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Research Article

Anti-inflammatory and analgesic effects of *Lonchocarpus cyanescens* root in mice

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Background: The root of *Lonchocarpus cyanescens* is one common remedy of the Ibibios of Akwa Ibom State**,** Nigeria for the treatment of pain and inflammatory disorders.

Objective: To study and validate the anti-inflammatory and analgesic potentials of the ethanol extract and fractions of *L. cyanescens* root in mice.

Methodology: The ethanol extract and the partitioned fractions were tested using carrageenan-induced inflammation, xylene–induced ear oedema models as well as on pains induced chemically and thermally in mice.

Results: *L. cyanescens* root extract and fractions demonstrated anti-inflammatory effects in all the models, suppressed acute oedema as well as exhibited dose and time dependent analgesic properties with butanol fraction showing the highest effects.

Discussion: Since the extract and its fractions significantly affected oedema and pain in the various models of this study, it therefore justify the use of the root traditionally in the treatment of pain and inflammatory diseases.

Keywords: Anti-inflammatory, analgesic, pain, *Lonchocarpus cyanescens*

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1. Introduction

Lonchocarpus cyanescens otherwise called indigo vine (West African wild indigo) is described as a shrub or tree with a height of about 5-7m that grows in fringe deciduous and savannah forest and occurs from Guinea to Cameroon (Hutchinson et al, 1958; Iwu, 1993). The bark is implicated in the treatment of bone pains in ivory coast (Trabifezan, 1997), diabetes by lgede people of Nigeria (Igolis et al, 2005) and the leaves and roots for treating boils and yaws by the Ibibio's of Akwa Ibom State of Nigeria (Ajibesin et al, 2008). Iwu and Anyanwu (1982) reported the anti-inflammatory and anti-arthritic uses of this shrub using the entire herb.

This study was carried out due to the use of the roots to treat inflammatory disorders by the Ibibio people of Akwa Ibom State of Nigeria to examine the anti-inflammatory and analgesic effects of *L. cyanescens* roots on oedema and nociception in mice.

2. Materials and Methods

2.1 Collection of Plant Materials

The plant material used in this study was obtained from Itak Ikot Akap in Ikono Local Government Area, Akwa Ibom State, Nigeria. It was identified by Dr. (Mrs.) Margaret Bassey of the Department of Botany and Ecological Studies, University of Uyo, Nigeria with voucher number UUH 925 and its specimen was deposited at the herbarium of the Department of Pharmacognosy and Natural Medicine, Faculty of Pharmacy, University of Uyo, Nigeria. The dried root was oven-dried at 45°c, pulverized by grinding and extracted cold with 60% ethanol for 72 hours and concentrated at 40 °C. The resultant concentrated

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ethanol extract was divided into two parts. One part was partitioned successively with n-hexane, chloroform, ethyl acetate and butanol to yield the different fractions. These fractions were concentrated and both the crude extract and fractions stored in refrigerator at -4^{o}C from where they were used for the experiments.

2.2 Phytochemical Analysis

The method of Sofowora (1993) was employed and the following bioactive constituents such as alkaloids, flavonoids, glycosides, saponins and tannins among others tested.

2.3 Animals

Adult albino mice weighing 20-30g of either sex were used in this study. The animals were housed under standard environmental conditions with free access to food (Standard mash, guinea feed) and water, except for the day of experiments. The care and the handling of the animals were in accordance with the internationally accepted standard guide for the care and use of laboratory animals (1996) and as adopted and promulgated by the National Institute of Health and the related ethics regulation of Faculty of Pharmacy, University of Uyo, Nigeria. All animals were handled with humane care.

2.4 Acute toxicity testing (LD_{50})

Acute toxicity study was done using the method of Lorke's (1983) with little modifications. Mice were randomized and divided into groups of three mice per group. The animals were starved of food 24hours prior to the experiment. The ethanol extract was administered intraperitoneally (IP) in a dose range of 100-3000mg/kg body weights.

2.5 Carrageenan-induced oedema

In this model, carrageenan was used as the phlogistic agent. Increase in the mice hind paw circumference was used as a measure of acute inflammation (Winter et al, 1962). Male and female albino mice were randomly divided into six groups of six animals in each group. Oedema of the hind paw was induced by injection of 0.1mL of freshly prepared 1% carrageenan suspension in distilled water. Animals in Group 1 received distilled water (10ml/kg, IP), groups 2-4 received 30-90 mg/kg of ethanol extract intraperitoneally, group 5 received 100mg/kg of acetyl salicylic acid (ASA) and group 6 received 60 mg/kg of extract plus ASA 100 mg/kg, intraperitoneally 30 minutes before 0.1ml of carrageenan was injected into the plantar surface of the right hindpaw. Linear circumference measurements of the injected hind paws were taken before the administration of the phlogistic agent (t=0) and at 30 minutes intervals for 5 hours after. Venier calipers were used to assess the average (mean) oedema (Nwafor and Okwuasaba, 2003). The fractions were also evaluated at the same dose level (60 mg/kg) with sodium carbonate (Na_2CO_3) as control.

2.6 Xylene-induced ear oedema

Male and female albino mice were randomly divided into six groups of six animals in each group. Two (2) drops of xylene topically applied to the inner surface portion of the right ear and allowed for 15 minutes was used to induce Inflammation (Mbagwu et al, 2007). Group 1 received distilled water (10ml/kg; ip), animals in groups 2-4 were made to receive 30-90 mg/kg of extract intraperitoneally, group 5 animals received dexamethasone and group 6 received extract (60 mg/kg) plus dexamethasone (4mg/kg, IP) 30 minutes before induction of inflammation. The animals were sacrificed using chloroform anaesthesia and their left and right ears cut off. The difference in weights indicated the degree of xylene-induced oedema (Tjolsen et al, 1992). The fractions were assessed at a dose of 60 mg/kg with sodium carbonate as control.

2.7 Acetic acid-induced writhing in mice

Administration of 3% acetic acid intraperitoneally resulted in The abdominal constrictions resulting from the intraperitoneal (IP) injection of 3% acetic acid which consisted of abdominal contractions with stretching of of hind limbs, were carried out according to the method described by Santos et al, 1994. Male and female albino mice were randomly divided into six groups of six animals in each group. Group 1 animals received distilled water (10 ml/kg, IP), animals in groups 2-4 were made to receive 30-90 mg/kg of extract intraperitoneally, group 5 animals received 100 mg/kg of acetyl salicylic acid 30 minutes prior to receiving 3% acetic acid. The reduction in the number of abdominal constrictions between control mice and those treated with extract was taken as the analgesic activity (Nwafor and Okwuasaba, 2003). This procedure was repeated for the fractions at a dose of 60 mg/kg.

2.8 Formalin-induced paw licking in mice

The procedure used was similar to that described earlier by Hunskaar and Hole (1987) and Nwafor and Okwuasaba (2003). Twenty microlitre (20 µL) of 2.5% formalin solution (0.9% formaldehyde) was made up in phosphate buffer solution (PBS concentration: NaCI, 137 mM; KCI, 2.7 mM and phosphate buffer, 10 mM) and injected into the under surface of the right hind paw subcutaneously. The time that the animals spent in licking the injected paw was taken as a measure of pain with the first phase of response at 5 minutes and second phase (15-30 minutes) after formalin injection. Thirty minutes before the challenge with buffered formalin, albino mice were randomly divided into six groups of six animals in each group. Animals in group 1 were pretreated with distilled water (10ml/kg), groups 2-4 extract (30-90 mg/kg, IP), group 5 ASA (100mg/k, IP) and groups 6 (60 mg/kg, IP) plus ASA (100 mg/kg, IP). The fractions were also evaluated at a dose of 60 mg/kg with sodium carbonate as control.

2.9 Thermally-induced pain in mice

The effect of the extract on hot plate was investigated in adult mice. The procedure was basically similar to the one earlier described by Vaz et al (1996). Adult mice were put into a glass beaker of 50cm diameter and placed on a hot plate that was kept at 45 ± 1 °C. The time(s) between being placed on the hot plate and licking the paws were recorded. Animals were grouped as earlier described above and pretreated same 30 minutes prior to being placed on the hot plate.

2.10 Statistical analysis

Results are expressed as mean ± S.E.M. The differences were then estimated using the one way ANOVA followed by the Turkey Kramar multiple comparison test. A probability level of 5% was considered significant.

2.7 Ethical approval

Permission and approval for animal studies were obtained from the College of Health Sciences Animal Ethics Committee, University of Uyo.

3. Results

3.1 Phytochemical screening

The results reveal the presence of saponin, alkaloid, flavonoids, tannins among other components as presented in **Table 1** (Supporting Information).

3.1 Acute toxicity

The extract was seen to produce signs of toxicity which included decreased motor activity, decreased respiratory rate, decreased body and limb tone with eventual death and the intensities of these effects were proportional to the doses that were administered. The LD_{50} (calculated as the geometrical mean of the minimal dose that killed all the animal (900mg/kg) and the maximal dose (100mg/kg) that killed none of the animals) was 300mg/kg and the dosages for the experiments used were $^{1}/_{10^{th}}$, $^{2}/_{10^{th}}$ and $^{3}/_{10^{th}}$ of the LD_{50}.

3.2 Carrageenan-induced oedema in mice

The extract dose dependently demonstrated a significant anti-inflammatory effect against acute inflammation. The suppression was statistically significant (P< 0.001 – 0.05) and maximal after 4 hours of pretreatment with carrageenan (**Table 2**). The percentage inhibitory effect of the fractions revealed that butanol fraction exhibited the highest activity (**Table 3** – Supporting Information).

Table 2: Antiinflammatory activity of *L. cyanescens* ethanol root extract on carrageenan-induced oedema in mice

Dose (mg/kg)	Mean diameter (cm) ±SEM at time Intervals (min)					
	0	30	60	120	240	300
Control	0.29 ± 0.01	0.38 ± 0.01	0.37 ± 0.01	0.36 ± 0.01	0.35 ± 0.0	0.35 ±0.01
30	0.28 ± 0.01	0.38 ± 0.01	0.36 ± 0.01	0.34 ± 0.01	0.31 ± 0.01[b]	0.30 ±0.01[a]
60	0.26 ± 0.01	0.38 ± 0.00	0.35 ± 0.01[c]	0.33 ± 0.01[a]	0.28 ± 0.01[b]	0.28 ±0.01[a]
90	0.26 ± 0.01	0.37 ± 0.01	0.35 ± 0.01[b]	0.32 ± 0.01[a]	0.28 ± 0.01[a]	0.27 ±0.01[a]
60 + ASA 100	0.26 ± 0.01	0.30 ± 0.01[a]	0.28 ± 0.01[b]	0.28 ± 0.01[a]	0.26 ± 0.01[b]	0.26 ±0.01[a]
ASA 100	0.26 ± 0.01	0.31 ± 0.01[a]	0.29 ± 0.00[a]	0.29 ± 0.00	0.28 ± 0.01[a]	0.25 ±0.04[a]

Significance relative to control, [a]p< 0.001, [b]p< 0.01, [c]p< 0.05,
ASA = Acetyl Salicylic Acid,
(n = 6).

Table 4: Effect of ethanol extract of *L. cyanescens* root on xylene-induced topical oedema in mice

Doses (mg/kg)	Weight difference (cm) ±SEM	% Inhibition
Control	0.025 ± 0.002	
30	0.012 ± 0.002[a]	52
60	0.017 ± 0.003	32
90	0.013 ± 0.002	48
60 + Dexa 4	0.013 ± 0.002[a]	48
Dexa 4	0.012 ± 0.003[a]	52

Significance relative to control, [a]p< 0.05,
Dexa = Dexamethasone,
n = 6

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Table 5: Effect of ethanol extract of *L. cyanescens root* on formalin–induced hind paw licking in mice

Dose Mg/kg	Number of paw lickings at time intervals (min)				
	5	15	20	25	30
Control	17.83 ± 1.74	0.83 ± 0.37	1.00 ± 0.033	0.67 ± 0.19	0.33 ± 0.19
30	16.50 ± 1.95	0.33 ± 0.30	0.50 ± 0.46	0.00 ± 0.00[a]	0.00 ± 0.00[a]
60	11.83 ± 0.86[c]	0.00 ± 0.00[b]	0.00 ± 0.00[b]	0.00 ± 0.00[a]	0.83 ± 0.37[b]
90	9.50 ± 0.39[b]	0.00 ± 0.00[a]	0.00 ± 0.00[b]	0.00 ± 0.00[a]	0.00 ± 0.00[a]
60 + ASA 100	9.50 ± 0.39[b]	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00[a]
ASA 100	8.50 ± 1.10	0.00 ± 0.00[a]	0.00 ± 0.00[a]	0.00 ± 0.00[a]	0.00 ± 0.00[a]

Significance relative to control; [a]p< 0.001, [b]p < 0.01, [c]p < 0.05
ASA = Acetyl salicylic acid
n= 6

Table 7: Effect of ethanol extract of *L. cyanescens* on thermally–induced pain in mice

Doses (mg/kg)	Reaction time (sec.) (Mean ±SEM)
Control	2.50 ± 0.24
30	5.18 ± 0.39
60	6.13 ± 0.56[b]
90	8.13 ± 1.68[a]
60 + ASA 100	10.78 ± 1.09[a]
ASA 100	11.38 ± 1.20[a]

Significance relative to control: [a]p < 0.001, [a]p < 0.001, [b]p < o.05
ASA = acetylsalicylic acid
n = 6

Table 8: Effect of ethanol extract of *L. cyanescens* root on acetic acid-induced writhing in mice

Dose (mg/kg)	Number of writhings at time intervals(min)					
	5	10	15	20	25	30
Control	0.83 ± 0.6	13.3 ± 3.26	13.0 ± 3.82	9.17 ± 1.99	5.17 ± 0.78	4.50 ± 0.91
30	0.00 ± 0.00[b]	6.33 ± 1.87[c]	12.17 ± 1.95	7.83 ± 1.36	3.88 ± 1.14	3.64 ± 0.96
60	0.00 ± 0.00[b]	1.00 ± 0.33[a]	3.83 ± 0.37[c]	3.50 ± 0.39[b]	2.00 ± 0.41[b]	1.17 ± 0.37[b]
90	0.00 ± 0.00[b]	3.17 ± 0.37[a]	1.83 ± 0.37[b]	2.50 ± 0.48[b]	0.67 ± 0.61[a]	1.00 ± 0.00[b]
60 + ASA 100	0.00 ± 0.00[b]	0.00 ± 0.00[a]	0.83 ± 0.50[a]	0.83 ± 0.33[a]	0.83 ± 0.29[a]	0.83 ± 0.44[b]
ASA 100	0.00 ± 0.00[b]	0.00 ± 0.00[a]	0.00 ± 0.47	1.17 ± 0.28[a]	0.33 ± 0.19[a]	0.33 ± 0.19

Significance relative to control, [a]p < 0.001, [b]p < 0.01, [c]p < 0.05
ASA = Acetyl salicylic acid
n= 6

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3.3 Xylene-induced topical oedema in mice ear

Pretreatment of the mice with extract showed a reduction in mice oedema following topical application of xylene. This reduction was in a dose-dependent manner (**Table 4**) and was statistically significant ($p< 0.05$).

3.4 Formalin – induced paw licking in mice

The reduction in number of paw lickings by both the extract and fractions compared with controls (distilled water for crude, Na_2CO_3 for fractions) were statistically significant ($p< 0.001$ - 0.05) as shown in **Table 5**. Butanol fraction demonstrated the highest activity (**Table 6** – Supporting Information).

3.5 Thermally induced pain in mice

The effect of extract of *L. cyanescens* root on hotplate-induced pain in mice as presented in **Table 7** showed that the extract in a dose-dependent manner increased the mice reaction time to heat. The increase in the reaction time were statistically significant ($p< 0.001$ – 0.05)

3.6 Acetic acid-induced writhing in mice

The extract and fractions reduced abdominal constructions stretching of hind limbs in a dose related manner. The reductions were significant (**Table 8** and **Table 9** – Supporting Information).

4 Discussion

The ethanol extract and fractions of *L. cyanescens* root demonstrated marked anti-inflammatory effects in the various animal models tested. The observed effects of the crude extract was dose-dependent.

The extract caused progressive reduction of the oedema of the mice hindpaw by carrageenan, and also suppressed acute oedema induced by topical administration of xylene in mice. Xylene is known to cause immediate irritation of the mouse ear, resulting in accumulation of fluid and oedema which is characteristic of acute inflammation. Suppression of this inflammatory response is an indication of anti-phlogistic effect. This model supports the existence of constituents in the extract that may be used where topical anti-inflammatory effect is needed.

The extract caused a significant ($p<0.001$ - 0.05) dose related inhibition of paw oedema, therefore showing systemic anti-inflammatory effect similar to that of acetyl salicylic acid (ASA 100mg/kg), a cyclo-oxygenase inhibitor (Singh et al, 1996). Butanol fraction demonstrated the highest anti-inflammatory effect in inhibiting paw oedema caused by carrageenan. Results of the phytochemical analysis showed that *L. cyanescens* root contains bioactive constituents such as flavonoids, tannin among others which have been implicated for anti-inflammatory potentials (Trease and Evans, 1989; Nwafor et al, 1998), hence the marked anti-inflammatory activity could have been caused by these metabolites present in the extract.

Two mechanisms account for increased vascular permeability resulting in oedema formation. One is local release or formation of various autocoids and the other which is neurogenic involves the stimulation of primary sensory neurons and subsequent release of mediators (substance P) from peripheral nerve endings of fibres (Gabbiani et al, 1970; Gamse et al, 1980; Amico Roxas et al, 1984). The non-neurogenic plasma extravasations partly depends on the neurogenic component's stimulation of peripheral neurons leading to release of substance P from peripheral sensory ending with consequent release of histamine from mast cells (Lembeck and Holzer, 1979). Therefore, the effect of the extract and fractions in opposing these mechanisms could possibly account for their anti-inflammatory properties.

The extract and its fractions also caused dose and time dependent analgesia against chemically and thermally-induced pains in mice. Acetic acid is known to produce inflammatory pain by increasing capillary permeability (Amico Roxas et al, 1984), formalin also exhibits pain of neurogenic and inflammatory origin (Vaz et al, 1996, 1997), while hot plate induces pain due to narcotic involvement (Turner, 1965; Besra et al, 1996). Since the extract and its fractions significantly affected pain in the various models of this study, it therefore suggests that its antinociceptive effect may partly be related to its anti-inflammatory, neurogenic and narcotic potentials (Nwafor and Okwuasaba, 2003). Among the fractions, butanol fraction demonstrated the highest analgesic effect by reducing the number of abdominal constrictions and stretching of hind limbs and formalin-induced paw licking.

5. Conclusion

This study has shown that the ethanol extract and fractions of *L. cyanescens* root caused anti-inflammatory and analgesic effects which may partly be related to its chemical constituents such as flavonoids, tannins, saponins etc. and these effects are comparable to that of Aspirin. However, more work is advocated to fully determine the exact mechanism(s) of action and the component(s) responsible for these anti-inflammatory and analgesic actions. The results from this work therefore support the ethnobotanical claims of *L. cyanescens* root in the management of pains and inflammatory diseases.

Conflict of Interest declaration

The authors declare no conflict of interest

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