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Anti-inflammatory activity of *Curcuma albiflora* Thw. grown in Sri Lanka

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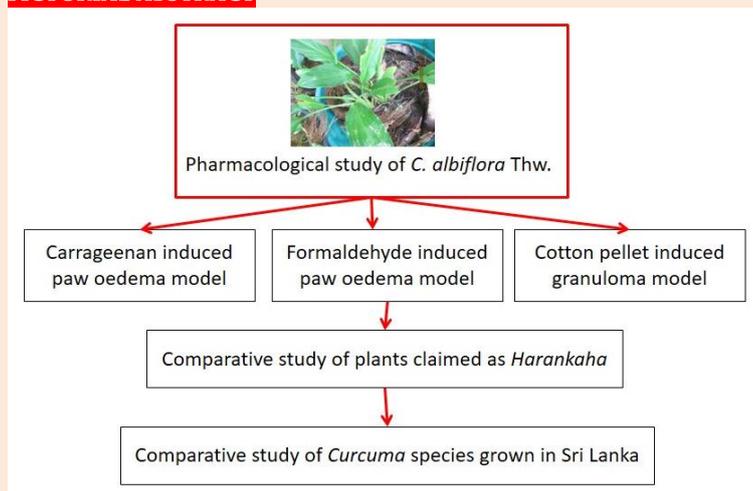
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ABSTRACT

Introduction: Among five species of *Curcuma* (*C. albiflora*, *C. aromatica*, *C. longa*, *C. oligantha*, and *C. zedoaria*), *Harankaha* is an important anti-inflammatory drug have been used in Sri Lankan Traditional Medicine. There are three species under the same vernacular name *Harankaha*; *C. albiflora*, *C. zedoaria* and *Zingiber zerumbet*. Amongst, *C. albiflora* is an unexplored and endangered. Current study was conducted to compare anti-inflammatory activity among above mentioned species. **Methods:** Plants were collected 2016-2017 in Sabaragamuwa province. Voucher specimens were authenticated from National Herbarium, Peradeniya, Sri Lanka. Whole plant extract from composite samples was prepared using 50% ethanol (in water) by continuous extraction (6 h). Thirty rats were assigned into six groups. Groups were treated in the following manner; control (distilled water), three *C. albiflora* drug groups; 200 mg/kg, 400 mg/kg, and 600 mg/kg, standard group; indomethacin 4 mg/kg. **Results:** The 200 mg/kg significantly impaired the paw oedema, at 1h (by 61%). *C. albiflora* inhibited 1st phase of acute anti-inflammatory process. The drug group (400 mg/kg and 600 mg/kg) significantly ($P < 0.05$) reduced the paw oedema from the day 5 to 7 by 400 mg/kg. Since, *C. albiflora* showed low (as 19.5% on 400 mg/kg) anti-inflammatory activity on cotton pellet granuloma test, it can be concluded that anti-inflammatory activity of *C. albiflora* is not linked with prostaglandin synthesis. **Conclusion:** It can be concluded from the current study, *C. albiflora* Thw. grown in Sri Lanka and plants claimed as *Harankaha*, which seems to have marked anti-inflammatory activity.

KEYWORDS *Curcuma*, anti-inflammatory, *in-vivo*, *Curcuma albiflora*, *Curcuma zedoaria*

PICTORIAL ABSTRACT



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Genus *Curcuma* is important in Traditional Medicine in Sri Lanka. Amongst, *C. albiflora* is an unexplored and endangered^[1]. *C. albiflora* is named as *Harankaha* locally, indeed there are two other species with the same vernacular name (*C. zedoaria* and *Zingiber zerumbet*)^[2]. *Harankaha* is claimed as an anti-inflammatory medicinal plant. Therefore, current study was conducted to prove or disprove unexplored *C. albiflora* possessing anti-inflammatory activity and compare anti-inflammatory activity among species of the *Curcuma* genus which grown in Sri Lanka; *C. albiflora*, *C. aromatica*, *C. longa*, *C. oligantha*, and *C. zedoaria*.^[2] Moreover, three species claimed as *Harankaha* also comparatively studied in terms of anti-inflammatory activity.

Plants were collected from 2016 to early 2017 in Sabaragamuwa province. Voucher specimens of the plants were authenticated from National Herbarium, Peradeniya, Sri Lanka.

Whole plant extract from composite samples was prepared using 50% ethanol (in water) by continuous extraction (6 h). Anti-inflammatory experiments were performed at the animal house in department of zoology, University of Colombo. Required concentrations (200 mg/kg, 400 mg/kg, and 600 mg/kg) were prepared using water as solvent. The animal dose was calculated based on human equivalent dose. Wistar healthy female rats from MRI, Colombo weighing 180 - 240 g were used. The study protocol

and procedures were reviewed and approved by FGS, Colombo ethics committee and conducted in accordance to the WHO guidelines. Rats were fed commercial pelleted diet and water ad libitum. Thirty rats were assigned into six groups. Groups were treated in the following manner; control (distilled water), three *C. albiflora* (CA) drug groups; 200 mg/kg, 400 mg/kg, and 600 mg/kg, standard group; indomethacin 4 mg/kg^[3,4].

Inflammations were induced by 0.05 ml of 1% carrageenan (in 1% methyl cellulose) into the plantar surface of the left hind paw under mild anesthetic ether anesthesia. Treatments were performed prior 1h of 1st reading. The paw volumes were measured before the injection of carrageenan, and 1h, 2h, 3h, and 4h after the treatment^[3,4].

Inflammations were induced by 0.1 ml of 2% formaldehyde in distilled water into the plantar surface of the left hind paw under mild anesthetic ether anesthesia on days 1 and 3. Treatments were performed for 7 consecutive days. The paw volumes were measured before the injection of formaldehyde (on days 1 and 4), and 1h after the treatment and on day 1, 4h after the injection of formaldehyde^[3,4].

Granulomatous lesions were induced by surgically implanting two cotton pellets subcutaneously in the dorsal region of the rats near the axilla. *C. albiflora* extract was administered orally before 1 h of the surgery. Rats were anaesthetized using ketamine (0.6 ml kg⁻¹) and autoclaved sterile pellets of cotton (8 ± 0.5 mg each) were implanted. The rats of the control group were administered with water and standard group by Indomethacin (5 mg/kg). Drugs and water was administered for consecutive 7 days. Rats were anaesthetized on the eighth day using ketamine and the pellets were dissected out carefully and dried at 60 °C (3 d)^[3,4]. Mean weight of the granuloma tissue formed around each dried pellets were recorded.

Calculation and statistical analysis was performed using Minitab 17 (version 17.1.0.0). Results were expressed as mean ± standard deviation. Anti-inflammatory activity results were analyzed by ANOVA by comparing control group values using Turkey test.

The effect of oral treatment of *C. albiflora* whole plant extract on the carrageenan induced paw oedema of rats was reported in Table 1. The effect of *C. albiflora* extract on the formaldehyde-induced paw oedema in Wistar rats was reported in Table 2. Wet cotton pellets which were dissected out on the 8th day and mean dry weight of cotton pellets were showed in the Figure 1. The effect of *C. albiflora* on cotton pellet granuloma test in Wistar rats is presented in Table 3.

Table 1. Effect of oral treatment of *C. albiflora* whole plant extract on the carrageenan induced paw oedema of rats

Dose (mg/kg)	Paw oedema (ml)			
	1h	2h	3h	4h
Control	0.33 ± 0.02	0.37 ± 0.03	0.48 ± 0.05	0.55 ± 0.06
200 CA	0.19 ± 0.06	0.31 ± 0.04*	0.40 ± 0.05	0.40 ± 0.06
400 CA	0.14 ± 0.05	0.28 ± 0.06	0.38 ± 0.05	0.52 ± 0.06*
600 CA	0.18 ± 0.07	0.20 ± 0.12	0.35 ± 0.08	0.48 ± 0.02
4 Indomethacin	0.12 ± 0.02	0.04 ± 0.01*	0.11 ± 0.04*	0.23 ± 0.03*

Values are means ± SEM (n=6), *p values < 0.05 as compared with control (Turkey's test), CA: *Curcuma albiflora*

Table 2. Effect of *C. albiflora* extract (water) on the formaldehyde-induced paw oedema in Wistar rats

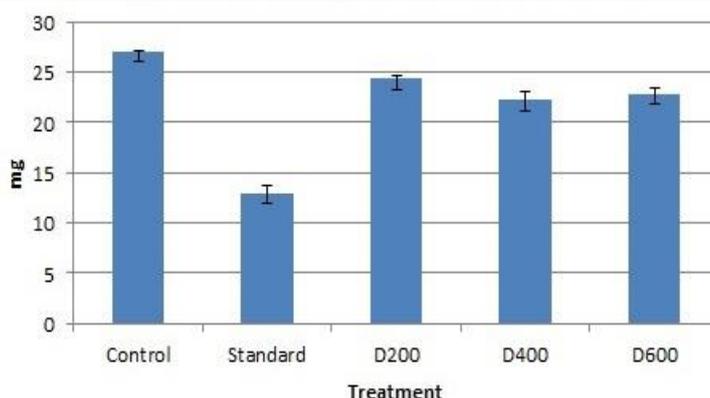
Dose (mg/kg)	Paw oedema (ml)						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Control	0.39±0.05	0.60±0.03	0.65±0.05	0.77±0.07	0.94±0.08	0.54±0.06	0.47±0.05
200 CA	0.29±0.03	0.75±0.07	0.64±0.03	0.86±0.05	1.02±0.12	0.61±0.06	0.51±0.05
400 CA	0.22 ±0.05*	0.13±0.05**	0.32±0.04**	0.55±0.04*	0.09±0.01**	0.07±0.02**	0.04±0.01**
600 CA	0.20±0.04*	0.15±0.04**	0.36±0.03**	0.57±0.06*	0.16±0.08	0.13±0.03**	0.12±0.04**
4 Indomethacin	0.19±0.05*	0.23±0.05**	0.37±0.09*	0.52±0.06*	0.07±0.07**	0.04±0.02**	0.02±0.01**

Values are means ± SEM (n=6), *p values < 0.05 and **p values < 0.01 as compared with control (Turkey's test), CA: *Curcuma albiflora*

Figure 1. Cotton pellet experiment



1.1 Wet cotton pellets after surgical removal



1.2 mean of dry weight of cotton pellets of each treatment groups

Table 3. Effect of *C. albiflora* on cotton pellet granuloma test in Wistar rats

Dose mg/kg	Mean of wet cotton pellets(mg)	Percentage inhibition	Mean of dry cotton pellets(mg)	Percentage inhibition
Control Group	37.57 ±0.93		27.60±1.02	
200 CA	34.48±0.26	8.2%	24.88±0.69*	8.1%
400 CA	30.75±0.12	18.2%	21.78±0.37**	19.5%
600 CA	33.56±0.65	10.7%	23.44±0.74**	13.4%
4 indomethacin	22.03±0.35	41.4%	13.18±0.25	51.3%

Values are means ± SEM (n = 6). *p < 0.05 and **p<0.01 as compared with the control (Turkey's test), CA: *Curcuma albiflora*

The 200 mg/kg significantly impaired the paw oedema, at 1h (by 61%). In contrast, the 400 and 600 mg/kg tested significantly inhibited the paw oedema measured; 1h (by 45-58%), 2h (by 24-46%), 3h (by 21-27%). Therefore it showed the anti-inflammatory effect of *C. albiflora* was inversely dose dependent (Table 1). Indomethacin induced significantly impairment of oedema at all-time points measured (58-89%). Initial phase lasting primarily mediated via production of cox-1, histamine, serotonin, bradykinins etc. Since *C. albiflora* inhibited 1st phase, anti-inflammatory effect may relate with above mentioned pathways. *C. albiflora* showed its anti-inflammatory activity in initial phase. As per the formaldehyde induced paw oedema experimental results, the drug group (400 mg/kg and 600 mg/kg) significantly ($P < 0.05$) reduced the paw oedema from the day 5 to 7 by 400 mg/kg when compared with the control (Table 2). This effect related prostaglandin synthesis can be proved by cotton pellet induced granuloma test. From the present study, it can be concluded that 400 mg/kg treated group showed higher inhibition percentage than 200 and 600 mg/kg treated groups. According to the cotton pellet induced granuloma test results *C. albiflora* showed low (as 19.5% on 400 mg/kg) anti-inflammatory activity on cotton pellet granuloma test, it can be concluded that anti-inflammatory activity of *C. albiflora* is not linked with prostaglandin synthesis (Table 3).

Harankaha is an important plant, but there are three species under same vernacular name; *C. albiflora*, *C. zedoaria*, and *Z. zerumbet*. Previous study reports anti-inflammatory phytochemicals present in essential oil of *C. zedoaria* and *Z. zerumbet*. Whereas essential oil of *C. zedoaria* consists of camphor (11.82%), benzofuran (2.96%), beta pinene (0.41%), alpha pinene (0.23%), *Z. zerumbet* consists of alpha humulene (22.52%), beta eudesmol (7.48%), camphor (3.04%), caryophyllene (2.33%), alpha pinene (1.25%), beta pinene (0.09%) as anti-inflammatory phytochemicals^[5,6]. Essential oil of *C. albiflora* consisted anti-inflammatory phytochemicals as alpha pinene (14.51%), alpha bisabolene (3.51%), caryophyllene (2.57%), alpha copaene (0.85%). Furanodiene and furanodienone from *C. zedoaria* rhizome demonstrates anti-inflammatory activity on TPA-induced ear edema^[7]. *C. zedoaria* shows 54- 56% inhibition in initial phase and 56-59% in late phase by the concentration 200 mg/kg of petroleum ether on carrageenan induced paw oedema test. However it shows the 58% inhibition at 2h by the concentration of 200 mg/kg of chloroform^[8]. Therefore, it shows anti-inflammatory activity of *C. zedoaria* on both the initial and late phases. In contrast, *C. albiflora* showed anti-inflammatory activity on initial phase. Chien showed zerumbone and 3-O-methyl kaempferol as the major bioactive component, which possesses anti-inflammatory activity in *Z. zerumbet*^[9]. Aqueous and methanol extracts and essential oil of *Z. zerumbet* shows significant anti-inflammatory activity. The aqueous extract exhibited significant anti-inflammatory activity only at the doses of 50 and 100mg/kg producing an activity between 1-4h after PGE₂ administration^[10]. Nearly half percent inflammatory inhibition for the first 2h. The all the dosages of methanol extract (25-100mg/kg; s.i.) shows significant ($P < 0.05$) antioedema and anti-inflammatory activities using the acute (carrageenan-induced paw edema test) and chronic (cotton pellet-induced granuloma test) models of inflammation, respectively^[10]. Twenty five mg/kg methanol extract, the onset of antioedema was 2.5h after the carrageenan administration. Fifty mg/kg of methanol extract significantly reduced the weight of exudates by 47% and granuloma tissues by 52% in the granuloma test^[11]. Essential oil of *Z. zerumbet* attenuates the second phase of the formalin-induced pain test, which is associated with inflammatory-mediated pain. The dosages of 100 and 300 mg/kg (i.p) of essential oil in the first 3h after its administration in the paw edema test and the 30-300mg/kg (i.p.) essential oil shows anti-inflammatory activities in the range of 42-75%.^[10] As per the review of above three *Harankaha* plants, they have anti-inflammatory activity. However, *C. zedoaria* and *Z. zerumbet* shows higher anti-inflammatory activity.

Among five *Curcuma* species grown in Sri Lanka, Curcuminoids extracted from *C. longa* rhizome demonstrates significant anti-inflammatory activity on TPA-induced ear edema^[12]. *C. longa* has been used in several cultures for wound healing for long time. At present, aqueous extract of *C. longa* is applied on wound as house hold remedy. It is popularized against to treat sprains^[13]. Curcumin is claimed as a one of major active compounds of *C. longa*, which possesses anti-inflammatory activity. It is effective in acute (carrageenan induced), sub-acute (formaldehyde induced) and chronic models (cotton pellet) of inflammation, indicates effective on transudate and proliferative phase of inflammation^[14]. Whereas 50 mg/kg of curcumin shows 31.5% inhibition, 200 mg/kg shows 66.2% inhibition by the experiment of carrageenan induced oedema in mice. Curcumin inhibites significantly formaldehyde induced arthritis (40mg/kg/day)^[14]. The granuloma pouch test was positive in the range 80-160 mg/kg. Low ulcerogenic index of curcumin (0.60) indicates potent anti-inflammatory activity than phenylbutazone (1.70)^[14]. Pet ether extract of *C. longa* shows 23.45 ± 0.15 mg dry mass in the cotton pellet granuloma test, which is nearly the result given by standard drug cortisone (20.89 ± 0.15 mg)^[14]. In formaline treated granuloma pouch arthritis indicates significant effect ($p < 0.001$) in terms of granuloma weight of the pouch; hydrocortisone treated group gave weight as 2.87 ± 0.18 mg, which is closer to pet ether treated group results (3.7 ± 0.21 mg)^[14]. Adjuvant arthritis model shows *C. longa* as a potent anti-inflammatory drug, since secondary lesions and histamine content were significantly reduced^[14]. Anti-inflammatory activity of curcumin is greater than phenylbutazone, and triethyl curcumin^[15]. The various concentration of ethyl acetate extract of *C. longa* (doses of 90, 180, and 360 mg/kg b.w.) shows 51.2, 35.8, and 48.75% inhibitions respectively on xylene induced ear oedema test. Further ethyl acetate extract of *C. longa* (doses of 45, 90, and 180 mg/kg) inhibits 38.7, 34.1, and 32.1% respectively on dry weight of cotton pellet-induced granuloma test, which indicates a measure of inhibition of proliferative phase^[16]. Essential oil of *C. oligantha* consists of anti-inflammatory phytochemicals; caryophyllene (15.07%), alpha copaene (1.89%), humulene (8.24%), phytol (13.38%), alpha pinene (1.6%), beta pinene (2.8%), gamma curcumene (0.5%), beta eudesmol (1.2%), bisabolol oxide (1.1%). Its antimicrobial activity has been proved by Ahmed^[17]. Anti-inflammatory activity of *C. oligantha* is needed to assess whether it has anti-inflammatory activity, still it has not been studied extensively arising research gap. However, it seems to have anti-inflammatory activity in concern its chemical profile. Essential oil of *C. aromatica* also consists of anti-inflammatory phytochemicals; camphor (26.32%), germacrene D (3.45%), caryophyllene oxide (6.33%), p-cymene, alpha pinene (2.6%), beta pinene (1.2%), carvacrol (1.4%)^[18-20]. Hexane extract of *C. aromatica* shows maximum peak area of 40.46% for germacron^[21]. The anti-inflammatory effect of the ethanol extract of *C. aromatica* at the end of 3h shows 35.18% inhibition on carrageenan induced paw oedema model. *C. aromatica* has been found to have marked anti-inflammatory potential due to the presence of preliminary phytochemicals; flavonoids and tannins^[22]. Xiang founds anti-inflammatory action of *C. aromatica* essential oil by significantly down-regulating expression of tumor necrosis factor- α and cyclooxygenase-2^[23]. As per the review of all five *Curcuma* species grown in Sri Lanka, it can be considered as important genus, which possesses marked anti-inflammatory activity. However, *C. albiflora* seems to have lower anti-inflammatory activity compare to *C. zedoaria*, *C. aromatica*, and *C. longa*. *C. oligantha* has not been studied extensively to its anti-inflammatory activity.

It can be concluded from the current study, *C. albiflora* Thw. grown in Sri Lanka and claimed as *Harankaha*, has marked anti-inflammatory activity.

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Conflict of interest Authors declare no conflicts of interest.

Contributors Mr. Herath contributed to the literature study, perform experiment data acquisition, data analysis, and manuscript writing. Dr. Wijayasiriwardene and Dr. Premakumara contributed to the manuscript editing, experimental design, and analysis of the study.

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