.15 ^c	33.89±0.24 ^c

Values are expressed as mean ± SEM. Significance relative to control. ^a $p<0.05$; ^b $p<0.01$; ^c $p<0.001$. n = 6.

Table 2. Antipyretic effect of *Mammea africana* stembark extract on Dinitrophenol-induced pyrexia.

Treatment/ Dose(mg/kg)	Time Intervals (hrs)							
	Basal Temp	0	0.5	1.0	2.0	3.0	4.0	5.0
Control	34.42±0.34	36.33±0.21	36.46±0.12	36.54±0.18	36.60±0.54	36.48±0.15	36.20±0.25	36.24±0.12
Extract 30	34.16±0.20	36.15±0.16	36.33±0.24	36.29±0.38	35.97±0.20	35.35±0.42	34.50±0.26 ^a	34.05±0.54 ^b
Extract 60	34.55±0.12	36.36±0.22	36.25±0.22	36.16±0.17	35.81±0.37	35.23±0.23	34.32±0.24 ^a	33.76±0.16 ^b
Extract 90	35.11±0.32	36.86±0.54	36.20±0.18	35.83±0.35	35.31±0.47	34.86±0.31	33.55±0.28 ^c	33.22±0.19 ^c
ASA 100	35.16±0.12	36.91±0.20	36.12±0.26	35.65±0.29	35.10±0.15	34.59±0.12 ^a	33.40±0.12 ^c	33.12±0.26 ^c

Values are expressed as mean ± SEM. Significance relative to control. ^a $p<0.05$; ^b $p<0.01$; ^c $p<0.001$. n = 6

Table 3. Antipyretic effect of *Mammea africana* stembark extract on yeast-induced pyrexia.

Treatment/ Dose(mg/kg)	Time Intervals (hrs)							
	Basal Temp	0	0.5	1.0	2.0	3.0	4.0	5.0
Control	34.38±0.18	35.60±0.21	36.65±0.15	36.85±0.31	37.20±0.19	37.41±0.26	37.76±0.18	37.44±0.16
Extract 30	34.74±0.26	36.02±0.18	36.24±0.20	36.52±0.34	36.26±0.23	36.11±0.25	36.02±0.26	35.92±0.26
Extract 60	35.08±0.15	36.14±0.78	36.30±0.12	36.10±0.43	36.01±0.10	35.91±0.14 ^a	35.65±0.17 ^b	35.21±0.18 ^c
Extract 90	35.10±0.22	36.13±0.28	36.20±0.29	36.15±0.22	35.88±0.31 ^a	35.55±0.16 ^a	35.33±0.12 ^b	35.25±0.20 ^c
ASA 100	35.20±0.17	36.29±0.18	36.35±0.32	36.10±0.17	35.78±0.25 ^a	35.42±0.26 ^c	35.30±0.14 ^c	35.05±0.26 ^c

Values are expressed as mean ± SEM. Significance relative to control. ^a $p<0.05$; ^b $p<0.01$; ^c $p<0.001$. n = 6.

DISCUSSION

In this study, the stembark extract of *M. africana* was investigated for anti-pyretic activity using standard experimental models. The extract inhibited significantly amphetamine, dinitrophenol and yeast-induced pyrexia. Amphetamine causes rise in body temperature by acting on the brain, causing the release of biogenic amines from their storage sites in nerve terminals. Thus resulting in elevated level of cAMP and subsequent increased synthesis of prostaglandins from arachidonic acids produced in neurons by receptor-mediated hydrolysis of phospholipids (Westfall and Westfall, 2006). This leads to hyperthermia. Dinitrophenol causes hyperthermia by uncoupling oxidative phosphorylation resulting in the release of calcium from mitochondrial stores and also blocks

calcium reuptake. This results in increased level of intracellular calcium, muscle contraction and hyperthermia (Kumar *et al.*, 2002). Yeast induces hyperthermia by stimulating the synthesis of prostaglandins (Al-Ghamdi, 2001), in the hypothalamus. The extract may have reduced pyrexia by reducing brain concentration of prostaglandin E₂ especially in the hypothalamus through its action on COX-2 or by enhancement of the production of the body's own antipyretic substances such as vasopressin and arginine (Chandrasekharan, 2002). The hypothermic activity of the extract could have also been mediated by vasodilatation of superficial blood vessels leading to increased dissipation of heat following resetting of hypothalamic temperature control center (Rang *et al.*, 2007). This action may be

due to the phytochemical compounds in this plant. Therefore, the temperature lowering activity of the extract may not be unconnected with the inhibition of one or combination of the above-mentioned mechanisms. The phytochemical compounds in this plant may in part be responsible for the observed antipyretic activities of the stem bark extract.

CONCLUSION

From the results of this study, the stem bark extract of *Mammea africana* possesses antipyretic activity which is due to the activities of its phytochemical constituents.

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Competing Interests: The authors have not declared any conflict of interests.

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