Anti-Inflammatory Activity of Whole Plant Extracts of selected Kenyan *Ruellia* Species

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Abstract

Ruellia species (Fam. Acanthaceae) is a perennial creeper with many reported biological activities. Studies on extracts of *Ruellia* species revealed *in vivo* analgesic activity in mice. The objective of this study was to determine the anti-inflammatory activity of aqueous and methanolic whole plant extracts of selected Kenyan *Ruellia* species (viz. *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata*) in Wistar albino rats. Anti-inflammatory activity of species was evaluated by determining the percentage inhibition of carrageenan-induced rat paw swelling. The aqueous and methanolic *Ruellia* extracts (250, 500, 1000 and 1500mg/kg) and positive controls (diclofenac sodium 20mg/kg and ibuprofen 200mg/kg) were administered orally prior to carrageenan injection. Determination of swelling was done every hour for six hours following carrageenan injection using a digital water plethysmometer. Both aqueous and methanolic *Ruellia* extracts exhibited dose-dependent anti-inflammatory activity. The aqueous extract of *R. prostrata* was the most potent. The highest percentage inhibition of swelling was exhibited at the 6-hour point by 1500mg/kg of the aqueous extract of R. prostrata (79.12%), followed by *R. bignoniiflora* (70.83%) and *R. lineari-bracteolata* (68.82%). At the same time point, diclofenac sodium (20mg/kg) and ibuprofen (200mg/kg) displayed percentage inhibition in swelling of 67.87% and 60.53%, respectively. Aqueous extracts were consistently more potent than the corresponding methanolic extracts. All test groups showed significantly increased activity ($p \leq 0.05$) compared to the negative (untreated) control. The aqueous extracts of whole plant parts of Kenyan *Ruellia* species possess significant anti-inflammatory activity, and there is need to investigate these species further for the management of inflammatory conditions such as rheumatoid arthritis. This study also reported anti-inflammatory activity of *R. bignoniiflora* and *R. lineari-bracteolata* for the first time.

Keywords: *Ruellia, R. prostrata, R. bignoniiflora, R. lineari-bracteolata, anti-inflammatory, carrageenan.*

Introduction

Ruellia (Fam. Acanthaceae), is a genus of flowering plants commonly known as *Ruellias* or wild petunias. Acanthaceae Family contains about 300 genera and 2500 species. They are distributed in Indonesia and Malaysia, Africa, Brazil, Central America, and Pakistan, with only a few species distributed in temperate regions [1, 2].

Some of these species have medicinal and ornamental value. Many species of the genus have reported antinociceptive, analgesic, antioxidant, antiulcer, antidiabetic, antispasmodic, anti-inflammatory properties. The genus has been traditionally used for the treatment of joint disorders of varied aetiology [3]; painful conditions, high blood pressure, eczema, flu, bronchitis, asthma, fever, ulcer, and diabetes [2, 4].

Several studies have reported on the anti-inflammatory activities of other *Ruellia* species such as *R. prostrata* [5], *R. tuberosa* [6] and *R. patula* [7]. Aqueous and methanolic extracts of *R. prostrata*, have shown antioxidant activity [8]; [9]. *R. bignoniiflora* and *R. lineari-bracteolata* aqueous and methanolic extracts showed antioxidant activity [10]. These findings reveal a possible trend between *Ruellia* species and anti-inflammatory activity.

Previous studies revealed the analgesic and antinociceptive activities of the aqueous and methanolic extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* [11]. Since these Kenyan *Ruellia* species displayed high analgesic activity in both acute pain and progressive pain models, the current study aimed to investigate these Kenyan *Ruellia* species for *in vivo* anti-inflammatory activity using Wistar albino rats.

Methodology

Study sites

Plant materials were collected from their natural habitats i.e., *R. prostrata* (Muthetheni and Kavoo areas) in Machakos

County, *R. bignoniiflora* (Kibwezi) in Makueni County, and *R. lineari-bracteolata* (Isiolo) in Isiolo County. Animal experiments were carried out from the Small Animal Facility for Research and Innovation animal house in Jomo Kenyatta University of Agriculture and Technology.

Sample collection, preparation and extraction

Upon identification by a plant taxonomist, the species were collected from their natural habitats and Voucher specimens, (UoN/ 2010/598 of 16/12/2010 for *R. prostrata*; UoN/2013/811 of 15/3/2013 for *R. bignoniiflora*, and UoN/2015/003 of 3/7/2015 for *R. lineari-bracteolata*) were deposited at the University of Nairobi Herbarium.

The plant materials were dried under a shade for 2-3 months, and ground into a fine powder using an electric grinder. Organic extraction was done by cold maceration for 6 hours using absolute methanol, whereas aqueous extraction was done using hot maceration also for 6 hours. The organic extracts were concentrated *in vacuo* using a rotary evaporator (BUCHI R-200, Labortechnik Switzerland), whereas aqueous extracts were obtained by freeze drying (Alpha 1-4 LD, Christ, Germany). The extracts were stored in refrigerator at 4°C until required.

Laboratory Animals

Wistar albino rats of either sex (6-8 weeks old) of weight 150–250g were used for the study. All animals were purchased from the Small Animal Facility for Research and Innovation (SAFARI) located in JKUAT. Standard laboratory conditions of ambient temperature 22°C±3°C, humidity 50-60% and artificial lighting of a 12-hour light and 12-hour dark cycle was maintained. Conventional laboratory diets were used, and an unlimited supply of drinking water was provided. Approval for the use of laboratory animals was sought from Animal Care and Use Committee (ACUC) of the Kenya Medical Research Institute (KEMRI).

Evaluation of the anti-inflammatory activity

Anti-inflammatory activity of the extracts of the various *Ruellia* species was evaluated by determining their ability to inhibit the swelling of the rat hind paw induced by injection of the inflammatory agent carrageenan [12]. Rats were randomly assigned into groups of 6 animals each. The two positive control groups received either diclofenac sodium 20mg/kg or ibuprofen 200mg/kg. The treatment groups were treated with one of the plant extracts at a dose of either 250mg/kg, 500mg/kg, 1000mg/kg or 1500mg/kg. One group of rats remained untreated (negative control). The extracts were administered by the oral route 1 hour before carrageenan injection, whereas the positive control groups were treated orally 30 minutes before carrageenan injection.

Following injection of 0.1mL of λ-carrageenan (1% w/v in normal saline) into the sub plantar region of the left rat hind paw, the extent of the induced swelling was determined by volume displacement using a digital water plethysmometer (LE 7500, Panlab Harvard Apparatus, Spain). Paw volume measurements were taken every hour for 6 hours.

Data analysis

The data was analyzed using Minitab Statistical Software Version 18.0 (Pennsylvania State University). Average paw volumes were calculated at each time point for each group of rats and expressed as mean ± standard error of the mean (SEM). The percentage inhibition of rat paw swelling was then calculated at each time point for each treatment group relative to the untreated (negative control) group. One-way Analysis of Variance (ANOVA) was used to analyze for significant differences in percentage inhibition of rat paw swelling between the different treatment groups. Significant differences in percentage inhibition between the different treatment groups identified by one-way ANOVA were further explored using the Tukey's *post hoc* multiple comparison test. A value of $p \leq 0.05$ was considered significant.

Results

The findings for the percentage inhibition of swelling in the rat hind paw by the aqueous extracts R. prostrata, R. bignoniiflora and R. lineari-bracteolata are presented in Table 1.

Table 1. Percentage inhibition of swelling in the rat hind paw by the aqueous extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata*.

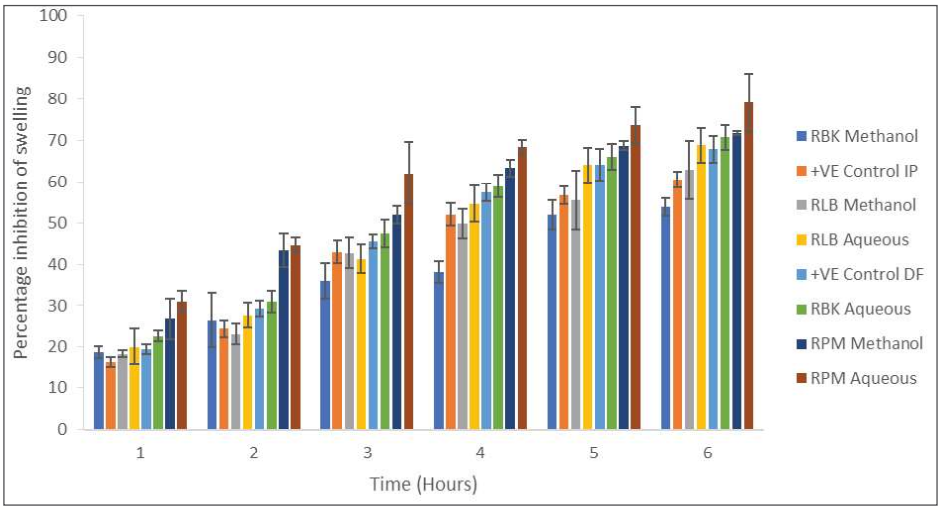
Dose (mg/kg)	Type of extract	Time in hours					
		1	2	3	4	5	6
		Percentage inhibition of rat hind paw swelling (n=6)					
	Untreated Control	0.00±0.00^{d}	0.0±0.00^{b}	0.00±0.00^{c}	0.00±0.00^{c}	0.00±0.00^{b}	0.00±0.00^{b}
	IP	16.31±1.36^{c}	24.42±2.10^{b}	43.00±2.73^{a}	52.00±2.72^{a}	56.82±2.18^{a,b}	60.53±1.84^{a}
	DF	19.46±1.21^{b,c}	29.19±1.92^{a,b}	145.51±1.62^{a}	57.38±2.16^{a}	64.07±3.82^{a,b}	67.87±3.27^{a}
250	RPM	21.83±4.22^{a,b,c}	29.24±3.93^{a,b}	37.32±7.38^{a}	43.28±7.29^{b}	45.2±10.7^{b}	54.20±8.26^{b}
	RBK	14.77±3.15^{a}	18.38±4.81^{a}	29.55±5.45^{a}	37.28±5.74^{b}	43.31±8.89^{b}	46.55±3.48^{b}
	RLB	13.37±2.41^{b}	19.14±2.79^{a}	27.99±2.70^{a}	37.76±4.39^{a}	45.71±3.42^{a}	47.71±5.14^{a}
500	RPM	24.05±2.72^{a,b,c}	35.65±6.85^{a,b}	47.57±5.67^{a}	58.58±4.25^{a,b}	64.51±5.39^{a,b}	67.73±1.69^{a}
	RBK	19.15±1.24^{a}	25.96±1.53^{a}	39.14±2.15^{a}	43.18±2.97^{a,b}	49.41±6.55^{a,b}	57.63±5.19^{a,b}
	RLB	17.97±1.46^{b}	21.64±5.09^{a}	35.90±5.48^{a}	44.45±5.11^{a}	51.95±7.80^{a}	53.85±3.46^{a}
1000	RPM	27.96±1.55^{a,b}	38.42±3.06^{a,b}	57.66±7.19^{a}	65.57±3.54^{a,b}	68.23±5.74^{a,b}	66.89±4.48^{a}
	RBK	20.22±1.18^{a}	28.22±1.64^{a}	42.45±1.43^{a}	51.78±1.96^{a,b}	62.13±2.27^{a,b}	67.61±1.87^{a}
	RLB	18.61±4.63^{b}	25.26±2.39^{a}	38.58±1.92^{a}	50.03±2.08^{a}	57.02±2.51^{a}	63.53±1.96^{a}
1500	RPM	31.05±2.53^{a}	44.60±1.76^{a}	62.08±7.51^{a}	68.52±1.70^{a}	73.71±4.30^{a}	79.12±7.11^{a}
	RBK	22.64±0.99^{a}	31.02±2.63^{a}	47.36±3.39^{a}	59.00±2.71^{a}	66.01±3.17^{a}	70.83±2.99a
	RLB	20.07±4.45^{b}	27.63±2.96^{a}	41.32±3.39^{a}	54.65±4.47^{a}	64.04±4.24^{a}	68.82±4.08a

Key: IP-Ibuprofen 200mg/kg; DF-Diclofenac sodium (20mg/kg) standard; RPM-*Ruellia prostrata*; RBK-*R. bignoniiflora*; RLB-*R. lineari-bracteolata* Values are expressed as Mean ±SEM. Values with the same superscript down the column are not significantly different ($p>0.05$).

The percentage inhibition in rat hind paw swelling by *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* aqueous extracts was dose-dependent. All test groups showed significant inhibition of rat hind paw swelling compared to the untreated control. The highest percentage inhibition of swelling was exhibited by aqueous extract of *R. prostrata* (79.12%), followed by *R. bignoniiflora* (70.83%) and *R. lineari-bracteolata* (68.82%) at the 6-hour point and doses of 1500mg/kg. This percentage inhibition of the *Ruellia* extracts was higher than the 67.87% inhibition observed for diclofenac sodium at 20mg/kg and the 60.53% inhibition observed for ibuprofen at 200mg/kg at the same time point. There was no significant difference in percentage inhibition of swelling in the rat hind paw ($p>0.05$) between *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* at doses of 1000mg/kg and 1500mg/kg.

Comparable findings were observed for the methanolic extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* (Table 2). The highest percentage inhibition of swelling exhibited by the methanolic extracts were *R. prostrata* (71.87%) followed by *R. lineari-bracteolata* (68.82%) and R. bignoniiflora (53.33%) at the 6-hour point and doses of 1500mg/kg.

However, the methanolic extracts of the three Ruellia species consistently displayed lower percentage inhibition of swelling than their corresponding aqueous extracts. A comparison of the effects of 1500mg/kg doses of the aqueous and methanolic extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* on the percentage inhibition of swelling in the rat hind paw versus time is shown in Figure 1.



Key: IP-Ibuprofen 200mg/kg; DF-Diclofenac sodium (20mg/kg) standards; *RPM-Ruellia prostrata;* RBK-*R. bignoniiflora;* RLB-*R. lineari-bracteolata*.

Figure 1. Comparison of % inhibition of rat paw swelling of 1500mg/kg doses of the aqueous and methanolic extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata*.

Table 2: Percentage inhibition of swelling in the rat hind paw by the methanolic extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata.*

Conc. (mg/kg)	Type of extract	Time in hours					
		1	2	3	4	5	6
		Percentage inhibition of rat hind paw swelling (n=6)					
	Untreated Control	0.0±0.00^{d}	0.0±0.00^{b}	0.00±0.00^{c}	0.00±0.00^{b}	0.00±0.00^{b}	
	IP	16.31±1.36c	24.42±2.10b	43.00±2.73a	52.00±2.72a	56.82±2.18a,b	60.53±1.84a
	DF	19.46±1.21b,c	29.19±1.92a,b	45.51±1.62a	57.38±2.16a	64.07±3.82a,b	67.87±3.27a
250	RPM RBK RLB	16.95+3.24^{a} 14.00+3.59^{a} 9.15±2.67^{a}	21.33+4.18^{b} 15.55+2.42^{a} 12.15±5.06^{a}	32.97+6.89^{a} 17.88+4.27^{c} 27.26±1.95^{a}	37.19+3.63^{b} 18.22+2.05^{d} 32.90±4.75^{b}	40.84+6.85^{b} 34.75+2.52^{b} 37.06±2.70^{b}	49.59+8.95^{b} 43.26+3.54^{b} 44.86±4.00^{b}
500	RPM RBK RLB	19.15+1.02^{a} 16.84+1.28^{a} 13.71±3.78^{a}	26.06+2.5^{a,b} 20.55+2.60^{a} 16.29±4.35^{a}	42.39+2.62^{a} 24.32+1.43^{b,c} 32.92±5.01^{a}	52.48+2.13^{a,b} 30.72+1.78^{c,d} 41.96±2.41^{a,b}	57.59+2.7^{a,b} 44.59+6.75^{a,b} 47.58±2.34^{a,b}	60.71+1.99^{a} 45.75+3.32^{b} 50.26±2.81^{a,b}
1000	RPM RBK RLB	22.67+1.54^{a} 17.458+0.83^{a} 16.42±2.05^{a}	35.99+4.77^{a,b} 24.77+4.32^{a} 20.52±2.89^{a}	48.38+2.88^{a} 32.94+4.68^{a,b,c} 36.46±2.06^{a}	60.00+2.97^{a} 35.43+4.37^{b,c,d} 46.83±2.43^{a,b}	63.57+3.57^{a} 47.54+3.62^{a,b} 52.73±2.52^{a,b}	65.47+4.63^{a} 50.11+2.05^{a,b} 58.12±2.61^{a,b}
1500	RPM RBK RLB	26.79+4.96^{a} 18.72+1.45^{a} 18.36±0.808^{a}	43.41+4.12^{a} 25.84+2.63^{a} 23.17±2.60^{a}	51.93+2.21^{a} 37.43+2.53^{a,b,c} 42.76±3.70^{a}	63.33+2.04^{a} 43.39+4.15^{a,b,c} 49.81±3.68^{a,b}	68.78+1.13^{a} 50.564.24^{a,b} 55.62±7.21^{a,b}	71.87+0.45^{a} 53.33+5.42^{a,b} 62.88±7.04^{a,b}

Key: IP-Ibuprofen 200mg/kg; DF-Diclofenac sodium (20mg/kg) standard; RPM-*Ruellia prostrata*; RBK-*R. bignoniiflora*; RLB-*R. lineari-bracteolata*; Conc.- concentration. Values are expressed as Mean ±SEM. Values with the same superscript down the column are not significantly different ($p>0.05$).

Discussion

Carrageenan-induced oedema is considered a multi-mediated process that liberates a diversity of inflammatory mediators such as prostaglandins and leukotrienes which are released through the cyclooxygenase pathway and lipoxygenase pathways [13]. It is believed to be biphasic, with the first phase (≤1 hr.) involving the release of 5-hydroxytrypramine (5-HT) and histamine, while the second phase (>1 hr.) is mediated by prostaglandins, the cyclooxygenase products. The transition between the two phases is provided by kinins [14-16]. A correlation between the development

of oedema induced by carrageenan and early exudative stage of inflammation has also been reported [15, 16]. It can, therefore, be argued that suppression of the first phase of inflammation is due to inhibition of release of early mediators, whereas inhibition of the second phase of inflammation is due to the inhibition of the cyclooxygenase pathway.

The present study showed that the aqueous extract of whole plant parts of the Kenyan *Ruellia* species possessed a significant anti-oedematogenic effect on rat hind paw oedema induced by carrageenan. Both the *Ruellia* species and reference drugs in the present study displayed the highest anti-inflammatory activity at the 6-hour point. Therefore, the inhibitory effect of the extracts of the *Ruellia* species in the present study on carrageenan-induced oedema over a period of 6 hours was similar to the effect of non-steroidal anti-inflammatory drugs of inhibiting the second phase of the inflammatory response. This suggests that the extracts acted by inhibiting the second phase of inflammation mediated by arachidonic acid metabolites which produce oedema [17]. It has also been reported that the carrageenan-induced oedema is a significant predictive test for anti-inflammatory agents acting by the inhibition of mediators of acute inflammation [18]. The anti-inflammatory activity of extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* species in the present study, may be attributed to the presence of flavonoids, polyphenols and saponins in the plant [19].

Conclusion

The aqueous extracts of whole plant parts of Kenyan *Ruellia* species possess significant anti-inflammatory activity. Both the aqueous and methanol extracts of *R. prostrata, R. bignoniiflora* and *R. lineari-bracteolata* showed significant dose-dependent anti-inflammatory activity compared to the negative (untreated) control. Aqueous extracts were consistently more potent than the corresponding methanolic extracts. Overall, the aqueous extract of *R. prostrata* showed the most promising analgesic and anti-inflammatory activities, followed by the aqueous extract of *R. bignoniiflora*. Anti-inflammatory activity of the aqueous extract of *R. prostrata* (1500 mg/kg) was superior to that of diclofenac sodium (20 mg/kg) and ibuprofen (200 mg/kg) standards. To the best of the researcher's knowledge, this is the first ever report of the anti-inflammatory activities of *R. bignoniiflora* and *R. lineari-bracteolata*.

Recommendations

Bioactive phytocompounds from the Kenyan *Ruellia* species should be isolated, identified and characterized using standard spectroscopic technique such as liquid chromatography-mass spectrometry, ^{1}H proton and ^{13}Carbon Nuclear magnetic resonance, 2-dimensional COSY nuclear magnetic resonance. This could be accompanied by in silico studies that could predict the targets of drug action, to establish the most probable mechanism of action. The bioactive compounds present in *R. prostrata* and *R. bignoniiflora* should also undergo in vivo toxicity evaluation. Promising findings could justify subsequent formulation and clinical trials of these compounds as potential anti-inflammatory and anti-arthritic drugs.

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Conclict of Interests

Authors have declared no conflict of interest.

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