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EVALUATION OF IN-VIVO ANALGESIC AND ANTIINFLAMMATORY ACTIVITIES OF ETHANOLIC LEAF EXTRACT OF CORDIA MYXA

Tekimudi Lovakumari*, K. Ravi Shankar, S. Amala and V. Bhaargavi

Aditya College of Pharmacy, Surampalem, Pin no.533437.

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***Corresponding Author**
Tekimudi Lovakumari
Aditya College of Pharmacy, Surampalem, Pin no.533437.

ABSTRACT

The presented research deals with the evaluation of analgesic and anti-inflammatory activities of the ethanolic extract of Cordia myxa leaves on albino Wister rats. Analgesic activity was observed in albino Wister rats of both sexes using paradigms such as the tail flick method, the eddy hot plate method. While anti-inflammatory activity was observed using the carrageenan-induced paw edema method. In the tail flick method and eddy's hot plate method, rats were treated with the extract at doses (100 mg/kg and 200 mg/kg) Po was observed at 0, 15, 30, 60, 120 minutes. Rats treated with the extract were compared with standard tramadol (5 mg/kg). In the tail flick method, Cordia myxa extract at a dose of 200 mg/kg significantly increases the latency of the nociceptive reaction of the tail withdrawal from the heat source. In the eddy's hot plate method, the extract at a dose of 200 mg/kg significantly increases the latency of jumping and licking responses. In the carrageenan-induced paw edema method, rats were treated with the extract at doses (100 mg/kg and 200 mg/kg) Po and observed at 0, 1, 2, 3, 4 hours and compared with standard Diclofenac sodium (10 mg/kg). Leaf extract at a dose of 200 mg/kg showed maximum percent inhibition of paw edema in rats at 4 h.

KEYWORDS: Analgesic activity, Anti-inflammatory activity, Carrageenan, Eddy's hot plate method.

INTRODUCTION

Inflammation is a physiological process that involves the intervention of the immune system. The key role of inflammation is to protect organisms against microbial infections, and in some instances, it acts as a physiological defense mechanism against certain diseases such as cancer.[1] However, under certain circumstances, inflammation can become harmful, leading

to serious pathological conditions. The prolonged overexpression of inflammatory factors can alter several physiological processes by activating numerous signaling pathways, especially the transcriptional factor nuclear factor kappa B (NF-κB), which regulates the expression of multiple inflammatory genes that induce the inflammatory process.[2] Cellular inflammation can be the driving factor for several diseases, leading to cell death and organ damage, or cellular stimulation, thus initiating tumor formation. Chronic inflammation is considered as an integral part of developing various diseases, including diabetes, heart diseases, cancer, digestive disorders, autoimmune diseases, or neurodegenerative disorders. Non-steroidal anti-inflammatory drugs (NSAIDs) continue to be the mainstays of managing pain and inflammation of chronic course conditions. Despite their efficacy, prolonged use of NSAIDs was found to be associated with renal and gastric adverse drug reactions (ADRs); linked to NSAID-mediated inhibition of the cyclooxygenase 1 (COX-1) enz. Gastrointestinal erosions, ulcerations and bleeding have, for long, been the most commonly reported ADRs, with a 15–30% incidence rate of peptic ulcers among NSAID use. Cardiovascular ADRs, particularly increased risk of thromboembolic events and myocardial infarction, have been reported, and may be attributed to COX-2 mediated inhibition of prostacyclin synthesis Moreover, the use of COX-2 inhibitors is still associated with renal adverse reactions, due to the constitutive expression of both COX-1 and COX-2 in renal tissue. To meet the need for efficacious anti-inflammatory drugs that can overcome the debilitating side effects of currently available medications, scientists have directed their efforts toward identifying safe and effective anti-inflammatory agents from herbal medicines. Secondary metabolites of medicinal plants, including polyphenols, flavonoids, terpenoids, and alkaloids, are essential sources for developing anti-inflammatory and analgesic drugs.[6,7,8] Recent reports have revealed that these molecules exhibit an anti-inflammatory effect by suppressing inflammatory mediators involved in inflammatory processes, including cytokines, chemokines, and pro- and neo-inflammatory mediators.[9] There exist numerous examples of successful drug development from medicinal plants. Morphine was discovered from natural sources and remains one of the most potent analgesic drugs for pain management Morphine was isolated from poppy latex (*Papaver somniferum*). Typically, analgesics can be categorized as morphine and non-morphine analgesics. used for treating chronic pain, hyperalgesia, hepatic and renal colic, myocardial infarction, acute lung edema, and postoperative pain. However, these analgesics present several side effects, including addiction, nausea, constipation, and respiratory depression. In an attempt to overcome some side effects associated with morphine, numerous semisynthetic derivatives have been developed, including codethyline, pholcodine, and

diamorphine, as well as synthetic products such as pethidine, phenoperidine, and buprenorphine. Chemical screening of the Cordia myxa leaves and fruits led to the discovery of pyrrolizidine alkaloids, coumarins, flavonoids, saponins, terpenes, and sterols which are responsible for its anti-inflammatory and analgesic activity.

MATERIALS AND METHODS

Albino Wister rats weighing 150-200 grams were used in the experimental studies. Drugs used in the study include tramadol, paracetamol, diclofenac sodium, normal saline, gum arabic (0.5%), ethanol (95%) and instruments are Eddy plate (analgesiometer), plate, centrifugal UV – single beam spectrophotometer.

Two dose levels were chosen to determine the analgesic and anti-inflammatory activity. The plant extract was administered orally along with 2% gum acacia using an oral feeding tube attached to a syringe. Selected Albino Wister rats of both sexes weighing 150-200 grams were divided into 4 groups of two rats each. All animals were housed at room temperature and each group had a labeled cage. Animals were allowed time to adapt to the new environment and were provided with food and water ad libitum.

The main aim of this study is to evaluate the In-vivo analgesic and anti-inflammatory actives of Ethanolic leaf extract of Cordia myxa

1. Screening of analgesic effect of Ethanolic leaf extract of Cordia myxa

- **In-vivo methods**

1. Tail flick method using hotplate
2. Eddy’s hotplate method using Analgesiometer (thermal method)
3. Tail immersion method.
4. Screening of Anti-inflammatory activity of Ethanolic leaf extract of Cordia myxa.

- **In-vitro methods:** A. Protein denaturation method B. Egg albumin denaturation method
- **In-vivo method:** A. Carrageenan induced paw oedema method

Painful reaction in experimental animals can be produced by applying noxious stimuli like

- Thermal
- Chemical
- Physical presuure

1. Tail flick method using hotplate

Albino Wister rats of both sexes were chosen, and were numbered according to the group. Take basal reaction time to radiant heat by placing the tip (last 1-2 cm) of the tail on the radiant heat source. The end point is defined as the tail becoming disconnected from the heat source. Rats typically take 3 to 5 seconds to withdraw. A cutoff of 10-12 seconds has been established to prevent tail injury. Any animal whose withdrawal duration is shorter than 3 to 5 seconds was not included in the study. Take at least 3-5 basal reactions for each rat at a gap of 5 minutes to confirm normal behavior of the animals. Inject 100 & 200 mg/kg of an ethanolic leaf extract *Cordia myxa* and 5 mg/ kg of Tramadol. Take note of the reaction times at 0, 15, 30, 60, and 120 minutes following the administration of the drug. Maximum analgesia is considered when the reaction time reaches 10 seconds and the tail is removed from the source of heat to avoid tissue damage. Using this technique, the analgesic efficacy of an ethanolic leaf extract *Cordia myxa* was tested. Calculated the percentage increase in reaction time at a specified interval.

Percentage (%) inhibition = (Pt – Po/Po) × 100

(Pt = pain threshold at time "t" intervals Po = pain threshold at “0” interval)

2. Eddy’s hot plate method

Albino Wister rats of both sexes weighting about (150-200 grams) were selected and numbered according to groups. Animals were located on hot plate which was maintained at stable temperature• (55ºC). Take the basal reaction time by observing the hind paw licking or jumping response. Animals were given with doses of 100 & 200 mg/kg of extract and tramadol (5 mg/kg) to record the response time of animals on hot plate at 0, 15, 30, 60, 120 minutes after drug administration. Response duration of animals expanded with tramadol, where 15 seconds was taken as maximum analgesia. Animals were displaced from hot plate to prevent damage to paws. The analgesic effect of Ethanolic leaf extract of Cordia myxa was determined by this process. Calculate the percent development in response time at each interval. Percentage (%) inhibition = (Pt – Po/Po) × 100 Pt = pain threshold at time "t" intervals Po = pain threshold at “0” interval.

3. Tail immersion method

Albino Wister rats of both sexes weighting about (150-200 grams) were selected and numbered according to groups. The rats lower 5 cm of tail is immersed in water held at a steady temperature (55ºC) in a beaker. The time it took for the tail to pull itself out of the

water in seconds was used as a reaction time, with a cut off time of 10 seconds for immersion. The reaction time was determined 1 hour before and after extracts (100 & 200 mg/kg) or distilled water (10 ml/kg) were given orally. 30 minutes before the test diclofenac sodium (10 mg/kg) was given.

Percentage (%) inhibition = (Pt – Po/Po) × 100

(Pt = pain threshold at time "t" intervals)

1. In-vitro methods

A. Protein denaturation method

- Test solution (0.5ml) which contains 0.45ml of Bovine Serum Albumin and 0.05ml test samples of various concentrations (10, 25, 50, 100 & 200 µg/ml). • Test control (0.5ml) which contains 0.45ml Bovine serum albumin and 0.05mlof distilled water. • Product control (0.5ml) in which that contains 0.45ml of distilled water and 0.05ml of test samples of various concentrations (10, 25, 50, 100 & 200 µg/ml).
- Standard (0.5ml) in which that contains 0.45ml of Bovine serum albumin and 0.05ml of various concentrations of Diclofenac sodium (10, 25, 50, 100 & 200 µg/ml). The above mixtures are maintained at P H 6.3 with IN HCI. They are incubated for 20 minutes at 37ºC and temperature is raised and kept the samples at 57ºC for 3 minutes. Later cooled the sample to room temperature, 2.5 ml of phosphate buffer (6.8 PH) was added to the samples. The absorbances should be seen with the help of UV-Visible Spectrophotometer at 660 nm. Percentage inhibition of protein denaturation was calculated by using the formula Percentage Inhibition = 100 – {(Abs. of Ts – Abs of Pc) / Abs. of Tc} × 100 Where Abs. of Ts = Absorbance of test solution Abs of Pc = Absorbance of product control Abs. of Tc = Absorbance of test control Control represents 100% protein denaturation and the result of sample extract was compared with Standard Diclofenac sodium.

B. Egg albumin denaturatiion method

This activity was carried out on plants extract by modified (Mizushima Y et al) meth Fig12: Separation of yolk and albumin Fresh eggs were taken and the yolk and white albumin portions are separated. The reaction mixture (5 ml) will have consisted of 0.2 ml of fresh egg albumin, 2.8 ml• of buffered phosphate saline (PBS, P H 6.4), and 2.0 ml of different concentrations of test samples (10, 25, 50, 100 & 200 µg/ml).

4. In-vivo methods

Carrageenan induced paw oedema in rats

Carrageenan was used to cause oedema in this process. The Ethanolic leaf extract of Cordia myxa (100 & 200 mg/kg) was suspended in 2% acacia was pretreated to the animals. The positive control animals receive Diclofenac sodium (10 mg/kg) whereas negative control group receives 2% acacia. 0.1ml of 1% w/v suspension of carrageenan in distilled water was given to sub-plantar region of left hind paw after 30 minutes. A mark was made on both the hind paws just below the tibio-torsal junction. The right paw serve as reference. With the help of plythesmometer the paw size was measured. Before and after one hour of carrageenan injection, paw size was to be measured immediately. The percentage inhibition of Oedema should be calculated by using the formula,

Percentage inhibition of paw oedema = $\{1-(Vt / Vc)\} \times 100$

Where Vt: Increase in paw volume in treated group Vc: Increase in paw volume in control group

RESULTS

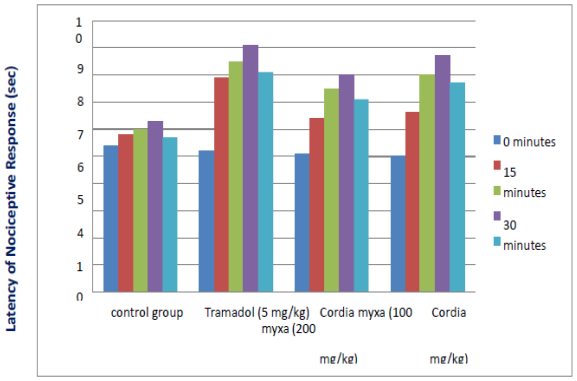
Phytochemical qualitative screening of Ethanolic leaf extract of Cordia myxa.

Compounds	Chemical test	Result
Carbohydrates	Molish test Benedicts test Fehling's	+ve +ve +ve
Flavanoids	Lead acetate test Zinc chloride test Naoh test	+ve +ve +ve
Glycosides	General test Legal's test Modified borntragors test	+ve +ve +ve
Proteins	Xanthropoitic test Millons test Biuret test	+ve +ve +ve
Saponins	Froth formation test	+ve
Alkaloids	Ferric chloride test	+ve
Tannins	Salkowski test Liebermann-bucchard test	+ve +ve
Triterpenoids	Dragondroff's test Mayer's test Hager's test	+ve +ve +ve

Analgesic activity

1. Tail flick method

Treatment Group	0 min		15 min		30 min		60 min		120 min	
	B.R.T	% inhr	B.R.T	% inhr	B.R.T	% inhr	B.R.T	% inhr	B.R.T	% Inhr
Control	5.4± 0.32	--	5.8± 0.17	--	6.0± 0.14	--	6.3± 0.74	--	5.7± 0.32	--
Group 1 (Tramadol-5 mg/kg)	5.2± 0.41	--	7.9± 0.35	51.9	8.5± 0.55	63.4	9.1± 0.44	75.0	8.1± 0.17	55.7
Group 2 (Extract of 100 mg/kg dose)	5.1± 0.13	--	6.4± 0.54	25.1	`7.5± 0.67	47.0	8.0± 0.65	56.0	7.1± 0.42	43.0
Group 3 (Extract of 200 mg/kg dose)	5.0± 0.57	--	6.6± 0.17	32.0	8.0± 0.48	60.0	8.7± 0.31	74.0	7.7± 0.72	54.0



Anti-inflammatory activity

1. In-vitro studies

A. Protein denaturation method

Maximum percentage inhibition of *Cordia myxa* was found to be **71.0% at 200µg/ml.** Whereas standard Diclofenac sodium showed the maximum inhibition **78.2% at 200µg/ml.**

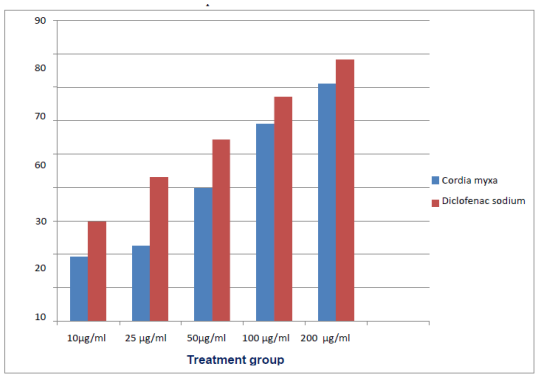
Table 7: In-vitro Anti inflammatory effect of Ethanolic leaf extract of *Cordia myxa* by protein denaturation method.

S. NO	Concentration	% Inhibition	
		Cordia myxa Extract	Diclofenacsodium
1	10 µg/ml	19.1±0.15	29.7±0.32
2	25 µg/ml	22.4±0.43	42.9±0.21

3	50 µg/ml	39.8±0.51	54.4±0.41
4	100 µg/ml	59.0±0.43	67.2±0.22
5	200 µg/ml	71.0±0.43	78.2±0.19

*P< 0.001 when compared with standard values**.**

Values are expressed as mean ± SEM



In-vitro Anti-inflammatory effects of Diclofenac Sodium (std drug) and Ethanolic extract of *Cordia myxa* by protein denaturation method.

A. Egg Albumin Denaturation Method

Table 8: In-vitro Anti-inflammatory effect of Ethanolic leaf extract of *Cordia myxa* by Albumin Denaturation method.

S.NO	Concentration	% Inhibition	
		***Cordia myxa* extract**	**Diclofenacsodium**
1	10 µG/ML	18.5±0.02	35.7±0.32
2	25 µG/ML	25.6±0.15	46.9±0.21
3	50 µG/ML	31.4±0.43	58.4±0.41
4	100 µG/ML	56.8±0.51	69.4±0.19
5	200 µG/ML	70.6±0.43	77.4±0.19

2. In-vivo study

Carrageenan induced paw oedema in rats

- *Cordia myxa* shows maximum percentage inhibition of paw oedema at **4th hr at doseof 200 mg/kg by 71.5%.**
- Diclofenac sodium shows maximum percentage inhibition of paw oedema at **4th hr at dose of 10 mg/kg by 73.4%.**

Values are expressed as mean ± SEM; n=3. *P< 0.001 when compared with standard values.

Table 9: In-vivo Anti-inflammatory effect of Ethanolic leaf extract of Cordia *myxa* in Carrageenan induced paw oedema in rats.

Treatment	Mean increase of paw diameter(cm)				
	0 hour	1 hour	2 hour	3 hour	4 hour
Control	0.38 ±0.21	0.59±0.33	0.98±0.29	1.3±0.58	0.98±0.64
Diclofenac sodium (10mg/kg)	0.27±0.35	0.34±0.26 (42.3%)	0.46±0.32 (53.0%)	0.57±0.46 (56.1%)	0.26±0.71 (73.4%)
Leaf extract (100 mg/kg)	0.34±0.54	0.40±0.51 (32.2%)	0.58±0.41 (40.8%)	0.70±0.34 (46.2%)	0.45±0.25 (54.0%)
Leaf extract (200 mg/kg)	0.29±0.14	0.36±0.33 (39.1%)	0.49±0.19 (50.3%)	0.60±0.67 (53.8%)	0.28±0.27 (71.5%)

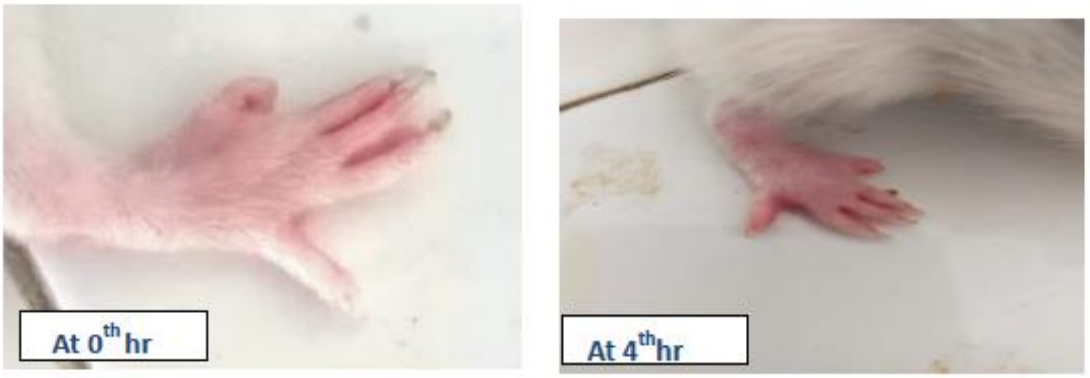
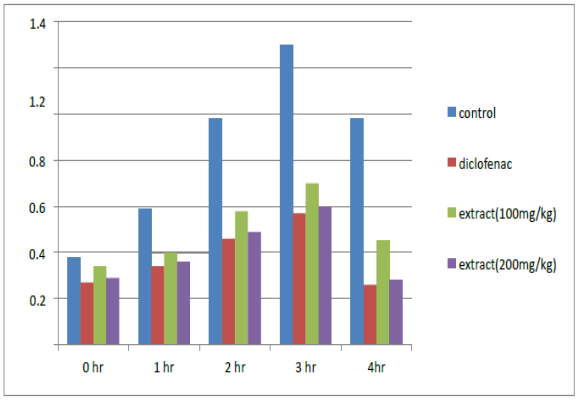
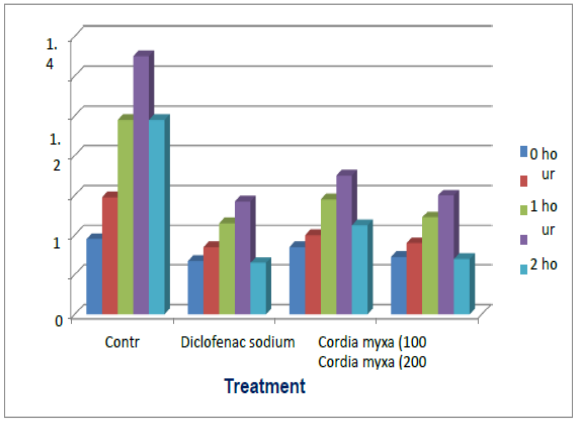


Figure 16: Carrageenan induced paw oedema.

Effect of Diclofenac sodium and Ethanolic leaf extract of *Cordia myxa* on carrageenan induced paw oedema





DISCUSSION

According to phytochemical studies alkaloids, glycosides, flavanoids, coumarins, triterpinoids, phenols, carbohydrates and tannins were present in ethanolic leaf extract of *Cordia myxa*. *the* flavonoids are reported to have analgesic and anti-inflammatory activities. Terpenoids also possess significant analgesic and anti-inflammatory activities. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. When an injury occurs, pain is first evoked by stimulation of the nociceptors causing potassium and kinins to be released from the damaged cells. The significant antinociceptive activity of *Cordia myxa* might be due to the presence of analgesic principles acting with the prostaglandin pathways. To investigate *Cordia myxa* has true analgesic potential, Tail flick method, Eddy's hot plate method and Tail immersion methods were used. In all these methods, the extract increased the tolerance capacity of the animals and hence also indicates the possible involvement of a higher center. In all these methods it is proven that *Cardia myxa* shown like similar analgesic property as strandard drugs. standard drug tramadol (5 mg/kg) significantly inhibited pain perception by 85.71% at 60 minutes. The ethanolic extract (200 mg/kg) significantly inhibited nociceptive response in rats at 30 minutes by 83.8%. Mainly brain and spinal cord produce major part in pain mechanism. The dorsal part in spinal cord as well as substance P, endogenous opioids, somatostatin and other hormones which are the source of pain and inflammation. The tail flick method and tail immersion methods are well determined models for measure of central analgesic effects of medication through opioid receptors. In tail flick and tail immersion methods standard drug tramadol (5 mg/kg) significantly inhibited pain perception by 75% at 60 minutes whereas the ethanolic extract (200 mg/kg) significantly inhibited nociceptive response in rats at 60 minutes by 74% and 72.4% respectively. Proteins being the essential nutrient for human body, serves as fuel source. Inflammation is caused due to denaturation of proteins. (Tidmore

T et al.,). The ethanolic leaf extract of *Cordia myxa* was successful in inhibiting heat induced protein denaturation at a dose of 200 µg/ml by 78.2% in protein denaturation method and 70.6% in egg albumin denaturation method.even with carageenan induced inflammation cardia myxia showing equalent anti-inflammatory activity like standard.

CONCLUSION

Since from the ages of ancient times, people have been using plants in several ways as a source of medicine. In conclusion, result collected through this investigation determined significant analgesic and anti-inflammatory effects of *Cordia myxa* leaf extract in laboratory animals and this justify the regional uses of plant to cure in humans. In advanced studies, we use to formulate a new methodology for desolation and purification of elements present in *Cordia myxa* plant which may act as a control drug to a broad range of inflammation. These studies determine the recognition, purification and design of definitive phytochemical elements that causes biological effects. From examination, it was proved that ethanolic leaf extract of *Cordia myxa* plant had shown analgesic, anti-inflammatory activities. The existence of alkaloids, glycosides, flavanoids, triterpenoids, and tannins may be caused for these anti- inflammatory and analgesic activities. This study says that ethanolic leaf extract of Cordia myxa exhibited significant Analgesic effect against nociceptive stimulus produced by eddy's hot plate method, tail flick method and tail immersion method and Anti- inflammatory activity by protein denaturation method, egg albumin denaturation method and Carrageenan induced paw oedema method.

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