

Toxicity Assessment and Evaluation of Analgesic, Antipyretic and Anti-Inflammatory Activities on *Cordia obliqua* Leaf Methanol Extract

Richa Gupta¹, Ghanshyam Das Gupta^{2*}

ABSTRACT

Background: *Cordia obliqua* Willd. Plant belongs to genus *Cordia* and family Boraginaceae. Commonly it is known as Clammy Cherry and in Hindi Lasora. Earlier very few researches were carried out to explore its medicinal importance as compared with other *Cordia* species.

Objective: To determine maximum safe dose and explore analgesic, anti-inflammatory and antipyretic activities of *Cordia obliqua* leaf methanol extract. **Materials and Methods:** As per our previous study report, the leaf methanol extract is rich in phyto-constituents and has good antioxidant effect; so only methanol extract was studied here. The maximum safe dose of methanol extract was found by acute oral toxicity study according to OECD guidelines 423. For analgesic effect, hot plate and tail flick method, for anti-inflammatory, Carageenan induced rat paw edema and for antipyretic study, yeast induced pyrexia method were used.

Results: The extract dose up to 2000mg/Kg was found safe with no any side effects. Three dose levels were tested for all activities. The medium (250 mg/Kg) and high (500 mg/Kg) dose of methanol extract was found effective in all activities when compared with standard. The result for antipyretic activity was found better than other activities. **Conclusion:** It can be concluded that *Cordia obliqua* leaf is safe and effective drug for relief of pain, fever and inflammation.

Key words: Carageenan induced edema, Clammy Cherry, Hot plate, Tail flick, Yeast induced pyrexia.

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INTRODUCTION

Higher plants are a rich source of various secondary metabolites with a number of important medicinal activities. So, plants have been used by human being in traditional medicine since ages due to their therapeutic potential.¹ *Cordia obliqua* Willd. is a well-known plant of Boraginaceae family and *Cordia* genus? It is found scattered throughout mid-Himalayas up to an elevation of 1,470 meters. It is a deciduous tree with medium size (height 10.5 meters) and vigorous growth. It is commonly known as Clammy Cherry and in Hindi, called as Lasora.² Traditionally, the plant is used as anthelmintic, expectorant, purgative, diuretic and in treatment of chronic fever, dry cough, joints pain, spleen diseases and burning of throat. The leaves are useful in treatment of headache and ulcer. Its fruits are sweet and used in raw form as vegetable and pickle. Scientifically, this plant is used as hypotensive, respiratory stimulant, diuretic, anti-inflammatory and antimicrobial.³

Till this work done, no any activity of *C. obliqua* leaves is reported except antimicrobial. So, this research work was carried out to explore the pharmacological importance and determine the chemical nature of

leaves. For this methanol extract of leaves was selected because as our previous study, methanol extract is rich in various Phyto-constituents and has good antioxidant effect.⁴

At first, acute oral toxicity study was performed to determine maximum safe dose of leaf methanol extract and then various activities like analgesic (by Hot plate and Tail flick method), anti-inflammatory (by Carageenan induced rat paw edema method) and antipyretic (by yeast induced pyrexia method) were performed.

MATERIALS AND METHODS

Plant material

The *Cordia obliqua* Willd. leaves were procured from Jammu. These were authenticated and identified by Dr. (Mrs) Sunita Garg, Chief Scientist, Raw Material Herbarium and Museum (RHMD), Council of Scientific and Industrial Research-National Institute of Science and Information Resources (CSIR-NISCAIR), New Delhi, with the reference no. NISCAIR/RHMD/Consult/-2014/2383-163. A plant sample was deposited in herbarium of Phar-

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macognosy department, ASBASJSM College of pharmacy, Bela (Ropar) for future reference.

Extraction method

About 1 Kg of leaf drug was dried under shade and then coarsely powdered. The successive extraction was performed using soxhlet apparatus with a number of solvents such as Hexane, Chloroform, Methanol and water in order of increasing polarity. All the four extracts were separately concentrated using Rotary vacuum evaporator and then kept in desiccator for further use. The yield of methanol extract was found 1.2% w/w and it was dark Green in color and non-sticky. As per the previous study, methanol extract contains maximum number of Phyto-constituents as well as maximum total phenol and total flavonoid content. So, leaf methanol extract was selected for biological activity study.

Animals

The Albino rats of the body weight range 180-200g were used for the present study. The rats were maintained under standard conditions of environment and feed with standard pellet diet. Before starting of experiment, the animals were given time of seven days to get acclimatized with laboratory environment conditions. The animals were fasted for 18hrs before the experiment. After sufficient period of acclimatization, they were used to evaluate anti-inflammatory, anti-pyretic and analgesic activities. The experimental protocol was subjected to the scrutinization of IAEC of ASBASJSM College of Pharmacy, Bela and was duly approved under the Protocol No. ASCB/IAEC/07/14/92 and care of animals were carried out according to the guidelines of CPCSEA, New Delhi (Regn. No. 724/PO/a/02/CPCSEA).

Chemicals and drugs

Indomethacin (Glenmark Generics Ltd, Goa), Paracetamol (Yarrow Chem, Mumbai) and Carageenan (Himedia, Mumbai) were used for present study.

Acute Toxicity Study

The acute toxicity for the methanol extract dose was determined in albino rats by adopting Acute Toxic Dose method of CPCSEA (OECD guidelines No. 423). Animals were weighed and divided in four groups of three animals in each. They were administered group wise increasing dose of extract like 5, 50, 300 and 2000 mg/kg Body Weight (BW) to determine changes in parameters for assessing toxicity. The animals were maintained under standard environmental conditions and allowed free access to water and food. These were observed continuously after drug administration at regular time interval on first day to fourteen consecutive days for behaviour profile, neurological profile and autonomic profile.⁵

Analgesic activity

The analgesic activity of leaf methanol extract was determined by using two methods- (1) Tail Flick method or Tail immersion method based on thermal radiant heat as a pain source; (2) Hot plate method based on jumping of animal or withdrawal of paws from hot plate at 55°C. These both methods determine central analgesic effect of drug.⁶

In both methods, Animals were divided in five groups of six animals in each, one control group, one standard group and three groups for three dose levels of leaf methanol extract- low dose (125mg/kg BW), Medium dose (250mg/kg BW) and high dose (500mg/Kg BW) per oral.

Tail Flick method

The animals received vehicle Normal saline 10ml/kg BW (Group I) and standard drug Indomethacin 10 mg/kg BW per oral (Group II). Analgesic activity at three doses of leaf methanol extract (Group III, IV, V respectively)

was assessed by observing the reaction time in the treated groups. Reaction time in seconds was used as the unit for measurement of pain and analgesic effect was indicated by increase in reaction time. Time between placing the tail of the rat on the radiant heat source and sharp withdrawal of the tail was recorded as "reaction time". While noting down the reaction time, cut off time of ten sec was used in all experiments as maximum latency to rule out thermal injury. Animals were discarded that has showed a mean reaction time outside the range of five-six sec. In all the groups, tail-flick test was performed prior to drug administration, and at 0, 30, 60, 90 and 120 min after drug administration, and the reaction time at each time interval was calculated.^{7,8}

Hot plate method

The animals were acclimatized of laboratory conditions 1h before the start of experiment. Animals were then subjected to pre-testing on hot plate apparatus maintained at 55±0.1°C. During pre-testing, the animals were rejected showing latency time more than 15sec. Then animals were divided in five groups of six animals in each. The group I was control group and treated with Normal saline (10ml/kg BW), Group II was treated with standard drug Indomethacin (10mg/kg BW) and group III, IV and V were treated with three dose level of leaf methanol extract. At first, the latency time in sec was noted after 30 min of treatment by placing the animals on Hot plate. In order to prevent the tissue damage, a cut-off time of 15 sec was used for all animals. The latency time was recorded for all animals at 0, 30, 60, 90 and 120 min.⁹⁻¹¹

Antipyretic activity

The antipyretic activity was determined by using Yeast induced Pyrexia method using Paracetamol as standard drug.

Yeast induced Pyrexia method

Animals were divided into five groups of six animals in each group. The initial rectal temperature of each animal was recorded by insertion of digital thermometer to a depth of 2 cm into the rectum. The pyrexia was induced by injecting a suspension of 15% of brewer's yeast in normal saline, sub-cutaneously in the volume of 1ml/100g of animal weight. The site of injection was massaged to spread the suspension beneath the skin. The room temperature was kept at 22-24°C. Immediately after yeast administration, food was withdrawn. A stabilized temperature was produce in 18 h. and recorded. The measurement was repeated after 30 min. Only animals with a body temperature of at least 38°C were taken into the test. Group 1 as control, received 10ml/kg of normal saline solution orally. The group II was administered with Paracetamol orally at dose of 100 mg/kg BW. The III, IV and V group received three doses of methanol extract 125mg/kg, 250mg/kg and 500mg/kg BW respectively. The test drug was given orally (0 h) and rectal temperature recorded at 1, 2, 3 and 4h. The difference in temperature between 0 h and at the end of 4 h was compared and analysed.⁸⁻¹²

Anti-inflammatory activity

It was determined by Carageenan-induced rat paw edema method using Indomethacin as standard drug.

Carageenan-induced rat paw edema

Albino Wister Rats were allotted to a total of six groups as Negative control, Positive control, standard treatment group and three groups for low, medium and high dose of leaf methanol extract 125mg/kg, 250mg/kg and 500mg/kg BW respectively. Edema was induced in the rats by injection of Carrageenan (0.1 ml, 1% w/v in normal saline) into the sub-plantar tissue of the right hind paw. The linear paw circumference was measured using the digital screw gauze. Measurements were made immediately before injection of the phlogistic agent and at hourly inter-

vals for 4 h in the animals injected with Carrageenan. Negative control group was given only Normal saline 10 ml/kg with no induction of inflammation and in all other group inflammation was induced by Carageenan injection. No any treatment was given to positive control group and in standard group Indomethacin (10 mg/kg BW) was administered orally 1 hr before injection of phlogistic agents. The extract dose was also administered orally 1 hr before inflammation induction.¹³⁻¹⁶

Statistical analysis

The results obtained represents the mean ± SEM, for number of animals used (n) = 6. The result was statistically analyzed by one-way ANOVA followed by Tukey's multiple comparison tests. The p-value<0.05 was considered to be statistically significant, p-value<0.01 was considered statistically more significant and p-value<0.001 was considered to be statistically highly significant when compared with control.

RESULTS

Acute Oral Toxicity study

It was determined that the maximum safe dose of extract in rats is 2000mg/kg by acute oral toxicity studies. The studies followed OECD guidelines 423. Based on observations, it was evident that there was no reduction in alertness, spontaneous motor activity, reactivity to sound and touch, body and limb tone. Respiration, urination, pupil size and pineal, corneal and righting reflexes were found normal for all 14 days of study. Abnormal signs pertaining to toxicity such as ataxia, body tremors, convulsions, lacrimation, salivation, diarrhoea, writhing, piloerection, sedation, coma, cyanosis etc. were not observed in all groups during experimental tenure of 14 days.

Analgesic activity

Tail Flick method

In study of analgesic activity by Tail Flick method, the methanol extract of *Cordia obliqua* Willd. leaf significantly increased the reaction time. The positive control group was compared with standard i.e. Indomethacin (10 mg/kg) and three different doses (125 mg/kg, 250 mg/kg and 500 mg/kg) of methanol extract. In this activity only high dose (500 mg/kg) has been shown significant (p<0.05) effect after 90 min of treatment. The reference drug Indomethacin has also shown only significant (p<0.05) effect Table 1, Figure 1a.

Hot Plate method

In study of analgesic activity by Hot Plate method, the methanol extract of *Cordia obliqua* Willd. leaf significantly increased the reaction time. The positive control group was compared with standard i.e. Indomethacin (10 mg/kg) and three different doses (125 mg/kg, 250 mg/kg and 500 mg/kg) of methanol extract. In this activity both doses (250 mg/kg and 500 mg/kg) has been shown highly significant (p<0.001) effect after 90 min of treatment. The reference drug Indomethacin has shown highly significant (p<0.001) effect Table 2, Figure 1b.

In the both methods, analgesic activity was confirmed for *Cordia obliqua* Willd. leaf methanol extract. The high dose is more effective as compared to low doses and analgesic effect is higher and comparable with standard drug after 1h of drug administration.

Antipyretic activity

In study of antipyretic activity by Yeast induced pyrexia method, the methanol extract of *Cordia obliqua* Willd. leaf significantly decreased body temperature. The positive control group was compared with standard drug i.e. Paracetamol (100 mg/kg) and three different doses (125 mg/kg, 250 mg/kg and 500 mg/kg) of methanol extract. In this activity study, all

Table 1: Effect of COME on Tail Flick reaction time in rats.

Group	Dose	Reaction time in sec at time in min.				
		0 min	30 min	60 min	90 min	120 min
Control	3.5±0.58	3.75±0.50	3.25±0.50	3.5±0.58	3.67±0.52
Standard (Indomethacin)	10 mg/kg	3.33±0.52	4.17±0.41	5.00±0.63	5.67±0.52*	5.83±0.41*
COME-1	125 mg/kg	3.00±0.62	3.50±0.55	3.67±0.52	4.16±0.41	4.33±0.51
COME-2	250 mg/kg	3.33±0.52	3.83±0.41	4.67±0.52	4.67±0.52	5.33±0.52
COME-3	500 mg/kg	3.33±0.52	4.16±0.75	4.67±0.52	5.50±0.52*	5.67±0.52*

Each column represents the mean ± SEM, number of animals used (n) = 6

*(p<0.05), **(p<0.01), ***(p<0.001)- compared with positive control, considered as significant, more significant, highly significant respectively.

One-way ANOVA followed by Tukey's multiple comparison test.

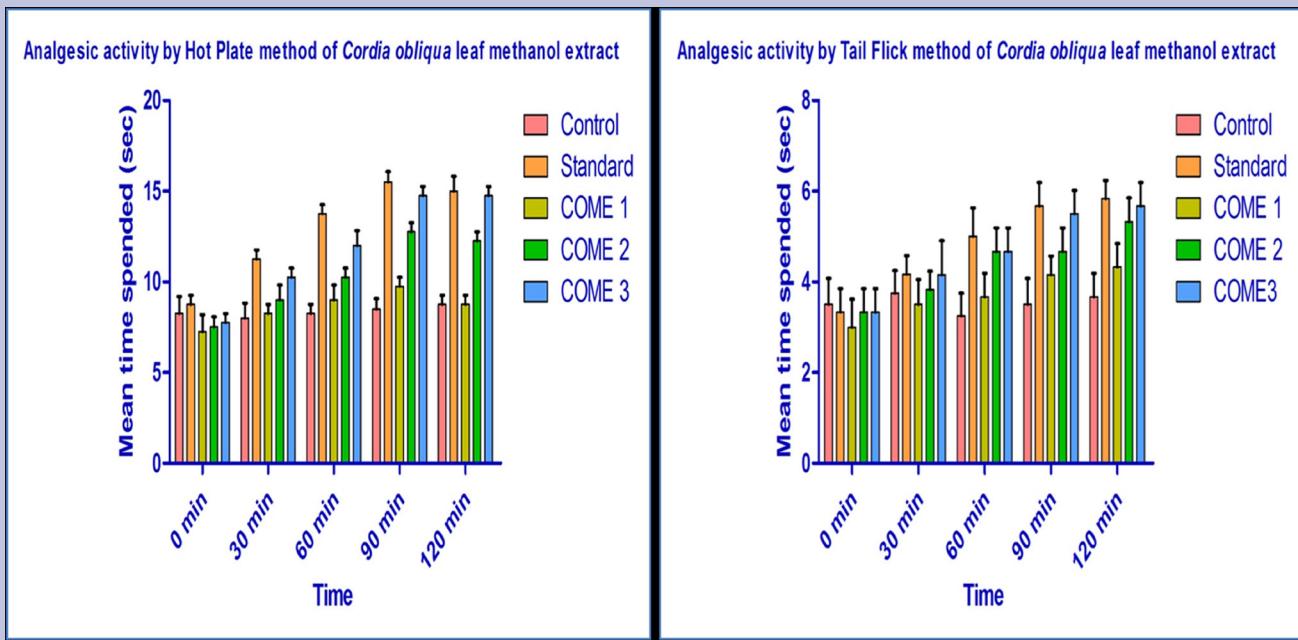
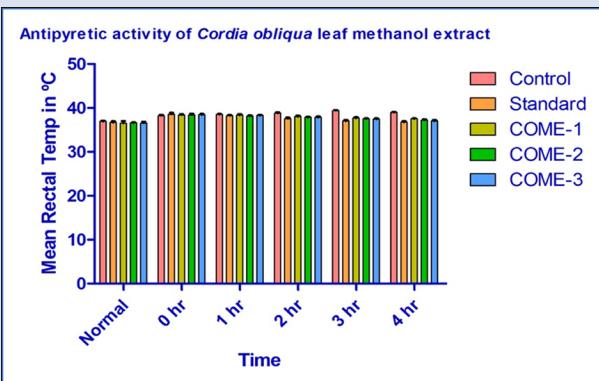
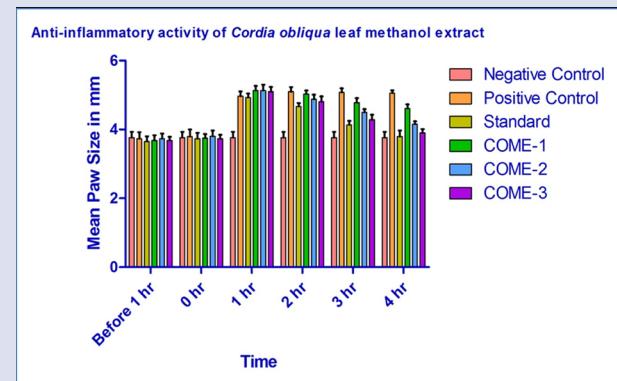
Table 2: Effect of COME on Hot Plate reaction time in rats.

Group	Dose	Reaction time in sec at time in min.				
		0 min	30 min	60 min	90 min	120 min
Control	8.25±0.95	8.00±0.82	8.25±0.5	8.50±0.58	8.75±0.5
Standard (Indomethacin)	10 mg/kg	8.75±0.5	11.25±0.5 **	13.75±0.5***	15.50±0.58***	15.00±0.82***
COME-1	125 mg/kg	7.25±0.95	8.25±0.5	9.00±0.82	9.75±0.50	8.75±0.5
COME-2	250 mg/kg	7.5±0.58	9.0±0.82	10.25±0.50	12.75±0.50***	12.25±0.50***
COME-3	500 mg/kg	7.75±0.5	10.25±0.5	12.0±0.82***	14.75±0.5***	14.75±0.5***

Each column represents the mean ± SEM, number of animals used (n) = 6

*(p<0.05), **(p<0.01), ***(p<0.001)- compared with positive control, considered as significant, more significant, highly significant respectively.

One-way ANOVA followed by Tukey's multiple comparison test.

**Figure 1:** Analgesic effect shown by *Cordia obliqua* leaf methanol extract.**Figure 2:** Antipyretic activity shown by *Cordia obliqua* leaf methanol extract.**Figure 3:** Anti-inflammatory activity shown by *Cordia obliqua* leaf methanol extract.

doses of methanol extract have shown highly significant ($p<0.001$) effect after 3h of drug administration. The reference drug Paracetamol has also shown highly significant ($p<0.001$) effect Table 3, Figure 2.

Anti-inflammatory activity

In Carrageenan induced animal model, the methanol extract of *Cordia obliqua* Willd. leaf significantly inhibited the edema. The positive control group was compared with standard i.e. Indomethacin (10 mg/kg) and three different doses (125 mg/kg, 250 mg/kg and 500 mg/kg) of methanol extract. The dose (250 mg/kg) has been shown highly significant ($p<0.001$) effect after 4h of drug administration and the dose (500 mg/kg) has also shown highly significant ($p<0.001$) effect after 3h of drug administration. The low dose has shown no any significant effect. The reference

drug Indomethacin has shown highly significant ($p<0.001$) effect Table 4, Figure 3

DISCUSSION

The results of present study showed that *Cordia obliqua* leaf methanol extract (COME) maximum safe dose was 2000mg/kg and it has good analgesic, antipyretic and anti-inflammatory activity when compared with suitable standard drug. The results support traditionally mentioned uses of this plant as well as pharmacological importance of genus *Cordia* according to previous studies.^{17,18}

The two models of thermal nociception, hot plate and tail flick method were used to evaluate the central analgesic activity of COME.⁶ In hot plate method the two-dose level (medium and high) of COME showed highly significant analgesic effect after 90 min of administration. In tail

Table 3: Effect of COME on Induction of yeast induces pyrexia in rats.

Drug	Dose	Rectal temperature in °C at time (hr)					
		Normal	0 hr	1 hr	2 hr	3 hr	4 hr
Positive control (15% brewer's yeast)	1ml/100gm	36.92±0.17	38.23±0.19	38.51±0.13	38.83±0.19	39.038±0.12	38.97±0.12
Standard (Paracetamol)	10 mg/kg	36.70±0.29	38.55±0.33	38.21±0.20	37.55±0.27***	37.03±0.23***	36.75±0.27***
COME-1	125 mg/kg	36.51±0.17	38.41±0.19	38.37±0.25	38.02±0.26	37.70±0.20***	37.51±0.15***
COME-2	250 mg/kg	36.59±0.14	38.41±0.27	38.16±0.16	37.85±0.14*	37.53±0.13***	37.23±0.21***
COME-3	500 mg/kg	36.55±0.31	38.43±0.23	38.26±0.19	37.86±0.19*	37.43±0.22***	37.00±0.26***

Each column represents the mean S.E.M.; number of animals used (n=6).

*(p<0.05), **(p<0.01), ***(p<0.001)- compared with positive control, considered as significant, more significant, highly significant respectively.
One-way ANOVA followed by Tukey's multiple comparison Test

Table 4: Effect of COME on Carrageenan Induced Paw Edema in rats.

Drug	Dose	Paw size in mm at time (hr)					
		Before 1 hr	0 hr	1 hr	2 hr	3 hr	4 hr
Negative Control	--	3.77±0.16	3.77±0.16	3.77±0.16	3.77±0.16	3.77±0.16	3.77±0.16
Positive control (carrageenan 1%)	0.1 ml	3.73±0.19	3.8±0.2	4.97±0.14	5.1±0.13	5.08±0.12	5.06±0.08
Standard (Indomethacin)	10 mg/kg	3.65±0.15	3.73±0.17	4.93±0.12	4.67±0.10	4.13±0.12***	3.8±0.17***
COME-1	125mg/kg	3.68±0.15	3.75±0.12	5.13±0.14	5.03±0.10	4.78±0.13	4.61±0.12
COME-2	250mg/kg	3.73±0.15	3.81±0.16	5.13±0.17	4.88±0.13	4.5±0.09*	4.16±0.08***
COME-3	500mg/kg	3.68±0.11	3.73±0.12	5.1±0.14	4.81±0.15	4.28±0.15***	3.9±0.11***

Each column represents the mean S.E.M.; number of animals used (n=6).

*(p<0.05), **(p<0.01), ***(p<0.001)- compared with positive control, considered as significant, more significant, highly significant respectively.

One-way ANOVA followed by Tukey's multiple comparison Test

flick method, only significant analgesic effect was observed with high dose level of COME after 90 min of administration. So, the result of hot plate method was comparatively better than result of tail flick method.

In the antipyretic study, the injection of Brewer's yeast subcutaneously, induces pyrexia by increasing Prostaglandin synthesis. It is called pathogenic fever and it is an important test for evaluation of antipyretic activity of all type of drugs.^{19,20} The possible mechanism of antipyretic action of Paracetamol may be inhibition of prostaglandin synthesis.²¹ In this study, all dose levels of COME significantly attenuated rectal temperature of yeast induced febrile rat. So, it can be postulated that COME contains some active principles that inhibit the release of prostaglandins.

For anti-inflammatory study, carrageenan-induced paw edema is well established animal model. Edema formation in rat paw due to carrageenan injection is a biphasic event of 1-5h; the initial phase of 1-1.5h is predominately a non-phagocytic edema followed by a second phase of 2-5h with increased formation of edema that may remain up to 5h.^{22,23}

The initial phase edema induction is due to the action of mediators such as serotonin, histamine and bradykinin on vascular permeability.²⁴

The late phase edema is the result of over production of prostaglandins.²⁵ In this study, the high dose (500mg/Kg) of COME has been found significantly effective in late phase of edema induction (after 3h of treatment). So, the possible mechanism of anti-inflammation action may be inhibition of prostaglandin synthesis. Further study may be carried out to find out the exact mechanism of action for analgesic, antipyretic and anti-inflammatory activity of COME.

CONCLUSION

In the conclusion, the methanolic extract of *Cordia obliqua* leaf, has been proved as a natural safe remedy for treatment of analgesia, pyrexia and inflammation. The result of this study supports the traditional use of this plant leaf as analgesic, antipyretic and anti-inflammatory drug. It is the first study related with biological activities of *Cordia obliqua* leaf. Further, the isolation of active phyto-constituents from plant will help in understanding the mechanism of action for tested activities and also identification of lead molecules of clinical utility.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

ABBREVIATION USED

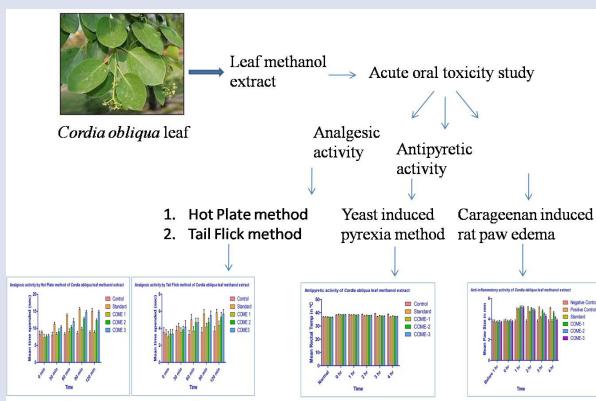
COME: *Cordia obliqua* methanol extract; C. obliqua: *Cordia obliqua*; BW: Body weight; SEM: Standard Error of Mean.

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GRAPHICAL ABSTRACT



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SUMMARY

- The methanol extract of *Cordia obliqua* leaf was selected for evaluation of analgesic, antipyretic and anti-inflammatory activities because it contains maximum amount of phytoconstituents.
- The extract dose up to 2000mg/kg was found safe with no any toxic and side effects.
- For analgesic study two methods were used Hot plate and tail flick. For anti-pyretic study yeast induced pyrexia method and for anti-inflammatory study carageenan induced rat paw edema method was used.
- Three dose levels (125mg/kg, 250mg/kg and 500mg/kg) of methanol extract were tested for all activities.
- The methanol extract was found effective in all activities as compared to standard drug. The effects were better with high dose level and the maximum activity was found against pyrexia.

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