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Antinociceptive, anti-inflammatory and antipyretic effects of ethanolic root bark extract of *Icacina senegalensis* in rodents

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ABSTRACT

To investigate the ethanolic root bark extract of *Icacina senegalensis* for antinociceptive, anti-inflammatory and antipyretic activities in rats and mice. Acetic acid-induced abdominal constriction and tail immersion tests were used to evaluate the antinociceptive activity of the extract. Egg albumin and carrageenan-induced paw oedema were used to study the anti-inflammatory activity, whereas the anti-pyretic studies were evaluated on yeast and amphetamine-induced pyrexia. The root bark extract (50, 100 and 200 mg/kg) significantly ($P<0.05$) showed inhibitory activity for all the models in the antinociceptive, anti-inflammatory and antipyretic assayed. Result shows that ethanolic root bark extract of *Icacina senegalensis* possesses phytochemicals with therapeutic potential against painful, inflammatory and feverish conditions, and thus explain the use of *Icacina senegalensis* for similar ailments in traditional medicine.

INTRODUCTION

Icacina senegalensis A. Juss (Family: Icacinaceae) is a savannah suffurex with glabrous or pubescent leafy shoots of about 2-3 feet high and a large fleshy tuber with creeping roots. The plant is indigenous to west and central Africa (Sarr *et al.*, 2011; Mbatchou and Dawada, 2012). It grows wild on light sandy soils in the savannah areas of Senegal, Gambia, Ghana, Nigeria, Guinea, Central African Republic, Congo and parts of Sudan. The leaf, stem and root are known for their therapeutic benefits due to the presence of numerous phytochemicals. The plant was reported to exhibit antimalarial activity (David-Oku *et al.,* 2014), antimicrobial (Obiajunwa-Otteh *et al.,* 2014), and antihyperglycemic actions (N'diaye *et al.*, 2008; Akuodor *et al.*, 2014). Despite its popular traditional application for the treatment of pains and feverish conditions, no scientific report of this plant on pains and feverish conditions has been verified. This study was therefore, aimed at investigating the analgesic, anti-inflammatory and anti-pyretic activities of the ethanolic root bark extract of *Icacina senegalensis* in rodents.

MATERIALS AND METHODS

Collection of the root bark

The roots of *Icacinia senegalensis* were collected from a farm land in Orlu, Imo state, Nigeria .The plant material was identified and authenticated by a taxonomist in the department of Botany, University of Calabar, Nigeria. A specimen of the plant with voucher number (620) is maintained at University of Calabar herbarium for reference.

Extraction of the root bark

The roots were properly cleaned, cut into pieces and air-dried at room temperature for 7 days. The roots were later ground to powder using mortar and pestle .Two hundred and fifty grams (250 g) of the grounded root powder was macerated in ethanol for 24 h and filtered. The filtrate was dried on a water bath at reduced temperature to recover the extract and the yield calculated to be 13.8% w/w. The root extract was subsequently reconstituted in distilled water at appropriate concentration for the experiment.

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Phytochemical screening

Phytochemical analysis of the ethanolic root bark extract was carried out adopting standard procedures to determine the following compounds; flavonoids, tannins, saponins, terpenoids, alkaloids, cardiac glycosides, steroids anthraquinones and phlobatanins (Mukherjee, 2006; Harborne, 1973).

Animals

Adult Swiss albino rats (150-180 g) of both sexes obtained from Physiology department, College of Medical Sciences, University of Calabar, Nigeria, were used for the study. The animals were housed in cages at room temperature and moisture, under naturally illuminated environment of 12:12 h dark/light cycle. They were fed on standard diet and had free access to water.

Acute toxicity study of the extract

The LD_{50} of the leaf extract was tested to determine the safety of the agent according to OECD No. 423 (2010). The study was done in two phases. First, nine rats were randomized into three groups of three per group and given 100, 600 and 1000 mg/kg of the extract orally. The animals were observed for the 4 h and 24 h for signs of toxicity and mortality. In the second phase, 2000, 3000 and 5000 mg/kg of the extract was administered to another set of three rats per group. The rats were also observed for signs of toxicity and mortality for 72 h.

Acetic acid-induced writhing test

Analgesic activity of ethanolic root bark extract of *I. senegalensis* 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 50,100 and 200 mg/kg p.o. of the root bark extract. 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 50,100 and 200 mg/kg of the ethanolic extract of *I. senegalensis* orally. 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 ± 1^{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.

Egg-albumin-induced inflammation test

Adult albino rats of both male and female fasted for 24 hrs and selected into 5 groups of 6 rats per cage were recruited for the study. Distilled water (20 ml/kg) was given to group 1. The root bark extract (50,100, and 200 mg/kg) and 150 mg/kg of acetyl salicylic acid (aspirin) were administrated to the group 2, 3, 4 and 5 respectively.

All were administered orally. One hour after, inflammation was induced in rats by injection of 0.1ml of fresh egg-albumin into the subplantar of the right hind paw (Winter *et al*, 1962; Akah and Nwabie, 1994; Agbaje, 2008). The paw volumes were measured at 0, 20, 40, 60, 80, 100 and 120 minutes respectively by using plethysmometer.

Carrageenan-induced inflammation test

Adult albino male and female rats fasted for 24 hrs and selected into 5 groups of 6 rats per cage were employed for the study. Distilled water (20 ml/kg) given to group 1. The root bark extract (50,100, and 200 mg/kg) and 150 mg/kg of acetyl salicylic acid (aspirin) were administered to group 2, 3, 4 and 5 respectively.

All were administered orally. One hour after, inflammation was induced in rats by injecting carrageenan ((0.1 ml of 1% solution in normal saline) into the subplantar of the right hind paw (Winter *et al*, 1962; Agbaje, 2008). The paw volumes were measured at 0, 20, 40, 60, 80, 100 and 120 minutes respectively by using plethysmometer.

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, the root bark extract (50, 100 and 200 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

The procedure as described by Mbagwu et al (2007) was employed with little modification. 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. 30 minutes 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). The root bark extract of *I. senegalensis* (50, 100 and 200 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 5 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

Phytochemical sreening

Phytochemical analysis of the ethanolic root bark extract of *I. senegalensis* showed the presence alkaloids, flavonoids, saponons, tannins, terpenoids steroids and cardiac glycosides as secondary metabolites. These constituents have been variously implicated in different biological activities (Panda and Kar, 2007).

Acute toxicity

The acute oral toxicity test showed normal behaviour of the treated rats. There was no mortality observed at a high dose of 5000 mg/kg. Hence the experimental doses used (50, 100 and 200 mg/kg *p.o.*) were within the safe margin.

Analgesic effect

Acetic acid-induced writhing in mice

The ethanolic root bark extract of *I. sanegalensis* dose dependently decreased acetic acid-induced abdominal constrictions in mice. The effect was significant ($P<0.05$) when compared to control. The activity of the root bark extract was comparable to that of aspirin, the standard drug (table 1).

Tail immersion test

The root bark extract of *Icacina senegalensis* significantly ($P<0.05$) protected the mice from the thermal stimuli. Morphine exerted greater protection than the root bar extract (Table 2).

Egg albumin induced oedema test

Administration of root bark extract of *Icacina senegalensis on* egg albumin induced oedema in mice caused a significant ($P<0.05$) dose-dependent anti-inflammatory activity. The effect of the standard drug, aspirin (150 mg/kg) was however higher than the extract (Table 3).

Carrageenan-induced oedema in rats

The effect of aqueous root bark extract of *Icacina senegalensis* on carragenan-induced oedema was shown in Table 4. The extract exhibited a dose-dependent anti-inflammatory effect. This effect was significant ($P<0.05$) when compared with control. However, data suggest more inhibitory activity with the standard drug, aspirin than in the root bark extract.

Yeast-induced pyrexia test

Data showed significant ($P<0.05$) anal temperature decrease for all the dose level in the different test doses of *Icacina senegalensis* root bark extract. Dose dependent was observed for all the dose levels used. Aspirin, (150 mg/kg) the standard drug showed higher activity than the root bark extract (Table 5).

Table 1: Effect of ethanolic root bark extract of *I. senegalensis* on acetic acid-induced writhing in mice.

Treatment	Dose (mg/kg)	Writhing	% Inhibition
Distilled water	20 ml/kg	20.54±1.4	-
I. senegalensis	50	7.28±0.34	64*
	100	4.16±0.24	80*
	200	3.10±0.16	85*
Aspirin	150	2.17±0.42	89*

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

Table 2: Effect of ethanolic root bark extract of *I. senegalensis* on Tail Immersion in 52±1 ^{0}C hot water (mice).

Treatment	Dose (mg/kg)	Pre-treatment		After-treatment		
		0 min	30 min	60 min	90 min	100min
Distilled water	20 ml/kg	7.65±1.40	8.0±0.45	9.36±1.51	10.33±1.60	13.33±1.22
I. senegalensis	50	7.58±0.55	9.12± 0.45	11.33±0.14	13.24±0.72*	14.67±0.08
	100	8.35±0.46	11.0±0.77	13.45±0.83	14.55±1.20*	15.83±1.05
	200	8.30±0.48	12.38±0.77	14.40±0.62	16.10±1.43*	17.00±0.62
Morphine	10	7.86±1.64	16.66±1.28	18.50±1.61	21.40±1.34*	23.50±1.09

Data are expressed as Mean ± SEM (n=6) * significantly different from control at P<0.0.

Table 3: Effect of ethanolic root bark extract of *I. senegalensis* on egg albumin- induced paw oedema in rats.

Treatment	Dose (mg/kg)	Paw oedema volume (ml) versus Time (min.)						
		0 min.	20 min.	40 min.	60 min.	80 min.	100 min.	120 min.
Distilled water	20 ml/kg	1.33±0.10	1.75±0.17	2.15±0.10	2.29±0.09	2.35±0.10	2.39±0.11	2.46±0.11
I. senegalensis	50	1.10±0.07	1.70±0.07	1.60±0.05	1.55±0.04	1.52±0.07	1.48±0.05	1.45±0.05*
	100	1.14±0.08	1.55±0.05	1.59±0.08	1.47±0.04	1.39±0.05	1.36±0.04	1.29±0.03*
	200	1.10±0.06	1.48±0.06	1.41±0.04	1.38±0.03	1.30±0.04	1.25±0.04	1.21±0.04*
Aspirin	150	1.18±0.05	1.52±0.05	1.40±0.03	1.36±0.02	1.27±0.03	1.22±0.04	1.18±0.03**

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

Table 4: Effect of ethanolic root bark extract of *I. senegalensis* on carrageenan-induced paw oedema in rats.

Treatment	Dose (mg/kg)	Paw oedema volume (ml) versus Time (min.)						
		0 min.	20 min.	40 min.	60 min.	80 min.	100 min.	120 min.
Distilled water	20 ml/kg	1.30±0.11	1.70±0.09	2.10±0.11	2.24±0.10	2.32±0.11	2.39±0.11	2.44±0.11
	50	1.15±0.05	1.65±0.04	1.61±0.04	1.55±0.04	1.47±0.07	1.44±0.05	1.41±0.05*
I.senegalensis	100	1.20±0.03	1.60±0.04	1.54±0.05	1.49±0.04	1.37±0.03	1.34±0.04	1.27±0.03*
	200	1.17±0.04	1.52±0.06	1.46±0.03	1.40±0.03	1.35±0.04	1.27±0.03	1.22±0.03*
Aspirin	150	1.22±0.05	1.55±0.04	1.42±0.03	1.38±0.02	1.30±0.03	1.24±0.04	1.20±0.03**

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

Table 5: Effect of ethanolic root bark extract of *I. senegalensis* on yeast-induced pyrexia in rats. Rectal Temperature (^oC)/ hours.

Treatment	Dose(mg/kg)	0 h	24 h	1 h	2 h	3 h	4 h	5 h
Control	20 ml/kg	36.34±0.04	37.66±0.12	37.75±0.14	37.80±0.16	37.85±0.16	37.95±0.15	37.99±0.15
I. senegalensis	50	35.12±0.20	36.75±0.14	36.58±0.16	36.45±0.13	36.22±0.16	36.06±0.21	35.98±0.20*
I. senegalensis	100	35.66±0.10	36.88±0.11	36.56±0.11	36.22±0.07	36.05±0.05	35.92±0.05	35.69±0.04*
I. senegalensis	200	35.59±0.10	36.79±0.09	36.42±0.11	36.16±0.09	35.91±0.10	35.84±0.11	35.65±0.11*
Aspirin	150	35.62±0.10	36.85±0.10	36.57±0.13	36.21±0.14	35.82±0.14	35.77±0.11	35.63±0.11*

Data are expressed as mean ± SEM (n=6) * significant at P<0.05 when compared to control.

Table 6: Effect of ethanolic root bark extract of *I. senegalensis* on amphetamin-induced pyrexia in rats. Rectal Temperature (^oC)/ hours.

Treatment	Dose(mg/kg)	0 h	0.5 h	1 h	2 h	3 h	4 h	5 h
Control	20 ml/kg	35.50±0.04	36.43±0.03	36.58±0.03	36.65±0.02	36.85±0.03	36.93±0.03	37.00±0.04
I. senegalensis	50	35.55±0.12	36.69±0.11	36.57±0.12	36.42±0.09	36.19±0.13	35.88±0.13	35.58±0.12*
I. senegalensis	100	35.51±0.04	36.77±0.04	36.62±0.05	36.35±0.10	36.15±0.08	35.74±0.06	35.54±0.04*
I. senegalensis	200	35.52±0.06	36.75±0.06	36.51±0.06	36.42±0.05	36.±170.06	35.68±0.06	35.49±0.06*
Aspirin	150	35.44±0.06	36.88±0.03	36.49±0.04	36.28±0.07	36.08±0.02	35.80±0.04	35.46±0.06*

Results are expressed as mean ± SEM (n=6)*significant at P<0.05 when compared to control.

Amphetamine-induced pyrexia test in rats

The root bark extract of *Icacina senegalensis* showed significant (P<0.05) and dose dependent decrease in pyrexia when compared to control as shown in Table 6. The effect of the extract was lower than the standard drug, aspirin (150 mg/kg).

DISCUSSION

In this study, different experimental models were used to evaluate the analgesic, anti-inflammatory and antipyretic activities of the ethanolic root extract of *I. senegalensis*. The root extract at the doses assayed was shown to exhibit analgesic activity, evident in all the models signifying it possesses both central and peripherally mediated effects. These activities were observed to be dose dependent.

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, particularly constituents of the arachidonic cascade (Nuhu *et al.*, 2007). The ethanolic root extract of *I. senegalensis* 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 the root extract. In this method, the root extract significantly exhibited reduction in the tail withdrawal latency which showed that it possesses analgesic activity. The observed effect may be through central pain pathway. The standard drug morphine which is known to act centrally, showed more activity than the extract. The root extract demonstrated effective analgesic activity mediated through peripheral and central mechanisms. This is further supported by the significant effect observed in both the acetic acid abdominal constriction and tail immersion.

The ethanolic root extract also exhibited marked inhibition in the carrageenan induced paw oedema, indicating effect on histamine, serotini, kinnins and prostaglandin which are known to be involved in both the early phase and later phase of carrageenan induced inflammation (Jothimavannan *et al.*, 2010; Vane and Booting, 1987).

The root extract actively suppressed egg albumin induced paw oedema by blocking the release of histamine and serotonin. These two mediators are released by egg albumin. Therefore, the root extract can be said to be effective in suppressing both the acute and later phases of inflammation which are mediated by kinnin, serotonin, histamine and prostaglandins. The activity exhibited by the extract suggest that it possesses active constituents with anti-inflammatory activities (Umukoro and Ashorobi, 2006).

The ethanolic root extract of *I. senegalensis* also showed remarkable antipyretic activity in both brewer's yeast and amphetamine induced pyrexia in rats.

Antipyretic drugs have been reported to inhibit prostaglandin E_2 elevation by antagonizing the effect of cyclo-oxyginase-2, hence reduce elevated body temperature (Agbaje *et al.*, 2011; David *et al.*, 2001). It was found that *I. senegalensis* root extract exhibited a reasonable suppression in the rectal pyrexia comparable to the standard drug acetylsalicylic acid (ASA). This result is of the view that the extract possesses some inhibitory activity on PG biosynthesis, shown to be involved in the regulation of body temperature. In conclusion, the ethanolic root extract of *I.*

senegalensis has exhibited significant analgesic, anti-inflammatory and antipyretic activities. These observed effects are exerted via peripheral and central activity of the extract.

Conflict of interest

The authors declare no conflict of interest.

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