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Analgesic and Anti-inflammatory Effects of the Leaf Extracts of *Pseudocedrella kotschyii* Harms (Meliaceae)

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Abstract: The n-butanol soluble portion of the ethanolic extract of the leaves of *Pseudocedrella kotschyii* Harms, was evaluated for anti-nociceptive and anti-inflammatory activities in mice and rats, respectively. The n-butanol portion of the ethanolic extract (50 and 100 mg kg^{-1} body weight i.p.) exhibited a significant analgesic (acetic acid-induced writhes) and anti-inflammatory (raw egg albumin and formalin induced-oedema) effects. The analgesic and anti-inflammatory effects of the n-butanol portion of the ethanolic extract was comparable to piroxicam (20 mg kg^{-1} body weight i.p.), an analgesic and non-steroidal anti-inflammatory drug. The extract had an intraperitoneal LD_{50} of 1131 mg kg^{-1} body weight in mice. Preliminary phytochemical screening of the extract revealed the presence of carbohydrates, glycosides, steroids, tannins, saponins, flavonoids and terpenoids Present results make the n-butanol portion of the ethanol extract worthy of further investigation.

Key words: Analgesic, anti-inflammatory effects, piroxicam, *Pseudocedrella kotschyii*, Meliaceae

INTRODUCTION

Pseudocedrella kotschyii Harms (Meliaceae), is a medium-sized tree of a monotypic genus, widely distributed in sub-Saharan zone of Central Africa, westerly limited in Senegal and easterly limited in Sudan and Uganda. It extends southwards to the savanna zones of southern Nigeria and Congo-Kinshasa. The plant is known locally in Nigeria as tuna or tunas in Hausa, bodel in Fulfulde and emibegbe or emigbegeri in Yoruba languages (Dalziel, 1955).

Folk remedies in different West African Countries, use it to treat numerous diseases. In Nigerian traditional medicine, the roots and the leaves are used for treating rheumatism and other diseases (Dalziel, 1955). The bark is used in Togo in infusions for gastrointestinal, febrile and rheumatic conditions and a decoction is used as wash for ulcers. A decoction of root-bark and leaves is used as a sitz bath for piles. The pulped leafy twigs are used as a medicine for stomach pains and headache (Kerharo and Bouquet, 1950).

Previous phytochemical studies (Delaveau *et al*., 1979), revealed the presence of steroids, triterpenes, saponins and tannins in the trunk wood of *P. kotschyii*. Ekong and Olagbemi (1967) have isolated a variety of limonoids from the trunk wood, including 7-deacetoxy-7-oxogedunin and

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pseudrelones A, B and C. The isolation of 24-methylenecycloartanol, cycloeucalenol, pseudrelone B and β-sitosterol from the trunk wood of *P. kotschyii* were also reported (Ekong *et al*., 1968). Taylor (1979), have also reported the isolation of pseudrelone B from the stem bark of the plant.

In recent years, secondary plant metabolites (phytochemicals) with analgesic and anti-inflammatory properties have actively been investigated as alternatives to synthetic compounds. Among these phytochemicals, Flavonoids seem to be the most potent candidates because they show broad pharmacological activities and are widely distributed in many edible plants and beverages (Havesteen, 1983).

Pharmacological evaluations of the alcoholic and aqueous extracts obtained from the various parts of this plant showed that it exhibited antimicrobial activities (Kpakote *et al*., 1998; Sote and Wilson, 1999; Tahir *et al*., 1999).

To the best of our knowledge, there are no reports in the literature on the analgesic and anti-inflammatory activities of leaves extract of this plant. The present study was carried out in an attempt to investigate the potential analgesic and anti-inflammatory effects of *P. kotschyii* employing the acetic acid-induced writhing test in mice and raw egg albumin and formalin-induced oedema tests in rats.

MATERIALS AND METHODS

Plant Material

The leaves of *Pseudocedrella kotschyii* were collected in March 2004 from Samaru-Zaria, Kaduna State, Nigeria. Mal. M. Musa and U.A. Gallah of the Herbarium Unit, Department of Biological Sciences, Ahmadu Bello University Zaria, Nigeria identified the specimen. A voucher specimen (No. 900243) was deposited in the Herbarium for further reference.

Extraction Procedure

The air-dried powdered leaves of *Pseudocedrella kotschyii* (750 g) was defatted with petroleum ether (60-80°C) and then extracted with ethanol (95%) using a soxhlet device. Solvent was removed under reduced pressure to afford 5.72 and 13.66% of residue that were coded PE and EE, respectively. 30 g of the ethanolic extract were shaken in water (400 mL) and residue insoluble matter removed by filtration. The aqueous filtrate was partition successively with ethyl acetate and n-butanol to afford an ethyl acetate soluble portion (12.98%) and n-butanol soluble portion (21.90%), which was coded as ET and BT, respectively.

The n-butanol soluble portion (BT) was screened for analgesic and anti-inflammatory activities using the methods described under the sections analgesic and anti-inflammatory activities, respectively.

Phytochemical Screening

The n-butanol soluble portion (BT) used for the pharmacological screening was tested for the presence of alkaloids, flavonoids, glycosides, tannins, saponins, steroids/or terpenoids according to the standard procedures (Sofowora, 1993; Trease and Evans, 1997).

Animals and Drugs

Swiss albino mice (20-25 g) and adult Wister rats (180-250 g) of either sex were used through out this study. The animals, kept under standard laboratory conditions were fed on standard feeds (Excel Feeds Plc, Zaria) and provided with drinking water *ad libitum*.

Piroxicam (Pfizer) was purchased from a Pharmacy retail store in Samaru-Zaria Nigeria and formaldehyde reagent (BDH Poole, UK). All drugs were freshly prepared to the desire concentration with distilled water just before use. The extract was also freshly prepared using distilled water.

Acute Toxicity Studies

The crude ethanolic extract (EE) of the leaves of *Pseudocedrella kotschyii* was subjected to acute toxicity tests (Lorke, 1983) to determine the LD_{50}.

Analgesic Activity

Acetic Acid-induced Writhing Test

Writhing activity was determined by the method of Koster *et al*. (1959). Mice were randomly divided into four groups (n = 6) and were administered 0.6% acetic acid (10 mL kg^{-1} body weight i.p.). The number of abdominal constrictions was registered over 15 min, starting 5 min after acetic acid injection. Mice were treated intraperitoneally as follows: group 1: distilled water (1 mL kg^{-1} as negative control); groups 2 and 3: BT (50 and 100 mg kg^{-1} body weight) and group 4: piroxicam (20 mg kg^{-1} body weight), 30 min before acetic acid administration, respectively. Treatment groups were compared with distilled water pre-treatment control and percent inhibition of writhes calculated as follows:

$$\text{Inhibition}(\%) = \frac{\text{Mean No. of writhes (control)} - \text{Mean No. of writhes (test)}}{\text{Mean No. of writhes (control)}} \times 100$$

(Usman *et al*., 2005)

Anti-Inflammatory Activity

Two tests were used to determine the anti-inflammatory effect of the intraperitoneally administered n-butanol soluble portion of the ethanolic extract of *Pseudocedrella kotschyii* in rats.

Raw Egg Albumin-induced Oedema Test

Acute inflammation was induced by the sub-planter administration of 0.1 mL of raw egg albumin in the left hind paw of the rats. Rats were randomly divided into four groups (n = 6) and were treated intraperitoneally as follows: Group 1; distilled water (10 mL kg^{-1} as negative control); groups 2 and 3: BT (50 and 100 mg kg^{-1} body weight) and group 4: piroxicam (20 mg kg^{-1} body weight), 30 min before administration of the raw egg albumin.

The paw volume was measured for 2 h at 20 min intervals after administration of the raw egg albumin using plethysmometre [Ugo basile LE 7150] (Winter *et al*., 1963).

Formalin Test

Acute Inflammation

Formaldehyde 2.5% was used as inflammagen. It was injected in 50 μL volumes in the sub-planter region of the left hind paw of the rats. The rats were divided into four groups (n = 6), 30 min before injection of formalin, the groups were treated intraperitoneally as follows: group 1; distilled water (10 mL kg^{-1} as negative control); group 2 and 3; BT (50 and 100 mg kg^{-1} body weight) and group 4; piroxicam (20 mg kg^{-1} body weight as positive control). Paw volume (mL) was measured at 0, 1, 2, 3, 4 and 5 h after formalin injection using plethysmometre (Ugo basile LE 7150).

Chronic Inflammation

Inflammation was induced by sub-planter injection of formaldehyde 2.5% to rats. Paw volume was measured on day 0 and then every day until the 5th day. Drug treatment was started 30 min before injection of formaldehyde and continued every 24 h (just after measurement of paw volume) until day 4.

Statistical Analysis

The results were expressed as Mean±SEM. Statistical significant differences between means were evaluated using Student's t-test and results were regarded as significant at $p<0.05$.

RESULTS

The phytochemical screening of BT of *Pseudocedrella kotschyii* used in the pharmacological tests has revealed the presence of tannins, saponins, glycosides, flavonoids and terpenoids/or steroids as major chemical constituents. Alkaloids were not detected in the extract.

The LD_{50} of the crude ethanolic extract (EE) in mice was determined to be 1131 mg kg^{-1} body weight (i.p.).

The extract at doses 50 and 100 mg kg^{-1} body weight i.p. reduced the number of abdominal constrictions by 82.42 and 83.59%, respectively. Piroxicam, as a reference drug, produced 76.62% reduction (Table 1). All the values were significant ($p<0.01$) compared with the negative control.

The results of Table 2a show that BT significantly inhibited the progressive increase in paw oedema. The anti-inflammatory effect of *P. kotschyii* was intense comparing favourably, at 100 mg kg^{-1} with that of piroxicam, a prototype of non-steroidal anti-inflammatory agent. BT showed maximum inhibition of 64.53% at dose of 100 mg kg^{-1} body weight after 100 min of drug treatment in raw egg albumin-induced oedema (Table 2b) whereas the standard drug produced 70.64% of inhibition after 20 min of drug treatment. The effect of the extract on formalin-induced acute paw oedema is shown in Table 3. BT of *P. kotschyii* significantly inhibited formalin-induced oedema in rats ($p<0.05$). BT produced the maximum inhibition of 71.09% at a dose of 100 mg kg^{-1} body weight after 2 h of drug

Table 1: The effects of BT of *P. kotschiyii* and piroxicam on acetic acid-induced writhing test in mice

Treatments	No. of abdominal constrictions	Inhibition (%)
Distilled water	21.33±3.05	–
BT 50 mg kg^{-1} body weight (i.p.)	3.75±1.49*	82.42
BT 100 mg kg^{-1} body weight (i.p.)	3.50±1.50*	83.59
Piroxicam 20 mg kg^{-1} body weight (i.p.)	4.23±1.24*	76.62

Values are mean number of withes±SEM (n = 6 per group), *$p<0.001$ significantly different from negative control

Table 2a: Inhibitory effects of BT of *P. kotschyii* and piroxicam on raw egg albumin-induced oedema in rats

	Paw volume (mL) at various times (min)					
Treatments	20	40	60	80	100	120
Distilled water	0.39±0.017	0.36±0.009	0.37±0.014	0.39±0.018	0.38±0.028	0.39±0.015
BT 50 mg kg^{-1} body weight (I.p.)	0.20±0.006[a]	0.17±0.024[b]	0.15±0.015[b]	0.20±0.025[b]	0.20±0.014[b]	0.20±0.017[b]
BT 100 mg kg^{-1} body weight (I.p.)	0.18±0.014[b]	0.14±0.008[b]	0.15±0.013[b]	0.16±0.015[b]	0.16±0.006[b]	0.18±0.008[b]
Piroxicam 20 mg kg^{-1} body weight (I.p.)	0.12±0.008[b]	0.16±0.026[b]	0.18±0.019[b]	0.20±0.007[b]	0.16±0.023[b]	0.19±0.023[b]

Values are mean number of inhibitory effect of oedema±SEM (n = 6 per group); data with different superscript in the same column are statistically significant: [a]$p<0.01$, [b]$p<0.001$ compared with the negative control

Table 2b: Percentage of oedema inhibition expressed by BT and piroxicam on albumin-induced oedema in rats

	Inhibition at various time (min) (%)						Mean inhibition
Treatments	20	40	60	80	100	120	(%)
BT 50 mg kg^{-1} body weight (I.p.)	48.95	52.55	58.38	48.51	46.26	48.10	50.46±1.79
BT 100 mg kg^{-1} body weight (I.p.)	54.89	60.92	60.17	59.99	64.53	54.05	58.43±2.04
Piroxicam 20 mg kg^{-1} body weight (I.p.)	70.64	54.42	51.13	50.22	57.71	51.06	55.86±3.17

Values are mean percentage inhibition of oedema in both extract and piroxicam treated groups (n = 6 per group)

Table 3a: The effects of single dose pre-treatment with BT and piroxicam on formalin-induced oedema in rats

	Paw volume (mL) at various time (h)				
Treatments	1	2	3	4	5
Distilled water	0.32±0.011	0.44±0.042	0.33±0.028	0.37±0.022	0.38±0.012
BT 50 mg kg^{-1} body weight (I.p.)	0.17±0.011[b]	0.22±0.031[b]	0.21±0.011[a]	0.14±0.011[b]	0.15±0.009[b]
BT 100 mg kg^{-1} body weight (I.p.)	0.17±0.008[b]	0.13±0.006[b]	0.16±0.010[b]	0.13±0.019[b]	0.15±0.010[b]
Piroxicam 20 mg kg^{-1} body weight (I.p.)	0.14±0.013[b]	0.16±0.010[b]	0.14±0.011[b]	0.14±0.012[b]	0.18±0.003[b]

Values are mean number of inhibitory effects of oedema±SEM (n = 6 per group); data with different superscript in the same column are statistically significant: [a]p<0.01, [b]p<0.001 compared with the negative control

Table 3b: Percentage of oedema inhibition expressed by BT of *P. kotschyii* and piroxicam on formalin-induced oedema in rats

	Inhibition at various time (h)					Mean inhibition
Treatments	1	2	3	4	5	(%)
BT 50 mg kg^{-1} body weight (i.p.)	44.98	49.42	36.03	62.72	60.63	50.76±4.96
BT 100 mg kg^{-1} body weight (I.p.)	46.57	71.09	52.79	63.65	59.73	58.77±4.25
Piroxicam 20 mg kg^{-1} body weight (i.p.)	54.51	63.50	57.36	63.19	64.61	60.63±1.99

Values are mean percentage inhibition of oedema in both extract and piroxicam treated groups (n = 6 per group)

Table 4: The effects of chronic administration of BT of *P. kotschyii* and piroxicam on the established rat paw inflammation induced by formalin

	Paw volume (mL) at various days				
Treatments	1	2	3	4	5
Distilled water	0.38±0.037	0.34±0.022	0.34±0.039	0.32±0.023	0.38±0.025
BT 50 mg kg^{-1} body weight (I.p.)	0.28±0.021[a]	0.18±0.016[c]	0.22±0.012[a]	0.19±0.013[b]	0.19±0.028[c]
BT 100 mg kg^{-1} body weight (I.p.)	0.17±0.014[c]	0.15±0.020[c]	0.17±0.011[b]	0.17±0.024[b]	0.14±0.011[c]
Piroxicam 20 mg kg^{-1} body weight (I.p.)	0.20±0.007[c]	0.24±0.200[b]	0.24±0.150[a]	0.16±0.021[b]	0.16±0.020[c]

Values are mean number of inhibitory effect of oedema±SEM (n = 6 per group); data with different superscript in the same column are statistically significant: [a]p<0.05, [b]p<0.01, [c]p<0.001 compared with the negative control

treatment when compared with that of the control group. The anti-inflammatory effects produced by piroxicam were similar with that of *P. kotschyii* in that action was sustained for at least duration of the studies in the two tests. Further more daily administration of the leaves extract decreased the established inflammation (Table 4).

DISCUSSION

The objectives of the present study was to study the analgesic and anti-inflammatory effects of the leaf extracts of *P. kotschyii* in order to clarify the traditional claim for the anti-rheumatic effects of the of this plant in some part of West African folk medicine.

The abdominal constriction response induced by acetic acid is a sensitive procedure to establish peripherally acting analgesics. Local peritoneal receptors are postulated to be partly involved in abdominal constriction response (Bentley *et al*., 1981). The method has been associated with prostanoids in general, example increase level of PGE_2 and $PGF_{2\alpha}$ in peritoneal fluids (Derardt *et al*., 1980) as well as lipoxygenase products by some researchers (Levini *et al*., 1984; Dhara *et al*., 2000). Inhibition of acetic acid-induced writhing in mice suggests that the analgesic effect of the extracts may be peripherally mediated via the inhibition of the synthesis and release of prostaglandins (Koster *et al*., 1959). Writhes can be described as a wave of constriction and elongation passing caudally along the abdominal wall with twisting of the trunk and extension of the hind limbs in mice. This is due to the nociceptive property of acetic acid (Surender and Mafumdar, 1995). The percentage of inhibition, clearly shown in Table 1, also indicates that the extract at 50 and 100 mg kg^{-1} produced a higher inhibition when compared to piroxicam (20 mg kg^{-1}), a known standard analgesic drug. These

effects were observed to have no significant ($p<0.01$) difference between the two test doses (Table 1). Although this test is a non-specific model, it is widely used for the evaluation of peripheral anti-nociceptive activity (Genè *et al*., 1998); so called the abdominal constriction response, it is very sensitive and able to detect anti-nociceptive effects of compounds at dose levels that may appear inactive in the other method like the tail-flick test (Bentley *et al*., 1983; Usman *et al*., 2005). Therefore, the results of the acetic acid-induced writhing strongly suggest that the mechanism of action of this extract may be linked to lipoxygenase and/or cyclo-oxygenases.

The anti-inflammatory effects of BT from *P. kotschyii* leaves were tested in two different models of oedema that is the raw egg albumin and formalin-induced oedema tests. BT produced a marked anti-inflammatory effect on both raw egg albumin and formalin-induced paw oedema, which was in the same order of magnitude as that observed after piroxicam administration.

The egg albumin-induced hind paw oedema method is useful to detect activity in acute inflammation (Akah *et al*., 1993; Akah and Nwambie, 1994; Amos *et al*., 2002). The BT caused marked inhibition of egg albumin-induced hid-paw edema in rats (Table 2). BT showed maximum inhibition of 64.53% at dose of 100 mg kg^{-1} body weight after 100 min of drug treatment in raw egg albumin-induced oedema (Table 2) whereas the standard drug produced 70.64% of inhibition after 20 min of drug treatment.

The extract also exhibited potent anti-inflammatory activities against formalin-induced oedema. Formalin-induced paw oedema is one of the most suitable test procedures to screen chronic anti-inflammatory agents, as it closely resembled human arthritis (Greenwald, 1991). BT of *P. kotschyii* significantly inhibited formalin-induced oedema in rats ($p<0.05$). BT produced the maximum inhibition of 71.09% at a dose of 100 mg kg^{-1} body weight after 2 h of drug treatment when compared with that of the control group. The nociceptive effect of formalin is biphasic; an early neurogenic component followed by a later tissue-mediated response (Wheeler and Cowan, 1991). The result suggests the usefulness of *P. kotschyii* extract in the treatment of inflammation-associated diseases like arthritis. In the test of more chronic inflammation, formalin-induced, the potency of the extract was observed. The extract show significant anti-inflammatory action in the more chronic formalin test. Daily administration of the leaves extract decreased the established inflammation (Table 4). The anti-inflammatory effects produced by piroxicam (20 mg kg^{-1} body weight) were similar with that of *P. kotschyii* in that action was sustained for at least duration of the studies in the two tests.

The co-existence of both anti-nociceptive and anti-inflammatory effects which was observed with this extract is well-defined for various non-steroidal anti-inflammatory drugs (NSAIDS) particularly salicylates and their congeners (Beuoist and Misse, 1979; Famaey, 1983). These NSAIDs exert anti-inflammatory effect principally by inhibiting the synthesis of prostaglandin (Vane, 1971) an eicosanoid mediator of the inflammatory response (Foegh and Ramwell, 2001). In addition to their involvement in the inflammatory response, prostaglandins cause pain (Roberts and Morrow, 2001) and sensitize the skin to painful stimuli (Dray, 1995) probably because they sensitize pain receptors to mechanical and chemical stimulation (Roberts and Morrow, 2001) such as the pain-producing effect of mediators (e.g., histamine, kinins etc.) which are released in tissue injury and inflammation. It is therefore interesting that the extract behaved liked NSAIDS in this study which correlates well with the traditional application of the plant.

Phytochemical analysis of the extract has revealed the presence of flavonoids, saponins, terpenoids and tannins which are known to be responsible for the anti-inflammatory and analgesic activities of some plants (Duke, 1992; Ahmadiani *et al*., 2000; Usman *et al*., 2005). Among these phytochemicals, Flavonoids seem to be the most potent candidates because they show broad pharmacological activities and are widely distributed in many edible plants and beverages (Havesteen, 1983). A variety of *in vitro* and *in vivo* experiments have shown that selected flavonoids isolated from medicinal plants have been proven to possess antiallergic, anti-inflammatory, antiviral

and antioxidant activities. Certain Flavonoids possess potent inhibitory activity against a wide array of enzymes such as protein kinase C, protein tyrosine kinases, phospholipase A2 and others (Middleton, 1998). Other Flavonoids are known to target prostaglandins, a group of powerful pro-inflammatory signaling molecule (Manthey, 2000; Rajnarayana *et al*., 2001). Studies have shown that this effect is due to flavonoid inhibition of key enzymes involved in prostaglandin biosynthesis (that is: lipoxygenase, phospholipase and cycloxygenase). Manthey *et al*. (2001) reported that flavonoids also inhibit phosphodiesterases involved in cell activation, much of whose effect is upon the biosynthesis of protein cytokines that mediate adhesion of circulating leucocytes to sites of injury. Protein kinases are another class of regulatory enzymes affected by flavonoids. Thus, the inhibition of these key enzymes provides the possible mechanism by which this extracts acts on inflammation. It is therefore, possible that both the anti-nociceptive and anti-inflammatory effects observed with this extract may be attributed to its flavonoids, saponins terpenoids and/or tannins contents. The results presented in this study should be taken as a basis for further investigation for determination of the exact mode of action of individual constituents of the extracts.

CONCLUSIONS

In conclusion, the n-butanol soluble portion of the ethanolic extracts of leaf of *Pseudocedrella kotschyii* possesses significant antinociceptive and anti-inflammatory effects in laboratory animals at the doses investigated. The results support the traditional use of this plant in the treatment of rheumatic conditions and also suggest the presence of biologically active principles, which may worth further investigation and structure elucidation. Further studies are in fact currently under way to isolate and characterize the active principle(s) of the n-butanol soluble portion of the ethanolic extract.

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