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Inquiry of analgesic and anti-inflammatory activities of *Xanthosoma sagittifolium* L.: An effective medicinal plantMd. Sarwar Hossain^{1*}, Md. Sahab Uddin², Md. Asaduzzaman², Mst. Shirajum Munira², Md. Josim Uddin³, Md. Rajdoula Rafe², Md. Mosiur Rahman²¹School of Biosciences and Veterinary Medicine, University of Camerino, Camerino, MC, Italy²Department of Pharmacy, Southeast University, Dhaka, Bangladesh³Department of Pharmacy, International Islamic University Chittagong, Chittagong, Bangladesh

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ABSTRACT

Objective: To examine the analgesic and anti-inflammatory activities of *Xanthosoma sagittifolium* L. (*X. sagittifolium*) leaves.**Methods:** The fresh leaves of *X. sagittifolium* were extracted with methanol followed by fractionation using ethyl acetate fraction (EAF), *n*-hexane fraction, chloroform fraction and aqueous fraction. The analgesic activity was determined by acetic acid-induced writhing test and tail immersion test using Swiss albino male mice. Carrageenan-induced paw edema test was used to resolve the anti-inflammatory activity using Wistar albino male rats.**Results:** The results displayed that among these four samples, EAF had maximum analgesic efficacy ($P < 0.001$) measured by acetic acid-induced writhing test (71.37%). In case of tail immersion test, EAF also exerted maximum activity (5.03 s, $P < 0.001$) at 180 min compared to *n*-hexane fraction, chloroform fraction and aqueous fraction at maximum concentration. In case of anti-inflammatory test, EAF remained ascendancy in its activity ($P < 0.001$) and it inhibited 72.92% of paw edema at maximum concentration at 180 min with respect to remaining fractions.**Conclusions:** The above evidences suggest that EAF of *X. sagittifolium* leaves is a potential source of natural compounds having analgesic and anti-inflammatory activities.

1. Introduction

Plants exhibiting medicinal property have been used as medicine to treat various diseases from ancient civilization generally known as medicinal plants[1]. Medicinal plants provide a rich source of novel therapeutic drugs that make a huge contribution to human society and life. As stated by the World Health Organization, still now most of the people depend on medicinal plants for their initial health care all over the world[2].

Inflammation is the reaction to the cell injury and numerous mediators such as serotonin, histamine, prostaglandins, bradykinin etc. are plentiful in inflammatory cell; prostaglandins are abundant

substances involved in the inflammation[3]. These mediators even in small quantities can elicit pain response[4]. The medicinal properties of medicinal plant have great value to researchers[5], and the study of plants that have been traditionally used for the treatment of pain-related disorders should still be seen as a prolific and rational research scheme in the hunt for novel analgesic and anti-inflammatory drugs[6].

Xanthosoma sagittifolium L. (*X. sagittifolium*), belongs to the family of Araceae, popularly regarded as a medicinal plant in the Southeast Asia region. In Bangladesh, it is widely distributed and known as Mukhi Kochu[7]. This plant is natural to the tropical America and cultured in South America and tropical Central since ancient time. Only in comparatively recent times (19th century), it has been spread widely all over the tropical world. Now this plant is cultivated in the Caribbean, tropical America, West Africa and the Pacific and to a very limited extent in some other parts of the humid tropics[7,8]. Experimentally, *X. sagittifolium* is shown to possess antimicrobial, antioxidant, antidiabetic and hypolipidaemic activity[7-9]. In addition to this, *X. sagittifolium* species are used to prevent osteoporosis in Brazilian traditional medicine[10].

The current study was carried out to evaluate the analgesic and

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The treatment and maintenance of the animal were accompanied in line with the Principle of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) and the Animal Care and Use Procedures of Southeast University, and the study protocol was approved by the ethics committee of the Department of Pharmacy, Southeast University, Dhaka, Bangladesh.

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anti-inflammatory activities of different fractions *i.e.*, ethyl acetate fraction (EAF), *n*-hexane fraction (NHF), chloroform fraction (CLF) and aqueous fraction (AQF) of methanolic extract of *X. sagittifolium* in different experimental model.

2. Materials and methods

2.1. Chemicals and drugs

Methanol, *n*-hexane, ethyl acetate and chloroform were bought from Sigma-Aldrich, USA. Acetic acid and carrageenan were bought from Merck, Germany. Diclofenac-sodium and indomethacin were obtained from Square Pharmaceuticals Ltd., Dhaka, Bangladesh.

2.2. Collection and identification of plant materials

The fresh leaves of *X. sagittifolium* were obtained from Bogra District, Bangladesh, in June 2015 and identified by the taxonomist of Bangladesh National Herbarium, Mirpur, Dhaka, Bangladesh. A voucher specimen No. DACB-41076 was placed at the herbarium for forthcoming reference.

2.3. Drying and grinding of plant materials

The plant materials were washed with water, then dried in the shade with infrequent shifting to dry and finally ground with a motorized grinder and deposited in a close-fitting container till extraction.

2.4. Extraction and fractionation of plant materials

The dried powder material (leaves) with a weight of 1.2 kg for extraction was refluxed by the help of methanol for 3 h. The entire filtrate obtained was concentrated to dryness in rotary evaporator at 40 °C to get the methanol extract (13 g). An aliquot (10 g) of the concentrated methanolic extract was fractionated by the help of modified Kupchan method^[11] and the resultant fractions were solvable NHF (2.95 g), CLF (2.58 g), EAF (1.09 g) and AQF (3.38 g) used for the experiment purposes.

2.5. Tested animals

Swiss albino male mice (25–30 g) and Wistar albino male rats (120–135 g) were used to evaluate the analgesic and anti-inflammatory activities. Animals were kept in standard laboratory settings and had free entrance to food and water. The animals were permitted to adapt to the environment for 7 days before starting the study. The animals were divided into various groups, each having six animals which were starved overnight before the experiments. The treatment and maintenance of the animal were accompanied in line with the Principle of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) and the Animal Care and Use Procedures of Southeast University, Dhaka, Bangladesh.

2.6. Administration of drugs and test compounds

A solution of diclofenac-sodium was ready by using normal

saline (pH 7.4) and administered to Swiss albino male mice by using oral route at the dose of 10 mg/kg body weight. On the other hand, indomethacin solution was also prepared by using normal saline and administered to Wistar albino male rats by using oral route at the dose of 10 mg/kg body weight. Weighed quantity of plant fractions was dissolved in the normal saline (pH 7.4) and then orally administered to animals at 50, 100 and 200 mg/kg body weight. The doses of diclofenac-sodium, indomethacin and plant fractions were selected based on literature review^[12-14].

2.7. Experimental design

For analgesic activity, the Swiss albino male mice (25–30 g) were divided into fourteen groups containing six mice in each group. Group I was treated with normal saline (control). Group II was treated with diclofenac-sodium at the dose of 10 mg/kg body weight. Group III was treated with NHF at the dose of 50 mg/kg body weight (NHF 50). Group IV was treated with NHF at the dose of 100 mg/kg body weight (NHF 100). Group V was treated with NHF at the dose of 200 mg/kg body weight (NHF 200). Group VI was treated with CLF at the dose of 50 mg/kg body weight (CLF 50). Group VII was treated with CLF at the dose of 100 mg/kg body weight (CLF 100). Group VIII was treated with CLF at the dose of 200 mg/kg body weight (CLF 200). Group IX was treated with EAF at the dose of 50 mg/kg body weight (EAF 50). Group X was treated with EAF at the dose of 100 mg/kg body weight (EAF 100). Group XI was treated with EAF at the dose of 200 mg/kg body weight (EAF 200). Group XII was treated with AQF at the dose of 50 mg/kg body weight (AQF 50). Group XIII was treated with AQF at the dose of 100 mg/kg body weight (AQF 100). Group XIV was treated with AQF at the dose of 200 mg/kg body weight (AQF 200).

For anti-inflammatory activity, the Wistar albino male rats (120–135 g) were also divided into fourteen groups containing six mice in each group. All of the grouping were same except Group II that was treated with indomethacin at the dose of 10 mg/kg body weight.

2.8. Acute toxicity study

Healthy adult Swiss albino mice (25–30 g) were used for acute toxicity test. The test was executed using gradual increasing dose of different fractions of methanolic extract of *X. sagittifolium* (50, 100, 200, 500, 1000 mg/kg body weight) in the test groups. Water was administered to normal group. The mice were allowable to feed *ad libitum*, and observed for the period of 48 h to detect any mortality or behavioral changes and finally for 14 days to notice any mortality. The acute toxicity test was performed in accordance with the procedures of the Organisation for Economic Cooperation and Development^[15].

2.9. Analgesic activity

2.9.1. Acetic acid-induced writhing test

In this test, the analgesic action of the fractions was analyzed using acetic acid-induced writhing test according to the method stated by Koster *et al.* in Swiss albino male mice^[16]. The vehicle (control), diclofenac-sodium (standard) and test samples (fractions) were administered orally to the mice 30 min before intraperitoneal

injection of 0.7% v/v acetic acid. After a break of 5 min, the mice were observed for the particular contraction of the body mentioned as 'writhing' for the subsequent 10 min. The percentage of inhibition of writhing that represents the analgesic activity was calculated by using the following equation:

$$\% \text{ of inhibition of writhing} = [(W_c - W_t)/W_c] \times 100$$

where W_c is the average writhing of control group and W_t is the average writhing of treated group (i.e., fractions or standard).

2.9.2. Tail immersion test

In this test, the analgesic action of the fractions was analyzed using tail immersion test according to the method stated by Aydin *et al.* in Swiss albino male mice^[17]. About 1 h after administration of vehicle (control), diclofenac-sodium (standard) and test samples (fractions), the marked tip of tail of the mice up to 5 cm was submerged in the water bath that was thermo-statistically controlled at $(55 \pm 1)^\circ\text{C}$. Sudden tail removal from the hot water was mentioned as the latency to tail flick. The maximum cut off time for dipping was 180 s to evade the tail injury. The initial reading (i.e., 0 min) was taken before administration of standard and test sample and then reaction time was measured after 30, 60, 120 and 180 min.

2.10. Anti-inflammatory activity

In this test, the anti-inflammatory action of the fractions was studied using carrageenan-induced hind paw edema model as said by the method stated by Winter *et al.* in Wistar albino male rats^[18]. After 30 min administration of the vehicle (control), diclofenac-sodium (standard) and test samples (fractions), 0.1 mL of 1% w/v suspension of the carrageenan in normal saline was injected subcutaneously into the sub-plantar region of the right hind paw of rats. The volume of the paw was measured at 30, 60, 120 and 180 min after injection of carrageenan by means of a micrometer screw gauge. The percentage of inhibition of the inflammation was measured from the following formula:

$$\% \text{ of inhibition of paw edema} = [(I_c - I_t)/I_c] \times 100$$

where I_c is the average inflammation (i.e., hind paw edema) of control group at a specified time and I_t is the average inflammation of the treated group (i.e., fractions or standard) at the same time.

2.11. Statistical analysis

All results were stated as the mean \pm SEM of three duplicate experiments. The investigation was executed by using the SPSS statistical package (version 16.0; SPSS Inc, Chicago). All *in vivo* results were subjected to ANOVA subsequently Dunnett's test and $P \leq 0.05$ was considered to be statistically significant compared to control group.

3. Results

3.1. Evaluation of acute toxicity

The behavior of the animals was closely observed and the fractions did not cause any behavioral, motor and neuronal responses, weight loss and mortality in mice during up to 1000

mg/kg body weight. Therefore, these fractions were considered as safe.

3.2. Evaluation of analgesic activity by acetic acid-induced writhing test

Table 1 shows the effect of different fractions of methanolic extract of *X. sagittifolium* in acetic acid-induced writhing test in mice. The oral administration of various doses of NHF, CLF, EAF and AQF significantly ($P < 0.001$) blocked writhing initiated by acetic acid in a dose-dependent mode. Maximum inhibition (71.37%) was observed at 200 mg/kg body weight for EAF. The inhibitory effect of diclofenac-sodium (78.50%) was greater than that of the highest dose of EAF.

Table 1

Analgesic effect of different fractions of methanolic extract of *X. sagittifolium* leaves in acetic acid-induced writhing test in mice.

Treatment groups	Average number of writhing	% Inhibition of writhing
Control	64.80 \pm 2.41	–
Diclofenac-sodium	13.93 \pm 2.11***	78.50
NHF 50	29.28 \pm 1.56***	54.81
NHF 100	26.19 \pm 1.07***	59.58
NHF 200	22.09 \pm 2.00***	65.91
CLF 50	38.21 \pm 1.69***	41.03
CLF 100	34.47 \pm 1.77***	46.81
CLF 200	29.96 \pm 1.51***	53.77
EAF 50	26.03 \pm 1.19***	59.83
EAF 100	22.60 \pm 1.90***	65.12
EAF 200	18.55 \pm 1.45***	71.37
AQF 50	45.55 \pm 2.24***	29.71
AQF 100	40.99 \pm 1.73***	36.74
AQE 200	36.81 \pm 1.12***	43.19

Values are expressed as mean \pm SEM ($n = 6$). ***: $P < 0.001$ compared to the control group.

3.3. Evaluation of analgesic activity by tail immersion test

Table 2 shows the effect of different fractions of methanolic extract of *X. sagittifolium* in tail immersion test in mice. EAF, NHF, AQF and CLF (50, 100 and 200 mg/kg body weight) significantly ($P < 0.05$, $P < 0.01$, $P < 0.001$) increased latency to tail flick compared to control group. The highest inhibition of nociception was exhibited by EAF 200 at 180 min. The maximum inhibition of nociception was also observed by diclofenac-sodium at 180 min, which was higher than that in the highest dose of EAF.

3.4. Evaluation of anti-inflammatory activity by carrageenan-induced paw edema test

Tables 3 and 4 show the result of the anti-inflammatory effect of different fractions of methanolic extract of *X. sagittifolium* in carrageenan-induced paw edema test in rats. All of the fractions displayed dose-dependent anti-inflammatory activity at various time intervals and results were statistically significant ($P < 0.05$, $P < 0.01$, $P < 0.001$) compared to control group (Table 3). EAF showed maximum inhibition (72.92%) of inflammation at 200 mg/kg body weight at 180 min, whereas standard indomethacin showed 89.58% inhibition of paw edema at the last moment given in Table 4.

Table 2Analgesic effect of different fractions of methanolic extract of *X. sagittifolium* leaves in tail immersion test in mice.

Treatment groups	Latency to tail flick (s)				
	0 min	30 min	60 min	120 min	180 min
Control	3.14 ± 0.06	3.15 ± 0.04	3.19 ± 0.05	3.19 ± 0.05	3.13 ± 0.13
Diclofenac-sodium	3.21 ± 0.07	5.31 ± 0.14***	5.42 ± 0.12***	5.45 ± 0.09***	5.41 ± 0.08***
NHF 50	3.11 ± 0.06	3.24 ± 0.05	3.34 ± 0.04**	3.44 ± 0.04***	3.42 ± 0.04***
NHF 100	3.17 ± 0.07	3.41 ± 0.07***	3.51 ± 0.04***	3.66 ± 0.04***	3.66 ± 0.04***
NHF 200	3.15 ± 0.07	3.51 ± 0.06***	3.63 ± 0.04***	3.79 ± 0.05***	3.79 ± 0.05***
CLF 50	3.16 ± 0.06	3.20 ± 0.06	3.23 ± 0.06	3.25 ± 0.06	3.24 ± 0.05
CLF 100	3.18 ± 0.05	3.23 ± 0.04	3.27 ± 0.04	3.30 ± 0.04*	3.30 ± 0.04**
CLF 200	3.16 ± 0.07	3.19 ± 0.08	3.23 ± 0.08	3.26 ± 0.09	3.26 ± 0.09*
EAF 50	3.18 ± 0.08	3.34 ± 0.08***	3.50 ± 0.04***	3.58 ± 0.05***	3.51 ± 0.04***
EAF 100	3.23 ± 0.06	3.80 ± 0.07***	3.95 ± 0.05***	4.46 ± 0.10***	4.45 ± 0.06***
EAF 200	3.23 ± 0.07	4.19 ± 0.08***	4.71 ± 0.12***	5.01 ± 0.14***	5.03 ± 0.14***
AQF 50	3.19 ± 0.04	3.24 ± 0.04	3.32 ± 0.04*	3.40 ± 0.04***	3.39 ± 0.04***
AQF 100	3.16 ± 0.08	3.24 ± 0.08	3.32 ± 0.07*	3.38 ± 0.08***	3.36 ± 0.08***
AQF 200	3.14 ± 0.07	3.24 ± 0.07	3.31 ± 0.07*	3.37 ± 0.08***	3.36 ± 0.07***

Values are expressed as mean ± SEM (n = 6). *: P < 0.05, **: P < 0.01, ***: P < 0.001 compared to the control group.

Table 3Effect of different fractions of methanolic extract of *X. sagittifolium* leaves in carrageenan-induced paw edema test in rats (mm).

Treatment groups	Initial paw volume	Volume of paw edema at different time interval			
		30 min	60 min	120 min	180 min
Control	0.88 ± 0.07	1.53 ± 0.08	1.64 ± 0.12	1.77 ± 0.06	1.84 ± 0.10
Indomethacin	0.83 ± 0.06	1.10 ± 0.06	1.05 ± 0.05***	0.96 ± 0.04***	0.93 ± 0.07***
NHF 50	0.50 ± 0.06	1.02 ± 0.08***	1.07 ± 0.06***	1.03 ± 0.06***	0.95 ± 0.07***
NHF 100	1.21 ± 0.05	1.69 ± 0.07	1.67 ± 0.08	1.63 ± 0.06**	1.56 ± 0.06**
NHF 200	1.01 ± 0.07	1.35 ± 0.09	1.37 ± 0.08***	1.34 ± 0.04***	1.30 ± 0.05***
CLF 50	1.19 ± 0.04	1.72 ± 0.06*	1.78 ± 0.08*	1.74 ± 0.09	1.70 ± 0.05*
CLF 100	1.15 ± 0.06	1.64 ± 0.10	1.63 ± 0.05	1.62 ± 0.09**	1.57 ± 0.10***
CLF 200	1.09 ± 0.07	1.46 ± 0.04	1.49 ± 0.09**	1.48 ± 0.08***	1.46 ± 0.10***
EAF 50	1.25 ± 0.04	1.75 ± 0.05**	1.80 ± 0.11**	1.75 ± 0.07	1.67 ± 0.06***
EAF 100	0.81 ± 0.04	1.26 ± 0.05***	1.25 ± 0.05***	1.21 ± 0.04***	1.12 ± 0.07***
EAF 200	0.87 ± 0.07	1.20 ± 0.08***	1.21 ± 0.04***	1.18 ± 0.07***	1.13 ± 0.04***
AQF 50	0.94 ± 0.06	1.48 ± 0.12	1.55 ± 0.06	1.54 ± 0.05***	1.49 ± 0.09***
AQF 100	1.05 ± 0.08	1.56 ± 0.07	1.55 ± 0.06	1.55 ± 0.09***	1.53 ± 0.05***
AQF 200	0.97 ± 0.08	1.38 ± 0.10	1.42 ± 0.08***	1.38 ± 0.08***	1.38 ± 0.06***

Values are expressed as mean ± SEM (n = 6). *: P < 0.05, **: P < 0.01, ***: P < 0.001 compared to the control group.

Table 4

Inhibition of inflammation at various time intervals in carrageenan-induced hind paw edema test in rats.

Treatment groups	% Inhibition of paw edema			
	30 min	60 min	120 min	180 min
Control	–	–	–	–
Indomethacin	58.46	71.05	86.46	89.58
NHF 50	20.00	25.00	40.45	53.13
NHF 100	26.15	39.47	52.81	63.54
NHF 200	47.69	52.63	62.92	69.79
CLF 50	18.46	22.37	38.20	46.88
CLF 100	24.62	36.84	47.19	56.25
CLF 200	43.08	47.37	57.18	61.46
EAF 50	23.08	27.63	43.82	56.25
EAF 100	30.78	42.11	55.06	67.71
EAF 200	49.23	55.26	65.17	72.92
AQF 50	16.92	19.74	32.58	42.71
AQF 100	21.54	34.21	43.82	50.00
AQF 200	36.92	40.79	53.93	57.29

Values are expressed as mean ± SEM (n = 6).

4. Discussion

The drive of the current study was to create the basis for the ancient use of *X. sagittifolium* on wound healing by means of the

evaluation of the analgesic and anti-inflammatory actions on *in vivo* models. In this study, Swiss albino male mice were used to study the analgesic effects and Wistar albino male rats were used to study anti-inflammatory activity[19].

Intraperitoneal injection of acetic acid in mice provokes serous membranes and produces a stereotyped performance in mouse characterized by abdominal shrinkages and twisting of dorsal abdominal muscles, which is introduced as writhing[20]. Writhing response due to acetic acid-induction is a vulnerable technique to evaluate analgesic activity mainly peripherally acting and characterize pain sensation. This type of pain inducement leads to releasing free arachidonic acid from the phospholipid of the cell[21]. The response is supposed to be arbitrated by acid-sensing ion channels, peritoneal mast cells and prostaglandin pathways[22-24]. It is well recognized that non-steroidal anti-inflammatory as well as analgesic drugs assuage the inflammatory pain by hindering the creation of pain mediators in the peripheral target sites. In this study, different fractions of methanolic extract of *X. sagittifolium* leaves produce significant analgesic activity at different concentration probably by interfering with the local reaction caused by the help of irritant or by blocking the synthesis, release or antagonizing the act of pain mediators at the target sites. The maximum inhibitory activity was shown by the EAF of methanolic extract of *X. sagittifolium* (71.37% inhibition at the concentration of 200 mg/kg body weight). There is another technique, tail immersion test that was used to

explore central analgesic activity. The drugs exert their function against tail immersion induced pain, endorsed their actions via μ -opioid receptor instead of kappa and delta receptor[25,26]. Likely, EAF of methanolic extract of *X. sagittifolium* produced better activity in acetic acid-induced writhing test.

Carrageenan-induced edema has been widely used in animal model for evaluating the acute inflammatory activity. The first phase (1–2 h) of the carrageenan model is generally facilitated by serotonin, histamine and increased genesis of prostaglandins in the surrounding damaged tissue and the late phase is continued by prostaglandin release, facilitated by prostaglandins, bradykinin and polymorphonuclear cells formed by tissue macrophages[27]. These results of this study indicated that EAF of methanolic extract of *X. sagittifolium* produced maximum blockage of paw edema compared to remaining fractions. An earlier study on analgesic and anti-inflammatory activity of methanol extract of *X. sagittifolium* rhizomes was also reported[14].

The aforementioned studies suggested powerful analgesic and anti-inflammatory actions of *X. sagittifolium* leaves. The consequences of this study suggest that *X. sagittifolium* leaves may be used as a substitute of herbal natural therapy in order to treat diseases related to pain and inflammation. Due to the analgesic as well as anti-inflammatory actions, *X. sagittifolium* may have valuable effects in conjunction with drugs having superior analgesic and anti-inflammatory properties. Thus, the current study permits further elaborate inquiry involving components of *X. sagittifolium* for the better understanding of their analgesic plus anti-inflammatory activity and for the potential development of innovative class of analgesic as well as anti-inflammatory drugs.

Conflict of interest statement

We declare that we have no conflict of interest.

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