



International Research Journal of Pharmaceutical and Applied  
Sciences (IRJPAS)

Available online at [www.irjpas.com](http://www.irjpas.com)  
Int. Res J Pharm. App Sci., 2012; 2(6): 159-163



### Research Article

## ANALGESIC AND ANTIPYRETIC ACTIVITIES OF *TERMINALIA CHEBULA* RETZ. FRUITS EXTRACTS IN EXPERIMENTAL ANIMALS

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(Received: 10 December 2012; Accepted: 20 December, 2012; Published: 29 December, 2012)

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**Abstract:** The present study was undertaken to evaluate the analgesic and antipyretic activities of ethanolic extract of *Terminalia chebula* Retz. (EETC) fruits in experimental animal models. The study was carried out using Albino mice (20-30g) and rats (120-130 g) of either sex. The EETC was prepared by Soxhlet extraction process. The analgesic activity of *Terminalia chebula* was assessed by using hot plate method in rats and acetic acid induced writhing in mice. The antipyretic activity was assessed by Brewer's yeast-induced pyrexia in rats. Doses of ethanolic extract of *Terminalia chebula* used for the present study were 400mg/kg and 600mg/kg. EETC produced a significant decrease in the number of wriths in acetic acid induced writhing model of pain as well as showed a significant increase in the mean reaction time to heat stimuli in hot plate method at both 400mg/kg and 600mg/kg, p.o. doses. Single administration of EETC at doses 400mg/kg and 600mg/kg, p.o. showed significant antipyretic activity throughout the observation period of 3 hours, which was comparable to the standard paracetamol group. The present study suggested that ethanolic extract of *Terminalia chebula* Retz. has significant analgesic and antipyretic activities.

**Key words:** *Terminalia chebula*, antipyretic-analgesic, hot plate, acetic acid writhing, yeast induced pyrexia.

### INTRODUCTION

Medicinal plants are part and parcel of human society to combat diseases, from the dawn of civilization. Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide biological and medicinal activities, higher safety margins and lesser costs.<sup>1</sup> *Terminalia chebula* is a plant species belonging to the genus *Terminalia*, family *Combretaceae*.<sup>1</sup> It is commonly known as Chebulic myrobalan (harra in Hindi; hilikha in Assamese).<sup>2</sup> The Sanskrit name 'Haritaki' is rich with meaning, referring to the yellowish dye (harita) that contains the god Siva (Hari, i.e. the Himalayas) and that it cures (harayet) all the diseases.<sup>3</sup> It is moderate to large sized tree found throughout India, chiefly in deciduous forests and areas with light rain fall, but occasionally found in moist forest up to an altitude of 1500 meters.<sup>4</sup> Flowering takes place between April to August and fruit ripens from October- January.<sup>2</sup> *Terminalia chebula* has been extensively used in Ayurveda, Unani and Homoeopathic medicine and has become a cynosure of modern medicine. It is a component of the classic Ayurvedic combination called "Triphala" (three fruits).<sup>1</sup> The dried ripe fruits have traditionally been used in the treatment of asthma, sore throat, vomiting, hiccup, bleeding piles, gout, heart and bladder diseases. Its paste with water is found to be anti-inflammatory, analgesic and having purifying and healing capacity for wounds.<sup>5</sup> It is given as adjuvant herb in chronic fever.<sup>1</sup> It has been

used to treat various ailments like hemorrhoids, dental caries, bleeding gums and oral ulcers, diarrhoea, gastroenteritis, malabsorption syndrome, vesicular and renal calculi, neuropathy, paralysis, memory loss, epilepsy, depression, diabetes, tumors, skin diseases, as well as intermittent fever, rheumatism, arthritis, gout, etc.<sup>1,5</sup> The plant is reported to have antibacterial, antifungal, antiviral, antioxidant, hepatoprotective, cardioprotective, antidiabetic, hypolipidemic, antispasmodic, and various other activities.<sup>1</sup> Phytochemical studies revealed the presence of tannins like chebulic acid, chebulagic acid, chebulinic acid, corilagin, gallic acid, gallotannins and ellagic acid; fructose, amino acids, succinic acid, ascorbic acid, flavonol glycosides, triterpenoids, coumarin, betasitosterol, resin and anthroquinone.<sup>1,6</sup> A survey of literature revealed that no scientific study on the antipyretic activities has been reported on the fruits of the plant but however, Kaur S et al., 2010, demonstrated analgesic activity on tail immersion model of antinociceptive activity.<sup>7</sup> The present study was designed to evaluate the analgesic and antipyretic activities of the fruit extracts of the *Terminalia chebula* Retz.

### MATERIALS AND METHODS

#### Collection and identification of the of plant materials

The fruits of *Terminalia chebula* were collected during the month of October to December 2010

from the local market of Guwahati, Assam and were identified by Dr Triguna Ranjan Sharma, Lecturer, Department of Botany, Swadeshi Academy, Guwahati, Assam, India.

#### Preparation of extracts of *Terminalia chebula*

Shade dried fruits were grounded to fine powder in an electric grinder. 300 grams of the dried powdered material were extracted with 95% ethanol using Soxhlet apparatus at a temperature of 60°C for about 48 hours which was further evaporated to dryness to obtain the ethanolic extract. A final yield of 60 grams i.e. 20% w/w with respect to the original air dried powder was obtained. The extract was finally stored in air tight container in a refrigerator at 2-8 °C for further use in the experiment.

#### Experimental Animals

Albino mice (20-30g) and rats (120-130 g) of either sex were used for experimental study. They were acclimated to laboratory conditions for seven days before the commencement of the experiments, with alternate light-dark cycle of 12 hr each and were allowed free access to standard dry pellet diet and water *ad libitum*. Animals were fasted overnight with free access to water prior to each experiment. Experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC), CPCSEA Regd. No. 351; 3/1/2001, Gauhati Medical College & Hospital, as per the approved protocol (No.MCI 32/2012/3). The study was performed according to the CPCSEA (Committee for the Purpose of Control and Supervision of Experimentation on Animals) guidelines.

#### Acute Toxicity Studies

The acute toxicity study was carried out as per OECD guidelines 425. The mice were randomly selected, marked to permit individual identification, and kept in their cages for at least 5 days prior to dosing to allow for acclimatization to the laboratory conditions. Animals were fasted prior to dosing (food but not water was withheld for 3-4 hours). The fasted body weight of each animal was determined and the dose was calculated according to the body weight. Following the period of fasting, the *T. chebula* Retz fruits were administered orally at different dose levels of 175, 550 and 2000mg/kg. Food was withheld for a further 1-2 hours. The animal was observed for 48 for mortality. All the above animals were observed for a full observation period of 14 days.

#### Pharmacological evaluation

##### Acetic acid induced writhing in mice

The mice were divided into four groups of six animals each. The control group (Group I) mice received saline solution (0.9% w/v, NaCl) 2 ml/kg

p.o., standard group (Group II) received 40 mg/kg Ibuprofen p.o., Group III and IV received 400 mg/kg and 600mg/kg of EETC p.o. respectively. After 60 minutes, 0.1 ml of 1% acetic acid was injected intraperitoneally to each group.<sup>8</sup> The Number of writhes (abdominal muscle contraction), stretching of the hind limbs and trunk twisting were counted for 10 min after acetic acid injection. Percent inhibition was determined for each experimental group as  $(W_c - W_t / W_c) \times 100$ , where  $W_c$  is the average number of writhing in control group and  $W_t$  is the average number of writhing in test group.<sup>9</sup>

##### Thermal stimulus-induced pain (hot plate test) in rats

The rats were divided into four groups of six animals each. The test was carried out using Eddy's hot plate apparatus. The temperature was set at  $55 \pm 1$  °C.<sup>10</sup> The control group (Group I) received saline solution (0.9% w/v, NaCl) 2 ml/kg p.o., standard group (Group II) received Morphine 5 mg/kg s.c., Group III and IV received 400 mg/kg and 600mg/kg of EETC p.o. respectively. Analgesic activity of EETC was assessed by placing the animals on a hot plate and observing the reaction time (paw licking and jumping) in seconds with cut-off time of 15 sec (to prevent injury) The reaction time was noted at 0, 30, 60 and 120 minutes following drug administration.

##### Brewer's yeast-induced pyrexia

Rats were divided into four groups of six animals each. Fever was induced in rats by subcutaneous injection of 20 mg/kg of 20% suspension of Brewer's yeast in normal saline below the nape of the neck.<sup>10</sup> Initial rectal temperature were recorded. After 18h, animals that showed an increase of 0.3-0.5 °C in rectal temperature were selected. The control group (Group I) rats received saline solution (0.9% w/v, NaCl) 2 ml/kg p.o., standard group (Group II) received Paracetamol 150 mg/kg p.o.<sup>10,11</sup>, Group III and IV received 400 mg/kg and 600mg/kg of EETC p.o. respectively. Antipyretic activity of EETC was assessed by measuring the rectal temperature with thermometer at 0, 30, 60, 120 and 180 minutes following drug administration.<sup>12</sup>

##### Statistical analysis

All the data were entered into the statistical software, SPSS 16.0. Data were expressed as mean  $\pm$  SEM. Results were analyzed by one way analysis of variance (ANOVA), followed by Dunnett multiple comparison test. p value < 0.05 was considered as statistically significant.

**RESULTS AND DISCUSSION****Acute toxicity study:**

NOAEL of ethanolic extract of *Terminalia chebula* Retz. (EETC) was found to be 2000mg/kg/day.

**Acetic acid induced abdominal writhing:**

The standard drug Ibuprofen and ethanolic extract *Terminalia chebula* (EETC) at doses of

400mg/kg and 600mg/kg significantly decreased the number of acetic acid induced writhing in mice, when compared to control ( $p < 0.05$ ) [Table 1]. The maximal percentage of inhibition of writhing at 400mg/kg and 600mg/kg of EETC were 51.96% and 68.13% respectively, whereas the standard drug Ibuprofen showed a reduction of 74.51%.

**Table 1:** Effect of Ethanolic extract of *Terminalia chebula* fruit on Acetic acid induced writhing in mice

Group	Drugs	Dose (mg/kg)	Mean No. of Writhing±S.E.M (10Mins.)	% Inhibition of writhing
I	Normal saline	-	68.00±1.15	---
II	Ibuprofen (p.o.)	40	*17.33±0.99	74.51
III	EETC (p.o.)	400	*32.67±1.90	51.96
IV	EETC (p.o.)	600	*21.67±1.20	68.13
One way ANOVA			df 3, 20 F 285.460	

Values are Mean ± S.E.M. (n=6) Significance vs. control group: \* $p < 0.05$

**Thermal stimulus-induced pain (hot plate test) in rats:**

In the hot plate method, the standard drug (Morphine sulphate) and the ethanolic extract *Terminalia chebula* (EETC) at doses of 400mg/kg and 600mg/kg showed significant increase in reaction time i.e. 10.83±0.54 s, 8.33±0.21 s and 8.83±0.40 s, respectively at 30 min. when

compared to control (6.00±0.36s) [Table 2].  $p < 0.05$  was considered statistically significant. Similarly they showed a significant increase in reaction time at 60 and 120 minutes when compared to the control group. However the analgesic effect of EETC was less when compared to the standard drug (Morphine sulphate).

**Table 2:** Effect of ethanolic extract of *Terminalia chebula* fruit on Thermal stimulus induced pain (Hot Plate Test) in Rats.

Groups	Drugs	Dose mg/kg	Reaction Time in seconds			
			0 min	30 min	60 min	120 min
I	Control	-	6.17±0.47	6.00±0.36	6.17±0.30	6.17±0.40
II	Morphine (s.c.)	5	5.83±0.30	#10.83±0.54	#12.17±0.30	#14.50±0.34
III	EETC (p.o.)	400	5.83±0.30	#8.33±0.21	#9.33±0.33	#11.33±0.49
IV	EETC (p.o.)	600	6.00±0.25	#8.83±0.40	#10.17±0.30	#11.67±0.21
One way ANOVA				df 3, 20 F 24.912	df 3, 20 F 63.169	df 3, 20 F 85.033

Values are Mean ± S.E.M. (n=6) Significance vs. control group: # $p < 0.05$

**Antipyretic activity:**

The results of the antipyretic effect of the control, standard drug (Paracetamol) and the ethanolic extract *Terminalia chebula* (EETC) at doses of 400mg/kg and 600mg/kg are depicted in Table 3. The Paracetamol as well as EETC at doses

of 400 mg/kg and 600mg/kg started showing significant antipyretic activity after 1h (60 min.) of post dosing when compared with the control group. Antipyretic activity was observed up to 3 h (180 min.) after paracetamol and test extracts administration.

**Table 3:** Effect of Ethanolic extract of *Terminalia chebula* fruit on Brewer's yeast-induced pyrexia in Rats.

Groups	Drugs	Dose (mg/kg)	Rectal temperature in °C at time (min.)				
			0	30	60	120	180
I	Control	-	38.48 ± 0.15	38.65 ± 0.13	38.86 ± 0.09	38.96 ± 0.08	39.08 ± 0.09
II	Paracetamol (p.o)	150	38.56 ± 0.11	38.88 ± 0.07	**37.61 ± 0.14	**37.26 ± 0.16	**36.97 ± 0.16
III	EETC (p.o)	400	38.58 ± 0.17	38.86 ± 0.11	**38.18 ± 0.17	**37.94 ± 0.18	**37.80 ± 0.18
IV	EETC (p.o)	600	38.56 ± 0.14	38.81 ± 0.11	**37.89 ± 0.11	**37.61 ± 0.12	**37.38 ± 0.13
One way ANOVA					df 3, 20 F 15.700	df 3, 20 F 26.334	df 3, 20 F 39.019

Values are Mean ± S.E.M. (n=6) Significance vs. control group: \*\*p<0.05.

Acetic acid-induced writhing and Eddy's hot plate induced thermal stimulation are models of pain that mainly involve peripheral and central mechanisms, respectively. Analgesic effect observed in these two models with 400 mg/kg and 600mg/kg ethanolic extracts of *Terminalia chebula* (EETC) indicates the involvement of both peripheral and central mechanisms. The acetic acid-induced writhing has been associated with an increased level of PGE<sub>2</sub> and PGF<sub>2α</sub> in peritoneal fluids as well as lipoxygenase products.<sup>13</sup> The present results revealed a significant reduction in acetic acid-induced writhing, and increase reaction time to heat stimuli, strongly suggests that the mechanism of the extract may be linked partly to cyclooxygenase and/or lipoxygenase inhibition.<sup>10</sup> In addition, the flavonoids are known to inhibit prostaglandin synthetase.<sup>10,14</sup> Apart from flavonoids, tannins are also known to possess analgesic activity.<sup>13</sup> Since prostaglandins involved in pain perception are inhibited by flavonoids, it could be suggested that reduced availability of prostaglandins by flavonoids and tannins present in *Terminalia chebula* might be responsible for its analgesic effect.

It is well known that most of the anti-inflammatory and analgesic drugs possess antipyretic activity. The extract markedly decreased the rectal temperature of pyretic rats. This postulation is supported by the antipyretic effect of the extract, evidenced by its impact on the pathogenic fever induced by the administration of a yeast injection. Its etiology includes the production of prostaglandins in central nervous system which is the final common pathway responsible for fever

induction.<sup>10</sup> In general, NSAIDS produce their antipyretic action through the inhibition of prostaglandin synthetase within the hypothalamus.<sup>12,15</sup> Therefore, it appears that the flavonoids content of *Terminalia chebula* may also be responsible for its antipyretic activity by inhibiting prostaglandin synthesis in hypothalamus.

### CONCLUSION

The present study concludes that the ethanolic extract of *Terminalia chebula* (EETC) has analgesic and antipyretic activities in mice and rats at the doses of 400mg/kg and 600 mg/kg. However, this is a preliminary study and further study needs to be carried out for knowing the possible mechanism of actions and isolation of active principle(s) responsible for such activities.

### Acknowledgement:

The authors are grateful to Dr R. Borgohain for helping out with the necessary statistical analysis.

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