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In Rodents, Methanol Extract from *Ritchiea capparoides* leaf has Analgesic, Anti-Inflammatory, and Antipyretic Properties

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OO and AGC conducted the research. Author ICE carried out the analysis. Authors AGC and OCC drafted and prepared the manuscript. Author AOJ reviewed and approved the final version of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background*:* *Ritchiea capparoides* leaves are traditionally used in Southern Nigeria to cure fever, snake bites, aches, and malaria. Consequently, the analgesic, anti-inflammatory, and antipyretic properties of Ritchiea capparoides leaf ethanol extract were assessed in rodents in this work.

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Methods: Using acetic acid and tail immersion models in mice, the analgesic effect was investigated, and xylene, egg-albumen, brewer's yeast, and dinitrophenol models were used to investigate the anti-inflammatory and antipyretic properties in mice and rats at doses of 125 mg/kg, 250 mg/kg, and 500 mg/kg of the methanol extract. The plant's leaf extract was also subjected to oral acute toxicity testing and phytochemical screening.
Results: At $_p$<0.05 and $_p$<0.01, the methanol leaf extract and the common medication (aspirin) considerably reduced the amount of writhes brought on by acetic acid. The reaction times of the tested agent's standard and extract groups significantly increased. The extract significantly reduced oedema in the egg-albumin-induced paw oedema model, with dose-related inhibition of p<0.05 and p<0.01, similar to aspirin. When compared to dexamethasone, *Ritchiea capparoides* leaf extract likewise showed a significant p<0.05 and p<0.01 effect in the xylene-induced mouse ear oedema test. Rats with pyrexia caused by dinitrophenol and Brewer's yeast both showed a statistically significant decrease in rectal temperatures. Alkaloids, saponins, tannins, flavonoids, terpenoids, steroids, and cardiac glycosides are all present in the methanol leaf extract. It was discovered that the oral acute toxicity testing were more than 5000 mg/kg.
Conclusion: The findings supported the traditional use of *R. capparoides* as a medicine by demonstrating the plant's possible analgesic, anti-inflammatory, and antipyretic properties at the tested concentrations of methanol leaf extract.

Keywords: Ritchiea capparoides; leaf extract; antipyretic; analgesic; and anti-inflammatory.

1. INTRODUCTION

Herbs have demonstrated great effectiveness in immunological stimulation against a wide range of pathologic situations as well as in the prevention and treatment of disease [1]. Man was entirely dependent on medicinal plants to treat a variety of ailments before to the invention of synthetic medications [1]. Traditional healers in Nigeria frequently and extensively utilize chemicals that have been extracted from a variety of these plants [2]. Numerous plant products' constituents have demonstrated pharmacological and biological properties, including antiviral, antiplasmodial, anti-inflammatory, antipyretic, and antidiabetic actions [3]. It is therefore a good idea to look for new painkillers that have analgesic, anti-inflammatory, and antipyretic properties [4].

The evergreen climber *Ritchiea capparoides*, belonging to the Capridaceae family, can maintain itself as a shrub on its own and has compound palmate leaves. Since the plant can withstand dry seasons, leaves can be harvested all year round. The roots have a strong, pungent odor and are tuberous in nature. This herb is native to the tropics, as are other members of the capparidaceae family. It is primarily found in the lowland areas of rain forests, particularly next to bodies of water and virgin uplands. It can reach a height of a few meters as a shrub and can grow up to five meters in length as a climber, with several branches. Nearly all of Africa's tropical regions, especially those in West Africa, are home to the plant [5]. "Aka-ato or Nti-ato" is how they refer to it in Igboland [5]. In mice, the leaf extract demonstrated antinociceptive properties [6]. *R. capparoides* root extract is utilized as an antihelmintic ethnomedicinally [7]. Decoctions of the leaves and root are commonly used in the South-Western region of Nigeria to treat plasmodial and microbiological diseases [8,9]. It has also been claimed to have antifungal properties [10]. Preparations made from *R capparoides* leaves have been used to treat Guinea worms, swellings, wounds, ocular conditions, and conjunctivitis [11].

2. METHODS

2.1 Plant Collection

Ritchiea capparoides fresh leaves were gathered from Mazi Obasi Agwu's compound in Ugoni Okposi-Okwu, Ohaozara LGA, Ebonyi State. A taxonomist from the University of Benin's Ugwowo Campus in Benin City, Dr. E.I. Aigbokhan, identified and verified this plant. For future use, the voucher number UBH-R443 was placed in the Department's Herbarium.

2.2 Extraction of the Leaf

The gathered leaves were reduced in size using a mill and pestle after being air-dried for fourteen days at room temperature. For a full day, the 592 g of powdered plant leaf was immersed in 1.8 L

of methanol. A clean muslin sieve was used to strain the mixture into a conical flask.On a water bath set at a lower temperature of 40 ^{o}C, the filtrate was dried. Before the experiment, the extract yield was kept cold in a refrigerator.

2.3 Experimental Animals

Wistar rats and mice of both sexes, weighing 20–25 g and 150–180 g, respectively, were obtained from the University of Nigeria, Nsukka's department of veterinary medicine. The animals had unrestricted access to water and ordinary diet. Six of them were housed in hygienic, individual cages with bedding made of sawdust that was changed every two days. The study was carried out in accordance with Nnamdi Azikiwe University Research Policy and the ethical guidelines for the use and care of laboratory animals in the faculty of basic clinical sciences.

2.4 Phytochemical Screening

Simple chemical tests were used to perform phytochemical screening of the extract in order to determine whether secondary ingredients were present or absent, as described in the literature [12].

2.5 Acute Toxicity Test

The extract's acute toxicity (LD50) was calculated using the Lorke [13] technique. The mice utilized in this investigation were fed nothing but extract for the whole night prior to the experiment. Phase 1 involved giving the extract orally to three groups of three mice per cage at escalating doses of 10 mg/kg, 100 mg/kg, and 1000 mg/kg, respectively. For the first four hours and twenty-four hours, the treated mice were observed for indicators of toxicity and mortality. Phase 2 began when there was no death after 24 hours. The extract was administered orally to one mouse per group in four groups at doses of 1600 mg/kg, 2900 mg/kg, 5000 mg/kg, and 10 mL/kg distilled water. After then, the animals were watched for indicators of late toxicity and mortality for 24, 48, and 72 hours, respectively.

2.6 Analgesic Activity

2.6.1 Acetic acid induced writhing in mice

The analgesic effect of the methanol leaf extract was evaluated by means of the acetic acid-induced writhing method, as detailed by Essien et al. [14]. Both sex albino mice weighing 20–25 g were randomly assigned to 5 distinct cages containing 6 animals per. Group 1 (drug-free) received 10 mL/kg of normal saline, whereas groups 2-4 received 125 mg/kg, 250 mg/kg, and 500 mg/kg of the extract, respectively. The positive control was given acetyl salicylic acid (ASA) at a dose of 150 mg/kg. Each mouse received an intraperitoneal injection of 10 ml/kg of 0.7% acetic acid after thirty minutes. They were each given their own clear cage to be observed. For thirty minutes, the writhing motions of every mouse were recorded.

2.6.2 Tail immersion test in mice

For this investigation, the methodology outlined by Akuodor et al. [15] was employed. Thirty mature albino mice of both sexes were chosen at random, placed in five groups of six mice each, and kept free access to water for twenty-four hours. Groups 2, 3, and 4 were given oral doses of 125, 250, and 500 mg/kg of *R. capparoides*, respectively, while groups 1 and 5 got subcutaneous injections of 10 mg/kg of morphine and 10 mL/kg of distilled water, respectively. The tail was left hanging and fully exposed to be dunked in a water bath that was kept at 51±1°C thermostatistically (Grieve Cooperation, Illinois, U.S.A.). The length of time the tail spends in the heated before the animal removed its tail from the water, it was observed in a water bath. We measured the latency at 30, 60, 90, and 120 minutes.

2.7 Anti-inflammatory Activity

2.7.1 Egg-albumin-induced inflammation

For this investigation, the methodology outlined by Essien et al. [16] was employed. After being chosen at random, thirty mature Wistar rats of both sexes were divided into five groups, with six rats per cage. Group 2 received 150 mg/kg of aspirin orally, while Group 1 received 10 mL/kg of distilled water. *R. capparoides* was given orally to groups 3, 4, and 5, at doses of 125 mg/kg, 250 mg/kg, and 500 mg/kg, respectively. The initial size of each rat's right hind paw was measured and noted following a 30-minute treatment. Next, 0.2 mL of fresh egg albumin was subcutaneously injected into the right hind paw's sub-plantar region to cause inflammation in the rats. After that, the plethysmometer was used to measure the oedema volume every 30 minutes for 120 minutes.

2.7.2 Xylene induced ear oedema method

For the investigation, this approach as outlined by Akuodor et al. [17] was used. Five groups were utilized. Each group containing six individuals. The leaf extract was given to the animals orally at three different doses: 125 mg/kg, 250 mg/kg, and 500 mg/kg. The positive control group received 4 mg/kg of dexamethasone treatment, while the negative control group received 10 mL/kg of distilled water. Each mouse received one drop of xylene on the inner surface of the right ear to cause oedema one hour after treatment. Mice were slaughtered, weighed, and their bodies chopped off to identical size after three hours. One measure of inflammation was the mean difference between the left and right ears.

2.8 Antipyretic Activity

2.8.1 Brewer yeast induced pyrexia in rat

Ohanme et al.'s [18] Brewer yeast induced pyrexia method was used to assess the antipyretic efficacy. Twenty mL/kg of a 20% aqueous suspension of Brewer yeast in distilled water was given subcutaneously 24 hours before to therapy in order to cause hyperthermia. Five groups of thirty Wistar rats each were created. Groups 3, 4, and 5 received 125 mg/kg, 250 mg/kg, and 500 mg/kg of the extract, respectively, while groups 1 and 2 served as positive and negative controls (distilled water 10 mL/kg and ASA 150 mg/kg). Every medication was taken orally. A digital thermometer (Mediklin, China) was used to take rectal temperatures prior to the yeast injection, 24 hours after the injection, and 1, 2, 3, 4, and 5 hours after the medication was administered.

2.8.2 D-amphetamine induced pyrexia test

Using the D-amphetamine-induced pyrexia technique, the antipyretic properties of the secondary metabolites of the methanol leaf extract of *R. capparoides* were screened [19]. The animals (wistar rats) of both sexes were made to fast for a whole day. The chosen rats' starting body temperatures were noted. In each cage, there were six rats in each group. To produce pyrexia, 5 mg/kg of D-amphetamine was administered intraperitoneally to each of them. A day later, the animals' body temperatures were recorded as rising, and any rat that had a temperature below 0.6ºC was avoided. Groups 1 and 2 had positive controls (ASA 150 mg/kg) and negative controls (10 mL/kg distilled water), respectively. In contrast, *R. capparoides* methanol leaf extract was given orally to groups 3, 4, and 5, at doses of 125 mg/kg, 250 mg/kg, and 500 mg/kg, respectively.

2.9 Statistical Analysis

Results are shown as mean ± standard error of mean (SEM) and are subjected to one-way analysis of variance (ANOVA) and Dunnett's post hoc test analysis using the statistical software for social sciences (SPSS version 20). A difference in the mean that was statistically significant was defined as $p < 0.05$.

3. RESULTS

3.1 Phytochemical Analysis

Ritchiea capparoides leaf extract prepared with methanol underwent phytochemical screening, which identified the presence of alkaloids, cardiac glycosides, saponins, tannins, flavonoids, terpenoids, steroids, and balsam.

3.2 Acute Toxicity Studies

Seventy-two hours following the methanol leaf extract administration, no observable alterations, mortality, or toxicological indicators were noted. During the course of the investigation, every animal remained robust and energetic. As a result, it was discovered that the median lethal dose (LD50) was more than 5000 mg/kg.

3.3 Effect of Methanol Leaf Extract of *R. capparoides* on Acetic Acid Induced Writhing in Mice

The number of mice that writhed in response to acetic acid was significantly and dose-dependently reduced by *R. capparoides* leaf extract at $p < 0.05$ and $p < 0.01$, respectively. Compared to 125 mg/kg and 250 mg/kg, the extract's effects were greater at 500 mg/kg. This effect was similar to the prescription drug's (Table 1).

3.4 Effect of Methanol Leaf Extract of *R. capparoides* on Tail Immersion Test in Mice

The mice's response to thermal stimuli was dramatically lowered by the *R. capparoides* methanol leaf extract ($p < 0.05$ and $p < 0.01$). The

extract in this test demonstrated a dose-dependent decrease. But the conventional medication, morphine, provided better protection (Table 2).

3.5 Effect of Methanol Leaf Extract of *R. capparoides* on Egg-Albumen Induced Paw Oedema in Rats

It was shown that the methanol leaf extract of *R. capparoides* has dose-dependent anti-inflammatory effects. The extract at 125 mg/kg and 250 mg/kg showed considerable activity ($p < 0.05$), whereas the maximum dose (500 mg/kg) showed significant activity ($p < 0.01$). In this investigation, the reference medication (ASA) shows greater activity (Table 3). Five hours after the medication was administered, the anti-inflammatory effect started.

3.6 Effect of Methanol Leaf Extract of *R. capparoides* on xylene Induced Ear Oedema in Mice

Table 4 illustrates the anti-inflammatory action of R. capparoides methanol leaf extract against mice's xylene-induced ear oedema. At ($p < 0.01$), the extract significantly and dose-dependently reduced oedema; the highest dose of the extract was equivalent to the conventional medication, dexamethasone.

3.7 Effect of Methanol Leaf Extract of *R. capparoides* on Brewer Yeast Induced Pyrexia in Rats

Research on antipyretics Rats with Brewer's yeast-induced pyrexia were used to measure the antipyretic effect of the methanol leaf extract of *R. capparoides*, as shown in Table 5. The conventional medicine demonstrated considerable antipyretic efficacy at $p < 0.01$, while the extract demonstrated significant and dose-dependent antipyretic action at $p < 0.01$.

3.8 Effect of the Extract on Dinitrophenol – Induced Pyrexia in Rats

Table 6 displays the outcomes of the use of *R. capparoides* methanol leaf extract against D-amphetamine-induced pyrexia. The methanol extract-treated rats showed a dose-dependent, gradual ($p < 0.05$) decrease in body temperature. The extract had a lower impact than acetylsalicylic acid (ASA), the conventional medication.

Table 1. Effect of methanol leaf extract of *R. capparoides* on acetic acid-induced writhing in mice

Treatment	Dose (mg/kg)	Mean no of writhes	% Inhibition
Distilled water	20 mL/kg	103.67±3.87	-
R. capparoides	125	30.83±2.71	70[a]
R. capparoides	250	13.33±1.82	87[b]
R. capparoides	500	5.83±3.80	94[b]
R. capparoides	150	3.50±1.91	97[b]

Outcomes are mean ± SEM; n = 6; [a]p < 0.05; [bp] < 0.01 in relation to the control group

Table 2. Effect of methanol leaf extract of *R. capparoides* on tail immersion in mice time interval Time (min)

		Pre-treatment	After-treatment			
Treatment	**Dose mg/kg**	**0**	**30**	**60**	**90**	**120**
Distilled water	20mL/kg	10.17±0.45	10.00 ± 0.58	10.67±0.33	10.55±0.22	10.50±0.20
R. capparoides	125	6.50±0.43	8.50±0.50	10.83±0.83	11.67±0.71	13.17±0.60[a]
R. capparoides	250	7.50±0.76	9.33±0.76	11.83±0.70	13.50±0.56	16.80±0.68[b]
R. capparoides	500	8.00±0.52	10.17±0.79	12.50±0.88	14.67±0.56	17.50±0.34[b]
Morphine	10	7.50±0.62	17.50±0.72	19.17±0.60	21.17±0.87	23.33±0.95[b]

The findings are expressed as mean ± SEM; n = 6; [a]p < 0.05; [b]p < 0.01 in relation to the control.

Table 3. Effect of methanol leaf extract of *R. capparoides* on xylene-induced ear oedema in mice

Treatment	Dose (mg/kg)	Weight of right ear	Weigh of left ear	Increase in weight	% Inhibition
Distilled water	20 mL/kg	0.042±0.01	0.021±0.03	0.021±0.00	-
R. capparoides	125	0.036±0.05	0.019±0.02	0.017±0.00	55[a]
R. capparoides	250	0.030±0.04	0.017±0.03	0.017±0.00	60[b]
R. capparoides	500.	029±0.04	0.016±0.03	0.013±0.00	69[a]
Dexamethasone	4	0.022±0.03	0.012±0.03	0.010±0.00	76[b]

Outcomes are mean ± SEM; n = 6; [a]p < 0.05; [b]p < 0.01 in relation to the control group

Table 4. The effect of ethanol leaf extract of *R. capparoides*on on Egg-albumin-induced paws oedema in rats

Drug	Dose (mg/kg)	0	20	40	60	80	100	120
Distilled water	20 mL/kg	1.24±0.02	1.64±0.01	1.72±0.02	1.79±0.02	1.86±0.02	1.93±0.02	2.05±0.02
R. capparoideson	125	1.22±0.04	1.60±0.02	1.53±0.03	1.46±0.02	1.38±0.03	1.31±0.02	1.20±0.03[a]
R. capparoideson	250	1.24±0.02	1.63±0.01	1.56±0.02	1.48±0.02	1.30±0.02	1.24±0.02	1.16±0.02[b]
R. capparoideson	500	1.19±0.02	1.57±0.03	1.49±0.03	1.38±0.02	1.30±0.02	1.21±0.03	1.15±0.03[b]
Aspirin	150	1.17±0.04	1.61±0.02	1.49±0.02	1.39±0.03	1.30±0.03	1.22±0.03	1.12±0.03[b]

The results are mean ±SEM; compared to the control, (n = 6) [a]p < 0.05 and [b]p < 0.01

Table 5. Effect of methanol leaf extract of *R. capparoides* against yeast induced pyrexia in rats

		Yeast induction (h)		Drug administration (h)				
Treatment	**Dos (mg/kg)**	**0**	**24**	**1**	**2**	**3**	**4**	**5**
Distilled water	20 mL/kg	35.37±0.05	37.52±0.04	37.80±0.02	37.63±0.02	37.42±0.02	37.29±0.02	37.30±0.03
R. capparoides	125	35.26±0.03	37.25±0.03	36.41±0.01	36.20±0.02	35.62±0.03	35.37±0.03	35.24±0.02[a]
R. capparoides	250	35.25±0.02	37.27±0.02	36.50±0.03	36.22±0.01	35.61±0.02	35.36±0.03	35.22±0.03[a]
R. capparoides	500	35.23±0.02	37.30±0.02	36.47±0.02	36.15±0.01	35.55±0.03	35.30±0.02	35.10±0.03[a]
Aspirin	150	35.22±0.00	36.79±0.02	35.69±0.04	35.43±0.02	35.40±0.01	34.60±0.02	34.30±0.03[b]

The findings, relative to the control, are mean ± SEM; (N=6) [a]p < 0.05; [b]p < 0.01

Table 6. Effect of methanol leaf extract of *R. capparoides* on de-amphetamine induced pyrexia in rats (hours)

		D-amphetamine induction (h)		Drug administration (h)				
Treatment	**Dose (mg/kg)**	**0**	**24**	**1**	**2**	**3**	**4**	**5**
Distilled water	20 mL/kg	35.25±0.04	37.39±0.04	37.61±0.04	37.67±0.02	37.46±0.05	37.26±0.03	37.70±0.03
R. capparoides	125	35.27±0.04	37.29±0.02	36.43±0.03	36.23±0.03	35.51±0.02	35.30±0.02	35.25±0.02[a]
R. capparoides	250	35.20±0.03	37.30±0.02	36.40±0.02	36.23±0.02	35.52±0.02	35.31±0.02	35.23±0.03[a]
R. capparoides	500	35.24±0.02	37.30±0.02	36.33±0.02	36.20±0.03	35.48±0.02	35.26±0.02	35.21±0.01[a]
Aspirin	150	35.25±0.03	37.31±0.02	36.39±0.03	36.22±0.03	35.49±0.01	35.31±0.01	34.17±0.01[b]

The mean ± SEM results show that, as compared to the control, (N=6) [a]$p < 0.05$ and [b]$p < 0.01$

4. DISCUSSION

Based on claims of usage in herbal medicine, this study was conducted to determine the possible pharmacological characteristics of *R. capparoides* methanol extract. The results of this investigation show that *R. capparoides* demonstrated analgesic efficacy against chemically generated pains (writhing) at the levels used [20]. A different study found that testing the peripheral analgesic impact of herbal remedies can be done quickly and reliably using mice's reactions to acetic acid [14]. In the current study, acetic acid-induced writhing was prevented by *R. capparoides* and acetylsalicylic acid (aspirin) extracts. According to the extract's peripheral analgesic characteristics, local peritoneal receptor blockage may be the mechanism of action [21]. Nevertheless, the results confirm the plant's value as an analgesic in Nigeria, regardless of whether this model assesses peripheral pain reducing effect exclusively or not. It has been found that acetic acid injections cause the release of prostaglandins and other cyclokinase, which are known pain mediators [22]. This result implies that the extracts may have worked by preventing cycloxygenase from converting arachidonic acids into prostaglandins [22]. The analgesic properties exhibited by *R. capparoides* support their use as analgesics in traditional medical practice, as well as in the local Nigerian population.

Moreover, the analgesic efficacy of this leaf extract was verified using a centrally acting model of analgesia (tail immersion). Spinal reflex is thought to be involved in this assay technique, which is utilized to show whether the central analgesic mechanism is involved [23,15]. It has been noted that whereas peripherally acting drugs, such acetylsalicylic acid, have only been shown to have analgesic effect in the writhing test, centrally acting drugs, like morphine, have this activity in both kinds of studies [24]. Above all, it should be noted that acetylsalicylic acid's effects on the writhing assay are limited to its ability to either directly or indirectly block prostaglandin activity by stopping cyclo-oxygenase activity [25]. The central analgesic mechanism is implicated in the crucial action of the tail immersion test.

The induction of paw oedema by egg albumin has been shown to be a useful method for evaluating anti-inflammatory drugs and is frequently employed to assess the anti-oedematous properties of natural products [26]. This method of determining the potency of acute inflammation is extremely sensitive [27]. Bradykinin and polymorphonuclear leucocytes with proinflammatory factors such prostaglandins are necessary for the development of oedema [28]. *R. capparoides* leaf extract might not have demonstrated effect on the early stages of inflammation; as a result, it might work by preventing prostaglandin release. Aspirin and other nonsteroidal anti-inflammatory drugs may not prevent the first phase of edema brought on by egg albumin, but they may counteract the drug's effects on the second, faster phase [29].

In mice, xylene irritates the ear, causing fluid to build up and oedema as well as an increase in the enzyme myeloperoxidase activity. Suppression of this reaction could be an indication of antiphlogistic behavior [15]. In mice, the methanol extract of *R. capparoides* leaf significantly reduced the amount of ear oedema [30]. This activity suggests the suppression of phospholipase A2 which has been involved in the pathophysiology of inflammation resulting from xylene [31]. On the other hand, the reference medication, dexamethasone, significantly reduced the ear weight of the positive control rats, indicating that PLA2 was inhibited.

Antipyretic agents have been shown to antagonize cyclooxygenase activity through increase in prostaglandin E2 by suppressing high temperature [31]. Increase in temperature may result from damaged tissue, infections, and other factors. This process usually give rise to mediators (interleukins and others), which progresses to prostaglandin E2 formation with increase body temperature [32]. The extract under study reduced rats' anal temperature whose effect was similar to that observed in aspirin. The methanol leaf extract of *R. capparoides* was able to bring fever to a control by getting rid of inflammatory symptoms at both peripheral and nervous system thermoregulator zones. This could bring down pyrogenic secreting cytokines while reducing prostaglandin E2 synthesis from cyclooxygenase possibly through the mechanism reputed for paracetamol [33].

The therapeutic potentials of medicinal plants are mostly attributed to the combination of their secondary metabolites. Flavonoids have been reported to target prostaglandins involved in late

phase of acute inflammation and pain and they have therefore been associated with analgesic, anti-inflammatory and antipyretic activities [34, 35]. Therefore, it is not surprising to have seen these activities in *R. capparoides* leaf extract. There was no lethality observed during the LD50 test which proves the relative safety of the herbal agent.

5. CONCLUSION

The current study's findings support the plant's traditional applications for treating various illnesses by demonstrating the analgesic, anti-inflammatory, and antipyretic properties of the methanolic leaf extract of *R. capparoides.*

CONSENT

It is not applicable.

ETHICAL APPROVAL

The Nnamdi Azikiwe University, Nnewi Campus Ethics Committee, the U.S. National Institutes of Health's Publication number 85, amended in 1996, and the Faculty of Basic Clinical Sciences' guidelines were followed when conducting the experiments.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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