EVALUATION OF ANTIPYRETIC AND ANALGESIC ACTIVITY OF *ARTOCARPUS HETROPHYLLUS* IN EXPERIMENTAL ANIMAL MODELS

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Summary

The objective of the present study was to investigate the antipyretic and analgesic activities of ethanol extract of *Artocarpus hetrophyllus* fruit seeds. The antipyretic activity of *A. hetrophyllus* (25mg/kg, 50mg/kg and 100mg/kg) was studied in Brewer's yeast induced pyrexia in rats. The analgesic activity of *A. hetrophyllus* (25mg/kg, 50mg/kg and 100mg/kg) was studied using Eddy's hot plate method and tail flick method in mice. The ethanol extract of *A. hetrophyllus* showed reduction in normal body temperature and yeast provoked elevated temperature in a dose dependant manner. The effect became significant at 60 min at the highest dose of 100 mg/kg. Meanwhile the analgesic activity evidence by increase in the reaction time by Eddy"s hot plate method and tail flick method in mice. The results suggest that *A. hetrophyllus* contains biologically-active substances with potential values in the treatment of fever and pain. These provide scientific evidence to support the isolation and development of biologically active components as antipyretic agents.

Key words *Artocarpus hetrophyllus,* analgesic activity, eddy's hot plate, tail flick

Introduction

The jackfruit (*Artocarpus heterophyllus*) is a species of tree in the mulberry family (Moraceae), which is native to parts of South and Southeast Asia. It is called Katahal in Hindi, medium-size evergreen tree typically reaching 8–25 m (26–82 ft) in height that is easily recognized by its fruit. Its fruit is the largest tree borne fruit in the world, seldom less than about 25 cm in diameter. The jackfruit is something of an acquired taste, but it is very popular in many parts of the world. Seeds are light brown to brown, rounded, 2–3 cm in length by 1–1.5 cm in diameter, and enclosed in a thin, whitish membrane and has a sweet taste. Up to 500 seeds can be found in each fruit. The nutritious seeds are boiled or roasted and eaten like chestnuts, added to flour for baking, or cooked in dishes[1-4]. A review of the literature revealed that the antipyretic and analgesic property of fruit seeds of *Artocarpus heterophyllus* has not been subjected to scientific evaluation. The present study was carried out in an experimental animal model to reports the antipyretic and analgesic property on fruit seeds of this plant.

Materials and Methods

Plant material: The proposed study of *A. hetrophyllus* were collected from the Sukhi sevaniya village, Bhopal, Madhya Pradesh, with the help of local tribal and field botanist. The collected material was authenticated by Dr. Dolly Malhotra, Professor, Department of Biotechnology, M.V.M. College, Bhopal.

Preparation of ethanol extract: The powder of seeds (300gm) of *A. heterophyllus*, was packed well in Soxhlet apparatus and extracted with ethanol until the completion of the extraction. The extract was filtered while hot, and the resultant extract was distilled in vacuum under reduced pressure in order to remove the solvent completely and dried in a desiccators.

Animals: Male wistar albino rats and mice were kept in quarantine for 10 days under standard husbandry conditions (27.3^{o}, Relative humidity 65 ±10%) for 12 hrs in dark and light cycle respectively and were given standard food and water *ad. libitum*. The study was permitted by the Institution Animal Ethical Committee with Reg. No. CPCSEA/1230/a.

Acute oral toxicity study: Acute oral toxicity was performed by following OECD guideline – 420 fixed dose procedure for ethanolic extract and it was found that dose increasing upto 2000 mg/kg body wt. shown no toxicity or mortality in experimental rats. The LD_{50} of the ethanolic bark extract as per OECD guidelines – 420 is greater then 2000 mg/kg[5].

Antipyretic studies: The procedure described by Al-Ghamdi was adopted for this study. The body temperature of each albino Wistar rat was recorded by measuring rectal temperature at predetermined intervals. Albino wistar mice were fasted overnight with

water *ad libitum* before the experiments. Pyrexia was induced by subcutaneously injecting 20% (W/V) brewer's yeast suspension (10 ml/kg) into the animal's dorsum region. The rectal temperature of each rat was again recorded after 24 h of yeast administration. Mice that did not show a minimum increase of 0.5 $^{\circ}$C in temperature 24 h after yeast injection were discarded. Thirty selected mice were grouped into five and immediately treated as follows: group I received normal saline, group II received 10 mg/kg paracetamol, while groups III, IV and V received ethanol extracts 25, 50 and 100 mg/kg respectively i.p. Rectal temperature of all the mice was then recorded by inserting digital thermometer into the rectum of each mice at thirty minutes[6,7].

Analgesic activity:

(i) Hot plate method: The animals were divided into five groups with five mice in each group. Group I animals served as control, animals of Group II received Diclofenac sodium at 10 mg/kg body weight while animals of Group III, Group IV and Group V were treated with 25, 50 and 100 mg/kg body weight (s.c.) of the ethanol extract. The animals were placed on Eddy's hot plate kept at a temperature of 55±0.5°C. A cut off period of 15s was observed to avoid damage to the paw. Reaction time was recorded when animals licked their fore or hind paws, or jumped prior to and 0, 30, 60 and 90 min after administration of the samples[8,9].

(ii) Hot Tail Flick method: The animals were divided into five groups with five mice in each group. Group I animals served as control, animals of Group II received Diclofenac sodium at 10 mg/kg body weight while animals of Group III, Group IV and Group V were treated with 25, 50 and 100 mg/kg body weight (s.c.) of the ethanol extract. The animals were placed on Eddy's hot plate kept at a temperature of 55±0.5°C. A cut off period of 15s was observed to avoid damage to the paw. Reaction time was recorded when animals licked their fore or hind paws, or jumped prior to and 0, 30, 60 and 90 min after administration of the samples[10,11].

Statistical Analysis: The results are expressed as mean ± SEM of six independent experiments. Statistical significance between group was evaluated by one-way analysis of variance (ANOVA) followed by Dunnet's test. A $P < 0.05$ value was considered as statistically significant.

Result and Discussion

The ethanol extract of *A. hetrophyllus* fruit seeds significantly ($P<0.05$) decreased the fever induced by yeast in rats. From the result, the ethanol extracts (25 mg/kg, 50 mg/kg and 100 mg/kg) fever lowering effect comparable with the standard drug, paracetamol, at 10 mg/ml concentration (table 1). Thus, it is possible that active compound(s) for antipyretic action may be included in the ethanol extract. The fever condition entails enhanced formation of cytokines such as interleukins, interferon and tumor necrosis factor, and the cytokines increase the synthesis of prostaglandin E2. Paracetamol

suppresses this response by inhibiting the synthesis of prostaglandin E2. The extract may be involved in the inhibition of some of these substances inducing fever.

The result of hot plate test indicated a significant increase in reaction time at 0.5, 1 and 1.5 hours as comparable to the reference drug diclofenac sodium (10 mg/kg; s.c.) which is showed in table 2. The results obtained from hot tail flick experiments are shown in table 3, in this model, administration of ethanol extract (25 mg/kg, 50 mg/kg and 100 mg/kg) showed significant ($p<0.05$) protection against the pain induction.

The result from hot tail flick test also gave additional evidences for the analgesic activity of the extract. The activity may be attributed due to the presence of phytoconstituent as bioactive compounds.

In conclusion, the present study demonstrated that ethanol extract of *A. hetrophyllus* fruit seeds has intrinsic antipyretic and analgesic activity which needs to be investigated with more information on the bioactive principles responsible for the action. The results indicate that the ethanol extract possesses significant antipyretic and analgesic activity.

Table 1: Antipyretic activity of ethanol extract of *A. hetrophyllus* on Brewer's yeast induced pyrexia in rats

Treatment	Dose	Rectal Temperature (°C)				
		0.0h	0.5h	1.0h	1.5h	2.0h
Control	-	38.15±0.14	38.08±0.20	38.23±0.15	38.48±0.18	38.02±0.22
Paracetamol	10mg/kg	38.17±0.21	36.8±0.18*	35.93±0.12*	35.5±0.18*	35.45±0.15*
A. hetrophyllus	25mg/kg	38.42±0.8	38.3±0.13	37.95±0.10	37.48±0.20*	37.57±0.24
	50mg/kg	38.45±0.07	38.18±0.10	37.47±10*	36.85±0.20*	36.75±0.18*
	100mg/kg	38.38±0.10	37.88±0.07	36.98±0.16*	36.03±0.23*	35.85±0.23*

*** Significantly different from the control at P<0.05,**

Table 2: Effects of ethanol extract of *A. hetrophyllus* on thermal stimulus induced pain (Hot Plate Test) in mice

Treatment	Dose	Licked Time Recorded in Second			
		0.0h	0.5h	1.0h	1.5h
Control	-	2.22±0.20	2.27±0.20	2. 4±0.20	2.19±0.25
Standard	10mg/kg	2.23±0.31	5.80±0.47*	9.40±0.35*	15.84±0.60*
A. hetrophyllus	25mg/kg	2.12±0.19	3.25±0.15	5.22±0.27*	5.35±0.39*
	50mg/kg	2.19±0.16	3.53±0.29*	6.27±0.46*	7.7±0.24*
	100mg/kg	2.19±0.26	4.30±0.36*	7.99±0.57*	11.89±0.40*

*** Significantly different from the control at P<0.05, Standard drug – Diclofenac Sodium**

Table 3: Effects of ethanol extract of *A. hetrophyllus* on pain threshold in hot tail flick test in mice

Treatment	Dose	Tail Flick Response in Second			
		0.0h	0.5h	1.0h	1.5h
Control	-	1.93±0.17	1.81±0.20	1.93±0.20	1.90±0.19
Standard	10mg/kg	1.96±0.27	5.05±0.28*	7.54±0.36*	10.38±0.55*
A. hetrophyllus	25mg/kg	1.90±0.19	2.81±0.23*	3.79±0.20*	4.70±0.23*
	50mg/kg	1.82±0.19	3.26±0.30*	4.87±0.24*	6.54±0.35*
	100mg/kg	1.91±0.23	3.46±0.15*	6.16±0.19*	8.93±0.23*

*** Significantly different from the control at P<0.05, Standard drug – Diclofenac Sodium**

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