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Relative Anti-inflammatory and Analgesic Activities of the Whole Fruit, Fruit Bark, Pulp and Seed of *Lagenaria breviflora* Roberty

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ABSTRACT

Ethanol extracts of seeds, pulp, bark or whole fruit of *Lagenaria breviflora* Roberty were investigated for their individual anti-inflammatory and analgesic activities. These extracts were evaluated using formalin-induced paw lick in Wistar rats, acetic acid-induced writhing, hot plate and tail flick tests in mice. Each experiment consisted of thirty animals randomly, but equally divided into six groups of 100, 200, 400 or 800 mg kg^{-1} b.wt. of extract pre-treated, indomethacin (10 mg kg^{-1} b.wt.) pre-treated and a control group administered with distilled water (10 mL kg^{-1} b.wt.). Values were expressed as Mean±Standard Error of Mean (SEM). The data were analyzed using one way ANOVA and difference of means were considered significant at $p<0.05$. The different extracts showed varying degrees of same pattern of anti-inflammatory or analgesic effect on the rats or mice. Itching of the paws persisted significantly longer in control or indomethacin treated-rats than in seed, pulp, bark or whole fruit extract treated-rats for both phases of formalin-induced paw licks. All the extracts effectively reduced abdominal writhing but not as effective as indomethacin. The extract treated rats tolerated thermal induced pain longer than the control or indomethacin treated rats, with very significant difference for the bark and the whole fruit groups. All the fruit parts exhibited significant anti-inflammatory and analgesic activities. The bark extract was the most potent extract of the three component parts of the fruit, followed by the pulp and then seed extracts. The bark exhibited the strongest bioactivity and invariably may contain the largest concentration of the bioactive anti-inflammatory/analgesic compound(s) in the fruit of *Lagenaria breviflora*.

Key words: Anti-inflammatory, analgesic, seed, pulp, bark, *Lagenaria breviflora*

INTRODUCTION

Plants in the family Cucurbitaceae have been reported for their anti-inflammatory, analgesic, antioxidant or anti-proliferative activities (Bowman *et al*., 2000; Smit *et al*., 2000; Tannin-Spitz *et al*., 2007; Haritunians *et al*., 2008; Wakimoto *et al*., 2008; Bernard and Olayinka, 2010). *Cayaponia tayuya, Cucurbita andreana, Picrorhiza scrophulariiflora* and *Wilbrandia ebracteata* of Cucurbitaceae family were investigated (Peters *et al*., 1999; Smit *et al*., 2000; Jayaprakasam *et al*., 2003) and were reported to contain the anti-inflammatory/analgesic compound called cucurbitacins. Cucurbitacins are a group of diverse highly oxygenated triterpenoid molecules isolated from plant members of this family. Cucurbitacins of

different types have been identified as the bioactive compounds and overwhelming evidences validate their biological activities in these plants (Vouldoukis *et al*., 2004; Semiz and Sen, 2007; Kumar *et al*., 2008; Gill *et al*., 2009, 2010; Marzouk *et al*., 2010; Bernard and Olayinka, 2010).

Lagenaria breviflora Roberty belongs to the family Cucurbitaceae (Morimoto *et al*., 2005; Schaefer *et al*., 2009). The whole fruit of *L. breviflora* which is used for medicinal purposes has three distinct parts viz bark, pulp and seeds (Elujoba *et al*., 1985, 1991). The fruit has been reported to have several biological activities, including anti-implantation (Elujoba *et al*., 1985), miracicidal and cercaricidal (Ajayi *et al*., 2002), antibacterial activities with low toxicity (Saba *et al*., 2009a, b). Studies also showed that the ethanol extract of whole fruit of the plant exhibited potent anti-inflammatory, analgesic, anti-oxidant or anti-ulcerogenic activities and were comparable to diclofenac, indomethacin and ibuprofen (Onasanwo *et al*., 2010, 2011).

The current study seeks to explore the individual anti-inflammatory or analgesic potential of the seeds, pulp or bark of the fruit of *L. breviflora* which was achieved by testing the various extracts using the models of inflammation and analgesia studied.

MATERIALS AND METHODS

Plant materials: Fresh fruits of *Lagenaria breviflora* Roberty were obtained from the Teaching and Research Farm of University of Ibadan and identified at the Department of Botany and Microbiology, University of Ibadan, Nigeria. Fresh fruits were washed, cut into small pieces and weighed out in small portions for the whole fruit extraction. The seeds, pulp and bark of the fruit were separated and the different parts were soaked in ethanol (96%) in labelled plastic containers. The ethanolic solution was drained regularly and replaced with fresh ethanol every 3 days. Each batch of harvested solvent were stored in plastic containers and refrigerated at 4°C. The extract obtained was clarified by filtration through celite on water pump and was then concentrated *in vacuo* using a rotation evaporator (Rotavapor R-210, Switzerland) at low temperatures. The remaining moisture was finally removed by placing small volumes in porcelain dishes in the oven set at low temperatures of 40°C.

Experimental animals: Male Wistar rats (150 -180 g) were used for the anti-inflammatory study, while Swiss mice (20-30 g) of both sexes were used for the analgesic study. The experimental animals were housed in 12 h light: dark condition and maintained on standard rat diet and mouse cube, respectively. Water was provided *ad libitum*.

Thirty rats were randomly and equally divided into six groups of five for each experiment: four groups were administered with extract concentration of 100, 200, 400 and 800 mg kg^{-1} b. wt., the fifth group was administered with 10 mg kg^{-1} b.wt. of indomethacin as the reference drug while the sixth group was administered with distilled water (10 mL kg^{-1} b.wt.). Thirty mice were also randomly and equally divided into six groups of five for each experiment and administered with the extract or indomethacin as described above. Extracts prepared from the seeds, pulp, bark or the whole fruit were evaluated separately using the same anti-inflammatory and analgesic models. The experimental animal use and ethical committee approved the research protocols adopted.

Anti-inflammatory study

Formalin-induced paw licking test in rats: Twenty microliter of 2.5% formalin was injected into the plantar surface of the left hind-paw of the rat (Tjolsen *et al*., 1992). Sixty minutes after treatment with fruit extract (100, 200, 400 and 800 mg kg^{-1}, p.o.) or indomethacin

(10 mg kg^{-1} b.wt.) or distilled water (10 mL kg^{-1} b.wt.). The amount of time spent licking the injected paw was indicative of pain. The numbers of lickings within 0-5 min (first phase) and 20-30 min (second phase) were counted after injection of formalin. The initial, acute nociceptive response within 0-5 min after injection of formalin indicated the first phase while within 20-30 min indicated the second's chronic second (chronic) phase. These phases represented neurogenic and inflammatory pain responses, respectively.

Analgesic study

Acetic acid-induced abdominal writhing test in mice: The mice were injected intraperitoneally with 0.1 mL 10 g b.wt. of 30.6% acetic acid solution 1 h after treatment with fruit extract (100, 200, 400 and 800 mg kg^{-1}, p.o.) or indomethacin (10 mg kg^{-1} b.wt.) or distilled water (10 mL kg^{-1} b.wt.) to induce the characteristic writhing. The number of writhing was observed between 5-15 min.

Hot plate test in mice: Pain reflexes in response to a thermal stimulus as described by Sood *et al.* (2009) were measured using a hot plate apparatus (Ugo Basile, Italy). The control group of mice received normal saline distilled water (10 mL kg^{-1}, p.o.). The test group mice were treated with fruit extract (100, 200, 400 and 800 mg kg^{-1}, p.o.) or indomethacin (10 mg kg^{-1} b.wt.). Mice were habituated to the apparatus for 1 min before the start of the test. They were placed on the hot plate of 25.4×25.4 cm at 55±1.0°C which is surrounded by an opened-top acrylic cage (19 cm tall), with the start/stop button on the timer. A 10 sec cut-off time was used to prevent tissue damage. The latency measures were taken both before and 60 min after drug/extract administration as the time elapsed between placing the mice on the hot plate and forepaw licking, hind paw flicking or jumping. The mouse was immediately removed from the hot plate and returned to its home cage.

Tail flick test: This experiment was conducted according to the modified method adopted by Sanchez-Mateo *et al.* (2006) using hot water bath. Groups of five mice each were administered with the extract (100, 200, 400 and 800 mg kg^{-1} b.wt.), 10 mg kg^{-1} b.wt. indomethacin or distilled water, respectively as earlier mentioned. Thereafter, the terminal 2 cm of the mice tail were immersed a water bath containing hot water maintained at 55±1°C by a circutine (Haake-Vison, Germany). Responses of the mice were taken at 30, 60 and 90 min after treatment.

Statistical analysis: Data were analysed using one way Analysis of Variance (ANOVA) on GraphPad Prism 4.0 version. The result obtained were expressed as Mean±SEM. The statistical significant difference between the mean values were determined at $p<0.05$.

RESULTS

Anti-inflammatory or analgesic effect of ethanolic seed extract of *L. breviflora*: The seed extract of *L. breviflora* caused dose dependent, significant inhibition of the formalin-induced inflammatory response in both early and late phases. Inflammatory inhibition was significantly higher in extract treated rats compared to those administered with indomethacin, except for the rats administered with 200 mg kg^{-1} b.wt. (Table 1). The mean numbers of abdominal writhes were lower in rats administered seed extract compared to the rats in the control group but higher than the number of writhes in rats administered with indomethacin (Table 2). Reaction to thermal pain

Table 1: The effect of ethanolic extract of seed, pulp, bark or whole fruit of *L. breviflora* or indomethacin on response (sec) to pain in formalin paw lick test in rats

Treatments (mg kg^{-1})	Early phase (0-5 min)	Late phase (20-30 min)
S100	60.62±1.43^{a}	12.24±0.99^{ab}
S200	48.14±5.55^{a}	16.92±1.86^{a}
S400	47.96±1.90^{a}	13.44±1.18^{ab}
S800	42.66±3.08^{ab}	10.64±1.60^{ab}
P100	36.36±2.77^{ab}	10.82±1.84^{ab}
P200	37.72±2.23^{ab}	12.46±1.90^{a}
P400	38.90±2.65^{ab}	15.58±1.84^{a}
P800	35.96±2.17^{ab}	14.78±1.67^{a}
B100	60.48±8.35^{a}	8.86±2.50^{ab}
B200	48.84±2.27^{a}	10.72±0.94^{ab}
B400	48.00±3.74^{a}	15.54±4.69^{a}
B800	41.18±3.18^{ab}	12.66±1.68^{ab}
W100	59.80±21.21^{a}	19.55±2.85^{a}
W200	53.28±4.45^{ab}	18.33±3.87^{a}
W400	39.00±6.15^{ab}	9.62±0.70^{ab}
W800	18.30±2.76^{ab}	8.50±2.40^{ab}
Indomethacin (10 mg kg^{-1})	61.80±1.64^{b}	22.88±0.89^{b}
Control	109.66±8.41^{ac}	73.10±6.88^{a}

Values with same letters within column are statistically significant at $p \leq 0.05$

Table 2: The effect of ethanolic extract of seed, pulp, bark or whole fruit of *L. breviflora* or indomethacin on abdominal writhing in mice injected with acetic acid intraperitoneally

Group				Total No. of writhes
Control				48.00±3.81^{a}
Indomethacin (10 mg kg^{-1})				19.80±5.11^{b}
	Plant extracts (mg kg^{-1})			
	100	200	400	800
Seed	36.80±2.40^{b}	29.00±3.56^{a}	28.40±3.76^{a}	43.20±2.15^{b}
Pulp	32.60±3.98^{a}	27.00±2.83^{a}	25.60±2.71^{a}	21.00±4.01^{a}
Bark	23.80±7.92^{a}	27.20±2.25^{a}	25.60±6.38^{a}	20.00±6.43^{a}
Whole fruit	27.60±1.94^{a}	26.60±1.21^{b}	11.80±2.56^{a}	8.40±1.03^{ab}

Values with same letters within column are statistically significant at $p \leq 0.05$

in the hot plate test was non-significantly ($p>0.05$) longer at 0 min post-treatment in all the rats administered with the seed extract compared to those in the control group or indomethacin treated group. At 30 or 60 min post-treatment, the response was non-significantly longer compared with the control, but shorter compared with indomethacin group. The same pattern was observed for reaction to thermal pain in the tail flick test but the differences were not significant (Table 4).

Anti-inflammatory or analgesic effect of ethanolic pulp extract of *L. breviflora*: The frequency of licking of paws was significantly higher in the control rats for both phases of formalin test. Licking of paws was less frequent in extract treated than in indomethacin treated rats (Table 1). The extract dose dependently reduced the number of writhes and the difference was significant compared with the control group. The numbers of writhes in indomethacin group were non-significantly lower than for extract treated rats (Table 2). Reaction time to thermal pain was significantly longer in extract treated rats than the control rats but shorter than for indomethacin

Table 3: Effect of ethanolic extract of seed, pulp, bark or whole fruit of *L. breviflora* or Indomethacin on reaction (sec) to thermal pain induced in hot plate method in mice

Treatment (mg kg^{-1})	0 min	30 min	60 min
S100	5.26±0.32	6.76±1.15	6.86±0.35
S200	4.70±0.61	6.32±0.63	7.60±0.48
S400	4.98±0.41	7.02±0.51	7.02±0.87
S800	5.40±0.50	6.82±1.37	7.68±0.53
P100	7.43±0.80^{ab}	11.46±0.56^{ab}	11.48±0.80^{a}
P200	8.56±0.22^{ab}	11.30±0.56^{ab}	11.42±0.85^{a}
P400	7.08±0.45^{b}	12.22±0.92^{ab}	15.90±1.05^{ab}
P800	7.22±0.89^{ab}	10.56±0.98^{a}	10.78±1.11^{a}
B100	9.44±0.45^{ab}	12.56±1.15^{ab}	10.76±1.48^{a}
B200	8.76±0.83^{ab}	13.86±0.46^{ab}	10.04±0.25^{a}
B400	9.74±1.54^{ab}	12.28±0.85^{ab}	12.80±0.73^{ab}
B800	8.38±0.52^{ab}	14.50±1.16^{ab}	9.32±0.92^{a}
W100	9.52±1.03^{ab}	12.66±1.14^{ab}	13.50±1.23^{ab}
W200	8.08±0.69^{ab}	13.04±0.99^{ab}	12.10±0.83^{a}
W400	9.08±0.66^{ab}	10.90±1.14^{ab}	12.14±1.74^{a}
W800	9.10±0.61^{ab}	11.38±0.51^{ab}	10.46±0.99^{a}
Indomethacin (10 mg kg^{-1})	4.06±0.62^{b}	7.02±0.86^{b}	8.36±1.02^{b}
Control	4.20±0.68^{a}	4.32±0.76^{a}	4.62±0.51^{a}

Values with same letters within column are statistically significant at $p \leq 0.05$

Table 4: Effect of ethanolic extract of seed, pulp, bark or whole fruit of *L. breviflora* or indomethacin on response (sec) to thermal pain induced by tail flick method in mice

Treatment (mg kg^{-1})	30 min	60 min	90 min
S100	3.44±0.39	2.72±0.27	2.02±0.30
S200	2.66±0.18	2.68±0.34	2.18±0.26
S400	2.80±0.30	3.58±0.73	3.56±0.62
S800	7.08±1.59	2.90±0.66	3.16±0.77
P100	2.94±0.25	3.40±0.65	4.02±0.49
P200	3.10±0.23	4.10±0.44	5.12±1.01
P400	3.32±0.16	4.52±0.63	3.76±0.47
P800	2.89±0.25	4.90±0.57	3.36±0.17
B100	4.64±0.53	4.26±0.87	4.04±1.12
B200	7.84±5.80	3.30±0.64	3.30±0.44
B400	4.94±0.38	3.78±0.32^{a}	3.80±0.42
B800	6.54±1.13	5.64±1.22	5.68±1.72
W100	2.94±0.40	7.16±1.58^{a}	7.76±2.11^{ab}
W200	2.40±0.24	3.66±0.60	3.04±0.11
W400	2.72±0.24	5.28±1.27^{a}	4.20±0.78
W800	4.22±0.61	5.58±2.32^{a}	5.42±1.99
Indomethacin (10 mg kg^{-1})	2.86±0.26	3.24±0.81	3.22±0.48^{b}
Control	2.58±0.46	1.33±0.11^{a}	1.38±0.09^{a}

Values with same letters within column are statistically significant at $p \leq 0.05$

treated rats (Table 3). The extract also non-significantly prolonged the reaction period of rats to thermal pain compared to the control or indomethacin group (Table 4).

Anti-inflammatory or analgesic effect of ethanolic bark extract of *L. breviflora*: The frequency of licking of paws was lower in bark extract treated rats than in the control or indomethacin treated rats. Differences were significant in both phases for the control rats but only in the late phase for indomethacin treated rats (Table 1). The extract reduced the number of writhes and the difference was significant compared with the control group. The numbers of writhes in indomethacin group were non-significantly lower than for extract treated rats (Table 2). Bark extract treated rats tolerated thermal-induced pain significantly longer than the control or indomethacin treated rats at 0, 30 or 60 min post administration (Table 3). The extract prolonged the reaction of rats to thermal pain non-significantly longer than for the control or indomethacin treated rats (Table 4).

Anti-inflammatory or analgesic effect of ethanolic whole fruit extract of *L. breviflora*: Itching persisted significantly longer in the control or Indomethacin treated rats than in whole fruit extract treated rats for both phases of formalin-induced paw licks (Table 1). The extract reduced the number of writhes and the difference were significant compared with the control group. The numbers of writhes in indomethacin group were non-significantly lower than for extract treated rats (Table 2). Extract treated rats tolerated thermal-induced pain significantly longer than control or indomethacin treated rats at 0, 30 or 60 min post administration (Table 3). The extract prolonged the reaction of rats to thermal pain in tail flick test longer than for the control and indomethacin treated rats at 30 or 60 minutes post administration. The differences are only significant at 30 min post administration for control rats (Table 4).

Comparative potency study: The extract from the whole fruit was ranked first in the two analgesic models and second and third in the anti-inflammatory models with an aggregate score of 7. Next to the whole fruit is the bark which was ranked first in a model and second in three models, with an aggregate of 7. The pulp extract was next in line being ranked first in hot plate model, 3rd in formalin paw lick, 4th in writhing and tail flick test, with an aggregate of 12. The seed and Indomethacin were ranked at par with an aggregate of 16.

DISCUSSION

Findings from this study re-established the fact that the fruit of *L. breviflora* Roberty possesses potent anti-inflammatory or analgesic activities. Further facts emerging from this study is that extracts from each component part of the fruit; the seed, pulp or bark independently exhibit potent but varying degrees of anti-inflammatory or analgesic activities. Using bio-activity guided anti-inflammatory and analgesic models; there is enough evidence to suggest that the anti-inflammatory/analgesic activities of the whole fruit of *L. breviflora* are not restricted to a single section of the fruit. In this study, itching of the paws persisted significantly longer in the control or Indomethacin treated rats than in seed, pulp, bark or whole fruit extract treated rats for both phases of formalin-induced paw licks. Formalin paw lick test in rats is used to assess antinociceptive property and explain the possible mechanism of anti-inflammatory action. The neurogenic (early) phase is observed due to direct stimulation of nociceptors in the paw which culminates in centrally mediated pain with release of substance P, while the late phase is due to the release of histamine, serotonin, bradykinin and prostaglandins (Narendhirakannan *et al*., 2007; Zeashana *et al*., 2009; Alam *et al*., 2011; Shah *et al*., 2011). Drugs that act primarily on the central nervous system, such as opioids, inhibit both phases equally while peripherally acting drugs such as Non-Steroidal Anti-

Table 5: Ranking of the anti-inflammatory/analgesic potencies of the seed, pulp, bark or whole fruit extract of *L. breviflora*

	Formalin paw lick			Acetic acid test			Hot plate test (sec)			Tail flick test (sec)			Aggregate sum of the
	No. of licks	%	Score	No. of writhes	%	Score	Time taken	%	Score	Time taken	%	Score	scores
Seed	10.64±1.60	47	3rd	28.40±3.76	100	5th	7.68±0.53	37	5th	7.08±1.59	90	3rd	16
Pulp	10.82±1.84	47	3rd	21.00±4.01	74	4th	15.90±1.05	100	1st	5.12±1.01	65	4th	12
Bark	8.86±2.50	39	2nd	20.00±6.43	70	2nd	14.50±1.16	91	2nd	7.84±5.80	100	1st	7
Whole fruit	8.50±2.40	37	1st	8.40±1.03	30	1st	13.04±0.99	82	3rd	7.76±2.11	99	2nd	7
Indomethacin	22.88±0.89	100	5th	19.80±5.11	53	4th	8.36±1.02	53	4th	3.24±0.81	41	5th	16

The lower the aggregate score the higher the ranking

Inflammatory Drugs (NSAIDs) and steroidal anti-inflammatory drugs only inhibit the late phase (Garcia *et al*., 2004; Zeashana *et al*., 2009; Danquah *et al*., 2011). Abdominal writhing response establishes peripheral analgesic effect which might involve local peritoneal receptors (Chakraborty *et al*., 2004; Udegbunam *et al*., 2011; Ullah *et al*., 2012). The seed, pulp, bark or whole fruit extract effectively reduced writhing movement but were not as effective as Indomethacin in this study. The hot plate and tail flick tests employ thermal induced pain to assess antinociception. The hot plate test is effective in determining centrally acting analgesics by their ability to increase the time of response (Garcia *et al*., 2004; Uhegbu *et al*., 2012) while the tail flick test measures the response to a brief, noxious stimulus which appears to be a spinal reflex, modulated by supraspinal inhibitory mechanism. The test is selective for centrally acting analgesics (Ramabadran *et al*., 1989; Rasool *et al*., 2008; Gill *et al*., 2011) indicative of morphine like effect (Domer, 1990; Sabina and Rasool, 2007; Hossain *et al*., 2011) and also like NSAIDs which inhibit cycloxygenase in peripheral tissues, thereby interfering with the mechanism of transduction in primary afferent nociceptors (Fields, 1987; Rasool *et al*., 2008). In this study, the seed, pulp, bark or the whole fruit treated rats tolerated thermal induced pain longer than the control or Indomethacin treated rats and the difference was very significant for the bark and the whole fruit groups. This confirms that the mechanism of anti-inflammation and analgesia of these extracts are similarly mediated centrally and peripherally. Judging from the result in Table 5, the various fruit parts show a degree of anti-inflammatory/analgesic activity. However, the bark extract comes as the most potent extract of the three component parts of the fruit, followed by the pulp and then the seed extracts. The aggregate score of the bark is actually the same with that of the whole fruit, showing that even though other extracts contribute to the anti-inflammatory or analgesic activity of the whole fruit, the bark exhibited the strongest bioactivity and invariably may contain the largest concentration of the bioactive anti-inflammatory/analgesic compound in the fruit of *L. breviflora*. It is therefore safe to speculate at this stage that the bioactive compound(s) are common to the different parts of the fruit because of the similarities in their effects on the test models employed in this study. This assertion will be further confirmed when the ongoing effort to isolate and characterize the bioactive compound(s) is completed.

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