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Anti-inflammatory and antinociceptive effects of *Dolichandrone Falcata* fruit extracts in animal models

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ABSTRACT

Despite traditional claims about the pharmacological properties of Dolichandrone falcata and the successful isolation of bioactive compounds from its leaves, no in-depth scientific study has been carried out on their effects. The present study was carried out to determine the anti-inflammatory and antinociceptive activities of the methanol (DFFM) and ethyl acetate (DFFEA) extracts of Dolichandrone falcata fruits using animal models. An extract was obtained from air-dried, powdered fruits (900 g) using a Soxhlet extractor with methanol, it was then treated to obtain the ethyl acetate extract. The crude dried DFFM extract (90 g) and DFFEA extract (18 g) were used to prepare formulations, at doses of 100, 200 and 400 mg/kg, that were used in anti-inflammatory (carrageenan- and histamine-induced paw edema test) and antinociceptive (abdominal constriction, hot plate and tail flick tests) assays. The results obtained indicate that the extracts exhibited significant (P< 0.001) anti-inflammatory and antinociceptive effects, which were found to be dose dependent. The highest doses of both extracts were most significant and effective. This study showed that the methanol and ethyl acetate extracts of Dolichandronefalcata fruits possess potentially pharmacologically active constituents responsible for inhibition of inflammation and nociceptive effects.

Key Words: Bignoniaceae, *Dolichandrone falcata*, Anti-inflammatory, Antinociceptive

INTRODUCTION

Dolichandrone falcata Seem. (Bignoniaceae) is known as *medshingi* in the Toranmal region of Maharashtra, India. It is a small- to medium-sized deciduous tree, attaining a height of 20 to 50 feet, and is commonly found in hill forests [1]. It is occasionally seen in dry scrub forests. Sometimes it is grown in hedges along fields. The bark is used as a fish poison. A decoction of the fruits is used to bring about abortion [2]. The bark is ground into a paste and applied on fractured or dislocated bones [1]. Juice from the bark is used to treat menorrhagia and leucorrhea [3]. The plant is very rich in flavonoids. A few other substances have been isolated from the leaves, stem, bark, and fruit. Chrysin-7-rutinoside has been identified in the leaves [4]. Chrysin is a flavone that is commonly found in plants and that has been reported to have many different biological activities including anti-oxidant, anti-allergic, anti-inflammatory, anticancer, anti-estrogenic, and anxiolytic activities [5]. Although there are traditional claims about the pharmacological properties of *D. falcata* and bioactive compounds have been isolated successfully from it, no in-depth scientific study has been performed in this regard. The aim of the present study was to determine the anti-inflammatory and antinociceptive properties of the DFFM and DFFEA extracts of *D. falcata* fruits using different animal models.

MATERIALS AND METHODS

Plant Material

Dolichandrone falcata Seem. (Bignoniaceae) fruits were collected from the Toranmal Hills of the Satpura region of Maharashtra in May. Specimens were identified and authenticated by the Botanical Survey of India, Pune, and a voucher specimen of the sample (vishal 1) was deposited in the herbarium collection at the Department of Pharmacognosy, R.C. Patel Institute of Pharmaceutical Education and Research. The fruits were cleaned and dried in the shade and were pulverized to obtain a 40-mesh powder. This powder was stored in an airtight container.

Preparation of Extracts

Methanolic extract (DFFM). This extract was obtained from the dried fruit powder (900 g) with methanol (3 L × 4) by continuous hot extraction in a Soxhlet extractor. The methanol-containing extract was filtered and distilled on a water bath. The resulting methanol extract solution was concentrated in vacuum using a Rota Vapor. A greenish brown powder amounting to 10% (90 g) of the weight of the powder was obtained.

Ethyl acetate extract (DFFEA). Ten grams of the methanol extract was suspended in water (500 ml) and fractionated with *n*-hexane (800 ml × 3), chloroform (600 ml × 4), ethyl acetate (500 ml × 4), and *n*-butanol (500 ml × 4) successively. Evaporation yielded *n*-hexane (0.5 g), chloroform (3.5 g), ethyl acetate (2 g), and *n*-butanol (1.2 g) with the extract [6]. The ethyl acetate (DFFEA) extract was used for pharmacological screening.

Solutions of Standard Drugs and Chemicals

Solutions of acetylsalicylic acid (Reckitt Benckiser, 200 mg/kg), pentazocine (Ranbaxy, 5 mg/kg), and diclofenac sodium (Lupin, 10 mg/kg) were prepared for comparison by dissolving the respective drugs or chemicals in saline: CMC (Carboxy Methyl Cellulose). Carrageenan (λ4) (C3889-5G) and histamine (H-7375) were obtained from Sigma Aldrich, USA. Acetic acid (HPLC grade) was obtained from S. D. Fine-chem Ltd., Mumbai.

Pharmacological Studies

Test animals. Wistar rats (150-200 g; 8-11 weeks old) and Swiss albino mice (25-30 g; 7-10 weeks old) both male and female were obtained from R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, and Government Veterinary College, Mahu, MP (India). The animals were housed in the animal house of R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, in polycarbonate cages. The room was maintained at a temperature of 22 ± 2°C and a relative humidity of 60-70%. The animals were provided food and water *ad libitum*. All the experimental procedures and protocols used in the study were reviewed by the Institutional Animal Ethics Committee (Register Number: RCPIPER/IAEC/2008-09/13) and were in accordance with the guidelines of the CPCSEA, Ministry of Forests and Environment, Government of India. The animals were deprived of food for 24 h before experimentation but were allowed free access to water at all times. All studies were carried out on groups of six animals for both anti-inflammatory and analgesic activity.

Acute toxicity test. Acute toxicity tests were performed according to OECD-2001 guidelines. Swiss albino mice were weighed and marked, and a single high dose (3000 mg/kg) of DFFM and DFFEA as recommended by the OECD guidelines was administered to the first animal. The DFFM and DFFEA doses were administered separately to both the first test animals respectively. After a single administration, the animal was observed for signs of toxicity and unusual behavior each hour up to the 24th hour. If this animal was found to be dying, then a weaker dose was administered to the next animal. The same procedure was followed for that the second animal. If it survived, then the same dose was given to the next five animals. All the animals were observed for signs of toxicity and mortality for up to 14 days. The body weight of the animal was also measured. All the data obtained from the six animals were analyzed using the statistical program AOT425statPgm. This program was used to determine the LD50 value of the test drug.

Carrageenan-induced rat paw edema method. Rats of either sex (150-200 g) were divided into eight groups containing six animals each. The rats were fasted for 12 hours prior to induction of edema; however, water was provided *ad libitum*. To ensure uniform hydration and to minimize variability in the edematous response, rats were deprived of water only during the experiment. Inflammation of the right hind paw was induced by injecting 0.1 ml of 1% carrageenan solution in normal saline into the subplantar region of the paw [7]. A negative control group received saline: CMC (0.5%) solution [8], and a positive control group received diclofenac sodium (10 mg/kg) p.o. [9]. Three groups received DFFM at doses of 100, 200, and 400 mg/kg, respectively, p.o. The remaining three groups received DFFEA at doses of 100, 200, and 400 mg/kg, respectively, p.o. All the drug treatments were given 1 hour before the carrageenan injection. The paw volume was measured using a digital plethysmometer (Ugo Basile, 7140) before and 1, 2, 3, 4, 5, and 6 hr after the carrageenan injection [7, 10]. The edema was determined as the

increase in paw volume due to the carrageenan injection. The extracts and the reference drugs were dissolved in 0.5% carboxy methyl cellulose solution just before use.

Histamine-induced rat paw inflammation. Rats of either sex (weighing 150-200 g) were divided into eight groups containing six animals each. The rats were fasted for 12 hours prior to induction of edema; however, water was provided *ad libitum*. Inflammation of the right hind paw was induced by injecting 0.1 ml of histamine (1 mg/ml) in normal saline into the subplantar region of the paw. A negative control group received CMC (0.5%) solution [8], and a positive control group received diclofenac sodium (10 mg/kg) p.o [9]. The procedure used in the remainder of the test was the same as that utilized with carrageenan-induced edema. The percentage rise in paw volume was determined using the following formula.

$$\text{Percentage rise in paw volume} = [(V_t - V_0)/V_0] \times 100\%,$$

where V_t = paw volume at time t and V_0 = paw volume at time 0.

Antinociceptive (Analgesic) Activity

Acetic acid-induced writhing test. The analgesic activity was measured against chemical and thermal stimuli. The mice were divided into eight groups consisting of six animals each. The control group received normal saline: CMC (99:1) p.o, and the standard group received Aspirin (200 mg/kg, i.p.). The test groups received the DFFM and DFFEA extracts at doses of 100, 200, and 400 mg/kg p.o. separately. The acetic acid-induced abdominal writhing test was performed as described by Collier et al [11]. Nociception was induced by an i.p. injection of 1.0% acetic acid at a dose of 10 ml/kg body weight after 30 minutes of standard and test drug administration. The number of stretching or writhing movements noted was recorded from 5 minutes to 15 minutes after injection.

Hot-plate test. An Eddy's hot plate was used to measure response latencies according to the method described by Eddy and Leimback[12], with minor modifications. The paws of mice are very sensitive to high temperatures even if there is no damage to the skin. The response is in the form of jumping, withdrawal of the paws or licking of the paws. The animals were placed on the hot plate with its temperature at 55±0.5°C. A cut-off period of 15 seconds was used to avoid damage to the paws. The reaction time and the type of response were noted using a stopwatch. The latency was recorded before and after 30, 60, 90, and 120 minutes for both the test drug and the standard. The average reaction times were then calculated, and the percentage variation was calculated using the following relation [13]

$$\text{Percentage pain inhibition} = [(\text{Drug latency - baseline latency})/\text{baseline latency}] \times 100\%$$

Tail immersion method. The tail immersion test was conducted as described in [14]. This involved immersing the distal 3 cm of a mice's tail in a water bath containing water at a temperature of 55±0.5°C. Within a few minutes, the mice reacted by withdrawing the tail. The reaction time was recorded using a stopwatch. Each animal served as its own control, and two readings were obtained for the control at 0 and 10 minutes. The average of the two values was the initial reaction time (T_b). The test groups were given DFFM and DFFEA (100, 200, and 400 mg/kg, p.o.), pentazocine (5 mg/kg) and 1% CMC (p.o.). The reaction times (T_a) for the test groups were measured at 30, 60, 90, and 120 minutes after a latency period of 30 minutes following the administration of DFFM and DFFEA and the standard drug [15].

Statistical Analysis

Statistical analysis of all the results was carried out using two-way ANOVA followed by Bonferroni post test, except the results obtained in acetic acid induced writhings which was analyzed by using one-way ANOVA followed by Dunnett's multiple comparisons using the graph pad in stat 5 Demo. All the results obtained in the study were compared with those for the vehicle control group. P values <0.05 were considered statistically significant.

RESULTS

Acute Toxicity Test

Dolichandrone falcata fruit extracts did not produce any mortality even at a dose of 3000 mg/kg body weight p.o. *D.falcata* was thus found to be non-toxic. On the basis of these results, three doses (100, 200, and 400 mg/kg, p.o.) of *D.falcata*(DFFM, DFFEA)were selected for further pharmacological studies.

Carrageenan-induced rat paw edema

DFFM caused a significant inhibition in the percent rise of carrageenan-induced rat paw edema at doses of 200 and 400 mg/kg. The maximal inhibition in the percent rise of edema volume was achieved at a dose 400 mg/kg ($P< 0.001$), compared with the standard drug, diclofenac sodium (10 mg/kg). DFFEA failed to produce significant inhibition at doses of 100 and 200 mg/kg, but at higher dose of 400 mg/kg it exhibited significant inhibition by 4 hr. ($P< 0.01$) (Table 1).

Histamine-Induced Rat Paw Edema

DFFM at doses of 200 and 400 mg/kg caused a significant inhibition in the percent rise of histamine-induced rat paw edema. The maximal inhibition in the percent rise of edema volume was achieved at both doses of 200 and 400 mg/kg ($P< 0.001$), compared with the standard drug, diclofenac sodium (10 mg/kg). DFFEA at dose of 400 mg/kg ($P< 0.001$) produced significant inhibition in the percent rise of histamine-induced rat paw edema (Table 2).

Acetic Acid-Induced Writhing Test

The DFFM and DFFEA extracts of *D.falcata* fruits significantly reduced the writhing and stretching induced by 1.0% acetic acid at a dose of 10 ml/kg. Significant and dose-dependent protective effects were observed, with the DFFM and DFFEA extracts causing at doses of 100, 200, and 400 mg/kg p.o. an inhibition of the writhing response induced by acetic acid. The maximal inhibition of the nociceptive response was achieved by both extracts at dose of 400 mg/kg ($P< 0.01$) (Table 3).

Hot Plate Test

DFFM extract at oral doses of 100, 200, and 400 mg/kg elicited a significant analgesic activity as evidenced by an increase in the latency time in comparison with the negative control at the end of 30, 60, 90, and 120 minutes. The increase in latency time was found to be dose dependent and was found to be very significant ($P< 0.001$) at doses of 200 and 400 mg/kg. DFFEA extract also elicited a significant dose dependent analgesic activity at higher doses of 200 and 400 mg/kg ($P< 0.001$) (Table 4).

Tail Immersion Test

DFFM extract at oral doses of 100, 200, and 400 mg/kg elicited significant analgesic activity as evidenced by an increase in the time to flick the tail compared with the negative control at the end of 30, 60, 90, and 120 minutes. The increase in latency time was found to be dose dependent and to be very significant at doses of 200 and 400 mg/kg ($P< 0.001$). Similarly DFFEA at doses of 200 and 400 mg/kg produced significant analgesic activity ($P< 0.001$) (Table 5).

DISCUSSION

The present study on different animal models indicates that *D.falcata* has pharmacological potential as an antinociceptive and anti-inflammatory agent. The ability of DFFM and DFFEA to prolong the latency to discomfort in the acetic acid-induced writhing, hot plate and tail flick tests suggests that the extracts have potential to inhibit chemically and thermally induced noxious stimuli. The ability to inhibit/reverse these tests could also be associated with the extracts' potential to inhibit inflammation-induced [16] and non-inflammation-related [17] nociception, respectively. In general, several mechanisms of action could be used to explain the observed antinociceptive activity of DFFM and DFFEA. The ability to inhibit/reverse the centrally synthesized prostaglandins or COX [18] could be one of the possible mechanisms that contribute to the central antinociceptive activity of DFFM and DFFEA seen in the present study. Intraperitoneal administration of an agent that irritates the serous membranes provokes a stereotypical behavior in mice that is characterized by abdominal contractions, movements of the body as a whole, twisting of dorso-abdominal muscles, and a reduction in motor activity and coordination [19]. The present study did not aim at isolation and identification of bioactive compounds, but phytochemical screening of DFFM and DFFEA demonstrated the presence of flavonoids, steroids, tannins, and glycosides, which, it has been suggested, act synergistically to exert the observed pharmacological activity [20]. The presence of flavonoids in the DFFM and DFFEA could possibly lead to the observed activities. The anti-inflammatory activity of DFFM and DFFEA could also be linked to the ability of the extracts to influence the central COX activity or prostaglandin synthesis. This fact is supported by claims that the carrageenan-induced inflammation is a COX-dependent response and is not controlled with arachidonate lipo-oxygenase inhibitors but is more effectively controlled with arachidonate cyclo-oxygenase [21]. Interestingly, compounds such as flavonoids and triterpenes, in part, have been shown to possess anti-inflammatory activity, and the claim made by Attaway and Zaborsky [22] that compounds with anti-inflammatory activity also possess antinociceptive activity seems to support our findings on the pharmacological activities of DFFM and DFFEA. On the basis of the classes of compounds detected in DFFM and DFFEA, several mechanisms of action could be used to explain the observed activities of the extracts. Flavonoids are potent inhibitors of nitric oxide synthase type 2, which is involved in the synthesis of NO via an indirect blockade of the

cyclo-oxygenase and/or lipo-xygenase pathways [23] and of the protein kinase C and L-arginine/NO pathways [24], which are known to take part in a series of molecular events that lead to antinociceptive [25] and anti-inflammatory activities. Links between the release of NO from the endothelial cells during vasorelaxation, the ability of flavonoids to induce vasodilation, and the importance of vasodilation in the antinociceptive and anti-inflammatory mechanisms have also been reported and are worth mentioning [26]. The anti-inflammatory activity of DFFM and DFFEA, on the other hand, could be associated with the inhibitory effect of flavonoids on nuclear factor-κB [27]. To demonstrate whether DFFM and DFFEA were producing anti-inflammatory activity in this model by acting on histamine, the effect of DFFM and DFFEA on histamine-induced inflammation was studied.

Histamine-induced rat paw inflammation is the model used to study the anti-inflammatory activity of various agents. Histamine is one of the important mediators of inflammation. Histamine increases vascular permeability and acts with prostaglandins to induce edema [28]. These mediators are stored in the secretory granules and are released from mast cells during their activation. They are proposed to act through specific receptors on nearby vasculature and to induce plasma extravasation[29].

Table: 1. Anti-inflammatory activity of DFFM and DFFEA assessed using the carrageenan-induced paw edema test

Treatment	Dose (mg/kg)	Percentage rise in paw edema at different time intervals					
Time		1hour	2hour	3hour	4hour	5hour	6hour
Control	-	51±3.97	66±4.44	93.4±1.98	83.9±4.75	81.1±3.78	83.5±4.22
DFFM	100	39.1±1.92	50.5±2.00	78.0±3.78	53.4±2.96**	64.7±2.70	60.0±4.40*
DFFM	200	27.1±5.49*	44.4±1.46*	58.9±4.22**	43.2±2.49**	44.9±3.15***	54±6.3**
DFFM	400	20.1±4.17**	37.8±5.89**	52.6±6.26***	40.5±6.75***	32.5±5.47***	26.8±7.05***
DFFEA	100	34.5±6.73	67.2±10.4	90.1±8.06	82.5±6.23	71.8±5.03	69.5±5.24
DFFEA	200	36.3±3.79*	48.0±2.74	84.4±4.95	48±4.2*	58.3±4.87	55.4±1.42
DFFEA	400	20.5±2.13*	38.6±4.19	82.7±7.54	45±6.9**	64.7±5.55	62.9±6.76
STD (diclofenac sodium)	10	12±1.01***	19.1±0.49***	45.3±1.82***	34±3.6***	31.2±4.83***	29.6±4.05***

Values represent mean ±SEM, n = 6. DFFM: Dolichandrone falcata fruit methanol extract. DFFEA: Dolichandrone falcata fruit ethyl acetate extract. STD: Standard drug. Two-way ANOVA followed by Bonferroni post test.
**P < 0.05, **P< 0.01, ***P< 0.001 compared with control group.*

Table 2.Anti-inflammatory activity of DFFM and DFFEA assessed using the histamine-induced paw edema test

Treatment	Dose (mg/kg)	Percentage rise in paw edema at different time intervals		
Time		1hour	2hour	3hour
Control	-	58.2±3.02	70.6±2.62	74.6±4.32
DFFM	100	44.2±2.14*	40.2±2.76*	35.5±2.90**
DFFM	200	30.0±2.46*	26.5±0.893**	20.9±1.44***
DFFM	400	24.8±5.09*	12.9±2.40***	11.3±2.21***
DFFEA	100	41.0±1.55	44.4±1.14*	40.5±0.940*
DFFEA	200	42.1±4.60	33.8±4.76**	27.4±4.78**
DFFEA	400	25.4±5.47*	28.1±6.37**	23.1±5.99***
STD (diclofenac sodium)	10	13.7±0.835**	8.64±1.18***	7.13±0.954***

*Values represent mean ±SEM, n=6. DFFM: Dolichandrone falcata fruit methanol extract. DFFEA: Dolichandrone falcata fruit ethyl acetate extract. STD: Standard drug. Two-way ANOVA followed by Bonferroni post test. *P < 0.05, **P< 0.01, ***P< 0.001 compared with control group.*

Table 3.Antinociceptive activity of *Dolichandrone falcata* fruitson acetic acid-induced writhings in mice

Treatment	Dose (mg/kg)	No. of writhings
Control	-	52.5±7.14
DFFM	100	37.7±3.74*
DFFM	200	24.8±2.06**
DFFM	400	22.2±1.11**
DFFEA	100	39.5±2.57*
DFFEA	200	31.8±1.80**
DFFEA	400	29.5±1.52**
STD (Aspirin)	200	13.3±1.56**

Values represent mean ±SEM, n=6. DFFM: Dolichandrone falcata fruit methanol extract. DFFEA: Dolichandrone falcata fruit ethyl acetate extract. STD: Standard drug. One-way ANOVA followed by Dunnett's multiple comparison test.
**P < 0.05, **P< 0.01 compared with control group.*

In the histamine-induced rat paw inflammation model, DFFM and DFFEA and the reference drug, diclofenac sodium, significantly decreased the inflammation at the first hour after histamine injection. At the second and third hours, DFFM and DFFEA decreased the paw edema, after which the effect decreased slowly. In the late phases of this model DFFM and DFFEA and the reference drug, diclofenac sodium, showed anti-inflammatory activity. The present results support the ethno-medical use of *D.falcata* fruits in the treatment of inflammatory diseases. Further

experimentation is needed to understand the precise mechanism of action of the anti-inflammatory activities of the extracts.

Table 4.Antinociceptive activity of *Dolichandrone falcata* fruitin hot plate test in mice

Treatment	Dose (mg/kg)	Percentage pain inhibition in mice			
		30 min	60 min	90 min	120 min
Control	-	8.73±2.14	11.8±2.25	8.44±1.29	5.31±0.28
DFFM	100	21.3±1.99	50.4±5.24***	42.3±3.19**	36.5±2.94**
DFFM	200	30.8±2.78*	59.2±3.29***	46.4±4.84***	41.6±2.83**
DFFM	400	34.1±2.79*	64.1±3.01***	55.3±2.66***	51.1±4.97***
DFFEA	100	20.9±3.86	36.8±3.72**	26.8±2.24*	21.8±3.81*
DFFEA	200	21.1±4.74	41.3±6.28***	30.5±4.84**	28.5±4.02**
DFFEA	400	34.5±3.70**	52.7±4.32***	43.7±3.15***	37.8±2.99***
STD (pentazocine)	5	45.1±2.94**	72.7±2.88***	60.6±2.18***	57.5±3.80***

*Values represent mean ±SEM, n = 6. DFFM: Dolichandrone falcata fruit methanol extract. DFFEA: Dolichandrone falcata fruit ethyl acetate extract. STD: Standard drug. Two-way ANOVA followed by Bonferroni post test. *P < 0.05, **P< 0.01, ***P< 0.001 compared with control group.*

Table 5.Antinociceptive activity of *Dolichandrone falcata* fruitsin tail flick test in mice

Treatment	Dose (mg/kg)	Percentage pain inhibition in mice			
		30 min	60 min	90 min	120 min
Control	-	9.27±1.04	11.1±1.07	13.1±1.95	13.4±0.557
DFFM	100	37.5±3.32*	52.4±2.70**	49.3±3.35**	45.8±4.60**
DFFM	200	47.5±3.43**	66.2±4.20***	64.1±5.56***	62.6±3.91***
DFFM	400	46.1±3.82**	72.6±2.88***	68.5±3.65***	64.0±2.94***
DFFEA	100	18.8±3.06	34.2±3.26	30.3±2.71	24.7±3.32
DFFEA	200	26.0±3.77	41.2±3.95*	45.3±2.57*	36.6±3.84
DFFEA	400	47.4±2.70**	68.2±2.49***	60.8±3.14**	46.1±2.31*
STD (pentazocine)	5	43.8±1.42**	79.0±2.78***	76.9±2.20***	74.8±2.75***

*Values represent mean ±SEM, n = 6. DFFM: Dolichandrone falcata fruit methanol extract. DFFEA: Dolichandrone falcata fruit ethyl acetate extract. STD: Standard drug. Two-way ANOVA followed by Bonferroni post test. *P < 0.05, **P< 0.01, ***P< 0.001 compared with control group.*

CONCLUSION

The present study demonstrated that DFFM and DFFEA possessed various potential pharmacological properties, namely anti-inflammatory and antinociceptive activities. Phytochemical screening revealed the presence of compounds such as flavonoids, tannins, glycosides, and steroids, which, it has been suggested, act synergistically to produce the observed activities. Thus, the present study supports the folklore use of *D.falcata* fruits for the treatment of various ailments, and the plant's potential pharmacological activities merit further investigation.

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