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Full Length Research Paper

Investigation of the anti-inflammatory and antinociceptive activities of *Hymenocardia acida* Tul. (*Hymenocardiaceae*)

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Hymenocardia acida Tul. (*Hymenocardiaceae*) locally called Orupa, is traditionally used for the treatment of inflammation, including arthritis, rheumatic pain and toothache. The potential anti-inflammatory and antinociceptive activities of the aqueous leaf extract of this plant were evaluated in animal models. The extract (50, 100 and 200 mg/kg) significantly ($P < 0.05$) and dose - dependently inhibited carrageenan and egg albumin-induced rat paw oedema development compared with control group. At 3 h of post-carrageenan administration, the highest dose of the extract (200 mg/kg, p.o) inhibited oedema formation by 66.67%. The reference drug used, indomethacin (10 mg/kg, p.o), gave an inhibition of 72.22%. The inhibitory activity shown by the aqueous leaf extract of *H. acida* over a period of 6 h in the carrageenan and 3 h in the egg albumin-induced paw inflammation models was comparable to that exhibited by the reference drugs used, indomethacin and cyproheptadine (10 mg/kg, p.o). The extract elicited a significant analgesic activity in the tail immersion test as evidenced by the increase in latency time in seconds as compared with the control at the end of 20 min. In the acetic acid-induced writhing model, the extract showed a dose-dependent reduction in the number of writhes at 50, 100 and 200 mg/kg when compared to the control group. The 200 mg/kg dose produced a complete protective effect, as no abdominal constriction was observed. The results obtained in this study provide some justification for the folkloric uses of *H. acida* as a remedy for relieving pain and inflammation.

Key words: Anti-inflammatory activity, antinociceptive activity, carrageenan, egg-albumin, *Hymenocardia acida*.

INTRODUCTION

Inflammation is a complex multistep process comprising a dynamic cascade of biological phenomena, which can be subdivided into several stages and phases (Drozdova and Bubenchikov, 2005). Proinflammatory molecules like TNF α (tumor necrosis factor alpha), certain interleukins, prostaglandins and even pathogenic concentration of nitric oxide are instrumental in raising inflammatory response (Van der Vliet et al., 2000). Many current anti-

inflammatory drugs target these mediators at different levels, yet they lack specificity and their untoward effects restrict their long-term use (Dhikav et al., 2002). Hence, there is a constant demand for better therapeutic alternatives.

Many medicinal plants have been investigated for novel drugs or templates for the development of new therapeutic agents. *Hymenocardia acida* Tul. (*Hymenocardiaceae*), popularly known as 'Orunpa' has been used in folk medicine for many years in South-West, Nigeria and some other parts of tropical Africa. Decoction or infusion of the leaves and other parts of this plant, alone or mixed

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with other plant species are used for chest complaints, abdominal and menstrual pains and as poultices on abscesses and tumours (Burkill, 1994). The leaf is taken as snuff for headache or applied topically for rheumatic pains and toothache. Ethnobotanical survey further disclosed the folkloric uses of the leaves of the plant amongst others in inflammatory disorder, especially arthritic condition (Sofidiya et al., 2007).

The anti-inflammatory activity of the ethanolic crude extract of the stem bark of *H. acida* has previously been investigated (Sackeyfio, 1998). In the study, the ethanolic crude extract of the stem bark of this plant exhibited anti-inflammatory activity in adjuvant-induced arthritis and bovine serum albumin-induced pinnal inflammation respectively. However, there is no scientific report presently on the anti-inflammatory activity of the leaves of this plant which could possibly explain the use in some painful disorders and rheumatic diseases. Therefore, the main objective of the present study is to evaluate the anti-inflammatory and antinociceptive potential of the aqueous extract of *H. acida* leaves using *in vivo* experimental models in rats and mice.

MATERIALS AND METHODS

Plant material

The leaves of *H. acida* were collected in January 2004 at Olokemeji Forest Reserve (7.42 N 3.55 E), Ogun State, Nigeria. The plant was authenticated at the Forestry Research Institute of Nigeria, Ibadan, Nigeria, by Mr. Felix Usang. Voucher specimens (FHI 38672) were prepared and deposited at the herbaria of both the Institute and at the Pharmacognosy Department, Faculty of Pharmacy, University of Lagos.

Preparation of crude extract.

The leaves were air dried at room temperature, reduced to coarse powder, and a portion (250 g) was extracted with 2.5 L of distilled water on a shaker overnight at room temperature. The extract was filtered through whatman No.1 filter paper and the filtrate concentrated in a lyophilizer (freeze drier model B67 New Brunswick Scientific Co. Inc., New Brunswick N.J. USA). The yield of the extract was 11.4% w/w. The extract was then stored in the refrigerator for further use. Before use, a stock solution of 50 mg/ml was prepared for pharmacological experiments.

Preliminary chemical tests

Phytochemical screening of the powdered plant material was carried out to ascertain the qualitative chemical composition of the plant using commonly employed colour reactions and thin layer chromatography to identify the major constituents. The procedure was done according to the methods of Harborne (1998) and Asongalem et al. (2004).

Experimental animals

Male and female Wistar rats weighing 120 - 180 g were used to study the effect of the extract on inflammation, while albino mice

(male) weighing between 20 - 35 g were used for analgesic activity studies. The animals were obtained from the Nigerian Institute of Medical Research, Lagos, Nigeria and were kept at the Laboratory Animal Center of the College of Medicine, University of Lagos, Nigeria. They were maintained under laboratory conditions of temperature, humidity and light and were allowed free access to food (standard pellet diet, Pfizer Feeds, Plc, Lagos) and water *ad libitum*. All the animals were acclimatized to the laboratory environment for 3 weeks before the experiment. The experimental protocol was approved by the experimentation ethics committee on animal use of the College of Medicine, University of Lagos, Nigeria.

Anti-inflammatory studies

Carrageenan-induced rat paw model

Wistar rats of both sexes (120 - 180 g) were used in this study. The animals were divided into five groups of five rats each. A volume of 0.1 ml of 1% w/v carrageenan (Sigma-Aldrich Chemie GmbH, Steinheim, Denmark) in distilled water, was injected into the sub-plantar region of the right hind paw of rats (Akindele and Adeyemi, 2007). The linear paw circumference was measured immediately after carrageenan injection (0 h) and at intervals of 1, 2, 3, 4, 5 and 6 h using the cotton thread method (Bamgbose and Noamesi, 1981). Distilled water (5 ml/kg, p.o.) the aqueous extract (50, 100 and 200 mg/kg, p.o), and indomethacin (10 mg/kg, p.o) were administered orally 1 h before carrageenan injection. The mean increase in paw swelling was measured and the percentage inhibition of the inflammation was calculated from the formula:

$$\% \text{ Inhibition} = \frac{(\text{Ct} - \text{C}_0) \text{ control} - (\text{Ct} - \text{C}_0) \text{ treated}}{(\text{Ct} - \text{C}_0) \text{ control}} \times 100$$

Where Ct is the paw circumference at t time after carrageenan administration and C₀ is the paw circumference before carrageenan administration.

Egg albumin-induced rat paw oedema

Wistar rats of both sexes (120 - 180 g) were used for this assay. The rats were divided into five groups of five animals each. Rats were pretreated with the vehicle (distilled water, 5 ml/kg, p.o), the extract (50, 100 and 200 mg /kg, p.o) and cyproheptadine (10 mg/kg, p.o), 1 h before eliciting paw oedema. Acute inflammation was induced by injecting 0.1 ml of 0.1% freshly prepared solution of egg albumin into the subplantar region of the right hind paw of rats (Ojewole, 2006). The linear paw circumference was measured using the cotton thread method (Bamgbose and Noamesi, 1981) for 3 h at 30 min intervals after the administration of the phlogistic agent.

Antinociceptive activity

Acetic acid-induced abdominal writhing in mice

The writhing test was performed as described by Atta and Alkofahi (1998). Adult albino mice (22 - 32 g) were divided into five groups of five animals each. The animals were pretreated with the vehicle (distilled water 5 ml/kg, p.o), the aqueous extract of *H. acida* (50, 100 and 200 mg/kg, p.o.), and indomethacin (10 mg/kg, p.o.). This was followed by intraperitoneal injection of 1% (v/v) acetic acid (10 mg/kg) after 60 min. The mice were then placed in an observation box. 5 min after the intraperitoneal injection of acetic acid, the number of writhes during the following 20 min was counted. The

Table 1. Effect of aqueous leaf extract of *H. acida* on carrageenan-induced rat paw oedema.

Treatment	Dose (mg/kg)	0	1 h	2 h	3 h	4 h	5 h	6 h
Control		1.86 ± 0.06	1.98 ± 0.13	2.06 ± 0.10	2.22 ± 0.06	2.12 ± 0.06	2.18 ± 0.06	2.14 ± 0.04
<i>H. acida</i>	50	1.90 ± 0.03	2.00 ± 0.03 (16.67)	2.06 ± 0.02 (20.00)	2.12 ± 0.07 (38.89)	2.04 ± 0.02 (46.15)	2.00 ± 0.05 (68.75)	1.98 ± 0.02* (71.43)
	100	1.76 ± 0.02	1.84 ± 0.02 (33.33)	1.88 ± 0.04 (40.00)	1.94 ± 0.07* (50.00)	1.86 ± 0.06* (61.54)	1.84 ± 0.08* (75.00)	1.82 ± 0.07* (78.57)
	200	1.78 ± 0.07	1.86 ± 0.06 (33.33)	1.88 ± 0.02 (50.00)	1.90 ± 0.04* (66.67)	1.86 ± 0.05* (69.23)	1.84 ± 0.05* (81.25)	0.82 ± 0.04* (85.71)
Indomethacin	10	1.78 ± 0.04	1.84 ± 0.05 (50.00)	1.86 ± 0.02 (60.00)	1.88 ± 0.02* (72.22)	1.84 ± 0.05* (76.92)	1.82 ± 0.04* (87.50)	1.80 ± 0.05* (92.86)

Table showing mean increases in carrageenan-induced paw oedema (cm) with time after distilled water, *H. acida* (50, 100 and 200 mg/kg) or indomethacin administration to rats. Values are mean ± SEM (n = 5). *Significant (P < 0.05; Student's t-test) reduction in oedema formation compared with control. Values in parenthesis indicate inhibition (%).

number of writhes in each drug treated group was compared to that of the saline-treated group (control).

Tail immersion test

Distilled water (5 ml/kg, p.o), the extract at doses of 50, 100 and 200 mg/kg (p.o) and indomethacin (10 mg/kg, p.o) were administered to mice divided into groups of five animals each. 30 min post-treatment, the tail (up to one-third) was immersed in a water bath maintained at 55°C. The reaction time (in sec) was taken as the time when the animals withdrew their tails completely from the hot water in the bath (Parimaladevi et al., 2003). The response of the extract and indomethacin treated groups were compared with those of the animals in the distilled water-treated group (control).

Statistical analysis

Data obtained were expressed as mean ± standard error of mean (SEM). Student's t-test was used to compare test and control group values. Differences in the test versus control values were considered to be statistically significant at P ≤ 0.05.

RESULTS AND DISCUSSION

Anti-inflammatory

The aqueous extract of the leaves of *H. acida* was evaluated in rat paw oedema models induced by carrageenan and egg albumin. The extract produced a significant and dose-dependent inhibition of carrageenan induced inflammation (Table 1). At 3 h post-carrageenan administration, the highest dose of the extract (200 mg/kg) inhibited oedema development by 66.67%, while indomethacin (10 mg/kg, p.o), a cyclooxygenase inhibitor used in this assay as a reference, gave an inhibition of 72.22%. The extract (50, 100 and 200 mg/kg) also significantly (P < 0.05) and dose-dependently inhibited egg albumin-induced rat paw oedema compared with the control group. At 3 h, the percentage inhibition of 90% was observed with the dose 200 mg/kg of *H. acida* while cyproheptadine (10 mg/kg) produced 100% inhibition (Table 2).

As shown in Tables 1 and 2, the aqueous leaf extract of *H. acida* effectively suppressed the oedema produced by carrageenan and egg albumin in a dose-dependent manner. The carrageenan-induced rat paw oedema test has significant predictive value for anti-inflammatory agents acting by inhibiting the mediators of acute inflammation (Olajide et al., 2000). In the time course of oedematous inflammation induced by carrageenan, it has been shown that three main mediators are responsible for acute and chronic inflammatory reactions (Kasahara et al., 2002). The first phase of oedema is attributed to the release of histamine, serotonin or bradykinin by local cells. After a couple of hours, there is liberation of prostaglandins (Morris, 2003). This indicates that the extract possibly exhibits its anti-inflammatory action by inhibiting the synthesis, release or action of inflammatory mediators including histamine, serotonin and prostaglandin known to mediate acute inflammation induced by phlogistic agents, that are likely also involved in both egg albumin

Table 2. Effect of aqueous leaf extract of *H. acida* on egg albumin-induced rat paw oedema.

Treatment	Dose (mg/kg)	0	30 min	60 min	90 min	120 min	150 min	180 min
Control		1.86 ± 0.05	2.08 ± 0.06	2.12 ± 0.06	2.18 ± 0.05	2.20 ± 0.03	2.10 ± 0.05	2.06 ± 0.02
<i>H. acida</i>	50	1.92 ± 0.05	2.12 ± 0.04 (9.09)	2.12 ± 0.07 (23.08)	2.10 ± 0.04 (43.75)	2.08 ± 0.06 (52.94)	2.02 ± 0.08 (58.33)	2.00 ± 0.00 (60.00)
	100	1.92 ± 0.05	2.06 ± 0.05 (36.36)	2.06 ± 0.04 (46.15)	2.04 ± 0.05* (62.50)	2.02 ± 0.04* (70.59)	1.98 ± 0.06* (75.00)	1.96 ± 0.05* (80.00)
	200	1.86 ± 0.05	1.98 ± 0.05 (45.45)	1.98 ± 0.04 (53.85)	1.96 ± 0.05* (68.75)	1.94 ± 0.04* (76.47)	1.90 ± 0.06* (83.33)	1.88 ± 0.05* (90.00)
Cyproheptadine	10	1.90 ± 0.09	2.02 ± 0.04 (45.45)	2.00 ± 0.04 (61.54)	1.98 ± 0.02* (75.00)	1.96 ± 0.02* (82.35)	1.92 ± 0.06* (91.67)	1.90 ± 0.04* (100.00)

Table showing mean increases in egg albumin-induced paw oedema (cm) with time after distilled water, *H. acida* (50, 100 and 200 mg/kg) or cyproheptadine administration to rats. Values are mean ± SEM (n = 5). *Significant (P < 0.05; Student's t-test) reduction in oedema formation compared with control. Values in parenthesis indicate inhibition (%).

Table 3. Effect of aqueous leaf extract of *H. acida* on acetic acid-induced writhing in mice.

Group	Dose (mg/kg)	Number of writhing	Inhibition (%)
Control	-	61.75 ± 3.01	-
<i>H. acida</i>	50	39.50 ± 4.44*	36.0
	100	25.00 ± 2.61*	59.5
	200	0.00*	100
Indomethacin	10	17.50 ± 1.04*	71.7

The standard acetic acid-induced writhing in mice was employed. Acetic acid was intraperitoneally injected (1 % v/v) and extract and indomethacin were orally administered. Each value represents mean ±SEM or percentage inhibition of pain as compared to control animals, (n = 5). * P < 0.05 significantly different from control (Student's t-test).

and carrageenan induced acute oedema (Haiping, 2008).

The second phase of carrageenan-induced inflammation is also related to neutrophil infiltration and production of reactive free radical species derived from them (Dordevic et al., 2007). From our previous study *H. acida* demonstrated significant antioxidant potential *in vitro* (Sofidiya et al., 2009) indicating that the extract may also exert its anti-inflammatory effect partly through the

inhibition of neutrophil infiltration and free radical scavenging.

Antinociceptive

Oral administration of the extract and indomethacin significantly decreased the number of acetic acid-induced writhes in mice compared to the control (P < 0.05). The extract showed a dose-

dependent effect at 50, 100 and 200 mg/kg. At 200 mg/kg, there was complete protective effect, as no abdominal constriction was observed (Table 3). The acetic acid-induced abdominal constriction test is non-specific, as it does not indicate whether the activity was central and or peripheral (Chan et al., 1995; Magaji et al., 2008). However, the method is very sensitive and useful to detect the pharmacological activity of compounds in comparison with other methods like the tail-immersion test

Table 4. Effect of aqueous leaf extract of *H. acida* on tail immersion test in mice.

Group	Dose (mg/kg)	Pre-treatment	Post-treatment	Inhibition (%)
Control	-	2.80 ± 1.25	2.60 ± 1.16	-
<i>H. acida</i>	50	3.00 ± 1.34	4.00 ± 1.79	33.33
	100	4.00 ± 1.79	6.20 ± 2.77*	55.00
	200	4.00 ± 1.79	7.40 ± 3.31*	85.00
Indomethacin	10	3.20 ± 1.43	5.60 ± 2.50*	75.00

Table showing the reaction time (in seconds) of tail withdrawal from water maintained at 55 °C by mice before and after treatment with distilled water, *H. acida* (50, 100 and 200 mg/kg), or indomethacin. Values are mean ± SEM (n = 5). * P < 0.05 significantly different from control (Student's t-test).

(Bentley et al., 1981). With respect to the writhing test, the potent inhibitory effect exerted by the extract suggests that its analgesic effect may be peripherally mediated (Okpo et al., 2001). The observed analgesic effect of the extract can possibly be partly attributed to its anti-inflammatory effect. This is because in the visceral pain model, the processor releases arachidonic acid via cyclooxygenase and prostaglandin biosynthesis which plays a role in the nociceptive mechanism (Franzotti et al., 2002).

The extract also had a significant effect in the acute pain model as demonstrated in the tail immersion test. This was evidenced by increase in latency time in seconds compared with the control at the end of 20 min (Table 4). This effect of the extract indicates that it might be centrally acting, as centrally acting analgesic drugs elevate pain threshold of animals towards heat and pressure (Adeyemi et al., 2004).

Phytochemical screening

The phytochemical analyses revealed the presence of flavonoids, saponins, alkaloids, glycosides, tannins, triterpenoids and steroidal nucleus. A variety of *in vitro* and *in vivo* experiments have shown that flavonoids, tannins, triterpenoids and other secondary plant metabolites possess analgesic and anti-inflammatory properties in various experimental animal models (Yuan et al., 2006; Salminen et al., 2008; Garcí'a-Lafuente et al., 2009). An alkaloid, hymenocardine and five triterpenoid-friedelan-3-one, betulinic acid, lupeol, stigmasterol and sitosterol have been reported isolated and identified from the stem bark of this plant (Pais et al., 1968; Mpiana et al., 2009). Thus, these compounds may contribute to the observed anti-inflammatory and antinociceptive effects of *H. acida*.

Based on the results obtained in this study, it could be concluded that the aqueous leaf extract of *H. acida* demonstrated significant anti-inflammatory and antinociceptive activities, providing a scientific basis to explain, in part, the popular use of the plant in Nigerian folk medicine. It also suggests that the extract contains bioactive constituents that could be responsible for the observed activities.

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