

# Evaluation of Anti-Inflammatory and Antipyretic Effect of Aqueous Extract of *Tinospora Cordifolia* in Rats

Dr. Sumanlata<sup>1</sup>, Dr. Akanksha Suman<sup>2</sup>, Dr. Rajeev Kumar Sharma<sup>3</sup>,  
Dr. Adnan Khan<sup>4</sup>

<sup>1</sup>Professor and Head, <sup>2</sup>Associate Professor, <sup>3,4</sup>Professor,  
Department of Pharmacology, Muzaffarnagar Medical College, Muzaffarnagar, Uttar Pradesh.

Corresponding Author: Dr. Akanksha Suman

## ABSTRACT

Non Steroidal anti-inflammatory drugs (NSAIDs) are the mainstay for the treatment of inflammation and pyrexia. These drugs are synthetic in nature and are associated with many adverse effects which effect compliance of patients. Plants are used since ages as natural resources of medicines to treat various ailments. *Tinospora cordifolia* is widely available and its use is mentioned in various literatures. In the present study the aqueous extract of stem of *T. cordifolia* in graded doses (1.25g/kg, 2.5g/kg and 5gm/kg) was used to evaluate the anti-inflammatory activity by carrageenan and histamine induced rat paw edema and anti-pyretic activity by Brewer's yeast induced pyrexia model in albino rats. The statistical analysis showed significant anti-inflammatory and anti-pyretic activity comparable to that of standard drugs Diclofenac sodium and Paracetamol respectively. Present study showed the potential of *T cordifolia* as future anti-inflammatory and anti-pyretic drugs. This activity may be attributed to the presence of various phytoconstituents present in extract of *T. cordifolia*.

**Key words:** *T. cordifolia*, Anti-inflammatory, Anti-pyretic, Aqueous extract, Carrageenan, Histamine, Brewer's yeast.

## INTRODUCTION

Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is a complex reaction in tissues that consists mainly of response of blood vessels and leukocytes. It is a series of host responses directed as a protective attempt by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue. [1] Currently used non steroidal anti inflammatory drugs are synthetic nature and on prolonged use cause various adverse effects. [2]

In this context, there arises new scope for evaluation of herbal resources having significant anti inflammatory effects. Plants still remain a large untapped source of structurally novel compounds that might serve as a lead for the development of novel drugs

According to WHO, three quarter of world population depends on traditional herbal medicines for their health care needs. Indian Ayurveda and Chinese medicinal system are most acceptable traditional systems with research on Pharmacognosy, Chemistry, Pharmacology & Clinical Therapeutics. [3,4] Traditional Ayurvedic medicinal systems use several plants for the management and

treatment of various inflammatory disorders and in wound healing activities. [4]

*Tinospora cordifolia* (Guduchi) is a member of Menispermaceae family. It is also known as Giloe. [5] Guduchi is widely used in veterinary folk medicine/ ayurvedic system of medicine for its general tonic, antiperiod, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-allergic and anti-diabetic properties. The plant is used in ayurvedic medicines as Rasanayas to improve the immune system and the body resistance against infections. It is also known by the name magical herb due to its property to cure number of disease. [6] Moreover this plant extract has been traditionally used for the treatment of fever. [8] The whole plant is used medicinally, but Ayurvedic Pharmacopoeia of India approves the stem to be used medicinally, as alkaloid content is higher in stems than leaves. [9] Thus the present study was done to evaluate the anti-inflammatory and antipyretic activity of aqueous (aq) extract of stem of *Tinospora cordifolia*.

## MATERIALS AND METHODS

### Preparation of water-soluble extract of *T. cordifolia*

The stems of *T. cordifolia* (*Giloe*) were dried under shade, reduced to moderately coarse powder and 100g of this powder was soaked in 2 liter of water for 24 hours and then was boiled till it reduced to 100ml and filtered to get the aqueous extract. Thus, 100gm of *T. cordifolia* was present in 100ml, so 1ml of this extract is equivalent of 1g dry powder of *T. cordifolia* and preserved in refrigerator. The prepared extract was used for two days only. The fresh extract was prepared in the same way for the different sets of experiments.

The study was conducted in albino rats of either sex (100-200g) after taking approval from the Institutional Animal Ethical Committee (IAEC). The animals were provided the ideal conditions according to the CPCSEA norms. The food was withdrawn 12 hours before and during the experimental period.

### Anti-inflammatory Study

Carrageenan induced rat paw edema model [9]

The study was done using different phlogistic agents (carrageenan and histamine) in right hind paw of rats.

In this method also rats were divided into five groups of six animals in each group. The different groups were pretreated with standard drug and graded doses of aq extract of *T. cordifolia*, 60 minutes before injection of 0.1 ml of 1% carrageenan. Carrageenan was injected into the sub plantar region of the right hind paw of rats. The paw volumes were measured using plethysmograph at 0 and 3 hours after the administration of drugs. Maximum edema was produced at 3hrs of carrageenan administration. The average paw swelling in the group of the drug treated rats was compared with that of untreated rats (control group) and the percent of inhibition of the edema was determined using formula.

Percent (%) inhibition =  $1 - V_t/V_c \times 100$ , where  $V_t$ - edema volume in test group,  $V_c$ - edema volume in control.

Group I: control was treated with normal saline (5ml/kg of 0.9% NaCl) p.o

Group II: standard was given Diclofenac sodium 20mg/kg

Group III: 1.25gm/kg of aqueous extract of *T. cordifolia* (p.o)

Group IV: 2.5g/kg was challenged with aqueous extract of *T. cordifolia* (p.o)

Group V: 5g/kg was challenged with aqueous extract of *T. cordifolia* (p.o)

### Histamine induced hind paw edema (Parmar and Ghosh 1978) [11]

Histamine induced paw edema was induced using 0.1ml of 0.1% solution of Histamine acid phosphate was administered in the palmar aponeurosis of the right hind paw of rats and paw volume was recorded before and 1hr after the injection of histamine. ) and the percent of inhibition of the edema was determined using formula.

Percent (%) inhibition =  $1 - V_t/V_c \times 100$ , where  $V_t$ - edema volume in test group,  $V_c$ - edema volume in control.

Group I: control was treated with normal saline (5ml/kg of 0.9% NaCl)(p.o)

Group II: standard was given Diclofenac sodium 20mg/kg

Group III: 1.25gm/kg of aqueous extract of *T. cordifolia* (p.o)

Group IV: 2.5g/kg was challenged with aqueous extract of *T. cordifolia* (p.o)

Group V: 5g/kg was challenged with aqueous extract of *T. cordifolia* (p.o)

#### Anti pyretic activity of *T. cordifolia* [12]

The anti-pyretic activity was conducted on albino rats of either sex weighing 100-200 gm and rats were divided into 5 groups each with six animals in each group. The rectal temperature of each animal was recorded by digital clinical thermometer before inducing pyrexia. The room temperature remained constant during the experiments. Pyrexia was produced by injecting 10ml/kg of 20% suspension of dried brewer's yeast (*Saccharomyces cerevisiae*) in normal saline subcutaneously on the back of albino rats 20 hrs before performing the experiment. The rectal temperature was noted after 18 hrs for the development of pyrexia.

Group I: Control was treated with normal saline (5ml/kg of 0.9% NaCl) p.o

Group II: Standard was given Paracetamol 150mg/kg p.o

Group III: 1.25gm/kg of aqueous extract of *T. cordifolia* p.o

Group IV: 2.5g/kg was challenged with aqueous extract of *T. cordifolia* (p.o)

Group V: 5g/kg was challenged with aqueous extract of *T. cordifolia* (p.o)

#### STATISTICAL ANALYSIS

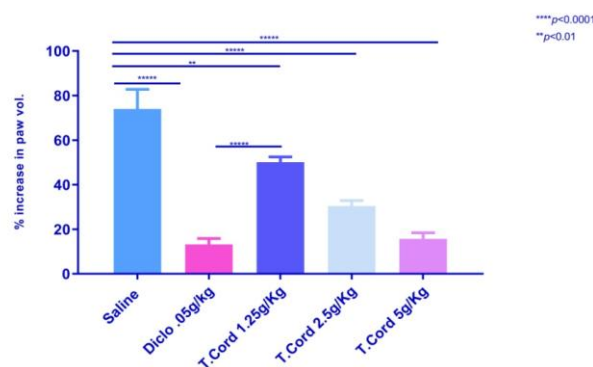
To examine the anti-pyretic activity of across time point two way ANOVA was performed with Tukey post hoc analysis. To examine early and late anti-inflammatory activity one way ANOVA was performed with Tukey post hoc analysis.

#### RESULTS

##### Carrageenan induced rat paw edema

Carrageenan administration produced  $74.0 \pm 8.78\%$  increase in paw volume. But pretreatment with diclofenac sodium produced highly significant reduction in paw edema  $13.17 \pm 2.68$ . Graded doses of *T. cordifolia* also prevented the edema significantly in dose dependent manner  $p < 0.0001$ . The prevention was less as compared to that of standard drug, but the difference was insignificant. (Fig. 1)

Fig. 1 *T. Cord* demonstrates anti-inflammatory activity in albino rats with Carrageenan induced paw edema



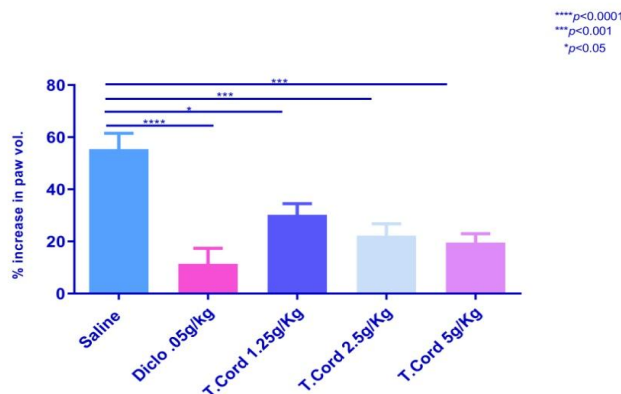
Aqueous extract of *T. Cord* stem was administered orally in graded doses of 1.25, 2.5 and 5.0 (g/Kg) in albino rats (n=6/group) with carrageenan induced inflammation at 3 hours in the right hind paw. *T. Cord* treatment showed a significant decline in the % paw volume compared to the control the doses 2.5 and 5 (g/Kg) were found equally potent as the Diclofenac sodium (.05g/Kg).

##### Histamine induced rats paw edema.

Histamine administration produced  $55.40 \pm 6.0\%$  increase in paw volume. But pretreatment with diclofenac sodium produced highly significant reduction in paw edema  $11.4 \pm 5.95$ .

Graded doses of *T. cordifolia* produced prevention in dose dependent manner and the effect was less than standard drug.(Fig. 2)

Fig. 2 *T.Cord* demonstrates anti-inflammatory activity in albino rats with Histamine induced paw edema

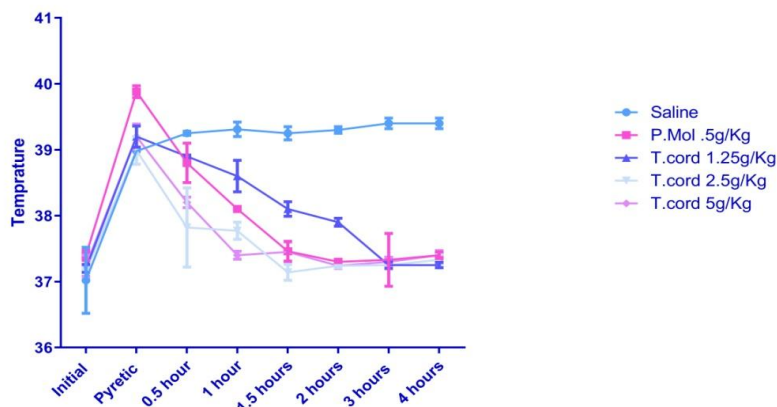


Aqueous extract of *T.Cord* stem was administered orally in graded doses of 1.25, 2.5 and 5.0 (g/Kg) in albino rats (n=6/group) with histamine induced inflammation at 1 hour in the right hind paw. *T.Cord* treatment showed a significant decline in the % paw volume compared to the control, none of the doses of *T.Cord* administered showed any significant difference in response compared to Diclofenac sodium (.05g/Kg).

### Yeast induced pyrexia.

The pyrexia was produced by injecting 10ml/kg of 20% suspension of dried brewers yeast (*Saccharomyces cerevisiae*) in normal saline s.c on back. Rats developed fever after 9-18hrs ranging between 38.71°C to 39.9°C in different groups. The pyrexia was noted at 30, 60, 90 and 120 minutes after administration of standard drug Paracetamol and graded doses of aq extract of *T. cordifolia*. Different doses of *T. cordifolia* produced a significant reduction in temperature. (Fig. 3)

Fig. 3 *T.Cord* demonstrates anti-pyretic activity in albino rats



Aqueous extract of *T.Cord* stem was administered orally in graded doses of 1.25, 2.5 and 5.0 (g/Kg) in brewer's yeast induced pyrexia in Albino rats (n=6/group). 0.5g/Kg Paracetamol was administered as a standard drug for comparison. *T.Cord* showed a significant anti-pyretic activity, 2.5 and 5 (g/kg) *T.Cord* doses with equipotent response compared to P.Mol (Table 1).

## DISCUSSION

The phytochemical screening of AETC has been shown the presence of alkaloids, glycosides, diterpenoid lactones sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. Three major groups of compounds, protoberberine alkaloids, terpenoids and polysaccharides are considered as putative active constituents of *T. cordifolia*. [13,14]

In our study aq extract of the stem of *T. cordifolia* produced a dose related reduction in rat right hind paw edema. At dose of 1.25g/kg there was significant reduction ( $p < 0.01$ ) but at 2.5g/kg and 5g/kg doses, the reduction in edema was highly significant as compared to control group, but no significant difference in 2.5g/kg and 50g/kg doses as compared to standard group. The observations were taken after 3

hrs of carrageenan administration as the maximum edema was noticed at 3 hrs. Similar study conducted by Siddalingappa C.M et al reported more potent anti-inflammatory activity of *T. cordifolia* as compared to standard drug Diclofenac. [15] The difference in result could be due to the use of aqueous extract of leaves while in our study aq. extract of stem was used. Although several research activities reported that anti inflammatory activity of water extract is more potent than alcoholic extract. [16,17]

Carrageenan is regarded as an established phlogistic agent for studying experimentally induced acute inflammation, as it is non-antigenic and does not produce any systemic side effects. [18] The inflammation induced by phlogistic agent biphasic in nature. The first phase is due to the production of histamine, bradykinin and cyclooxygenase products while second phase is related to neutrophil infiltration, as well as to the continuing of the production of arachidonic acid metabolites. Prostaglandins and nitric oxide synthesis is involved in inflammation, and the isoforms of inducible nitric oxide synthase (iNOS) and of cyclooxygenase (COX-2) are responsible for the production of a great amount of these mediators. It has been demonstrated that flavonoids are able to inhibit both enzymes, as well as other mediators of the inflammatory process such as reactive C protein or adhesion molecules. [19]

There is evidence of plant derived COX inhibitors in management of inflammatory disorders. Bowman et.al. reported role of dietary polyphenols mediated arachidonic acid peroxidase inhibition, [20] and thus PG synthesis inhibition. Since then many researchers have reported role of dietary polyphenols possessing COX-2 inhibitory and stimulatory effects. [21-23]

Arachidonic acid is metabolized by both cyclooxygenase (COX) and lipoxygenase (LOX) enzyme pathways, to generate PG, prostacyclins and thrombox-

anes, leukotrienes and hydroperoxy-eicosatetraenoic acid (HPETTEs), which play major role in inflammatory conditions. [24,25]

Jacob J and B. K. Prakash have reported presence of both alkaloids and flavonoids in *T. cordifolia*. And dual inhibition of COX and LOX enzymes for anti-inflammatory activity due to these phytoconstituents [26] another study also reported inhibition of LOX enzyme due to *T. cordifolia* [27] due to presence of protoberberine. [28]

#### **Antipyretic effect**

In saline treated control group, brewer's yeast induced pyrexia was significant and consistent, which was noticed even after 4hrs. Administration of aq extract of *T. cordifolia* produced dose dependent highly significant reduction in rectal temperature at 2.5g/kg. The temperature returned to normal in 2hrs. This effect was similar to that of standard drug paracetamol. At the 1.25g/kg dose, though the reduction in rectal temperature was significant but returned to normal after 3 hrs. Antipyretic activity of *T. cordifolia* was also demonstrated in the study conducted by Hussain L et al. [29] by water soluble methanolic extract. Vedavathy and Rao also reported antipyretic activity of water soluble fractions of 95% ethanolic extract of *T. cordifolia* against yeast induced pyrexia. [30]

Paracetamol is a standard antipyretic with analgesic effect. It is a poor inhibitor of cyclooxygenase in inflammatory lesions due to presence of peroxides. Its anti-pyretic effects in brain can be explained by its ability due to inhibit cyclooxygenase in brain where peroxide tone is low. [31]

Pyrexia is a result of secondary impact of infection, tissue damage, inflammation, graft rejection, malignancy or other diseased states. Mediators like IL-1 $\beta$ ,  $\alpha$ ,  $\beta$  and TNF- $\alpha$  increase the synthesis of PGE2 near pre optic hypothalamus area there by triggering the hypothalamus to elevate the body temperature. Flavonoids are known to target prostaglandins which are involved in pyrexia. [32,33] Jacob J and B.



K. Prakash have reported presence of both alkaloids and flavonoids in *T. cordifolia*, which can be attributed for its anti-pyretic effects. [25]

## CONCLUSION

Our study concludes that aq extract of *T cordifolia* is highly effective as an anti-inflammatory and anti-pyretic agent. Though further studies are required on long term basis to ascertain its adverse effects and interaction with other drugs. NSAIDS cause gastric irritation and ulceration, while *T. cordifolia* has gastro-protective and immune modulatory activity. Also there is no chance of drug dependence with its use. Moreover this plant is present in abundance throughout the year, so the procurement is easy, cost effective and does not require any expertise to prepare and is easy to administer. Anti-inflammatory and anti-pyretic activity is due to dual inhibition of COX and LOX enzymes. It can serve as a lead for the development of potential novel therapeutic agent possessing benefit of both COX and LOX enzymes inhibition with less adverse effects.

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