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Research Paper

STUDY OF ANALGESIC, ANTIPYRETIC AND ANTIINFLAMMATORY ACTIVITIES OF THE METHANOLIC EXTRACT OF *BLUMEA LANCEOLARIA* (ROXB.) DRUCE

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The methanolic extract of *Blumea lanceolaria* (Roxb.) Druce (200 and 400 mg/kg) was evaluated for analgesic, antipyretic and anti-inflammatory properties in mice and rats. The extract doses of (200 and 400 mg/kg) showed significant ($p < 0.01$) analgesic, antipyretic and anti-inflammatory activities were observed in all the experimental models tested. The extracts may be exerting its effects through central mechanisms. These findings confirms its ethnomedicinal use of the plant in the treatment of pain, fever and inflammation. The current results proved that the plant *Blumea lanceolaria* (Roxb.). Druce traditionally used by the tribal people of Mizoram is having good potential for analgesic, antipyretic and anti-inflammatory activities.

Keywords: Analgesic, Antipyretic, Anti-inflammatory, Blumea lanceolaria (Roxb.) Druce, Asteraceae

INTRODUCTION

Blumea lanceolaria (Roxb.) Druce (Asteraceae) commonly known as *Baurze* is a perennial herb, available in different states of India. The leaf extract of different *Blumea* species showed the presence of sesquiterpene lactones; isolantolactone derivative essential oil, glycoside (Rashmi *et al*., 1995) and acetylenic thiophenes (Viquar and Naser, 1996). It is used in the treatment of vermifuge, cholera, collysium, fever, scurvy, bronchitis (Timothy, 1998) and as antioxidants (Uttam *et al.*, 2008) which has been used in traditional folklore medicine for their analgesic, antipyretic and anti-inflammatory activities. It is also claimed to be useful in treating ulcer and anticancer activities by the tribal people of Mizoram, India (Sawmliana, 2003; and Chawngkunga, 2005). India is a rich source of medicinal plants and a number of plant derived oils and extracts are used against diseases in various system of

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medicine such as Ayurveda, Unani and Siddha. Only a very few of them have been scientifically explored. Plant derived natural products such as flavonoids, terpenes and alkaloids have received considerable attention in recent years due to their diverse pharmacological properties including analgesic, antipyretic and anti-inflammatory, activities (Osawa *et al*., 1990; and Keith *et al*., 1990).

However, there have been no published report to our knowledge on its analgesic, antipyretic and anti-inflammatory activities of this plant. Keeping this in view, the present study was undertaken to investigate for the first time the analgesic, antipyretic and antiinflammatory potential of the methanol extract of *Blumea lanceolaria* (Roxb.) Druce in experimental animal models.

MATERIALS AND METHODS

Plant material and Extraction

Leaves of *Blumea lanceolaria* (Roxb.) Druce were collected from Thenzawl area, Aizawl, Mizoram during July 2009. The plant material was identified by Botanical Survey of India, Shillong and the voucher specimen (BSI/ERC/2010)/RP/080 has been submitted there. The collected fresh leaves of the plant were cleaned, washed and dried in ventilated room under shade for three weeks, pulverized using grinder and passed through 40-mesh sieve to get the fine powder. The air- dried and powdered leaves (2.0 kg) were extracted at room temperature successively by soxhlet apparatus using petroleum ether (60-800C b.pt) followed by chloroform and methanol. The extraction was carried out exhaustively and the solvents were recovered by distillation under reduced pressure using rotary vacuum evaporator to obtain crude petroleum ether extract (113 g, 4.5%; w/w), chloroform extract (380 g ,16%; w/w) and methanol extract (300 g, 12%; w/w). For pharmacological studies, the methanol extract was used.

Animals

Adult Wistar albino rats (120-200 g), Swiss albino mice (20-30 g) of either sex maintained in the Animal Experimental Laboratory of Department of Pharmacy, RIPANS were selected for the experiments. The animals were grouped and housed in polyacrylic cages (38 x 23 x 10 cm), maintained under standard laboratory conditions (25 ± 2°C) with dark/light cycle (12/12 hour). They were allowed free access to standard dry pellet diet (M/S Hindustan Lever Limited, Kolkata, India) and water *ad libitum.* The animals were acclimatized to laboratory conditions for 10 days before commencement of the experiment. The minimum number of animals and duration of observation required to obtain consistent data were employed. “Principles of laboratory animal care” (NIH publication number 85-23, revised 1985) guidelines were followed. Permission and approval for animal studies were obtained from the Institutional Animal Ethics Committee.

Drugs and Reagents

Carrageenan (Sd-Fine Chemicals, Mumbai), carboxy methyl cellulose (LOBA Chemmie. Pvt Ltd., Mumbai), morphine sulphate injection vials, diclofenac sodium tablets, paracetamol tablets (Torent Pharmaceutical Ltd, Ahmedabad), acetic acid (Merck) and brewer’s yeast (Hindustan Lever limited, Kolkata) were used. Normal saline (0.9% w/v) was used as control in all studies while the dose levels of the MEBL (200 and 400 mg/kg, i.p.) suspended in 0.5 % CMC were employed for the test groups. Morphine sulphate (5 mg/kg, b.w. s.c..), paracetamol (33 mg/kg, b.w. i.p.), and diclofenac sodium (40mg/kg, b.w. i.p.) were used as reference drugs.

Acute Toxicity

Swiss albino mice were divided into five groups, each containing six animals. MEBL was administered orally at doses ranging from 5 mg to 2 g/kg following a standard methods (Turner, 1965; and Ecobicon, 1997) and Organisation for Economic Co-operation and Development (OECD) guidelines (OECD-423, 2000). Animals were individually and continuously observed for 4 h to detect changes in the autonomic or behavioural responses and then monitored for any mortality for the following 14 days. A group of animals treated with the vehicle (0.5% CMC) served as control. Based on the results of preliminary acute oral toxicity testing, the 'doses of 200 and 400 mg/kg were chosen for further experiments.

EVALUATION OF ANALGESIC ACTIVITY

Acetic Acid-Induced Writhing Test

The Acetic acid-induced writhing test was carried out according to the method given by (Koster, 1962) in mice. The rats used for this study were divided into four groups, each group consisting of six rats. First group serving as control group received 0.9% w/v Normal saline, second group received standard drug morphine sulphate (5 mg/kg, i.p.), another two groups received MEBL at the doses of 200 and 400 mg/kg, b.w. i.p.), 30 min later 0.6% acetic acid (10 ml/kg) was injected intraperitoneally to each mice. The number of writhings a response consisting of abdominal contractions and hind limbs strechings were counted for 20 mins beginning from 5 min after the acetic acid injection. A significant reduction in the number of writhes by MEBL treatment in the doses of 200 and 400 mg/kg, ip is compared to control and standard drug morphine sulphate (5 mg/kg, i.p.) was considered as an analgesic response.

$$\text{Percentage analgesic activity} = \frac{N / N \, X100}{N}$$

where N is the average number of stretching of control per group and N is the average number of stretching of test per group.

HOT PLATE METHOD

Hot Plate latency assay was carried out according to the method given by (Eddy *et al.,* 1950). The rats used for this study were divided into four groups, each group consisting of six rats. First group for the control, second group (positive control) for standard drug (morphine sulphate, another two groups for the extract (doses of 200 and 400 mg/kg). After 12 h of fasting test groups received MEBL (200 and 400 mg/kg) b.w. i.p. while the remaining two groups received 0.9 % w/v (control) and morphine sulphate (5 mg/kg, i.p.) respectively. Each animal was placed on a hot plate (Analgesiometer, Eddy's Hot Plate, Model KI-9514) maintained at 55^0C, 30 min after treatment. The time taken for the rats to respond to the thermal stimulus (usually by jumping) was noted as the latency (in second). The effect of MEBL, morphine sulphate and control were also determined after 60 and 90 min respectively.

TAIL FLICK TEST

The method of (Grey *et al.*, 1970) was used. The tail flick test was evoked by a source of radiant heat, which was focused on the dorsal surface of the tail. Adult, healthy rats were examined for latency to withdraw their tails from a noxious thermal stimulus using a tail-flick meter (Ugo Basile 7140, Italy). Each rat was tested twice before the administration of MEBL and the

reaction times were averaged to obtain a baseline. The intensity of heat stimulus was adjusted to achieve a mean tail-flick latency of 3-4 in control animals. The selected animals were divided into five groups, each group consisting of six rats. First group for the control, second group (positive control groups) for reference drug morphine sulphate, another two groups for MEBL (doses of 200 and 400 mg/kg). Each rat was then tested 30, 60, 90, 105, 120, 150 min after the administration of 200 and 400 mg/kg b.w. i.p., of the extracts. Control rats received 0.9 % w/v Normal saline. Morphine sulphate (5 mg/kg, s.c.) and were administered as a positive control.

EVALUATION OF ANTIPYRETIC ACTIVITY

Yeast-Induced Pyrexia

Rats were divided into four groups of six rats each (110-160 gm). The normal body temperature of each rat was measured rectally and recorded. (Lu *et al* ., 2004). Pyrexia was induced by injecting the yeast suspension by subcutaneous route of administration in hind limbs of the rats. The rats were acclimatized to remain quite in a restraint cage. A flexible thermometer coated with the lubricant was inserted 3-4 cm deep into the rectum and fastened to the tail by adhesive tape. The temperature was measured on a thermometer (60 sec). After measuring the basal rectal temperature, animals were given a subcutaneous injection of 10 ml/kg body weight of (w/v) yeast suspended in 0.5% (w/v) Carboxy methyl cellulose solution. Rats were then returned to their housing cages. After 18 h of yeast injection, the animals were again restrained in individual cages for the recording of their rectal temperature as described previously.

DRUG ADMINISTRATION

After 18 h of yeast injection the Normal saline solution (0.9 % Nacl, w/v) was administered orally to the control group I. The group II of animals received the standard drug Paracetamol (33 mg/ kg body weight) i.p. and the extracts of MEBL were administered intraperitoneally at doses of 200 and 400 mg/kg body weight to groups III- IV animals respectively. Rats were restrained for recording rectal temperature at the 18 h, immediately before extracts, normal saline or paracetamol administration, and again at one hour intervals up to the 21 h after yeast injection.

EVALUATION OF ANTI-INFLAMMATORY ACTIVITY

Carrageenan-Induced Rat Paw Edema

The carrageenan induced hind paw edema model was used for determination of the anti-inflammatory activity (Winter *et al*., 1962). Adult healthy wistar rats weighing 120-200 g, deprived of food overnight were divided into four groups, each group consisting of six rats. First group for the control, second group (positive control group) for reference drug and another two groups for MEBL. 0.1 ml of 1%w/v Carragenan was injected into the right paw of each rat under the subplantar aponeurosis. The test groups of rats were administered intraperitoneally with (200 and 400 mg/kg), ½ h before carragenan injection. At the same time the control group received 5 ml /kg of 0.9%w/v saline solution and the reference group received 40 mg/kg Diclofenac sodium (i.p.). The paw volume was measured upto 150 mins after the injection using a plethysmograph by dipping the foot in the mercury bath of the plethysmograph apparatus upto the anatomical hairline on lateral malleolus (Goldenberg and Ilse, 1997) and compared with the control animals. The inhibitory

activity was calculated according to the following formula (Chu and Kovacs, 1977):

$$\text{Percentage inhibition} = \frac{\text{100-(Oedema volume in the treated) x 100}}{\text{Oedema volume in the control}}$$

STATISTICAL ANALYSIS

Results of the study were expressed as mean ± S.E.M. All the statistical analysis have been done by one-way ANOVA followed by the Student's t test. P<0.01 was considered significant in all cases.

RESULTS AND DISCUSSION

Among several traditional claims, the usefulness of *Blumea lanceolaria* in fever, inflammation and pain have been emphasized more in literature was considered that investigations for this medicinal properties might give scientific authentication to the traditional claims. Moreover, this plant has not been subjected to above mentioned systematic pharmacological screening so far. In the present study, the analgesic, antipyretic and anti-inflammatory activity of the methanolic extracts of the leaves of *Blumea lanceolaria* has been established. All the extracts were found to significantly inhibit the analgesic, antipyretic and anti-inflammatory activity. In acute toxicity, no toxic symptoms were observed for the drug upto 2000 mg/kg body weight. So the dose of 200 and 400 mg/kg were selected to study the analgesic, antipyretic and anti-inflammatory activity. The extract showed significant peripheral analgesic activity (Table 1) at the tested dose level. The activity was comparable with morphine sulphate in all the analgesic activity. It exhibited significant (p<0.01) inhibition of the control writhes at the rate of 22.68, 50.52 and 79.89% respectively in the acetic acid induced writhing test. In case of hot plate test and tail flick test it showed significant increase in reaction time and increase in the tail flick latencies when compared to that of morphine sulphate , 5 mg/kg i.p. and control group as shown in (Table 2) and (Table 3). Subcutaneous injection of yeast suspension markedly elevated the rectal temperature after 24 h of administration. Treatment with the MEBL at the doses of 200 and 400 mg/kg significantly (p < 0.01) decrease the rectal temperature of the rats in a dose dependent manner. The antipyretic effect started as from the first hour and the effect was maintained for 4h, after administration of the extract (Table 4). Anti-inflammatory activity of MEBL was measured at the doses of 200 and 400 mg/kg b.w. i.p. against acute paw oedema induced by Carrageenan produced significant (p < 0.01) anti-inflammatory activity and the results were comparable to that of Diclofenac as a standard drug. The MEBL at the doses of 200 and 400 mg/kg showed an inhibition of (22.5%, 27.68%, 34.89%, 38.13% and 28.33%), (12.73%, 23.18%, 29.44%, 33.26% and

Table 1: Effect of the Methanolic Extract of *Blumea lanceolaria* on Acetic Acid Induced Writhing in Mices

Treatment %	Dose (mg/kg)	No.of Writhes per 30 mins	Inhibition
Control	–	64.66 ± 0.42	–
Morphine sulphate	5	13.0 ± 0.36**	79.89
MBL	200	50.0 ± 0.57*	22.68
MBL	400	32.0 ± 0.57**	50.52

Note: Values are expressed as mean ± SEM (n=6); ** P<0.01 compared with control; * P<0.05 compared with control (ANOVA followed by Student's *t*-test).

Table 2: Effect of the Methanolic Leaves Extract of *Blumea lanceolaria* (Roxb.) Druce on Hot Plate Method in Rats

Treatment	Dose mg/kg	Reaction Time(s)				
		30	60	90	120	150
Control	–	3.1 ± 0.03	3.05 ± 0.02	3.06 ± 0.03	3.01 ± 0.03	2.88 ± 0.04
Morphine Sulphate	5	8.11 ± 0.04	8.13 ± 0.02	8.11 ± 0.04	7.83 ± 0.07	7.2 ± 0.14
MBL	200	5.65 ± 0.04	5.88 ± 0.13	6.05 ± 0.12	5.73 ± 0.11	5.08 ± 0.07
MBL	400	6.23 ± 0.122	6.11 ± 0.09	6.08 ± 0.08	6.01 ± 0.08	5.85 ± 0.08

Note: Values are expressed as mean ± SEM (n=6); ** P<0.01 compared with control; * P<0.05 compared with control (ANOVA followed by the Students's *t*- test).

Table 3: Effect of the Methanolic Leaves Extract of *Blumea lanceolaria* (Roxb.) Druce on Tail Flick Method in Mice

Treatment	Dose (mg/kg)	Predrug Reaction Time in Sec	Average Tail Withdrawing Time in Sec					
			30 min	60 min	90 min	120 min	150 min	180 min
Control	–	3.06 ± 0.03	2.88 ± 0.07	2.95 ±0.05	3.01± 0.04	3.01 ±0.03	3.01 ±0.03	2.96 ± 0.02
Morphine Sulphate	5	3.06 ± 0.03	13.8 ± 0.13	14.16 ± 0.17	14.85 ± 0.08	14.88 ± 0.08	14.21 ± 0.20	14.21 ± 0.20
MBL	200	3.06 ± 0.03	8.28 ± 0.10*	8.68 ± 0.10*	9.26 ± 0.09*	9.73 ± 0.11*	9.01 ± 0.15*	9.01 ± 0.15**
MBL	400	3.06 ± 0.03	8.56 ± 0.03**	9.18 ± 0.11**	9.76 ± 0.15**	9.98 ± 0.06**	9.28 ± 0.17**	9.18 ± 0.11**

Note: Values are expressed as mean ± SEM (n=6); ** P<0.01 compared with control; and * P<0.05 compared with control (ANOVA followed by the Student's *t*-test).

Table 4: Effect of the Methanolic Extract of *Blumea lanceolaria* (Roxb.) Druce on Yeast Induced Pyrexia in Rats

Treatment	Dose (mg/kg)	Rectal Temperature (^{0}C) Before and After Treatment						
		Normal	18 h	1 h	2 h	3 h	4 h	5 h
Control	–	37.97 ± 0.17	38.70 ± 0.16	38.67 ± 0.16	38.67 ± 0.16	38.67 ± 0.04	38.70 ± 0.16	37.97 ± 0.17
Paracetamol	33	37.72 ± 0.14	38.40 ± 0.12	37.97 ± 0.19	37.90 ± 0.17	37.80 ± 0.17	37.90 ± 0.17	37.90 ± 0.17
MBL	200	37.77 ± 0.20	38.32 ± 0.19	38.22 ± 0.19	38.07 ± 0.17	38.10 ± 0.16	38.07 ± 0.17	38.10 ± 0.16
MBL	400	38.47 ± 0.17	38.45 ± 0.20	38.05 ± 0.17	37.95 ± 0.16	37.80 ± 0.14	37.80 ± 0.14	38.95 ± 0.16

Note: Values are expressed as mean ± SEM (n=6); ** P<0.01 compared with control; * P<0.05 compared with control (ANOVA followed by the Student's *t*-test.

17.81%) and 68.61%, 67.76%, 68.95%, 70.04% and 69.87% respectively (Table 5). Histamine is one of the most important inflammation mediators and it is potent vasodilator substance and increases the vascular permeability (Linardi *et al*., 2002 Cuman *et al*., 2001). This study showed that all the doses of MEBL effectively suppressed the oedema produced by histamine, so it may be

Table 5: Effect of the Methanolic Leaves Extract of *Blumea lanceolaria* (Roxb.) Druce on Carrageenin Induced Paw Edema in Rats

Treatment	Dose mg/kg	% Inflammation ± SEM at (hours)				
		1 hr	2 hr	3 hr	4 hr	5 hr
Control	–	0.72 ± 0.009	0.75 ± 0.004	0.82 ± 0.015	0.85 ± 0.01	0.73 ± 0.01
Diclofenac	40	0.22 ± 0.008** (68.61%)	0.25 ± 0.003** (67.78%)	0.25 ± 0.002** (68.95%)	0.25 ± 0.002** (70.04%)	0.22 ± 0.006** (69.89%)
MBL	200	0.55 ± 0.01 (22.5%)	0.54 ± 0.01 (27.68%)	0.53 ± 0.02** (34.89%)	0.53 ± 0.02** (38.13%)	0.52 ± 0.01** (28.33%)
MBL	400	0.62 ± 0.02 (12.73%)	0.58 ± 0.03** (23.18%)	0.58 ± 0.03 (29.44%)	0.57 ± 0.03** (33.26%)	0.6 ± 0.02 (17.81%)

Note: Values are expressed as mean ± SEM (n=6); ** P<0.01 compared with control; * P<0.05 compared with control (ANOVA followed by the Student's *t*-test).

suggested that its anti-inflammatory activity is possibly baked by its antihistaminic activity.

The MEBL also effectively suppressed the inflammation produced by serotonin induced by hind paw edema, which indicates that the MEBL may exhibit its anti-inflammatory action by means of either inhibiting the synthesis, release or action of inflammatory mediators viz. histamine, serotonin and protaglandinns that might be involved in inflammation. From the above results it is suggested that tha anti-oedematogenic effects of MEBL on Carrageenan paw oedema may be related to inhibition mediator formation. In acetic acid induced abdominal writhing which is the visceral pain model, the processor releases arachidonic acid via cyclooxygenase and prostaglandin biosynthesis plays a role in the nociceptive mechanism (Franzotti *et al*., 2002). Results of the present study showed that all the doses of the MEBL produced significant analgesic effect and this effect may be due to inhibition of the synthesis of the arachidonic acid metabolite. In addition, MEBL potentiates the analgesic activity of morphine. The hot plate test has been found to be suitable for evaluation of centrally acting analgesics. The validity of this test has been shown even in the presence of substantial impairment of motor performance (Plummer *et al.,* 1996). The present study findings indicate that the MEBL may be centrally acting. Fever may be the result of infection or one of sequelac of tissue damage, inflammation, graft rejection, or other disease states. Antipyretic are the drugs, which reduced the elevated body temperature. Regulation of body temperature requires a delicate balance between production and loss of heat and the hypothalamus regulates the set point at which temperature is maintained. In fever this set point elevates and a drug like paracetamol does not influence body temperature when it is elevated by the factors such as exercise or increase in ambient temperature (Goodman and Gilman, 1996). The MEBL possesses a significant antipyretic effect in yeast- induced elevation of body temperature in rats and this may be due to anti-inflammatory effect.

CONCLUSION

Based on the results of the present study it can be concluded that the methanol extract of *Blumea lanceolaria* (Roxb.) Druce has potential analgesic (both central and peripheral), antipyretic and anti-

inflammatory activities in dose dependent manner. Hence, our study gives a scientific approach to *Blumea lanceolaria* in consequent health benefits.

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