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RESEARCH ARTICLE

ANTI-PYRETIC AND ANTI-INFLAMMATORY ACTIVITY OF AQUEOUS EXTRACT OFSOLANUM XANTHOCARPUM BERRIES IN SUITABLE ANIMAL MODELS

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Abstract

Background: Use of traditional medicines for treating various diseases have become a topic of global importance because of their safety, less side effects and cost-effectiveness. The present study was undertaken to evaluate the anti-pyretic and anti-inflammatory activity of aqueous extract of Solanum xanthocarpum berries (SXB) in suitable animal models.

Methods: Anti-pyretic activity was assessed by dried yeast induced pyrexia in rats. Anti-inflammatory activity was evaluated using carrageenan induced paw oedema in rats. Three doses of the plant extract (500, 1000 and 1500 mg/kg) prepared by dissolving the drugs in 2% gum acacia were used. Paracetamol 33 mg/kg and aspirin 100 mg/kg were used as standard drugs for anti-pyretic and anti-inflammatory activity respectively. Vehicle served as a control drug.

Results: Acute toxicity study results demonstrated no mortality of animals after 24 hours. The aqueous extract of the plant significantly decreased the rectal temperature of the rats and significantly prevented increase in volume of paw oedema.

Conclusion: The aqueous extract of Solanum xanthocarpum berries exerts its anti-pyretic and anti-inflammatory activity activity. However, further studies with the plant are required to evaluate the dose dependent activity and also to determine the active principle responsible for exact mechanism for both antipyretic and anti-inflammatory activity.

Introduction:-

Body temperature is controlled by the hypothalamus. Neurons in both the pre-optic anterior hypothalamus and posterior hypothalamus receive two kinds of signals: one from peripheral nerves that reflect warm/cold receptors and the other form the temperature of the blood bathing the region. These two types of signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. Fever is an elevation of body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point [1].

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Fever can be produced by various organisms including bacteria, viruses, fungi, yeast, protozoa and also by many inflammatory and related reactions such as tissue damage and necrosis, malignancy, antigen-antibody reactions and tissue graft rejection [2].

The term inflammation was described by Celsus by the four Latin words: rubor (redness), calor (heat), dolor (pain) and tumor (swelling) [3]. It is a protective response of immune system to an injurious stimulus. It is a part of host's defense mechanism but when the response becomes too great, it may be worse than the disease state which is counteracted and in extreme cases, it may be fatal. Various mediators involved in the inflammatory process are histamine, bradykinin, prostaglandins, 5-hydroxytryptamine, leukotrienes and cytokines. PGE_2 and PGI_2 are the main prostaglandins involved in inflammatory process that increase local blood flow, permeability of the blood vessels and infiltration of the leucocytes. Activation of endothelial cells also lead to the recruitment of inflammatory cells like leukocytes. Platelet activating factor, complement factor and eicosanoids are also involved in this recruitment. Manifestations of inflammatory process are also contributed by the cytokines and growth factors like IL-2, IL-6, IL-8, granulocyte macrophages colony stimulating factor [4].

India is very rich in natural resources and the knowledge of traditional medicine and the use of plants as a source of medicine is an innate and a very important component of health care system. There are about 17,000 species of higher plants, of which approximately 8,000 species are considered to have medicinal values. The herbal medicines are safe and dependable compared to the available synthetic medicines that are costly and have adverse effects. During the past decade, use of traditional systems of medicine for treating various diseases have become a topic of global importance [5].

Solanum xanthocarpum, locally known as Leipung-khanga belonging to the family Solanaceae is a perennial herb with woody base commonly found in the North Eastern states of India. Flowers are purple in colour, fruit type is berry globose measuring about 6-8 mm in diameter, green in colour becoming reddish yellow when ripe [6]. The juice of berries is commonly used for sore throat, cough and asthma. Stem, flowers and fruits are carminative and also used in burning sensation of the feet accompanied by vesicular watery eruptions [7].

As such, considering its use by locals for treating various ailments, the present study was undertaken to evaluate the anti-pyretic and anti-inflammatory activity of aqueous extract ofSolanum xanthocarpum berries (SXB) in suitable animal models.

Materials And Methods:-

Plant material:

The fresh ripe berries of Solanum xanthocarpum were collected from around the Imphal area and was identified and authenticated by Professor and Head of Botany department, DM college of Science, Imphal.

Preparation of plant extract:

The berries were cleaned, dried under shade, powered by grinder and stored in an air-tight container for further use. 80 grams of powdered berries was extracted with distilled water using a Soxhlet apparatus. The brownish extract obtained was evaporated, shade dried, scrapped out, weighed and stored in a glazed porcelain jar for future use [8]. The percentage yield was 23.25% and the extract thus obtained was used for the anti-pyretic and anti-inflammatory study.

Toxicity studies:

Acute toxicity testing was be carried out as per Organization of Economic Cooperation and Development (OECD) guidelines 423 [9]. Toxicity testing was done by administrating aqueous extract ofSolanum xanthocarpum at doses 100, 200, 400, 800, 1600 and 3000 g/kg, p.o to groups of mice, each group consisting of 10 mice and mortality was observed after 24 hours.

Animals:

Wistar albino rats of 100-200 grams (both of either sex, non-pregnant) were obtained from the Central animal house, RIMS, Imphal after getting approval from the Institutional Animal Ethics Committee (IAEC). The animals were maintained at 24-28^{0}C temperature, relative humidity of 50–55% and under 12 h light and dark cycle (6–10 h light, 18–6 h dark). The animals were fed with standard animal feed and water was applied ad libitum. All the animals were acclimatized for 7 days to the laboratory conditions prior to experimentation.

Anti-pyretic activity:
The antipyretic activity of aqueous extract ofSolanum xanthocarpum was done yeast induced method of Brownlee with slight modifications [10]. Healthy albino rats of wistar strain of either sex weighing between 100-200grams were collected from central animal house, RIMS. The animals were fasted overnight during the experiment but had water ad libitum. Basal rectal temperature of the animalswere measured and 20% aqueous suspension of dried yeast was injected subcutaneously dissolved in 2% gum acacia at a dose of 20 ml/kg on the nape. After 18 hours of yeast injection, animals were restrained in individual cages for measuring rectal temperature. Rectal temperature was obtained by insertion of digital clinical thermometer to a constant depth of 3cm. After recording the temperature, animals were groups into 5 groups with six animals in each group. Group I was the control group who received 2% gum acacia in distilled water orally. Group II, III, IV were the test groups 1, 2 and 3 who received aqueous extract of SXB 500, 1000 and 1500 mg/kg orally respectively. Group V received the standard drug paracetamol at a dose of 33 mg/kg orally.

The drugs were suspended in 2% gum acacia and administered orally. The volume of the medicament was kept constant at 10 ml/kg body weight of the animals. Temperatures were recorded at hourly intervals upto 21 hours after yeast injection.

Anti-inflammatory activity:
The anti-inflammatory activity of aqueous extract ofSolanum xanthocarpum was done by carrageenan induced paw oedema using the method of Winter et al with slight modifications [11].Healthy albino rats of wistar strain of either sex weighing between 100-200grams were collected from Central animal house, RIMS. The animals were divided into 5 groups with six animals in each group. Group I was the control group who received 2% gum acacia in distilled water orally. Group II, III, IV were the test groups 1, 2 and 3 who received aqueous extract of SXB 500, 1000 and 1500 mg/kg orally respectively. Group V received the standard drug aspirin at a dose of 100 mg/kg orally. The drugs were suspended in 2% gum acacia and administered orally at a volume of 10 ml/kg body weight of animals.

Acute inflammation was produced by injection of 0.1ml freshly prepared 1% carrageenan in 0.9% sodium chloride solution in the sub-plantar region of the right hind paw of the rats, 1 hour after oral administration of drugs. The foot volume was measured in rats by modified plethysmographic method immediately and at 3 hours after carrageenan injection and the volume of oedema was recorded as the difference between the two readings.
The percentage of anti-inflammatory activity was then calculated by the formula as follows

Percentage of inhibition = $\left(\frac{Vc-Vt}{Vc}\right)$ x 100

where V_c means increase in paw volume in control group
V_t means increase in paw volume in drug treated group

Statistical analysis:
The data thus obtained were subjected to statistical analysis using one way ANOVA followed by Dunnet's 't' test for significant difference between different groups. P value of less than 0.05 was considered as significant.

Results:-

Acute toxicity:
The aqueous extract ofSolanum xanthocarpum berries was found to be safe in the doses used. There was no mortality upto a dose of 3000mg/kg, p.o. after 24 hours.

Anti-pyretic activity:

Group	Dose (mg/kg), p.o	Initial basal rectal temperature (°F) (Mean±SEM)	Temperature after 18 hrs of induction (°F) (Mean±SEM)	Temperature after treatment (°F) (Mean±SEM)		
				60 mins	120 mins	180 mins
GroupI (Control)	10 ml	99.8±0.47	101.1±0.62	101.3±0.31	101.2±0.50	101.1±0.28
Group II (Test 1)	500	99.6±0.42	101.3±0.46	101.0±0.44	99.90±0.48**	99.61±0.40**

Group III (Test 2)	1000	99.4±0.32	101.0±0.66	100.7±0.49	99.8±0.51**	99.4±0.34**
Group IV (Test 3)	1500	99.9±0.31	101.3±0.40	100.0±0.51*	99.8±0.38**	99.4±0.31**
GroupV (Standard)	33	99.6±0.36	101.4±0.38	99.90±0.49*	99.6±0.42**	99.2±0.42**

Table 1:- Anti-pyretic activity of the aqueous extract of SXB on dried yeast induced pyrexia in albino rats.

n=6 in each group, *p <0.05 when compared to the control at that particular hour, **p<0.001 when compared to the control at that particular hour

There was no significant difference in the mean initial basal temperatures of the different groups. After 18 hours of induction, there was significant rise in temperature of the control 101.1±0.62°F, test 1 (500 mg/kg) 101.3±0.46°F, test 2 (1000 mg/kg) 101.0±0.66°F, test 3 (1500 mg/kg) 101.3±0.40°F and standard drug paracetamol 101.4±0.38°F respectively in comparison to the initial basal temperature in each group but there was no significant difference in mean temperature in between the groups.

The reduction in the mean temperature by paracetamol after the 1st, 2nd and 3rd hour were 99.90±0.49°F, 99.6±0.42°F and 99.2±0.42°F respectively. The test drug (500 mg/kg) decreased the mean temperature at 1st, 2nd and 3rd hour to 101.0±0.44°F, 99.9±0.48°F and 99.61±0.40°F respectively. In case of test drug (1000 mg/kg), the mean temperature at 1st, 2nd and 3rd hour was 100.7±0.49°F, 99.8±0.51°F and 99.4±0.34°F respectively. The test drug (1500 mg/kg) reduced the mean temperature at 1st, 2nd and 3rd hour to 100.0±0.51°F, 99.8±0.38°F and 99.4±0.31°F respectively.

The aqueous extract ofSolanum xanthocarpum berries at doses 500, 1000 and 1500 mg/kg showed anti-pyretic activity in a dose dependant manner when compared to the control. However, the standard drug paracetamol (33mg/kg) is more effective than the test drug.

Anti-inflammatory activity:

Table 2:- Anti-inflammatory activity of the aqueous extract of SXB on carrageenan induced rat paw oedema.

Groups	Dose (mg/kg), p.o	Mean increase in paw volume (Mean±SEM) in ml	Percentage inhibition of paw oedema
Group I (Control)	10 ml/kg	0.63±0.01	
Group II (Test 1)	500	0.49±0.02*	22.2
Group III (Test 2)	1000	0.36±0.03*	42.8
Group IV (Test 3)	1500	0.26±0.02*	58.7
Group V (Standard)	100	0.21±0.02*	66.6

n=6 in each group. *p<0.001 when compared to the control

The mean increase in paw oedema in the control group was 0.63±0.01ml, test 1 (500 mg/kg) 0.49±0.02ml (p<0.001), test 2 (1000 mg/kg) 0.36±0.03ml (p<0.001), test 3 (1500 mg/kg) 0.26±0.02ml (p<0.001) respectively. The test drug at doses 500 mg/kg, 1000 mg/kg and 1500 mg/kg produced 22.2%, 42.8% and 58.7% inhibition of paw oedema respectively compared to 66.6% inhibition produced by 100 mg/kg of standard drug aspirin. Increasing dose of the test drug produced increased inhibition of paw oedema. Both the test and standard drug produced highly significant inhibition of paw oedema in comparison to the control (p<0.001).

Discussion:-

Yeast induced pyrexia is known as pathogenic fever that increase the synthesis of prostaglandin, and is regarded as a useful model for the screening of many plants derived medicines as well as synthetic drugs for their antipyretic activity [12,13]. The available antipyretic drugs, such as paracetamol and the non-steroidal anti-inflammatory drugs, exert their antipyretic action through inhibition of prostaglandin synthetase within the hypothalamus [14].

In our study the mean initial basal rectal temperature ranged from 99.4±0.32 to 99.9±0.31°F which corresponds to the findings of the study done by Khattak SG et al [15]. The rise of temperature after 18 hours of induction ranged from 101.0±0.66 to 101.4±0.38 °F which is similar to the findings of Mukherjee et al [16]. There was no significant

difference between the mean initial basal temperature of different groups and the mean temperature after 18 hours of pyrexia induction. The test drug SXB at doses 500 and 1000mg/kg did not produce any significant reduction in the mean temperature at the 1st hour when compared to the control ($p>0.05$). The test drug at dose 1500 mg/kg reduced the temperature significantly ($p<0.05$) at 1st hour. The test drug at doses 500, 1000 and 1500mg/kg reduced the rectal temperature of the pyrexic rats significantly from the 2nd hour to the 3rd hour, when compared to the control value of that particular hour. The standard drug paracetamol at dose 33mg/kg lowered the rectal temperature of the pyrexic rats from the 1st hour to the 3rd hour which is similar to the findings of Mutalik er al [17].

Carrageenan is a phlogistic agent of choice for testing anti-inflammatory drugs as it is known to be non-antigenic and there are no systemic effects and it has high degree of reproducibility [18]. After injection of the irritant substance carrageenan in rats there is accumulation of oedema fluid which cause biphasic reaction. Histamine and serotonin mediate the initial phase of the reaction while the latter phase of the reaction is mediated by arachidonic acids like prostaglandins and kinins. Although cyclo-oxygenase and lipo-oxygenase both pathways are involved in inflammatory process, inhibitors of cyclo-oxygenase are more effective in inhibiting carrageenan induced inflammation [19].

In this study the mean increase in paw volume of the control group was 0.63±0.01ml which corresponds to the findings of Ndebia et al [20]. The test drug at doses 500, 1000 and 1500 mg/kg produced 22%, 43% and 59% inhibition of paw oedema compared to 67% inhibition produced by 100 mg/kg of aspirin. The mean increase in paw volume of the standard drug was 0.21±0.02ml which has similarity to the study done by Smita et al [21]. The test drug SXB was found to be less effective than the standard drug aspirin.

Conclusion:-

The aqueous extract ofSolanum xanthocarpum berries demonstrated significant antipyretic and anti-inflammatory activity. However, further studies with the plant are required to evaluate the dose dependent activity and also to determine the active principle responsible for exact mechanism for both antipyretic and anti-inflammatory activity.

Conflicts of Interest

The authors declare no conflict of interest.

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