International Journal of Research in Medical Sciences
*Sumanlata et al. Int J Res Med Sci. 2019 Mar;7(3):938-942*
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20190953

**Original Research Article**

# Evaluation of the analgesic activity of the water soluble extract of stem of *Tinospora cordifolia* in experimentally induced pain in albino rats

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**Received:** 11 January 2019
**Accepted:** 09 February 2019

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## ABSTRACT

**Background:** Pain and pyrexia are the warning signals, primarily protective in nature, that cause discomfort and suffering and may even be unbearable and incapacitating. The modern drugs (like opioids, NSAIDs, corticosteroids) currently used for the management of pain, fever and inflammatory conditions, present with many known adverse effects. *Tinospora cordifolia* known as Giloe, widely used in folk medicine due to its property to cure a number of diseases. Hence the present study was undertaken to explore the analgesic activity of water-soluble extract of stem of T. cordifolia in albino rats in experimentally induced pain.
**Methods:** Present study was done in the department of pharmacology, albino rats were used to study the analgesic activity of *T. cordifolia* aqueous extract at the dose of 1.25g/kg,2.5g/kg and 5g/kg p.o. Various methods like Eddy's hot plate, tail flick test and acetic acid induced writhing were used for the anti- nociceptive study.
**Results:** In Eddy's hot plate and tail flick test an increase in reaction time was observed with peak effect at 90min. Results were similar to the standard drug Tramadol in acetic acid induced writhing increase in time of onset, decrease in number and duration of writhing was observed.
**Conclusions:** Aqueous extract of *T. cordifolia* was effective in all the three models of pain suggesting its possible action by central and peripheral mechanisms. Activity of *T. cordifolia* can be attributed to various phytoconstituents viz. protoberberine alkaloids, terpenoids, glycosides and polysaccharides. It can be developed as potent analgesic agent in future.

**Keywords:** Analgesic, Anti-inflammatory, Aqueous extract, Albino rats, *Tinospora cordifolia*, Writhing

## INTRODUCTION

Pain and pyrexia are the warning signals, primarily protective in nature, that cause discomfort and suffering and may even be unbearable and incapacitating, these are the most important symptoms that bring the patient to the physician.[1] The international association of study of pain definition states "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[2] Pain is a major symptom in many medical conditions and significantly interferes with a person's quality of life and general functioning. The modern drugs (opioids, NSAIDs, corticosteroids) currently used for the management of pain, fever and inflammatory conditions, present with many known adverse effects. Moreover, synthetic drugs are expensive, and many medicinal herbs have been used as therapy for the relief of pain without much adverse effects.[3] There are over 400 different tribal and other ethnic groups in India. Each tribal group has its own tradition, folk language, beliefs and knowledge about use of natural resources as medicines.[4]

*Tinospora cordifolia* (*T. cordifolia*) or Guduchi is a member of Menispermaceae family. It is also known as Giloe, Gurchi (Hindi) and Amrta (Sanskrit).[5] It is found almost everywhere in India and, even up to 1000 feet height in Himalayas. Its habitat ranges across a wide region in India spreading from Kumaon Mountains to Kanyakumari.[6] *T. cordifolia* is widely used in veterinary folk medicine/ayurvedic system of medicine for its general tonic, anti-spasmodic, anti-inflammatory, anti-arthritic, hepatoprotective, anti-allergic and anti-diabetic properties. The plant is used in ayurvedic medicine as "Rasayanas" 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 a number of diseases.[7] Hence the present study was undertaken to explore the analgesic activity of water soluble extract of stem of *T. cordifolia* in albino rats in experimentally induced pain.

## METHODS

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

The stems of *T. cordifolia* (Giloe) were dried under shade, reduced to moderately coarse power and 100g of this powder was soaked in 2liter of water for 24hours 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 rates 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 12hours before and during the experimental period. 30 animals were used for each set of experiment and animal were divided in 5 groups with 6 animals in each group.

- Group I: Control was treated with normal saline (2ml p.o) was given.
- Group II: Standard was given Tramadol (0.5mg/kg S.C.)
- Group III: 1.25g/kg was challenged with 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).

*T. cordifolia* was administered orally 30minutes before the onset of experiment.

Analgesic activity was noted at 30, 60, 90 and 120minute and then at hourly interval at 3, 4 and 5hours. The pain was produced by Eddy's hot plate, tail flick method and acetic acid induced Writhing for the study of analgesic activity.

### *Analgesic activity*

*Eddy's hot plate Method*

Rats weighing 100-200g were used and placed on the hot plate, which consists of electrically heated surface. Temperature of the hot plate was maintained at 55°C. Responses such as jumping, withdrawal of the paws and licking of the paws were observed. The time period (latency period) when animals were placed and until responses occur was recorded by the stopwatch and latency period was recorded after 0, 30, 60, 90 and 120min and then at hourly interval up to 5hours for each animal. These values were compared with the standard drug (tramadol) and control (normal saline) groups. This model evaluates the central pain.[8]

*Tail-flick test*

Antinociceptive (analgesic) activity of the extract was evaluated by the tail-flick method using analgesiometer for central cortical pain. The reaction time (in seconds) was the time taken by the rat to flick its tail due to pain. The first reading was omitted, and reaction time was taken as the average of the next two readings. The reaction time was recorded before (0min) and at 15, 30, 45, and 60min after the administration of normal saline, tramadol or graded doses of *T. cordifolia*. The maximum reaction time was fixed at 15sec to prevent any tail tissue injury. If the reading exceeds 15sec, it would be considered as maximum analgesia.[9]

*Writhing method*

Acetic acid 0.06% was injected intraperitoneally in each of the rats of this group to induce writhing. The rats reacted with a characteristic stretching behavior that is, a series of constrictions occur that travel along the abdominal wall, sometimes accompanied by turning movements of the body and extension of the hind limbs. This response of writhing was recorded. Gr.1, 2 and Test groups (3, 4, and 5) animals were administered normal saline orally, tramadol (S.C.) and *T. cordifolia* in graded doses orally 30minutes prior to administration of acetic acid. Later, rats were placed individually into glass chambers and number of writhes was recorded for 15min. This model evaluates peripheral pain.[10] The time period with the greatest percentage of inhibition was considered the peak time.

## RESULTS

The study was conducted in albino rats of either sex weighing 100-200g. The central analgesic activity was assessed by Eddy's hot plate and tail flick method while peripheral analgesic activity was assessed by acetic acid induced writhing, after taking the approval from IAEC.

Aq. extract of *T. cordifolia* was given orally. Administration of *T. cordifolia* produced a dose related significant response after 1 hour and the peak effect was observed at ½ -2hour and the effect lasted for 5hrs. The results were similar to that produced by standard drug tramadol (Table 1 and 2). There was no significant difference between the effect of tramadol and *T. cordifolia.*

**Table 1: Effect of graded doses of *Tinospora cordifolia* by Eddy's hot plate method in comparison to N. Saline and tramadol treated group in rats (n=6).**

| Name of Drugs | Reaction Time in Sec at | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0-M | 30-M | 60-M | 90-M | 120-M | 3-hr | 4-hr | 5-hr |
| N. Saline (5ml/kg) | 5.0±0.36 | 4.6 | 3.8 | 4.2 | 4.7 | 4.45 | 3.94 | 4.72 |
| Tramadol (5mg/kg) | 3.99±0.69 | ***17.12±2.73 | ***18.1±1.99 | ***19.8±2.59 | ***17.1±3.12 | **10.7±2.6 | *08.2±1.76 | 06.6±1.88 |
| T.C. (1.25g/kg) | 3.7±0.71 | **13.2±1.95 | **15.2±1.77 | ***17.3±2.55 | ***18.1±2.97 | ***16.1±2.02 | **12.4±1.79 | **11.6±1.9 |
| T.C. (2.5g/kg) | 5.2±0.59 | ***15.5±1.7 | ***16.4±1.82 | ***18.11±2.77 | ***19.4±2.69 | ***17.3±1.79 | **12.9±1.77 | **12.4±2.1 |
| T.C. (5g/kg) | 6.4±0.67 | ***16.01±2.1 | ***17.8±2.45 | ***19.81±3.01 | ***21.5±2.99 | ***17.8±1.79 | **14±1.65 | **12.5±2.01 |

*p ≤ 0.05, ** p≤ 0.01, *** p≤0.001

**Table 2: Effect of graded doses of *Tinospora cordifolia* by tail flick method in comparison to normal saline and tramadol treated group in rats (n=6).**

| Name of Drugs | Reaction Time in Sec at | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0-M | 30-M | 60-M | 90-M | 120-M (2-hr) | 3-hr | 4-hr | 5-hr |
| N. Saline (5 ml/kg) | 4.9±0.35 | 4.9±0.96 | 4.5±1.01 | 4.3±0.86 | 5.2±1.02 | 5.0±1.04 | 4.9±0.77 | 5.33±0.97 |
| Tramadol (5 mg/kg) | 5.8±1.02 | ***12.6±2.1 | ***13.1±2.6 | ***13.5±4.01 | ***14.7±3.59 | ***13.4±3.41 | **10.8±2.86 | **9.13±1.51 |
| T.C. (1.25g/kg) | 6.2±1.8 | **09.01±1.11 | **10.1±1.9 | ***12.05±2.58 | ***12.7±1.76 | **10.6±1.45 | **10.3±2.33 | **9.2±1.39 |
| T.C. (2.5 g/kg) | 5.6±0.67 | ***08.53±2.31 | ***11.21±2.3 | ***13.52±3.01 | ***14.2±2.88 | ***14.5±3.1 | ***13.5±1.95 | **10.6±2.08 |
| T.C. (5 g/kg) | 4.86±0.99 | **09.04±1.98 | ***12.13±2.22 | ***13.77±3.16 | ***13.0±2.89 | ***14.5±3.01 | ***14.01±3.04 | ***13.5±1.99 |

*p ≤ 0.05, ** p≤ 0.01, *** p≤0.001

**Table 3: Effect of graded doses of *Tinospora cordifolia* on acetic acid induced writhing in comparison to n. Saline and aspirin treated group in rats (n=6).**

| Number of Drugs | Writhing | | |
|---|---|---|---|
| | Onset in Minutes | Duration in Minutes | Number |
| N. Saline (5 ml/kg) | 10.01±2.3 | 108±5.1 | 45±2.82 |
| Aspirin (100 mg/kg) | 17.5±2.6** | 65±3.2*** | 10±1.0 |
| T.c 1.25g/kg | 11.3±1.99 | 78±4.01*** | 14±1.5*** |
| T.c 2.5g/kg | 12.5±1.83 | 70±4.06*** | 12±0.99*** |
| T.c 5.0g/kg | *15.30±2.67 | ***68±5.0 | 11±0.89*** |

*p ≤ 0.05, ** p≤ 0.01, *** p≤0.001

The peripheral analgesic activity was evaluated on the basis of increase in time of onset and decrease in number and duration of writhing as compared to control group. Result were equieffective as that of the standard drug aspirin. A highly significant increase in onset and reduction in number and duration of writhing with the test drug *T. cordifolia* (Table 3) was observed. However, the effect of *T. cordifolia* was dose related. Results were statistically analyzed for significance by using one-way ANOVA.

## DISCUSSION

*T. cordifolia* commonly known as giloe, a herbal plant is widely distributed in the Indian subcontinent and commonly used in alternative systems of medicines for treatment of conditions associated with pain. The plant mainly contains alkaloids, glycosides, steroids, sesquiterpenoids, aliphatic compounds, essential oils, mixture of fatty acids and polysaccchrides. The alkaloids include berberine, bitter gilonin, non-glycoside gilonin gilostero.[11]

The major phytoconstituent in *Tinospora cordifolia* include tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane furano diterpene, diterpenoid furano lactone, tinosporidine, columbin, b-sitosterol. Berberine, palmatine, tembertarine, magniflorine, choline and tinosporin are reported from the stem of the plant.[12,13]

Administration of AETC exhibited dose dependant highly significant increase in the reaction time at doses of 1.25g/kg, 2.5g/kg, and 5g/kg by various methods viz. Eddy's hot plate and tail flick method for central analgesic mechanism. The analgesic effect persisted for more than 5hrs duration similar to that of standard drug tramadol. The peak was noticed at 2hrs which lasted for 3hrs.

The peripheral analgesic activity was determined (indicated by delaying of onset, shortening of duration and reduction in number of writhing's) by using acetic acid induced writhing method. *T. cordifolia* showed highly significant effect in test groups in comparison to the control group but less potent than the standard drug aspirin. Study conducted by Siddalingappa also showed significant analgesic activity of aqueous extract of *T. cordifolia*.[14] Findings of our study are also in accordance with the results of Hossain MD et al which showed significant increase in pain threshold in hot plate and tail flick test in dose dependant manner and also significant inhibition of writhing response.[15] Phytochemical screening of AETC leaves revealed the presence of alkaloid, glycosides, diterpenoid lactones, sesquiterpenoid, phenolics aliphatic compounds and polysaccharides.[11,12] So, the observed analgesic activity may be attributed to any of their phytoconstituents.

Our study indicated that AETC has good analgesic effect which is similar to that of tramadol and produced better analgesia in 5g/kg dose but less potent than aspirin probably the central mechanism is more responsible for the analgesic effect.

## CONCLUSION

In conclusion further long term studies with higher doses are required to define the effective and toxic dose of *T. cordifoilia* extract to be used in routine Clinical practice as analgesic and anti-inflammatory. NSAID cause gastric irritation as side effect while *T. cordifoilia* has a gastro-protective activity.[16] It can be cost effective as compared to existing analgesics and has antioxidant and immunomodulatory activities also.[17,18] It is easily available and has no chances of causing drug dependence.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Sumanlata, Suman A, Sharma RK, Jindal M, Khan A. Evaluation of the analgesic activity of the water soluble extract of stem of Tinospora cordifolia in experimentally induced pain in albino rats. Int J Res Med Sci 2019;7:938-42.