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Original Article

AN INVESTIGATION OF THE ANALGESIC AND ANTI-INFLAMMATORY EFFECTS OF AERIAL PARTS OF *FLACOURTIA JANGOMAS*

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ABSTRACT

Objective: The present study was aimed to evaluate the analgesic and anti-inflammatory effects of leaf and stem part aqueous extract of *Flacourtia jangomas.*

Methods: Aqueous extract of leaves (ALE) and aqueous extract stem (ASE) part of *Flacourtia jangomas* were sequentially prepared by maceration process and subjected to a preliminary phytochemical screening. The anti-inflammatory activity was assessed by the carrageenan-induced acute rat paw oedema model and Analgesic activity was evaluated by acetic acid-induced writhing model and hot plate method in mice. The data were analysed by one-way ANOVA followed by post hoc Dunnet's test by using SPSS V.15 (student trail version).

Results: The preliminary phytochemical analysis of extracts of leaves and stems indicated the presence of carbohydrate, alkaloids flavonoids, phenols, tannins, saponins**.** The extracts showed significant anti-inflammatory and analgesic activities with a dose-dependent manner. The ethanolic extract from the leave extract of Flacourtia jangomas at the dose 200 mg/kg has 55.6% significant anti-inflammatory activity compared to the standard drugs (44.4%). Even at the low dose leave extract has more potent than aqueous stem extract. Where in analgesic effect by Hot plate method basal reaction time results showed that aqueous extract of stem part at the dose of 200 mg /kg has a significant effect at 120 mts 10.0 sec when compared with std pentazocine 13.0 sec. In peripheral analgesic method Acetic acid-induced writhing model results have not shown much more significant when compared with standard drug (42.1%). The potential to cause anti-inflammation by stem extract was comparatively less than that of leave extract. Thus it could be concluded that Flacourtia jangomas leave extract possess significant anti-inflammatory activity

Conclusion: Our findings suggest that *Flacourtia jangomas* extract is safe and has potential anti-inflammatory and analgesic activities, which promote this use as a food supplement against pain and inflammation related to inflammatory diseases.

Keywords: Anti-inflammatory, Carrageenan, Analgesics, Acetic acid, Pentazocine

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INTRODUCTION

Flacourtia jangomas is an important member of the family *Flacourtiaceae* showing a variety of medicinal uses and found in the lowland and mountain rain forest tree [1]. It is widely cultivated in southeast and East Asia and as escaped cultivation in number of places [2]. The family includes 87 genera and about 900 species and the genus Flacourtia includes 7 species. The species under study is very commonly found in lowland and mountain rain forest tree. It is widely cultivated in the southeast and East Asia and as escaped cultivation in a number of places [2] Aerial parts of the plant is used in the treatment of diabetics, asthma, anemia and antibacterial, antidiarrheal, antioxidant activities [3]. Fruits are widely eaten as pickles, jams, juice [4]. Dried roots are used to suppress toothache [5]. Phytochemical studies of *F. jangomas* revealed several bioactive constituents, including carbohydrates, protein, lipids, alkaloids, glycosides, tannins, etc [6]. *Flacourtia Montana*, a related species used as hepatoprotective, anti-inflammatory and antioxidant activities [7].

The plant has also been investigated pharmacologically for antidiabetics, antibacterial, antioxidant; analgesic, antifungal activities [8]. The related species of *F. Montana*, *F. spare, F. ignoramus*' and *F. romance* have been reported with various pharmacological activities like antibacterial, antidiabetic, anti-inflammatory and hepatoprotective [9]. The analgesic and anti-inflammatory activity of *Flacourtia jangomas* on the methanolic extract was already reported with methanolic extract. So we curious to know the same effect with high polar solvent to know the analgesic and anti-inflammatory activity in aqueous extract of *Flacourtia jangomas*

The current study aimed to validate the traditional use of *F. jangomas* in the management of inflammatory condition and pain. In the present study, we have chosen the plant *Flacourtia jangomas* used in herbal medicine to determine its anti-inflammatory activity and Analgesic activity.

MATERIALS AND METHODS

Animals

Swiss albino mice (20-25 g) and Wistar rats (200-250 g) of both sexes were obtained from the animal house facility Department of Pharmacology, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal. The animals were housed in plastic cages under standard conditions with 12 hrs light: dark cycle with free access to food and water. The study was conducted after obtaining approval (Reg. No. 1158/PO/AC/18) by the Institutional Animal Ethics Committee and was performed in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

Chemicals

The following chemicals were used in the experiments: Carrageenan, diclofenac sodium, Carboxymethylcellulose (CMC), Pentazocine, Acetic acid were purchased from (India).

Plant materials

The whole plant of *Flacourtia jangomas* (Flacourtiaceae) was collected from Pallikkara, Thiruvalla, Pathanamthitta (Dt), Kerala, in November, 2017 and identified by Dr. S. Senthil Kumar (Botanist) at the department of botany, Vivekanandha College of Arts and Sciences for women, Namakkal.

Phytochemical procedure

Extraction

Leaves and stem of *Flacourtia jangomas* were washed thoroughly with water to remove the soil particles, shade dried and grounded. About 800 g of leaf powder was extracted with 2500 ml of distilled

water by cold maceration. About 150 g of stem powder was extracted with 500 ml of distilled water by cold maceration. After completion of the extraction, it was filtered and dried to produce a semisolid mass. The dried extract was stored in a desiccator until use.

Preliminary phytochemical analysis

Flacourtia jangomas extract was subjected to preliminary phytochemical screening through qualitative chemical analysis for confirmation of the phytoconstituents [10, 11].

Acute toxicity tests

Swiss Albino rat weighing 200-250 g selected by random sampling were used in this study. Acute oral toxicity was performed as per OECD-423 guidelines. The animals were fasted overnight, provided only with water. The extracted was administered orally at the dose level of 5 mg/ kg body weight by gastric intubations and the animals were observed for 14 days. The animals were observed for toxic symptoms such as pain, Fur movement, Lachrymal secretion, Nose fluid secretion, Allergy, Pupil size and Diameter, eye colour, body weight, convulsion, mortality for 72h [12].

Pharmacological activity

Anti-inflammatory activity (Carrageenan induced paw oedema in rat)

Anti-inflammatory activity of the aqueous plant extract of *Flacourtia jangomas* was assessed by using a carrageenan induced acute paw oedema model. The albino Wistar rats of both sexes were divided into 6 groups of 4 animals each. Food was withdrawn overnight, but adequate supply of water was given to the rats before the experiment. Group 1 serving as control received 1% w/v carboxy methylcellulose suspension orally. Group 2 serving as standard received 20 mg/kg Diclofenac. Group 3 and 4 received 200, 400 mg/kg of *Flacourtia jangomas* leaf extract respectively. Group 5 and 6 received 200, 400 mg/kg of *Flacourtia jangomas* stem extract respectively. The drugs were given orally with the help of an oral catheter. After 1 hr a sub-plantar injection of 0.1 ml of 1% carrageenan was administered in the right hind paw to all the 6 groups. The paw volume was measured with the help of plethysmograph immediately after injection. The paw volume observed after 1, 2 and 3h [13]. Mean increase in the paw volume was measured and percent inhibition was calculated [14].

Percentages of inhibition were obtained using the following ratio:

$$\text{Percentage inhibition} = \frac{(\text{Vt} - \text{Vo})\text{control} - (\text{Vt} - \text{Vo})\text{treated}}{(\text{Vt} - \text{Vo})\text{control}} \times 100$$

Vt is the average volume for each group after treatment, Vo is the average volume for each group before any treatment.

Analgesic activity

Hot plate method

Analgesic activity of the aqueous plant extract of *Flacourtia jangomas* was assessed by heat. The Hot plate method was performed by Eddy and Leimbach. The pre-screened swiss albino mice showed the reaction time of 3 to 5 Sec and were selected and randomly divided into six groups of four mice per group. Group – 1 were given 1% CMC solution 10 ml/kg (control), Group – 2 were given pentazocine 4 mg/kg i. p.(standard), while Group - 3 and Group – 4 received 200 and 400 mg/kg of leaf extract of *Flacourtia jangomas*, Group – 5 and Group - 6 received 200 and 400 mg/kg of stem extract of *Flacourtia jangomas*. Extract respectively all by gastric gavage. Animals were placed on Eddy's hot plate maintained at 55 ± 1 ^{o}C. The reaction time in control and treated animals was recorded till they showed licking or jumping movements [15]. The cut-off time was considered as 10 Sec. The reaction time was recorded at 0, 30, 60, 90, and 120 min following administration of the test drug.

Acetic acid-induced writhing method

Acetic acid-induced writhing model was performed by the method of koster *et al.*, with slight modification. Twenty four albino mice of both sexes were randomly divided into six groups of four mice per group. Group – 1 were given 1% CMC solution 10 ml/kg (control), Group – 2 were given diclofenac sodium 20 mg/kg i. p. (Standard), while Group – 3 and Group – 4 were received 200 and 400 mg/kg of leaf extract of *Flacourtia jangomas,* Group – 5 and Group – 6 received 200 and 400 mg/kg of stem extracts of *Flacourtia jangomas.* Extracts respectively all by gastric gavage. One hour after administration of drug and extract, 0.6% glacial acetic acid (10 ml/kg) was given i. p. to all the mice to induce pain characterized by abdominal constrictions are wriths. The number of wriths observed in each mouse was counted for 10 mins and recorded [16-18]. The percentage protection against abdominal writhing was used to assess the degree of analgesia and was calculated using the formula,

$$\%\ \text{inhibition of writhing} = \frac{\text{No. of wriths in control} - \text{No. of wriths intreated group}}{\text{No. of wriths in control group}} \text{X100}$$

Statistical analysis

The results of the study were expressed as Mean ± SEM and statistical significance between control and treated groups, standard and treated groups evaluated by one-way ANOVA followed by post hoc Dunnet's multiple comparison test by using SPSS V.15 (Student trail version). P<0.05 was considered significant.

Table 1: Showing the preliminary phytochemical screening of leaf and stem part of *Flacourtia jangomas*

S. No.	Test	Aqueous extract of leaf	Aqueous extract of stem
1	CARBOHYDRATES		
	a) Molisch test	+	+
	b) Fehling's test	+	+
	c) Benedict test	+	+
2	ALKALOIDS		
	a) Dragondroff 's test	+	+
	b) Mayer's test	+	+
	c) Hager's test	-	-
3	SAPONINS:	+	+
4	GLYCOSIDES		
	a. Legal's test	-	-
	b. Balget's test	-	-
	c. Bontrager's test	+	+
5	FLAVONOIDS	+	+
6	PROTEINS and AMINO ACIDS	+	+
7	STEROIDS		
	a) Salkowski test	+	+
8	TANNINS and PHENOLIC COMPOUNDS:	+	+

+Presence -Absence

RESULTS

Preliminary phytochemical analysis

The aqueous extract of *Flacourtia jangomas* was subjected to a preliminary phytochemical screening revealed the presence of carbohydrates, alkaloids, saponins, glycosides, flavonoids, proteins, tannins and steroids.

Acute toxicity test

The aqueous extract of *Flacourtia jangomas* produced no toxic symptoms or mortality up to a dose level of 2000 mg/kg body weight orally in rats, Hence the drug was considered safe for further pharmacological screening. So 1/10th and 1/5th (200 mg and 400 mg, respectively) of toxic dose were selected for all *in vivo* experiments submaximal and maximal dose.

Anti-inflammatory activity

The anti-inflammatory effect of aqueous extract of *Flacourtia jangomas* was assayed in the carrageenan-induced paw edema in rat. The injection carrageenan when injected into a sub-plantar region of the rat paw produced localized edema that reached to its maximum at the 3rd h after injection. The localized inflammatory response to carrageenan was sustained for 4 h and gradually declined after this time.

As shown in table 2, *Flacourtia jangomas* produced a marked reduction in carrageenan-induced paw edema (55.6% at 200 mg/ kg leaf extract) at the 3rd h. The difference between the paw volume of the control and extracts treated animals was statistically significant ($p<0.001$) at the 2nd h of the observation. The standard drug Diclofenac sodium at 20 mg/kg produced about 44.4% inhibition of the carrageenan-induced edema as shown in table 1.

Table 2: Anti-inflammatory effect of leaf and stem part of *Flacourtia jangomas* on carrageenan-induced acute paw oedema in Wistar albino rats

Treatment	Increase in paw volume in ml (Mean ± SEM)					% inhibition after 3h
	0h	½ h	1h	2h	3h	
1% CMC	0.25 ± 0.03	0.55 ± 0.03	0.65 ± 0.03	0.55 ± 0.03	0.45 ± 0.03	-
Diclofenac sodium 20 mg/kg/*p. o* +0.1 ml Carrageenan	0.25 ± 0.03	0.35 ± 0.03 a***	0.30 ± 0.01 a**	0.30 ± 0.01 a***	0.25 ± 0.03 a***	44.4%
ALE-200 mg/kg/*p. o*+0.1 ml Carrageenan	0.20 ± 0.01	0.33 ± 0.03 a***	0.23 ± 0.03 a**,b*	0.23 ± 0.03 a***, b*	0.20 ± 0.01 a***	55.6%
ALE-400 mg/kg/*p. o*+0.1 ml Carrageenan	0.20 ± 0.01	0.35 ± 0.03 a***	0.23 ± 0.03 a***, b*	0.23 ± 0.03 a***, b*	0.23 ± 0.03 a***	48.9%
ASE-200 mg/kg/*p. o*+0.1 ml Carrageenan	0.23 ± 0.05	0.33 ± 0.03 a***	0.25 ± 0.03 a***	0.23 ± 0.03 a***, b*	0.25 ± 0.03 a***	44.4%
ASE-400 mg/kg/*p. o*+0.1 ml Carrageenan	0.25 ± 0.06	0.40 ± 0.01 a***	0.30 ± 0.01 a***	0.30 ± 0.01 a***	0.25 ± 0.03 a***	44.4%

Values are expressed as Mean ± SEM, n=4, the symbol represents statistical significance: a=comparison of Group-1 Vs Group-2,3,4,5 and 6; b= comparison of Group-2 Vs Group-1, 3,4,5 and 6. ***P<0.001, **P<0.01 and *P<0.05, one way ANOVA by Dunnet's multiple comparison test as compared to control and standard.

Table 3: Central analgesic activity of aqueous extract of *Flacourtia jangomas* on reaction time to hot plate method in mice

Treatment	Basal reaction time (sec)				
	Basal	30 min	60 min	90 min	120 min
1% CMC	7.3 ± 0.67	6.7 ± 0.88	8.3 ± 0.33	9.3 ± 0.76	9.7 ± 0.32
Pentazocine (4 mg/kg *i. p*	7.3 ± 0.20	9.3 ± 0.88*	15.0 ± 0.45**	13.0 ± 0.15	13.0 ± 0.23
ALE-200 mg/kg/p. o	7.6 ± 0.88	8.0 ± 0.15	11.0 ± 0.08	9.0 ± 0.58	9.7 ± 0.76
ALE-400 mg/kg/p. o	8.0 ± 0.52	8.7 ± 0.32	9.3 ± 0.85	9.3 ± 0.88	8.7 ± 0.32
ASE-200 mg/kg/p. o	9.0 ± 0.57	8.3 ± 0.23	12.7 ± 0.10*	10.3 ± 0.88	10.0 ± 0.45
ASE-400 mg/kg/p. o	8.0 ± 0.58	9.3 ± 0.67*	11.0 ± 0.73	10.0 ± 0.52	7.3 ± 0.88

Values are expressed as Mean ± SEM, n=4, the symbol represents statistical significance: a=comparison of Group-1 Vs Group-2,3,4,5 and 6; b= comparison of Group-2 Vs Group-1, 3,4,5 and 6. ***P<0.001, **P<0.01 and *P<0.05, one way ANOVA by Dunnet's multiple comparison test as compared to control and standard.

Table 4: Peripheral analgesic activity of *Flacourtia jangomas* on acetic acid induced writhing method in mice

Treatment	Total no. of writhing (in 10 min)	% Inhibition
1% CMC	44.33 ± 1.76	-
Pentazocine (4 mg/kg i. p +0.6% Acetic acid)	25.67 ± 4.84**	42.1 %
ALE-200 mg/kg/p. o+0.6% Acetic acid	28.00 ± 7.57*	36.8 %
ALE-400 mg/kg/p. o+0.6% Acetic acid	52.00 ± 1.58	-
ASE-200 mg/kg/p. o+0.6% Acetic acid	29.33 ± 4.18*	33.8 %
ASE-400 mg/kg/p. o+0.6% Acetic acid	52.67 ± 2.33	-

Values are expressed as Mean ± SEM, n=4, the symbol represents statistical significance: a=comparison of Group-1 Vs Group-2,3,4,5 and 6; b= comparison of Group-2 Vs Group-1, 3,4,5 and 6. ***P<0.001, **P<0.01 and *P<0.05, one way ANOVA by Dunnet's multiple comparison test as compared to control and standard.

DISCUSSION

Anti-inflammatory activity of *Flacourtia jangomas* was determined by the carrageenan-induced acute paw edema model, which is one of the most feasible methods of screen anti-inflammatory agents. The carrageenan-induced acute inflammation is biphasic, in the early phase (1-2 h after carrageenan injection), edema production is mediated by histamine, serotonin and kinins while in the late phase

(after 2 h), the inflammatory response is maintained by bradykinin and prostaglandins [19]. These mediators are well established for their role in an inflammatory reaction which is measured at 3 h. In the present investigation, *Flacourtia jangomas* exhibit marked anti-inflammatory activity in the early phase of carrageenan-induced edema test similar to diclofenac, a standard non-steroidal anti-inflammatory drug (NSAID). Aqueous extract of *Flacourtia jangomas* produced a significant ($p<0.001$) inhibition of carrageenan-induced paw edema at 2h in a dose-dependent manner. Therefore, it can conclude that the inhibitory effect of aqueous extract of *Flacourtia jangomas* on carrageenan-induced inflammation could be due to inhibition of the inflammatory enzyme cyclooxygenase and subsequent inhibition of prostaglandin synthesis, significant inhibition of paw edema in the yearly hours after carrageenan injection by *Flacourtia jangomas* could be attributed to the inhibition of prostaglandin [20].

Antinociceptive activities of aqueous extract of *Flacourtia jangomas* were evaluated by acetic acid-induced writhing method and hot plate method. This method allows the analysis of peripheral and centrally mediated antinociceptive responses respectively.

The hot plate method is commonly used to assess the centrally acting analgesics. The analgesic activity of *Flacourtia jangomas* was tested upon adult mice by the hot plate method. The aqueous extract of stem at lower dose of 200 mg/kg shows significant (p 0.05) analgesic activity when compared to standard pentazocine 4 mg/kg.

The aqueous stem extract (200 mg/kg) may be activate the opioid receptor at the interneuronal level, which produces hyperpolarisation of the neurons, result in the inhibition of the firing and the release of tachykinin neuropeptides, a neurotransmitter involved in pain transmission, thereby blocking the pain transmission that causes a prolongation of the hot plate latency by this model must be acting centrally [21].

The analgesic activity of *Flacourtia jangomas* was tested upon adult mice by acetic acid-induced writhing method. The aqueous extract of leaf and stem at low dose of 200 mg/kg shows significant ($p<0.05$) analgesic activity when compared to standard diclofenac sodium 20 mg/kg. Bradykinin, neurokinins and prostanoids are known mediators for acetic acid-induced writhing [22,24]. The effect of the aqueous leaf and stem extracts of *Flacourtia jangomas* at low concentration produces antinociceptive activity. It may be depressed the production of irritants and their by reduction in the number of writhes on the mice.

The abdominal contraction induced by acetic acid is a sensitive produced to establish peripherally acting antinociceptives. This response is thought to involve local peritoneal receptor [23]. The result of the current study indicates the analgesic effect of *Flacourtia jangomas*, might be mediated by inhibiting the synthesis or acting on peripherally acting nociceptive.

The present study reveals that the leaf and stem part of aqueous extract of *Flacourtia jangomas* found to possess the peripheral and central analgesic activity and significant anti-inflammatory activity.

CONCLUSION

In conclusion, our results reveals that among all the extracts of leaves and stem of *Flacourtia jangomas* aqueous extracts exhibited significant analgesic and anti-inflammatory activities. These findings validated the claim for the traditional use of this plant in the treatment of pain and inflammatory ailments activities. In addition to this, research regarding the mechanism responsible for these activities is also required which will guarantee its clinical worth.

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The study substantiates the traditional use of *F. jangomas* as a remedy of inflammatory and pain condition. The finding of this study will help natural product researcher to identify the active constituent of this plant and precise underlying mechanism as possible anti- inflammatory and analgesic drug candidate with good safety and tolerability profile.

AUTHORS CONTRIBUTIONS

All authors have contributed equally in this piece of work

CONFLICT OF INTERESTS

The authors declared no conflict of interest

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