

*Short Title: Evaluation of the Analgesic Activity of Terminalia bellerica Using the Hot Air Pain Model*

**A Randomized, Double Blind, Placebo-Controlled, Crossover Study to Evaluate the Analgesic Activity of Terminalia bellerica in Healthy Human Participants Using the Thermal Pain Model - Hot Air Pain Model**

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**ABSTRACT**

**Background**

Pain is a common and often disabling symptom associated with many medical conditions and may be triggered by external or internal stimuli. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used analgesics; however, their use is associated with adverse effects, necessitating the search for safer alternatives. Animal studies have demonstrated significant analgesic activity of the ethanolic and aqueous extracts of Terminalia bellerica (T. bellerica). Therefore, the present study was undertaken to evaluate the analgesic activity and safety of a standardized aqueous extract of T. bellerica in healthy volunteers using the hot-air pain model.

**Materials and Methods**

This randomized, double-blind, placebo-controlled, crossover study was conducted after obtaining informed consent and Institutional Ethics Committee approval. Twelve healthy adult participants were randomized in a double-blind manner to receive a single oral dose of either two 500-mg capsules of T. bellerica extract or identical placebo capsules. Thermal pain was assessed using a hot-air analgesiometer. Mean pain threshold and pain tolerance times were measured at baseline and 2 h after dosing. After a 2-week washout period, participants crossed over to receive the alternate treatment, and the procedure was repeated. Safety was assessed before and after the study. Data were analyzed using GraphPad Prism 7.

**Results**

Compared with baseline and placebo, T. bellerica significantly increased mean pain threshold time from  $33.53 \pm 1.53$  to  $38.19 \pm 1.93$ s ( $p < 0.001$ ) and pain tolerance time from  $47.75 \pm 2.37$  to  $51.41 \pm 2.14$ s ( $p < 0.001$ ). There was a significant increase in mean percentage change in pain threshold [13.91% ( $p < 0.001$ )] and pain tolerance time [7.82% ( $p < 0.01$ )]. No significant changes were observed with the placebo. Both treatments were well tolerated.

**Conclusion**

In the present study, T. bellerica significantly increased pain threshold and pain tolerance time compared with baseline and placebo and was well tolerated. Further studies are needed to evaluate its effects in patients with painful conditions.

**Keywords:** Terminalia bellerica, Analgesic activity, Experimental pain model, Hot air analgesiometer, Pain threshold, Pain tolerance.

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**Conflict of interest:** None

**INTRODUCTION**

Pain is a complex sensory and emotional experience associated with actual or potential tissue damage and serves as an important protective mechanism [1]. It

## RESEARCH PAPER

is one of the most common reasons for seeking medical care and is associated with a wide range of acute and chronic disorders. Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics; however, their long-term use is often limited by adverse effects. NSAIDs may cause gastrointestinal irritation and renal toxicity, whereas opioids are associated with respiratory depression, tolerance, and dependence [2]. Consequently, there is a continuing search for analgesic agents that are both safe and effective, including those derived from medicinal plants.

*Terminalia bellerica* (*Terminalia bellirica*) belongs to the Combretaceae family and is commonly known as Baheda or Bibhitaki. It is an important medicinal plant widely used for its diverse therapeutic properties [3]. It is one of the three constituents of the Ayurvedic formulation Triphala. It has been traditionally used for various therapeutic purposes, including the treatment of cough, sore throat, gastrointestinal disorders, inflammation, and fever [4]. Phytochemical studies have identified numerous bioactive compounds in *Terminalia bellerica* (*T. bellerica*), such as tannins, gallic acid, ellagic acid, flavonoids, glycosides, terpenoids, saponins, chebulinic acid, and chebulagic acid. These constituents are believed to contribute to its diverse pharmacological activities, including analgesic, anti-inflammatory, antioxidant, antidepressant, antidiabetic, antihypertensive, antimicrobial, antifungal, bronchodilator, antiulcer, antidiarrheal, antispasmodic, anticancer, and immunomodulatory effects [5,6].

Preclinical studies have reported the analgesic potential of *T. bellerica* in various animal pain models. Crude and aqueous extracts of *T. bellerica* showed significant analgesic activity in acetic acid-induced writhing, hot plate, and tail-immersion tests in rodents [7,8,9].

Although preclinical studies have shown promising analgesic effects of *T. bellerica*, clinical evidence in humans is still scarce. Experimental pain models in healthy volunteers provide a controlled and reproducible approach for assessing analgesic activity. Among experimental pain models, the hot-air pain model is a validated and reliable method for assessing pain threshold and pain tolerance. This model enables objective assessment of analgesic effects under standardized conditions while reducing inter-individual variability [10,11].

Therefore, the present study was undertaken to evaluate the analgesic efficacy and safety of a standardized aqueous extract of *T. bellerica* in healthy human participants using the hot-air thermal pain model.

### MATERIALS AND METHODS:

This study was conducted in the Department of Clinical Pharmacology and Therapeutics at Nizam's Institute of Medical Sciences. This was a randomized, double blind, placebo-controlled,

crossover study conducted after obtaining informed consent and approval from the Institutional Ethics Committee.

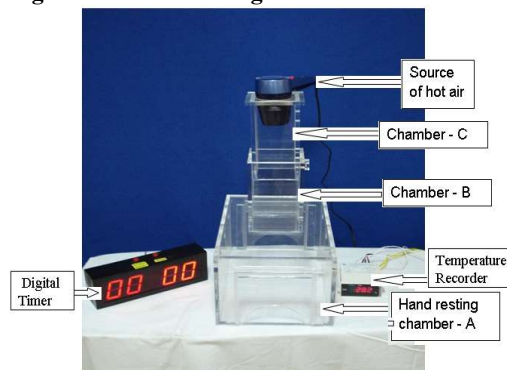
Healthy volunteers of either gender, aged between 18 and 45 years, with a normal body mass index (18.5–24.9 kg/m<sup>2</sup>), who provided written informed consent and were able to perform the tests as per the study protocol, and who had a pain threshold time of more than 30 seconds and a pain tolerance time of less than 180 seconds, were included in the study.

Uncooperative participants, those with prior wounds or fractures in the tested extremity, and those with a history of diabetes mellitus, hypertension, or gastrointestinal disorders were excluded from the study. Participants with any clinically significant abnormality detected during physical examination or laboratory investigations were also excluded. In addition, individuals with a documented history of treatment with amphetamines, cocaine, sympathomimetics, systemic glucocorticoids, or anabolic steroids; those who had used NSAIDs within the preceding 2 weeks; those receiving any investigational drug at the time of enrolment or within 3 months before the study; and those with a known history of hypersensitivity to the study drug were excluded.

The study medications consisted of *T. bellerica* (Ayuric®, Natreon Inc., USA) 500 mg capsules and identical matching placebo capsules supplied by Natreon Inc., USA. Each *T. bellerica* capsule contained an aqueous extract of the edible fruit of *T. bellerica*, standardized by HPLC to contain not less than 15% hydrolysable tannins, including chebulinic acid, chebulagic acid, and other low-molecular-weight tannins. The placebo capsule contained microcrystalline cellulose.

A hot air analgesiometer (Figure 1) was used to deliver the thermal pain stimulus. The device has been developed, validated, and described in detail in previous publications [10].

**Figure 1: Hot Air Analgesiometer**



### Study procedure

The study duration was three months. The study procedure was explained to the participants, and written informed consent was obtained. A detailed medical history was taken, and a physical and

## RESEARCH PAPER

clinical examination was done. Safety laboratory investigations were performed to assess hematological, hepatic, and renal parameters. Eligible participants were trained on the study procedures on two separate occasions before the study. On the study day, after a good overnight sleep, they were instructed to report to the department at 8:00 a.m. Participants were seated in a temperature- and humidity-controlled room for 30 minutes, after which baseline vital parameters were recorded. Participants were then asked to place their non-dominant hand, exposing the volar aspect of the forearm, into the lower chamber (A). They were blindfolded immediately before the delivery of the heat stimulus. The hot air analgesiometer was turned on by the investigator without prior notice. Participants were instructed to raise the index finger of their other hand as soon as they first perceived the heat sensation as painful, which was recorded as the pain threshold time in seconds. They were further instructed to raise the index finger a second time when the heat sensation became unbearable, which was recorded as the pain tolerance time in seconds, and then immediately withdraw their forearm from the chamber. The procedure was repeated three times, with an inter-stimulus interval of five minutes between successive measurements. The mean of the three measurements was calculated and used as the baseline value for analysis. At 9:00 a.m., a light breakfast was served to the participants. At 9:30 a.m., two capsules of *T. bellerica* 500 mg or identical matching placebo capsules were given to the participants with 240 mL of water, according to a computer-generated randomization sequence (simple randomization). Treatment allocation was concealed from both the participants and the investigator. They were instructed to sit upright in the chair after taking the drug. After 120 minutes, the thermal pain assessment procedure was repeated. Participants were instructed to report any adverse events experienced during the study period. After a 2-week washout period, participants crossed over to the alternate treatment according to the randomized crossover sequence, and all study procedures were repeated. Safety laboratory investigations were performed after the study and were found to be within normal limits. Both treatments were well tolerated, and no participant withdrew from the study because of adverse events.

### End points:

The primary endpoint of the study was the changes in pain threshold and pain tolerance time compared with baseline values. Pain threshold time was defined as the time at which participants first perceived the heat stimulus as painful, whereas pain tolerance time was defined as the time at which the heat stimulus was perceived as unbearable. The secondary endpoint was the assessment of the safety and tolerability of *T. bellerica* in healthy human participants.

### Statistical analysis

Data was expressed as Mean  $\pm$  S.D. Paired “t” test was done to determine the changes in pain threshold and tolerance time between and within study groups.  $p < 0.05$  level with 95% confidence interval was considered statistically significant. Statistical analysis was performed using the GraphPad Prism software 7 (GraphPad Software Inc., USA).

### RESULTS:

A total of 15 participants were screened, of whom 12 were enrolled in the study. Of the three excluded participants, two were excluded because the pain threshold time was less than 30 seconds, and the other was excluded because the liver function test values exceeded three times the upper limit of normal. The demographic characteristics are depicted in Table 1. There were no significant differences in baseline characteristics between the two groups.

**Table 1: Demographic characteristics of the study groups**

Parameter	Study group
Total no	n=12
Gender (M/F)	10/2
Age (years)	38.67 $\pm$ 4.87
Weight (kgs)	60.1 $\pm$ 5.19
Height (cms)	160.98 $\pm$ 5.0
BMI (Kg/m <sup>2</sup> )	22.46 $\pm$ 0.98

Aqueous extract of *T. bellerica* produced a significant ( $p < 0.001$ ) increase in mean pain threshold and mean pain tolerance time compared to baseline and placebo (Table 2). No significant change in pain threshold and pain tolerance time was observed with the placebo.

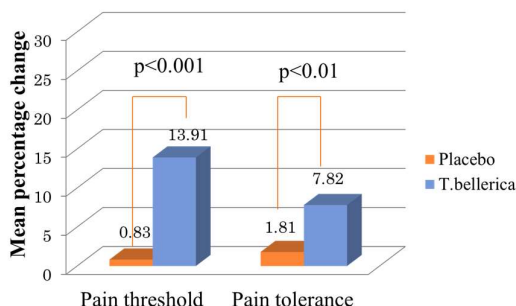
**Table 2: Mean Pain Threshold and Mean Pain Tolerance Time**

Treatment group	Mean Pain Threshold Time (in seconds)		Mean Pain Tolerance Time (in seconds)	
	At baseline (Mean $\pm$ SD)	Post-drug 2hr (Mean $\pm$ SD)	At baseline (Mean $\pm$ SD)	Post-drug 2hr (Mean $\pm$ SD)
Placebo	33.44 $\pm$ 1.14	33.72 $\pm$ 1.91 NS	47.39 $\pm$ 2.49	48.14 $\pm$ 2.36 <sup>N</sup> <sub>s</sub>
<i>T. bellarica</i>	33.53 $\pm$ 1.53	38.19 $\pm$ 1.93* #	47.75 $\pm$ 2.37	51.41 $\pm$ 2.14* #

Values are expressed as mean  $\pm$  SD, SD standard deviation, \* $p < 0.001$  compared to baseline value, #  $p < 0.001$  compared to placebo, NS-non-significant compared to baseline value.

A significant increase in the mean percentage change in both pain threshold (13.91% vs. 0.83%,  $p < 0.001$ ) and pain tolerance time (7.82% vs. 1.81%,  $p < 0.01$ ) was observed with *T. bellerica* compared with placebo (Figure 2).

**Figure 2: Mean percentage change in pain threshold and pain tolerance time**



Compliance was ensured, as all study medications were administered under direct supervision. Both medications were well tolerated; no participant discontinued the study because of adverse events. All safety laboratory parameters were repeated after the test procedure with placebo and standardised aqueous extract of *T. bellerica* and were found to be within normal limits.

## DISCUSSION

The present randomized, double-blind, placebo-controlled crossover study evaluated the analgesic activity of a standardized aqueous extract of *T. bellerica* in healthy human participants using the hot-air thermal pain model. A significant increase in both pain threshold and pain tolerance time was observed with *T. bellerica* compared with baseline and placebo treatment. A significant increase in the percentage change of these parameters was also observed following administration of *T. bellerica*, whereas placebo treatment did not produce any significant changes. These findings suggest that *T. bellerica* reduced sensitivity to thermal pain stimuli and enhanced pain tolerance in healthy volunteers. Several preclinical studies have demonstrated the analgesic potential of *T. bellerica*. Khan et al. reported antisecretory and analgesic activities of the crude extract of *T. bellerica* [7]. Similarly, Sharma et al. demonstrated significant analgesic activity of ethanolic and aqueous extracts of *T. bellerica* using the acetic acid-induced writhing and Eddy's hot plate methods in rodents [8]. The authors employed the acetic acid-induced writhing assay and the hot plate test to evaluate peripheral and centrally mediated antinociceptive activity, respectively. Kaur et al. further reported analgesic activity of ethanol extracts of *T. bellerica* and *T. chebula* in the tail-immersion model in mice [9]. More recently, Kodiattu et al. demonstrated significant analgesic activity of the aqueous extract of *T. bellerica* fruit pulp using Eddy's hot plate technique in mice [12]. The findings of the present study are consistent with

previous preclinical studies demonstrating the analgesic activity of *T. bellerica* in various animal models of nociception. Although the experimental models differ, both the animal studies and the present human study suggest a potential analgesic effect of *T. bellerica*. The hot air pain model used in the present study provides a controlled, quantifiable, and reproducible thermal stimulus for assessing pain threshold and pain tolerance time in healthy volunteers. Previous studies using the same model have demonstrated analgesic effects with *Terminalia chebula* and *Withania somnifera*, further supporting the validity of this model for assessing analgesic activity. [13,14].

The precise mechanism underlying the analgesic effect observed in this study remains unclear. The standardized extract used in this study contained chebulinic acid, chebulagic acid, and other hydrolysable tannins, which may have contributed to the observed analgesic effects [12]. However, further studies are required to elucidate the mechanisms responsible for the analgesic activity of *T. bellerica*.

All study medications were well tolerated, and no significant adverse effects were observed during the study period.

## Conclusion

In the present study, *T. bellerica* significantly increased pain threshold and pain tolerance time in healthy human participants in a thermal hot-air pain model and was well tolerated. Further studies are needed to assess its effects in patients with painful conditions.

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