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SHORT COMMUNICATION

Evaluation of Antipyretic Activity of *Calotropis gigantea* (Asclepiadaceae) in Experimental Animals

H. R. Chitme[1]*, Ramesh Chandra[2] and Sadhna Kaushik[3]

[1]Institute of Pharmacy, Bundelkhand University, Jhansi-284128, U.P., India
[2]Bundelkhand University, Jhansi-284128, U.P., India
[3]Department of Pharmacology, M.L.B. Medical College, Jhansi-284128, U.P., India

The roots of *Calotropis gigantea* have been used in leprosy, eczema, syphilis, elephantiasis, ulceration and cough in the Indian system of traditional medicine. The present communication evaluated its antipyretic activity by using yeast-induced and TAB (Typhoid) vaccine-induced pyrexia in rats and rabbits. In both yeast-induced and TAB vaccine-induced fever, the fever was significantly reduced and the body temperature was normalized by administration of 200 and 400 mg/kg dose intraperitoneally. Based on the results of the present study it can be concluded that the extract of *C. gigantea* has potential antipyretic activity against both yeast-induced and TAB vaccine-induced fever, indicating the possibility of developing *C. gigantea* as a cheaper and potent antipyretic agent. Copyright © 2005 John Wiley & Sons, Ltd.

Keywords: Calotropis gigantea; *C. gigantea*; Asclepiadaceae; antipyretic.

INTRODUCTION

Calotropis gigantea is used medicinally in Bangladesh (Kitagawa *et al.*, 1992) and Indonesia (Kiuchi *et al.*, 1998). Isorhamnetin-3-O-rutinoside, isorhamnetin-3-O-glucopyronoside, taraxasterol acetate and flavonol trisaccharide were isolated and characterized from the aerial parts of *C. gigantea*. Two new oxiopregnane-oligoglycosides named calotropis A and B have been isolated from the root of *Calotropis gigantea* and their chemical structures elucidated (Kitagawa *et al.*, 1992). The cytotoxic principles of '*Akond mul*' (root of *Calotropis gigantea*), cardenolide glycosides, calotropin frugoside and 4-O-beta-D-glucopyranosyl frugoside were also obtained (Kiuchi *et al.*, 1998). Recently, four new chemical constituents including one naphthalene derivative, named calotropinnaphthalene, two terpene derivatives, named calotropis sesquiterpenol and calotropbenzofuranon, and sucrose have been isolated from the roots (Gupta and Ali, 2000).

The roots of *C. gigantea* have been used to treat leprosy, eczema, syphilis, elephantiasis, ulceration and cough in the Indian system of traditional medicine (Kartikar and Basu, 1984). In the present communication the crude hydroalcohol (50:50) extract derived from the aerial part of *C. gigantea* was evaluated for its antipyretic activity in experimental animals.

* Correspondence to: Dr H. R. Chitme, H. S. K. College of Pharmacy, BVVS Campus, Bijapur Road, Bagalkot 587101, Karnatak, India.
E-mail: hrchitme@rediffmail.com

MATERIAL AND METHODS

Plant Material. The aerial parts of *C. gigantea* were collected around Jhansi city in 2001 from the wild. A voucher specimen has been deposited at the Institute of Pharmacy, Bundelkhand University, Jhansi, Uttarpradesh, India (BU/IOP/VOUCH/101). The aerial parts were dried under shade, powdered to a fine texture, and 100 g of the dried plant was repeatedly extracted with water:ethanol (50:50). The extract was concentrated under vacuum and the residue used in the experiments. The dried plant extracts were freshly dissolved or suspended in normal saline prior to administration.

Animals. Albino Swiss rats of either sex weighing 150–180 g were used for the Brewer's yeast-induced pyrexia. Male Swiss albino mice weighing 18–24 g were used for the acute toxicity study. White rabbits of body weight 1.5–2.0 kg were used for TAB vaccine-induced pyrexia. All animals were fed standard animal feed and tap water *ad libitum* before the experiments. Each experimental group consisted of six animals housed in separate cages.

Acute toxicity study (LD_{50}). The intraperitoneal (i.p.) acute toxicity (LD_{50}) profile of the extract was evaluated in Swiss albino mice according to the method of Lorke (1983). The LD_{50} was then calculated based on the pattern of death observed in the second step.

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TAB vaccine-induced pyrexia. The antipyretic activity was assessed by the method of TAB (Typhoid) vaccine-induced pyrexia (Saxena, 1979) with some modification. In this method the rabbits were divided into groups, each group consisted of six animals. The control group was treated with 2 mL/kg of saline. Other groups were treated as shown in Table 2. The normal rectal temperature of a group of rabbits was recorded by a telethermometer at hourly intervals for a period of 4 h. TAB vaccine was administered intravenously into the marginal ear vein of rabbits at a dose of 0.5 mL/rabbit. The temperature was recorded every 30 min until it approached normal. The extracts to be tested were administered 30 min prior to the administration of the TAB vaccine.

Brewer's yeast-induced pyrexia in rats. The antipyretic properties of *C. gigantea* were tested in rats in which hyperthermia had been induced following the method of Teotino *et al.* (1963). The initial rectal temperatures of the rats were recorded using a six channel electric thermometer connected with probes. Rats were made hyperthermic by a subcutaneous injection of 20% yeast suspension in 0.9% saline at a dose of 1 mL/100 g body weight. When the temperature was at a peak (18 h after yeast injection) the rectal temperature was recorded again. Those animals that showed a rise in rectal temperature of more than 1.2 °C were used. Test substances and control vehicle were given intraperitoneally and the rectal temperature of the animals was recorded at 1 h intervals for 4 h following the administration of drug or plant extract as shown in Table 1.

Statistical analysis. The experimental results are represented as mean ± SE (standard error of the mean). Student's *t*-test was used for the evaluation of data and $p < 0.05$ accepted as significant.

RESULTS

Acute toxicity

The 50% mortality was noted at 4600 mg/kg dose of the extract, within 3 h of drug administration. All the results were repeated thrice for confirmation.

TAB vaccine-induced pyrexia

When the extract was administered to rats with established TAB vaccine-induced fever, the fever was significantly reduced and the body temperature was normalized by administration of 200 and 400 mg/kg dose intraperitoneally. However, 100 mg/kg dose of extract had no effect on the rectal temperature of rabbits (Table 1).

Brewer's yeast-induced pyrexia in rats

As shown in Table 2, the hydroalcohol extract of *C. gigantea* at a dose of 200 and 400 mg/kg caused a significant lowering in rectal temperature of hyperthermic rats. This decrease persisted when an assessment was made 4 h after test drug administration and the efficacy was comparable to that of paracetamol at a dose of 150 mg/kg.

DISCUSSION

In the acute toxicity study, the therapeutic dose (ED_{50}) for antipyretic activity was found to be 150 mg/kg in

Table 1. Effect of *Calotropis gigantea* extract on TAB vaccine-induced pyrexia in rats

Treatment	Temperature after pyrexia (°C)	Rectal temperature after administration of drug (°C)				
		0 h	1 h	2 h	3 h	4 h
Saline (2 mL/kg, i.p.)	38.14 ± 0.219	38.08 ± 0.2167	38.64 ± 0.1673	39.3 ± 0.2	40.18 ± 0.2489	40.66 ± 0.238
Paracetamol (150 mg/kg, i.p.)	38.04 ± 0.181	37.98 ± 0.164	37.94 ± 0.164[a]	38.08 ± 0.13[c]	37.64 ± 0.167[c]	37.28 ± 0.216[c]
Extract (100 mg/kg, i.p.)	38.28 ± 0.294	38.28 ± 0.258	38.6 ± 0.374	39.12 ± 0.216	39.32 ± 0.228[b]	39.64 ± 0.167[c]
Extract (200 mg/kg, i.p.)	38.28 ± 0.13	38.16 ± 0.25	38.46 ± 0.151	38.8 ± 0.222[b]	39.18 ± 0.13	39.64 ± 0.336[b]
Extract (400 mg/kg, i.p.)	38.4 ± 0.158	39.28 ± 0.303	38.46 ± 0.343	37.98 ± 0.228[c]	37.66 ± 0.313[c]	37.28 ± 0.178[c]

Extract was administered i.p. 30 min before the injection of the pyrogen. Results are expressed as mean ± SE. The temperature was recorded every 30 min until it approached normal. [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ when compared with saline-treated group.

Table 2. Effect of *Calotropis gigantea* extract on Brewer's yeast-induced pyrexia in rats

Treatment	Temperature after pyrexia (°C)	Rectal temperature after administration of drug (°C)				
		0 h	1 h	2 h	3 h	4 h
Saline (2 mL/kg, i.p.)	37.53 ± 0.34	37.49 ± 0.14	37.7 ± 0.14	37.4 ± 0.14	37.36 ± 0.19	37.42 ± 0.31
Paracetamol (150 mg/kg, i.p.)	37.58 ± 0.27	37.56 ± 0.3	36.49 ± 0.12[c]	36.04 ± 0.64[b]	35.92 ± 0.18[c]	36.04 ± 0.41[c]
Extract (100 mg/kg, i.p.)	37.55 ± 0.25	37.52 ± 0.29	37.16 ± 0.16[b]	37.19 ± 0.12[b]	36.92 ± 0.33[a]	36.97 ± 0.19[a]
Extract (200 mg/kg, i.p.)	37.65 ± 0.164	37.63 ± 0.157	36.93 ± 0.08	37.04 ± 0.62	37.08 ± 0.27[a]	36.98 ± 0.19[a]
Extract (400 mg/kg, i.p.)	37.64 ± 0.133	37.58 ± 0.125	37.09 ± 0.71	37.06 ± 0.58	36.82 ± 0.13[c]	36.64 ± 0.68[a]

Extract was administered i.p. 30 min before the injection of the pyrogen. Values are expressed as mean ± SE from the experiments. The rectal temperature of animals were recorded at 1 h intervals for 4 h following the administration of drug or plant extract. [a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$ when compared with saline-treated group.

rats. The lethal dose (LD_{50}) was found to be 4600 mg/kg. Therefore, the therapeutic index of *C. gigantea* can be regarded as 30.66 mg/kg. Since this drug has a high therapeutic index, it is considered to be relatively safe. It was of interest to note that the extracts of *C. gigantea* aerial parts produced a rather modest decrease in the body temperature in hyperthermic rats. The cause of this decrease may be central and/or peripheral in origin. Clinically available antipyretic drugs, such as paracetamol and the non-steroidal antiinflammatory drugs, are able to lower the body temperature only in feverish patients. Neuroleptic drugs and other central depressants can also reduce the normal body temperature (Ali *et al.*, 1995). In general, non-steroidal antiinflammatory drugs produce their antipyretic action through inhibition of prostaglandin synthetase within the hypothalamus (Clark and Cumby, 1975; Zeil and Krupp, 1975). Therefore, it appears that the antipyretic action of the extract may also be related to the inhibition of prostaglandin synthesis.

TAB vaccine is a sterile suspension, 1 mL containing 1×10^9 *S. typhi* and 7.5×10^8 each of *S. paratyphi A* and *B* organisms in 5 and 10 mL vials. Administration is associated with local tenderness, fever and malaise lasting 1–2 days, which are common after the first dose (Tripathi, 1994). The yeast-induced hyperthermia in the rat model was, therefore, employed to further investigate the antipyretic activity of *C. gigantea*. It was found that only a dose of 400 mg/kg showed a significant decrease in rectal temperature similar to paracetamol. This result seems to support the view that the plant has some influence on prostaglandin biosynthesis, since prostaglandin is believed to be a regulator of body temperature (Milton, 1982).

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