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Antinociceptive and Antipyretic Effects of Aqueous Extract of *Borreria stachydea* Leaves

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Abstract

This study was undertaken to investigate the anti-nociceptive and anti-pyretic activities of the aqueous leaf extract of *Borreria stachydea* (AEBS). The anti-nociceptive activity was investigated using acetic acid- induced writhing and tail immersion models while antipyretic activity was examined using Brewer's yeast- and Amphetamine- induced pyrexia models. Acute toxicity study was also carried out on AEBS according to Lorke's method. Results of acute toxicity showed that AEBS produced no signs of toxicity or mortality up to a dose of 5000mg/kg. AEBS (100, 200 and 400 mg/kg) showed significant ($P<0.05$) and dose- dependent inhibitory activity in all the models of antinociceptive and antipyretic experiments. It was concluded that the aqueous leaf extract of *Borreria stachydea* possess anti-nociceptive and anti- pyretic activities. The plant extract therefore could be useful in the management of pain and pyrexia.

Keywords: Antinociceptive, Antipyretic, *Borreria stachydea*, Aqueous

Introduction

Pain is an unpleasant sensation that is often associated with actual or potential tissue damage that is caused by disease and/ or injury. The word "pain" comes from the Latin word "peona" meaning a fine or penalty (Coda and Bonica, 2001). Pain is not only a symptom used to diagnose several diseases and conditions but also has a protective function. The organism's ability to detect noxious stimuli and engage in appropriate protective behaviours against these stimuli is essential for its survival and wellbeing. Unrelieved pain may cause suffering and inability to perform daily activities hence imposing high health costs and economic losses to the victim and society (Ezeja *et al.,* 2011; Prystupa *et al.,* 2013).
Fever or pyrexia is an elevated body temperature above the normal level characterized by an increase in thermoregulatory set-point, which results from the interaction of the central nervous and immune system. Fever is caused or induced by substances called pyrogens such as microbial infections, trauma, drugs and chemicals. These pyrogens trigger the formation of cytokines like interleukins, tumor necrosis factor and interferon. These cytokines enhance the synthesis of prostaglandin E2 (PGE2) next to the pre-optic hypothalamus region hence elevating the body temperature through promoting heat generation mechanism and decreasing heat loss. Fever is usually accompanied by symptoms, such as sweating, chills and sensation of cold. It is exhibited in many illnesses for example; malaria, typhoid and arthritis (Kumar *et al.,* 2012; Anochie & Ifesinachi, 2013).

Reports of many cultures and traditional system of medicine across the world lend credence to the beneficial uses of medicinal plants in the management of pain and fever. A number of such plants have been used and still in use singly or as an adjuvant to orthodox drugs in managing a number of chronic diseases without any scientific data backing their pharmacological properties.

Borreria stachydea (DC) commonly known in English language as ant's wheat is an erect, hairy and weedy herb, about 30-60 cm high with mauve flowers. It belongs to Rubiaceae family (Dalziel, 1937). Through personal communication, we found out that this plant is used in traditional medicine to treat venereal diseases, inflammations, and gonorrhea. Borreria species possess wide variety of medicinal properties; however a few species have been screened for confirmation of their biological activities. To the best of our knowledge, no study has been carried out to determine the antinociceptive and antipyretic potentials of *B. stachydea.* Hence, this study investigated the antinociceptive and antipyretic potentials of the plant using different experimental models.

Materials and Methods

Materials

Chemicals and drugs

Acetic acid, Brewers' yeast, Methyl-cellulose, Amphetamine and Morphine were purchased from Sigma Chemical Co. Ltd (USA) while Aspirin was purchased from Adonai pharmacy shop, Nsukka, Enugu State.

Animals

Healthy adult Wistar rats (120-180 g) and mice (18-25 g) were used for this study. They were kept in stainless steel cages under standard laboratory conditions. They were maintained on clean water and standard rodent feed.

Methods

Plant collection and identification

The leaves of *Borreria stachydea* were collected from a natural habitat in Nsukka area of Enugu State, Nigeria. The plants were identified at the Department of Pharmacognosy, University of Nigeria, Nsukka.

Figure 1: Picture of *Borreria stachydea* in its natural habitat

Preparation of extract

The leaves of *Borreria stachydea* were dried under shade for five (5) days and pulverized using a manual blender. One thousand- five hundred (1500) gram of the pulverized leaves was soaked in distilled water for 48 h. The resulting mixture was filtered using Whatmann filter paper (Size No1) and the extract was concentrated using freeze- dryer. The extract of *Borreria stachydea* was code-named AEBS and stored in the refrigerator till when required.

Acute toxicity study

The oral median lethal dose (LD_{50}) of the extract was determined in rats according to the method of Lorke, (1983).

Acetic acid-induced writhing test

Analgesic activity of AEBS against acetic acid-induced writhing was carried out following the procedure of (Singh and Majumda, 1995; Akuodor *et al*, 2011). The adult albino mice used for this study were randomized into 5 groups of 6 mice in each cage. They were fasted for 24 hrs but were allowed free access to water. Group 1 which served as control received distilled water 20 ml/kg p.o.), while groups 2-4 received 100,200 and 400 mg/kg p.o. of AEBS. Group 5 received 150mg/kg of acetylsalicylic acid (aspirin). Thirty minutes post drug administration, each mouse was injected intraperitoneally with 0.7% of acetic acid at a dose of (20 ml/kg) to create pain sensation. Each mouse was later placed in a transparent observation box. The number of abdominal constrictions for each mouse was counted for 30 minutes, stating 5 min after injection of acetic acid.

Tail immersion test

This was based on the method described by Jansen and Jagenau, (1959) with slight modification. The mice selected for this study were grouped into 5 groups of 6 mice in each cage. The 24 h fasted mice were allowed access to water. Group 1 (control) received distilled water (20 ml/kg p.o.), while group 2-4 received 100,200 and 400 mg/kg of AEBS. Group 5 received 10 mg/kg of morphine subcutaneously. Thirty minutes post drug administration, each mouse was restrained in a horizontal cylinder leaving the tail hanging in a water bath maintained at $52\pm1^{o}C$, and the time taken for the animal to withdraw its tail out of the water was recorded. The latency was evaluated at 30, 60, 90 and 120 min. The initial reading was taken before administration of test samples.

Yeast-induced pyrexia test

Procedure as described by Okokon and Nwafor (2010) was adopted with slight modification. 24 h after induction of pyrexia (Brewer's yeast), the anal temperature of each rat was taken to confirm hyperthermia. Thereafter, AEBS (100, 200 and 400 mg/kg), normal saline (20 ml/kg) and the standard drug aspirin (150 mg/kg) were orally administered respectively. The anal temperature reading of each rat was recorded at 1 h interval for 5 h.

Amphetamine-induced pyrexia test

Thirty albino rats of both sexes fasted with access to water were recruited for this study. They were grouped into 5 with 6 in each cage. 1 h after induction of pyrexia with amphetamine, the anal temperature of each rat was taken to confirm hyperthermia. Normal saline was administered to group 1(control). AEBS (100, 200 and 400 mg/kg) were administered to groups 2-4, while group 5 received (150 mg/kg) of aspirin. All were given orally. Anal temperatures were recorded at 1 h interval for 6 h.

Statistical Analysis

Values are presented as mean ±SEM (standard error of the mean). The data were analyzed by One-way ANOVA and differences between the means were considered significant at $p<0.05$.

Results

Acute Toxicity

In the acute toxicity studies, the aqueous leaf extract of *Borreria stachydea* produced zero mortality up to a dose of 5000 mg/kg. No signs of toxicity were also observed with the extract up to same dose. The oral LD_{50} of the extract was then taken to be > 5000 mg/kg.

Acetic Acid-induced Writhing Test

Table 1 shows the effect of AEBS on acetic-acid-induced writhing in mice. The extract in a dose-dependent fashion significantly ($p<0.05$) produced reduction of writhing in mice. The 400 mg/kg dose of the extract produced an inhibition of 89.34% which was closest to that of aspirin (91.47%).

Table 1: Effect of Aqueous Leaf Extract of *Borreria stachydea* (AEBS) on Acetic acid-induced Writhing in Mice

Treatment	Writhing	% Inhibition
Control (20ml/kg DW)	25.43 ± 2.12	-
AEBS (100 mg/kg)	8.28± 0.21	67.44*
AEBS (200 mg/kg)	5.14± 0.17	79.79*
AEBS (400 mg/kg)	2.71 ± 0.25	89.34*
Aspirin (20 mg/kg)	2.17 ± 0.34	91.47*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at $p<0.05$

Tail Immersion

Similarly, AEBS dose- and time- dependently protected the mouse from the heat stimuli of the hot-bath. The highest dose of AEBS (400 mg/kg) produced an effect that is comparable to that of 10 mg/kg of morphine (Table 2).

Table 2: Effect of Aqueous Leaf Extract of *Borreria stachydea* (AEBS) on Mouse-tail Immersion in hot bath

Treatment/Duration of stay	0 min	30 min	60min	90 min	120 min
Control (20ml/kg DW)	7.15 ± 0.34	6.58 ± 0.45	8.91 ± 0.22	8.67 ± 0.19	9.45 ± 0.48
AEBS (100 mg/kg)	7.18 ± 0.31	7.34 ± 0.41	13.17 ± 0.35*	15.28 ± 0.26*	17.76 ± 0.63*
AEBS (200 mg/kg)	6.29 ± 0.24	7.76 ± 0.28	16.32 ± 0.12*	18.42 ± 0.33*	21.40 ± 0.56*
AEBS (400 mg/kg)	7.11 ± 0.31	7.48 ± 0.11	16.35± 0.45*	19.67 ± 0.96*	23.22 ± 0.34*
Morphine (10 mg/kg)	6.19 ± 0.44	6.32 ± 0.18	17.77 ± 0.34*	21.38 ± 0.39*	24.23 ± 0.88*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at p<0.05

Brewer's Yeast- induced Pyrexia

At 6h, AEBS at 200 and 400 mg/kg significantly (p<0.05) reduced the brewer's yeast- induced pyrexia. The anti-pyretic activity of the extract was comparable to that of the standard drug- aspirin.

Table 3: Effect of Aqueous Leaf Extract of *Borreria stachydea* (AEBS) on Brewer's yeast- induced pyrexia

Treatment	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Control (20ml/kg DW)	37.31±0.03	37.66±0.05	37.24±0.02	37.23±0.06	37.28±0.06	37.28±0.05	37.34±0.07
AEBS (100 mg/kg)	37.48±0.02	36.31±0.09	36.60±0.02	37.15±0.07	36.23±0.06	36.41±0.03	37.17±0.05
AEBS (200 mg/kg)	37.35±0.01	37.11±0.03	36.31±0.08	36.34±0.07	37.56±0.04	36.87±0.02	35.22±0.04*
AEBS (400 mg/kg)	37.63±0.08	36.26±0.03	36.14±0.02	37.61±0.08	36.74±0.09	36.69±0.06	35.16±0.08*
Aspirin (150 mg/kg)	37.44±0.07	36.41±0.08	36.23±0.05	36.33±0.01	36.41±0.04	36.64±0.08	35.33±0.05*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at p<0.05

Amphetamine- induced Pyrexia

AEBS significantly (p<0.05) and dose-dependently reduced amphetamine-induced pyrexia at 5 and 6 h (Table 4). The anti-pyretic activity of the extract was comparable to that of the standard drug- aspirin.

Table 4: Effect of Aqueous Leaf Extract of *Borreria stachydea* (AEBS) on Amphetamine- induced Pyrexia

Treatment	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr
Control (20ml/kg DW)	37.26±0.01	37.39±0.05	37.78±0.07	37.48±0.04	37.44±0.08	37.13±0.05	37.39±0.03
AEBS (100 mg/kg)	37.48±0.05	37.42±0.09	37.23±0.08	37.35±0.09	37.67±0.04	35.39±0.03*	36.56±0.07*
AEBS (200 mg/kg)	37.87±0.07	37.78±0.05	37.58±0.05	37.87±0.03	37.38±0.05	36.67±0.02*	35.33±0.07*
AEBS (400 mg/kg)	37.52±0.03	37.32±0.04	37.47±0.08	37.73±0.04	37.53±0.09	35.41±0.06*	35.89±0.04*
Aspirin (150 mg/kg)	37.43±0.03	37.27±0.07	37.36±0.07	37.28±0.07	37.28±0.14	35.83±0.09*	35.23±0.03*

Data are expressed as mean ±SEM (n = 6) *significantly different from control at p<0.05

Discussion

In the acute toxicity studies, the extract produced zero mortality and no signs of toxicity up to a dose of 5000 mg/kg. The oral LD_{50} of AEBS was then taken to be > 5000 mg/kg (Lorke's method). Therefore, the plant extract can be considered safe when consumed acutely.

Acetic acid induced writhing method has been widely used for the investigation of peripheral analgesic activity (Vongtau *et al.,* 2004). The writhing response is believed to be generated by the liberated endogenous substances such as serotonin, histamine, prostaglandins (PGs), bradykinins and substance P which stimulate nerve endings (Nuhu *et al.,* 2007). AEBS significantly inhibited the acetic acid induced writhing response in mice. The observed decrease in acetic acid induced writhes by the extract shows that the analgesic activity may be peripherally involved through the inhibition of synthesis or release of prostaglandins and other endogenous substances (Salawu *et al.,* 2008; Gupta *et al.,* 2003). The tail immersion test was carried out to further confirm the analgesic action of AEBS. The extract significantly exhibited reduction in the tail withdrawal latency which showed that it possesses analgesic activity. The standard drug used -morphine acts by inhibiting central nociceptive neurons and nociceptive spinal reflexes, thereby, blocking the transmission of nociceptive impulses through the dorsal horn (Fields and Basbaum, 1994; Oluwatoyin *et al*., 2008). The extract might have acted similarly via central mechanism.

Results of this study also revealed that AEBS possess significant antipyretic activity against induced pyrexia in the two models-Brewer's yeast and Amphetamine. Pyrexia begins whenever exogenous or/and endogenous stimuli which may include pyrogens are exposed to host cells-monocytes and macrophages (Arai *et al*., 1990). Formation of cascade of other pyrogenic cytokines like interleukin-1, TNF-α, interleukin-6 etc. follows. As a result of an interaction of cytokines and their receptors in the preoptic region of the anterior hypothalamus, phospholipase A is activated to catalyze arachidonate (substrate for COX), leading to synthesis of prostaglandins, that could further trigger the temperature to be elevated (Dinarello, 1997; Vane and O'Grady, 1993). The regulation of body temperature requires a subtle equilibrium between the production and loss of heat. As the temperature regulating structure is administrated by a nervous feedback mechanism, whenever the body temperature becomes very high, it dilates the blood vessels and increase sweating to reduce the temperature; but when the body temperature becomes very low, hypothalamus protect the internal temperature by 'vasoconstriction'. Under the influence of fever, this set point is elevated and a drug like paracetamol does not influence body temperature when it is elevated by factors such as exercise or an increase in ambient temperature. Antipyretic drugs have been reported to inhibit prostaglandin E2 elevation by antagonizing the effect of cyclo-oxyginase-2, hence reduce elevated body temperature (Agbeje *et al.,* 2008). Hence, AEBS suppressing the elevated temperature in both the yeast and amphetamine- induced fever models might have acted through a similar possible mechanism of action as orthodox anti-pyretic drugs.

Conclusion

Conclusively, the aqueous leaf extract of *Borreria stachydea* possess antinociceptive and anti-pyrexia effect in mouse possibly exerted via peripheral and central mechanisms.

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