

# Analgesic and Anti-inflammatory Activity of *Ficus glomerata* in Experimental Animal Models

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## ABSTRACT

The anti-inflammatory and analgesic activity of various extracts of *Ficus glomerata* Roxb. were evaluated in experimental animals. We have determined the anti-inflammatory and analgesic activity of various extracts of the dried fruits of *Ficus glomerata* by oral administration at doses of 200 and 400 mg/kg of body weight to healthy animals. The extracts were studied for their anti-inflammatory activity in carageenan induced hind paw edema in rats and the paw volume was measured plethysmometrically after 3 hours of injection. The extracts were also evaluated for analgesic activity using Eddy's hot plate method in mice. The extracts of *Ficus*

*glomerata* significantly reduced carageenan-induced hind paw edema in rats. The extracts showed significant analgesic activity, evidenced by increase in the reaction time by the Eddy's hot plate method in mice. The extracts showed a similar anti-inflammatory and analgesic effect compared to standard drugs indomethacin and diclofenac sodium, respectively. The present results indicated that the ethanolic extract of *Ficus glomerata* exhibited significantly more activity than other extracts in reducing the pain and inflammation in experimental models.

**KEYWORDS:** *Ficus glomerata*; anti-inflammatory; analgesic; pain; paw edema; writhing.

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## Introduction

The history of herbal medicines is as old as human civilization. Nature has provided a complete store house of remedies to cure all ailments of mankind. The knowledge of drugs has accumulated over thousands of years as a result of mans inquisitive nature so that today we possess many effective means of ensuring health care (Kokate, 2008). In general natural drug substances offer four

vital and appreciable roles in the modern system of medicine, thereby adequately justifying their legitimate presence in the prevailing therapeutic arsenal namely: serve as extremely useful natural drugs, provide basic compounds affording less toxic and more effective drug molecules, allow exploration of biologically active prototypes towards newer and better synthetic drugs, and allow modification of inactive natural products by suitable biological/chemical means into

potent drugs (Kar, 2003).

In recent times, focus on plant research has increased all over the world and a large body of evidence has been collected to show the immense potential of medicinal plants used in various traditional systems. Inflammation is the response of living tissues to injury; acute and chronic inflammations are a complex array of enzyme activation, mediator release, extravasations of fluid, cell migration, tissue breakdown and repair. Anti-

inflammatory agents exert their effects through a spectrum of different modes of action (Shikha et al., 2010). Pain is a sensorial modality which in many cases represents the only symptom for the diagnosis of several diseases. It often has a protective function throughout history and man has used several therapies for the management of pain. Medicinal herbs are highlighted due to their wide use and less side effects (Mate et al., 2008).

The genus *Ficus*, commonly known as figs, belongs to the family Moraceae (The Wealth of India, 2002) and constitutes an important group of trees with immense medicinal value. There are over 600 species of *Ficus*, of which four species, viz. *Ficus racemosa* Linn. (Cluster fig), *Ficus microcarpa* Linn. f. (Chinese or Malayan banyan), *Ficus religiosa* Linn. (Peepal tree or Sacred fig) and *Ficus benghalensis* Linn (Banyan tree) are medicinally important (Gracy et al., 2011). *Ficus glomerata* (syn. *Ficus racemosa*) is a widely cultivated plant all over India. It has been reported to have many medicinal properties (Nadkarni, 2002). The roots are used as a medicine against hydrophobia. Its fruits are effective against gastric ulcer (Rao et al., 2008), leprosy, diseases of the blood, fatigue, bleeding nose and cough. Its bark is helpful against asthma and its leaves are used against bronchitis and as anti-fungal agent (Vonshak

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**ABBREVIATIONS:** PE = petroleum ether; CH = chloroform; AC = acetone; ET = ethanol; AQ = aqueous; PG= prostaglandin.

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et al., 2003). It is used as carminative, astringent, vermifuge, and anti-dysentery drug.

The extract of fruit is used in diabetes (Kar et al., 2003) and leucoderma. The plant is used locally to relieve inflammation of skin wounds, lymphadenitis, sprains, and fibrositis. The alcoholic extract of the stem bark of the plant possessed anti- protozoal activity against *Entamoeba histolytica*. It is used in the treatment of mumps, small pox, haematuria (Khan and Sultana, 2005; Mandal et al., 2000), uterine disorders (Pulok et al., 1996), inflammatory conditions (Forestieri et al., 1996), hepatoprotective and anti-oxidant activity (Channabasavaraj et al., 2008).

The literature survey reveals inadequate information on the anti-inflammatory and analgesic activities of the fruit extracts of *Ficus glomerata* Roxb. This prompted us to investigate the anti-inflammatory and analgesic activities of the fruit extracts of *Ficus glomerata* Roxb.

## Material and Methods

### Collection and Authentication of Plant Material

The fruits of *Ficus glomerata* Roxb. (Family: Moraceae) were collected in the first week of March from fruiting trees in places around Bajpe, Mangalore, Karnataka, India. The plant material was taxonomically identified by Dr. Noeline J. Pinto, HOD, Dept of Botany, St. Agnes College, Mangalore, Karnataka.

The fruits were washed with water and then air dried for a week at 35-40 °C. The seeds were separated and kept aside and

only pulp was used. The material was then homogenized to a coarse powder using a mechanical grinder and stored at room temperature in a closed container for further experimental use.

### Extract Preparation

The powdered drug was repeatedly extracted in a Soxhlet apparatus using solvents of increasing polarity with petroleum ether, chloroform, acetone, ethanol and distilled water and refluxed for 48 hours with each solvent. The extracts were collected and concentrated by evaporation and dried in vacuo and used for subsequent experiments (Kokate et al., 2008).

### Chemicals

All the chemicals were of analytical grade and were either Sigma or Merck chemicals.

### Animals

and maintained under standard laboratory conditions of a 12 hour light and dark cycle with relative humidity  $55 \pm 5\%$  and at  $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ . They were allowed free access to standard dry pellet diet and water ad libitum.

### Acute Oral Toxicity Studies

Acute oral toxicity studies were performed according to OECD 423 guidelines (acute toxic class method). Three mice of either sex were selected for the study, and various extracts of *Ficus glomerata* Roxb. were administered with a higher dose of 2000 mg/kg (p.o.). The mice fasted overnight, with free access to water prior to test extract. Individual mice was observed after dosing at least once during the first 30 min, periodically during the first 24 hours with special attention given during the first 4 hour and daily thereafter for a total of 14 days (OECD/OCED 423,2001).

Animals were observed individually for behavioral, neurological and anatomic profiles. The observations were tabulated according to Irwin's table (Vogel, 2006).

### Screening of Anti-inflammatory Activity

Animal study protocol was approved by the Institutional and Animal Ethical Committee, CPCSEA. Wistar male rats (150-200 g) and Swiss albino mice (20-25 g) obtained from the institute's animal house were used for the studies. These animals were acclimatized to laboratory conditions for 7 days before commencement of experiments. The animals were grouped and housed in polyacrylic cages with no more than 6 animals per cage

Carrageenan induced paw edema in rats. Wistar rats weighing between 150-200 g were used for the study. Rats were divided into thirteen groups of six animals each.

Group I – Control: 1% Tween 80

Group II- negative control: carrageenan 1% w/v

Group III - standard: Indomethacin sodium (10 mg/ml, p.o.)

Group IV&V-petroleum ether extract (200 & 400 mg/kg, respectively, p.o.)

Group VI & VII-chloroform extract (200 & 400 mg/kg, respectively, p.o.)

Group VIII & IX- acetone extract (200 & 400 mg/kg, respectively, p.o.)

Group X & XI- ethanol extract (200 & 400 mg/kg, respectively, p.o.)

Group XII & XIII-aqueous extract (200 & 400 mg/kg, respectively, p.o.)

Indomethacin and test drugs were administered 30 minutes before carrageenan administration. Carrageenan 1% w/v in normal saline was injected into the sub-plantar region of left hind paw of all groups of animals with the right hind paw serving as a control. The hind paw volume was measured just before and 3 hours after carrageenan injection using a plethysmometer. The difference in the paw volumes indicated the degree of inflammation (Sreelekshmi et al., 2007; Kalpesh et al., 2008). Data is tabulated in Table 1.

Percentage inhibition was calculated as

$$\frac{V_c - V_t}{V_c} \times 100$$

Where,  $V_c$  = volume of control, and  $V_t$  = volume of test.

TABLE 1

Effect of Ficus glomerata fruit extracts on carageenan-induced paw edema in rats.

Group	Treatment	Paw volume	% inhibit
I	Control	0.0±0.0	0
II	Carageenan Only	0.70±0.02	0
III	Standard Indomethacin 5	0.20±0.02	71.42
IV	PE 200mg	0.50±0.02	28.57
V	PE 400 mg	0.50±0.02	28.57
VI	CH 200 mg	0.50±0.03	28.57
VII	CH 400 mg	0.50±0.03	28.57
VIII	AC 200 mg	0.30±0.02	57.14
IX	AC 400 mg	0.40±0.02	42.85
X	ET 200 mg	0.30±0.02	57.14
XI	ET 400 mg	0.30±0.02	57.14
XII	AO 200 mg	0.30±0.03	57.14
XII	AO 400 mg	0.30±0.03	57.14

ANOVA followed by Dunnet's multiple comparison test used. Values are expressed as MEAN±SEM, N=6.  
\*p<0.01, when compared with negative control (only carageenan)

TABLE 2

### Screening of Analgesic Activity

Eddy's hot plate model in mice. Swiss albino mice weighing about 25-30 g were selected for the study. All animals fasted for 18 hours. The hot plate was maintained at 55°C ± 5°C. A cut-off period of 15 seconds was observed to avoid damage to the paw. The reaction time in the control and treated animals was recorded at 0, 30, 60, 90 and 120 minutes following the administration of drugs.

The animals were divided into twelve groups of six animals each.

Group I – Control: 1% Tween 80

Group II - standard: diclofenac sodium (10 mg/ml, p.o.) Group III&IV-petroleum ether extract (200 & 400 mg/kg respectively, p.o.)

GroupV&VI-chloroform extract (200 & 400 mg/kg respectively, p.o.)

GroupVII & VIII- acetone extract (200 & 400 mg/kg respectively, p.o.)

Group IX & X- ethanol extract (200 & 400 mg/kg respectively, p.o.)

Group XI & XII-aqueous extract (200 & 400 mg/kg respectively, p.o.)

The increase in reaction time against control group was compared and calculated (Sandhya et al., 2011; Mohammed et al., 2007). Data is tabulated in Table 2.

### Statistical Analysis

All the values of the experimental results were expressed as mean  $\pm$  S.E.M. The values were analyzed by ANOVA and Dunnett's t-test for significant differences between various groups. Statistical analysis was carried out using Graph pad prism 4.0 (Graph pad software, San Diego, CA).

## Results

### Acute Toxicity Study

The various extracts of *Ficus glomerata* Roxb. did not produce any mortality at the highest dose employed. Selected doses were found

Analgesic activity of fruit extracts of *Ficus glomerata* by Eddy's hot plate method.

Group	Treatment	Reaction time in second				
		0 min	30 min	60 min	90 min	120 min
I	Control Tween	3.31+0.00	3.20+0.00	3.11+0.00	3.52+0.00	3.61+0.00
II	Standard	3.33+0.06	12.15+0.30	13.13+0.23	13.72+0.08	14.65+0.13
III	PE 200mg	3.23+0.04	3.33+0.06	3.23+0.01	3.55+0.04	3.53+0.03
IV	PE 400 mg	3.35+0.02	3.24+0.03	3.14+0.04	3.53+0.03	3.62+0.03
	CH 200 mg	3.34+0.03	3.21+0.03	3.13+0.03	3.52+0.02	3.65+0.03
VI	CH 400 mg	3.23+0.04	3.22+0.04	3.14+0.03	3.62+0.03	3.63+0.02
VII	AC 200 mg	3.34+0.04	7.59+0.03	8.67+0.01	9.48+0.01	10.26+0.03
VIII	AC 400 mg	3.53+0.03	9.01+0.04	10.27+0.03	11.37+0.02	11.93+0.03
IX	ET 200 mg	3.35+0.02	8.56+0.03	9.98+0.05	11.98+0.03	12.58+0.01
XI	ET 400 mg	3.23+0.01	9.36+0.02	10.28+0.02	12.05+0.03	13.01+0.04
XII	AO 200 mg	3.31+0.00	8.83+0.06	10.27+0.02	11.62+0.01	12.15+0.02
XIII	AO 400 mg	3.62+0.03	9.30+0.02	10.68+0.02	12.07+0.03	12.89+0.02

ANOVA followed by Dunnett's multiple comparison test used. Values are expressed as MEAN $\pm$ SEM, N=6. \*p<0.01 when compared to control

to be safe. Two doses (200 and 400 mg/kg, p.o.) were selected for further pharmacological studies.

### Anti-inflammatory Study

In this model and in a groups PE 200, PE 400, CH 200, CH 400, AC 200, AC 400, ET 200, ET 400, AQ 200, and AQ 400 (p < 0.01) the paw edema induced by carageenan was significantly reduced. The maximum paw edema reduction was shown by ET 200, ET 400, AQ 200, AQ 400 groups. In the standard indomethacin (10 mg/ml) group, difference in paw volume was 0.2 ml (Table 1).

### Analgesic Study

In this model, the analgesic effects in AC, ET and AQ groups increased significantly (p < 0.01) in comparison to the control group. The maximum effect of the test drug was observed at the dose of 400 mg/kg of ET extract at 120 minutes, which showed a value of 13.01 seconds. The standard drug diclofenac (10 mg/kg) showed maximum effect at 120 minutes with value of 14.65 seconds (Table 2).

## Discussion

Among several traditional claims, the utility of *Ficus glomerata* in inflammation and pain has been emphasized only in literature. Hence, results of present investigations might give scientific authentication to the traditional claims (Warokar et al., 2010).

Any injury or tissue damage is associated with pain and inflammation. Analgesics can act on peripheral or central nervous system. Peripherally acting analgesics act by blocking the generation of impulses at chemoreceptors site of pain while centrally acting analgesics not only raise the threshold for pain but also alter the physiological response to pain and suppress the patient's anxiety and apprehension. Pain and inflammation are an essential prelude to the repair process (Chandana et al., 2011).

Carageenan-induced paw edema was taken as a prototype of the exudative phase of acute inflammation. Inflammatory stimuli microbes, chemicals and necrosed cells activate the different mediator systems through a common trigger mechanism. The development of carageenan induced edema is believed to be biphasic. The early phase is attributed to the release of histamine and serotonin and the delayed phase is sustained by the leucotrienes and prostaglandins. Flavonoids and tannins are reported to inhibit PG synthesis. Most of the non steroidal anti-inflammatory drugs (NSAIDs) have well balanced anti-inflammatory and ulcerogenic activities which are considered to be due to PG synthetase inhibitor activity (Somnath et

al., 2008).

## Conclusion

From the above studies it can be suggested that the fruit extracts of *Ficus glomerata* possess promising anti-inflammatory and analgesic properties. These effect may be beneficial for the management of pain. Further studies on isolation and fractionation of the active components from the fruits of *Ficus glomerata* are underway to determine the exact constituents that are responsible for these activities.

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