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## Antipyretic Activity of *Byrsocarpus coccineus* Schum and Thonn. (Connaraceae)

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**Abstract:** The aqueous leaf extract of *Byrsocarpus coccineus* Schum and Thonn. (Connaraceae) was investigated for antipyretic activity in rats and rabbits using yeast, amphetamine and lipopolysaccharide induced pyrexia models. In control rats, yeast (10 mL kg<sup>-1</sup>, s.c.) caused elevation of rectal temperature of 1.68°C 19 h after administration. The extract (100, 200 and 400 mg kg<sup>-1</sup>, p.o.) produced a significant (p<0.05) dose dependent inhibition of temperature elevation. Peak inhibitory effect was observed at 1 h post therapy (42.05, 47.16 and 63.64% inhibition, respectively for the extract at 100, 200 and 400 mg kg<sup>-1</sup>). The effect at 400 mg kg<sup>-1</sup> was greater than that of acetylsalicylic acid, ASA (100 mg kg<sup>-1</sup>, p.o.; 43.18%). An elevation in rectal temperature of 1.88°C was provoked in control rats by amphetamine (10 mg kg<sup>-1</sup>, i.p.) 0.5 h after administration while in control rabbits, lipopolysaccharide from *E. coli* (0.2 µg kg<sup>-1</sup>, i.v.) elicited an elevation of 1.11°C, 1.5 h post challenge. In both models, the extract produced a significant (p<0.05) dose and time dependent direct reduction of elevated temperature with peak effect observed at 3.5 h post therapy. Percent reduction of fever values were 50.24, 61.11 and 84.33, respectively for the extract at 100, 200 and 400 mg kg<sup>-1</sup> (p.o.) in respect of the amphetamine test. The effect at 400 mg kg<sup>-1</sup> was about the same as that of ASA (85.31%) in this case, but it was lower (44.90%) compared to the standard drug (96.64%) in the lipopolysaccharide test. The results obtained in this study suggest that the extract possess antipyretic activity.

**Key words:** *Byrsocarpus coccineus*, antipyretic activity, pyrexia

### INTRODUCTION

*Byrsocarpus coccineus* is a plant commonly found across West and tropical Africa. It is a scandent shrub of savanna thickets and secondary jungle with delicate pink-tinged foliage and sweet-scented flowers. Ascribed local names in Nigeria include tsaamiyar-kasa (Hausa tribe, North), oke abolo (Igbo tribe, East) and Orikoteni; Amuje (Yoruba tribe, South-West).

In addition to its wide spread ornamental use, various preparations of the plant have been used to treat diverse ailments. These include mouth and skin sores, swellings, tumours, earache, muscular and rheumatic pains, venereal diseases, jaundice, pile and dysentery (Burkill, 1985). The plant extract has been shown to possess oxytocic (Amos *et al.*, 2002), antioxidant (Oke and Hamburger, 2002) and anti-diarrhoeal (Akindele and Adeyemi, 2006b) activities.

In previous studies, we reported the analgesic (Akindele and Adeyemi, 2006a) and anti-inflammatory (Akindele and Adeyemi, 2007) properties of the aqueous leaf extract of *B. coccineus*. Based on results obtained from these studies, we decided to investigate the antipyretic activity of the plant.

### MATERIALS AND METHODS

**Plant material:** The fresh plant was collected from a private garden in Iju-Ogundimu, Ifako/Ijaiye Local Government Area of Lagos State, Nigeria. Identification and authentication was done by Professor J.D. Olowokudejo of the Department of Botany, University of Lagos, Lagos, Nigeria and Mr. T.K. Odewo (Senior Superintendent) of the Forestry Research Institute of Nigeria (FRIN), Ibadan, Nigeria. A voucher specimen (FHI 106623) was deposited in the Herbarium of the Institute for reference.

**Extraction:** The air-dried leaves of *B. coccineus* were macerated in distilled water (10 g in 1 L) and the liquid was decanted 24 h after. The filtrate was evaporated to dryness at 40°C, giving a dark brown solid with a yield of 12.91%. The dried extract was weighed and dissolved in distilled water to give a concentration of 100 mg mL<sup>-1</sup> (pH 6.8) before administration to the experimental animals.

**Animals:** Albino rats (150-200 g) and adult rabbits (1.0-1.5 kg) of both sexes were used in this study. All the animals were obtained from the Laboratory Animal Centre

of the College of Medicine, University of Lagos, Lagos, Nigeria. The animals were maintained under standard environmental conditions and fed with standard diet (Livestock Feeds PLC) and water *ad libitum*. The experimental protocol was approved by the Experimentation Ethics Committee on Animal Use of the College of Medicine, University of Lagos, Lagos, Nigeria.

**Antipyretic activity**

**Yeast induced hyperthermia:** Five groups of six rats each were injected s.c. with 10 mL kg<sup>-1</sup> b.wt. yeast suspension (15% in 0.5% w/v methylcellulose) to induce pyrexia, after measuring the basal rectal temperature (T<sub>0</sub>°C) of each animal. Nineteen hours after yeast injection, the rectal temperature was recorded again and animals showing a rise in temperature of <0.6°C were discarded (Mukherjee *et al.*, 2002). Thereafter, treatment was carried out as follows:

- Group I : Distilled water (10 mL kg<sup>-1</sup>; p.o.),
- Groups II, III, IV : *B. coccineus* (100, 200 and 400 mg kg<sup>-1</sup>; p.o.) and
- Group V : Acetylsalicylic acid, ASA (100 mg kg<sup>-1</sup>; p.o.).

Rectal temperatures were then recorded at 20, 21, 22, 23 and 24 h (T<sub>x</sub>°C) after yeast injection.

**Amphetamine induced hyperthermia:** The basal rectal temperatures of rats fasted for 12 h were recorded (T<sub>0</sub>°C), prior to the induction of pyrexia by i.p. injection of d-amphetamine, 10 mg kg<sup>-1</sup> (Berkan *et al.*, 1991). After the confirmation of hyperthermia in the experimental animals 0.5 h after amphetamine administration, treatment was carried out as in the yeast model above. The rectal temperatures of the animals were then recorded 1, 2, 3 and 4 h (T<sub>x</sub>°C) post pyrexia induction.

**Lipopolysaccharide induced hyperthermia:** Rabbits used for the experiment were placed in separate holders and

allowed to stabilize for 1 h. Basal rectal temperatures (T<sub>0</sub>°C) were recorded using a narrow bulb rectal thermometer (readings taken twice and averaged). Pyrexia was then induced in groups of five rabbits each by injecting 0.2 µg kg<sup>-1</sup> lipopolysaccharide (from *E. coli*) i.v. through the marginal ear vein dilated with xylene (Vogel and Vogel, 1997). Rectal temperatures were taken 0.5, 1 and 1.5 h Post-Pyrogen Administration (PPA), after which distilled water (10 mL kg<sup>-1</sup>; p.o.), *B. coccineus* (400 mg kg<sup>-1</sup>; p.o.) and ASA (100 mg kg<sup>-1</sup>; p.o.) were administered. Rectal temperatures were then monitored at 0.5 h interval for 3.5 h post-therapy (2.0-5.0 h PPA). Only the 400 mg kg<sup>-1</sup> dose level of the extract was tested in this model because peak antipyretic effects were produced at this dose in the yeast and amphetamine models.

**RESULTS**

**Yeast induced hyperthermia:** As shown in Table 1, subcutaneous injection of yeast caused elevation of rectal temperature in control rats by 1.68°C 19 h after administration. Oral administration of the extract produced a significant (p<0.05) dose dependent inhibition of temperature elevation. Peak inhibitory effect was observed at 1 h post-therapy, i.e., 20 h post-yeast injection (42.05, 47.16 and 63.64% inhibition for *B. coccineus* at 100, 200 and 400 mg kg<sup>-1</sup>, respectively). The effect at 400 mg kg<sup>-1</sup> was greater than that of ASA (100 mg kg<sup>-1</sup> p.o., 43.18%).

**Amphetamine induced hyperthermia:** Amphetamine injected i.p. increased the rectal temperature of control rats from a baseline value of 37.96 to 39.83°C (Δ 1.87°C) 0.5 h after administration. The extract (p.o.) produced a dose and time dependent direct reduction of pyrexia. Peak effect was observed at 3.5 h post-therapy i.e., 4 h after amphetamine administration, with percent reduction of fever values of 50.24, 61.11 and 84.33%, respectively for

Table 1: Effects of *B. coccineus* on yeast induced hyperthermia in rats

Treatments	Dose	T <sub>0</sub>	T <sub>19h</sub>	T <sub>20h</sub>	T <sub>21h</sub>	T <sub>22h</sub>	T <sub>23h</sub>	T <sub>24h</sub>
----- (°C) -----								
Vehicle control (mL kg <sup>-1</sup> )	10	37.91±0.10	39.58±0.16	39.67±0.14 (-)	39.82±0.12 (-)	39.73±0.15	39.53±0.19	39.52±0.18
<i>B. coccineus</i> (mg kg <sup>-1</sup> )	100	38.44±0.25	-	39.46±0.24 <sup>α</sup> (42.05%)	39.62±0.25 <sup>β</sup> (38.22%)	39.83±0.11 (24.04%)	39.77±0.13 (18.40%)	39.73±0.16 (19.98%)
	200	38.97±0.19	-	39.90±0.20 <sup>γ</sup> (47.16%)	40.07±0.34 <sup>β</sup> (42.41%)	40.10±0.33 <sup>α</sup> (38.25%)	40.10±0.18 <sup>α</sup> (30.67%)	40.00±0.17 <sup>α</sup> (36.02%)
	400	38.89±0.12	-	39.53±0.19 <sup>γ</sup> (63.64%)	39.70±0.18 <sup>γ</sup> (57.59%)	39.97±0.14 <sup>β</sup> (40.98%)	40.08±0.12 (26.99%)	39.95±0.12 <sup>α</sup> (34.16%)
ASA (mg kg <sup>-1</sup> )	100	38.49±0.12	-	39.49±0.25 <sup>α</sup> (43.18%)	39.66±0.22 <sup>α</sup> (38.74%)	39.64±0.26 <sup>α</sup> (37.16%)	39.39±0.29 <sup>α</sup> (44.79%)	39.36±0.31 <sup>α</sup> (45.96%)

Values are mean±SEM (n = 6). α: p<0.05, β: p<0.02, γ: p<0.01 vs. control (Student's t-test), in respect of increase in temperature. Figures in parenthesis indicate inhibition (%) of temperature elevation

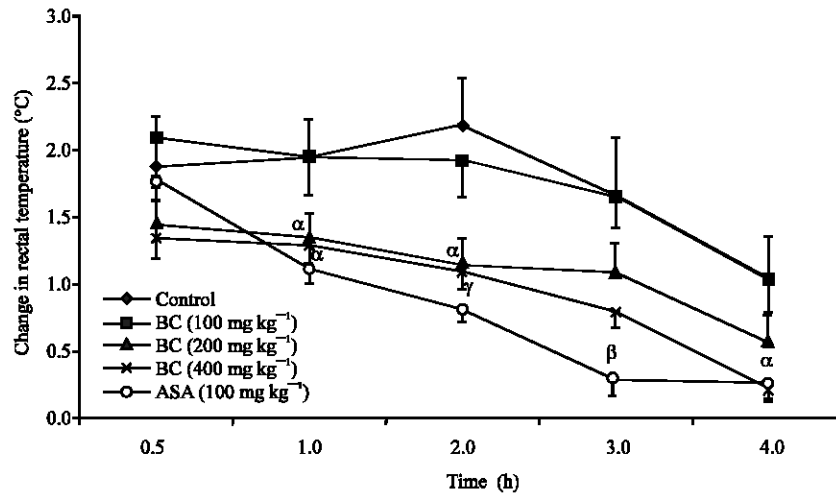


Fig. 1: Effect of *B. coccineus* on amphetamine induced hyperthermia in rats. Vertical bars are mean±SEM (n = 6). <sup>α</sup>: p<0.05, <sup>β</sup>: p<0.02, <sup>γ</sup>: p<0.01, (Student's t-test)

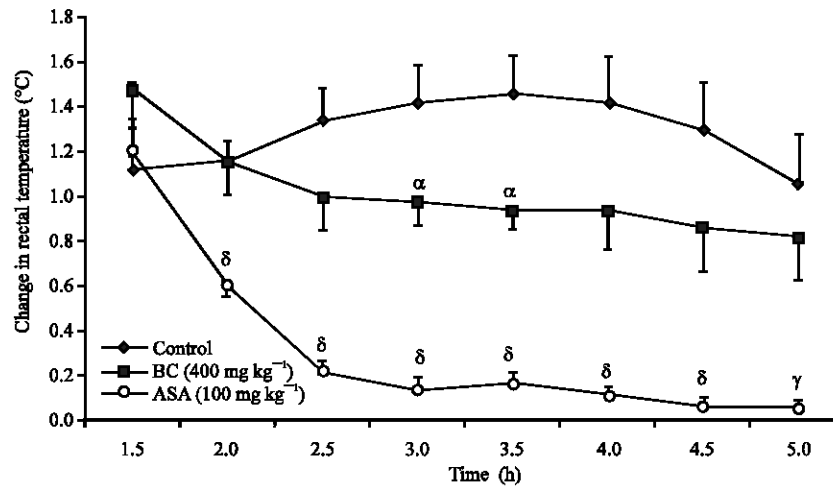


Fig. 2: Effect of *B. coccineus* on lipopolysaccharide induced hyperthermia in rabbits. Vertical bars are mean±SEM (n = 5). <sup>α</sup>: p<0.05, <sup>γ</sup>: p<0.01, <sup>δ</sup>: p<0.001, (Student's t-test)

*B. coccineus* at 100, 200 and 400 mg kg<sup>-1</sup>. At the highest dose, the extract significantly (p<0.05) reduced the rectal temperature from 39.55 to 38.42°C (Δ 1.13°C). This effect was comparable to that of ASA (85.31%), which reduced the rectal temperature from 39.78 to 38.27°C (Δ 1.51°C) as displayed in Fig. 1. On administration of amphetamine, mice manifested increased alertness, aggressiveness and locomotor activity, together with profuse sweating. Stereotyped behavior (consisting of repeated actions like licking, gnawing and rearing) was also observed in some animals. However, the manifestation of these CNS effects diminished post-treatment with increasing doses of the extract, relative to the observation in the control group.

**Lipopolysaccharide induced hyperthermia:** As shown in Fig. 2, intravenous injection of lipopolysaccharide from *E. coli* increased the rectal temperature of control rabbits from baseline value of 38.85 to 39.96°C (Δ1.11°C) 1.5 h after administration. The extract at 400 mg kg<sup>-1</sup> (p.o), which is the dose at which peak effects were produced in the yeast and amphetamine models, elicited a significant (p<0.05) time dependent direct reduction of pyrexia with peak effect observed at 3.5h post-therapy (5 h PPA). Rectal temperature was decreased from 40.60 to 39.94°C (Δ 0.66°C) corresponding to 44.90% reduction of fever. ASA reduced the temperature from 39.92 to 38.77°C (Δ 1.15°C), an effect (96.64%) that was significantly higher than that of *B. coccineus*.

## DISCUSSION

Fever is one of the most common signs of illness and it is best defined as an increase in temperature over what is normal for a given individual at that particular time of day (Wolff *et al.*, 1975). It is not merely an isolated temperature greater than 37°C. Normal body temperature is regulated by a centre in the hypothalamus, which ensures a balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic thermostat that leads to the set point of body temperature being raised (Rang *et al.*, 1999).

Certain prostaglandins, endogenous fatty acid derivatives present in brain and other tissues, are pyrogenic when injected into the hypothalamus of experimental animals. Fever, which is not blocked by systemic salicylates, develops within minutes of administration of nanogram amounts. Milton and Wendlandt (1971) therefore proposed that prostaglandins act as a molecular transmitter of pyrogenic stimuli in the hypothalamus. Abramson and Weissmann (1989) and Coelho *et al.* (1995) in their report on the mechanisms of antipyretic action of non-steroidal anti-inflammatory drugs and glucocorticoids, respectively, attributed the inhibition of fever during the febrile response to endotoxin, by these agents, to the inhibition of biosynthesis of prostaglandins and inhibition of increased plasma prostaglandin level, respectively. Their findings thus confirmed the earlier suggestion by Milton and Wendlandt (1971).

Indeed, non-steroidal anti-inflammatory drugs (NSAIDs), like acetylsalicylic acid, exert their antipyretic action by largely inhibiting prostaglandin (E-type) production in the hypothalamus (Rang *et al.*, 1999). Consequently, elevated plasma prostaglandin level, as observed in fever, is suppressed. Paracetamol, another reference antipyretic drug (not used in this study), also brings about the same effect by a selective action on a specific cyclooxygenase (COX) isoenzyme in the CNS.

The aqueous leaf extract of *B. coccineus* demonstrated effective antipyretic activity as evident in the inhibition of temperature elevation in the yeast model and a direct reduction of pyrexia in the amphetamine and lipopolysaccharide models. The antipyretic action of the extract may possibly be through inhibition of prostaglandin production, leading to suppression of elevated plasma level, especially since the extract had been shown to possess analgesic (Akindele and Adeyemi, 2006a) and anti-inflammatory (Akindele and Adeyemi, 2007) activities.

The behavioral observations made in amphetamine treated mice are expected since it is a psychomotor (CNS) stimulant (Rang *et al.*, 2003).

The plant extract has been shown to contain compounds like alkaloids, tannins, saponins, reducing sugars, glycosides and anthraquinones (Akindele and Adeyemi, 2006a). However, the active principle(s) responsible for the observed antipyretic effect of the extract is yet to be identified. Further investigations are going on in our laboratory to isolate and characterize the specific active components of the plant extract responsible for observed pharmacological actions. Also, we reported the safety of the extract when administered p.o., based on the fact that oral administration, up to 10 g kg<sup>-1</sup>, did not produce any mortality and visible toxic signs (Akindele and Adeyemi 2006a). However, the LD<sub>50</sub> when injected i.p. was estimated to be 141.3 mg kg<sup>-1</sup>.

In conclusion, the results obtained in this study suggest that the aqueous leaf extract of *Byrsocarpus coccineus* possesses antipyretic activity, in addition to the previously established analgesic and anti-inflammatory activities (Akindele and Adeyemi, 2006a, 2007).

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