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EVALUATION OF ANTIHISTAMINIC AND BRONCHODILATOR ACTIVITY OF A SIDDHA DRUG *NAAURUVI KUZHI THYLAM*

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ABSTRACT

The prevalence of allergy and asthma (*Suvasa irumal* ICD-DBA1.3) has risen in the recent years despite an improvement in the general health of the population. Bronchial asthma (*Suvasa irumal*) is one of the most complex disorders of the airway characterized by reversible airway obstruction inflammation, bronchial hyper-responsiveness and excessive mucous production. *Naauruvi Kuzhi thylam* (*NKT*) is a *Siddha* herbal formulation indicated in literature for the management of Asthma (*Suvasa irumal*). However the drug is not ethically validated hence the present study was focused to evaluate the in vitro antihistaminic action of *NKT* in isolated guinea pig ileum and in vivo bronchodilator activity was carried out in four groups of guinea pig each consisting of five animals. Group 1 was treated as control, Group II received *NKT* at the dose 250 mg/kg and Group III animals received *NKT* 500 respectively. Group IV animals received the standard drug Chlorpheniramine maleate 2mg/kg. Prior to drug treatment each guinea pig was exposed to an atomized fine mist of 2% w/v histamine dihydrochloride aerosol. The results were statistically analysed by one way analysis of variance (ANOVA) followed by Dunnet "t" test. The results conclude that the study drug NKT possess antihistaminic and bronchodilator activity.

KEYWORDS: *Naauruvi Kuzhi thylam* (*NKT*), *Traditional medicine*, Herbal medicine, Anti-histaminic action, Anti-asthmatic, Bronchodilator, Bronchial asthma (*Suvasa irumal*).

INTRODUCTION

Asthma (Suvasa irumala ICD-DBA1.3) is the most common disease in the. The symptoms of asthma are characterized by recurrent wheezing, breathlessness, chest tightness and

coughing.[1] Nearly 14 % of children and adolescents under 18 years of age are diagnosed with asthma at some point in their lives.[2] Since it is a chronic disease with recurrent episodes it is the most common cause of emergency visits hospitalizations, poor performance at work and missed school days.[3-5] Present day treatment for asthma management pose upon constant use of glucocorticoids, bronchodilators and leukotrine receptors antagonists either as oral drugs or as inhalers or both but none promise to provide complete relief but inturn associated with numerous side effects.[6,7] Therefore the world is in search for novel herbal remedies, which can serve the suffering patients towards long term management with lesser side effects.

Siddha is one among the well known global system of medicine which is constantly playing an important role in providing health care to large section of population, especially in developing countries. WHO estimates that nearly 4.3 billion people or 80% of the global population rely on traditional medicine for their primary health care needs.[8] The traditional *Siddha* system of medicine has several herbal formulations that are increasingly utilized to treat a wide variety of diseases. *Naauruvi Kuzhi thylam* is one such formulation that has been indicated in Siddha literature *Gunapaadam Mooligai Vaguppu* for the treatment of cough, Bronchial Asthma and other respiratory ailments (*Kapha diseases*)[9], but the knowledge about their mode of action is relatively deficient. In recent years there is an emerging interest regarding the pharmacological evaluation of various drugs used in traditional system of medicine. In order to achieve this object an attempt was made to assess the antihistaminic and bronchodilator activity as on *Naauruvi Kuzhithylam* for its antihistaminic and antiasthmatic actions.

MATERIALS AND METHODS

Drugs, Chemicals and Stock solution

Histamine solution was freshly prepared in normal saline (NaCl, 8.5 g/l), 2% Carboxy methyl cellulose (Loba chemie Pvt Ltd). All other chemicals used were of analytical grade. The *Naauruvi Kuzhi thylam* stock solution 100mg/ml was prepared and stored in refrigerator. The drug was mixed uniformly in saline solution to achieve 1mg/ml as main stock solution and used in *in-vitro* study.

Experimental animals

Guinea pigs of either sex 350- 450 were procured from animal house, Department of Pharmacology, Vels University and throughout the study. They were housed in stainless steel

cages (34×57×18 cm) at a population density of 5 guinea pigs per cage in a temperature regulated environment (26-29°C) with a 12 h light-dark cycle. Food and water were available *ad libitum* until a day before the experiment. Daily maintenance of the cages was conducted during the first quarter of the light cycle. Group sample sizes of five were utilized throughout the study. The guinea pig handling and experimental protocol were in accordance with the institutional animal care and use of Pharmacology Department and approved by the IAEC. The study was conducted after obtaining approval by CPCSEA. (_XIII/VELS/COL/18CPCSEA/IAEC/23.09.11).

EXPERIMENTAL PROCEDURES

In-vitro antihistaminic activity[][0]

Overnight fasted guinea pigs were killed by a blow on the head and exsanguinated. The abdomen was cut open, and a good length of the ileum was placed on a Petri dish containing Tyrode solution at 37°C. A 2.5 cm long piece of the distal part of the ileum was used for the study. Experiments were performed in organ baths containing 40 mL Tyrode solution at 37°C and bubbled with air and mounted in an organ bath containing Tyrode solution between two stainless steel hooks under 0.5 to 1 g initial tension. The lower hook was fixed at the bottom of the organ bath and upper one was connected to an isotonic transducer. The Tyrode solution composition (pH 7.4) was NaCl-8.0, KCl-0.2, $CaCl_2$-0.2, $MgCl_2$-0.1, $NaHCO_3$-1.0, NaH_2PO_4-0.05, and Glucose-.0 gms/liter. It was continuously aerated and maintained at 37 ± 0.5ºC The equilibrium period was 60 min and the bath solution was refreshed every 15 min. After equilibrium period, a dose response curve for histamine in variant molar concentrations, by maintaining 45 min time cycle was taken separately and the responses of the histamine, standard drug and the *Naauruvi Kuzhithylam* were studied at different dose levels. Their effect on contractions induced by histamine (0.5µg/mL) was also studied. The percentage inhibition of the *Naauruvi Kuzhithylam* on contractions induced by histamine was calculated.

Histamine induced bronchoconstriction in guinea pig[10]

Experimental bronchial asthma was induced in guinea pigs by exposing them to histamine. Overnight fasted guinea pigs of either sex (350-450) were selected and randomly divided in to four groups each consisting of five animals. The study was conducted after obtaining approval by CPCSEA. (_XIII/VELS/COL/18CPCSEA/IAEC/23.09.11). Group 1 was treated as control, Group II received *NKT* at the dose 250 and 500 mg/kg respectively. Group IV animals received the standard drug Chlorpheniramine maleate (CPM) 2mg/kg. All the doses

were given orally. Prior to drug treatment each guinea pigs were exposed to an atomized fine mist of 2% w/v histamine dihydrochloride aerosol (dissolved in normal saline) using a nebulizer in the histamine chamber. Guinea pigs exposed to histamine aerosol showed progressive signs of difficulty in breathing leading to convulsions, asphyxia and death. The time until signs of convulsion appeared is called pre-convulsion time (PCT) and was determined from the time of exposure to onset of convulsions. As soon as pre convulsion time was noted, animals were removed from the chamber and placed in fresh air to recover. The percentage protection offered by treatment was calculated by using the following formula:

$$\text{Percentage protection} = (1 - T_1/T_2) \times 100$$

Where; T_1 = the mean of PCT of control group animals.

T_2 = the mean of PCT of test group animals.

Statistical analysis

Data were expressed as Mean ± SEM. Differences between groups were analysed by one way analysis of variance (ANOVA) followed by Dunnet "t" test. Differences were considered significant when $P< 0.05$ and very significant when $P< 0.01$.

RESULTS AND DISCUSSION

From the previous acute toxicity study, it was confirmed that the test drug *Naauruvi Kuzhithylam* has LD50 > 5000 mg/kg body weight after oral administration in mice. Hence, as per the literature guidelines 1/10th of the dose was fixed to evaluate the anti-asthmatic activity.

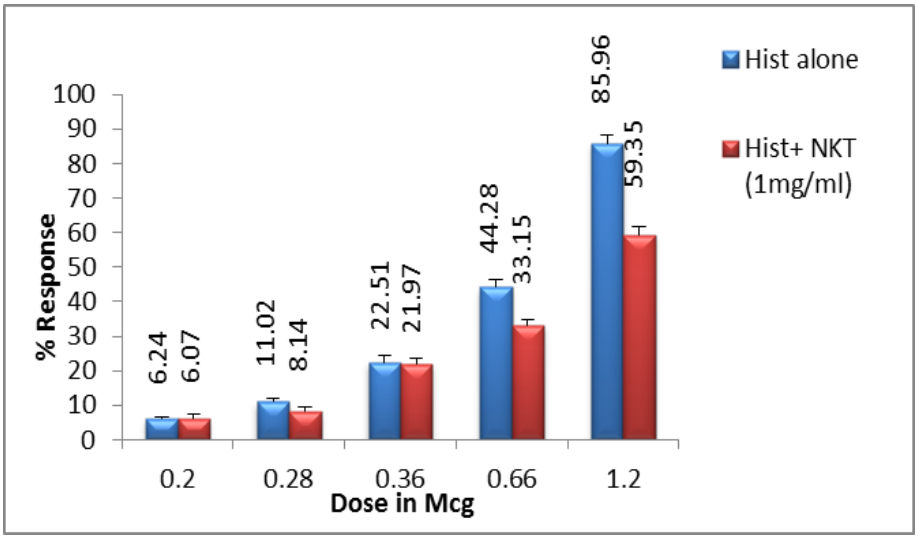

Figure 1: Effect of *Naauruvi Kuzhithylam* on isolated ileum preparation (Histamine).

Histamine has been recognized as the major mediator in allergic disorders. It is a potent vasoactive agent, bronchial smooth muscle constrictor, and stimulant of nociceptive itch nerves and responsible for clinical allergic symptoms[11]. Therefore in researches associated antihistaminic therapy such as Asthma, targeting the prevention of histamine release from mast cells or use of histaminergic receptor antagonist is vital. From the above Fig-1, it can be revealed that the study drug *Naauruvi Kuzhi thylam* showed significant antihistaminic effect at the dose levels of 0.28mcg, 0.66 mcg and 1.2 mcg.

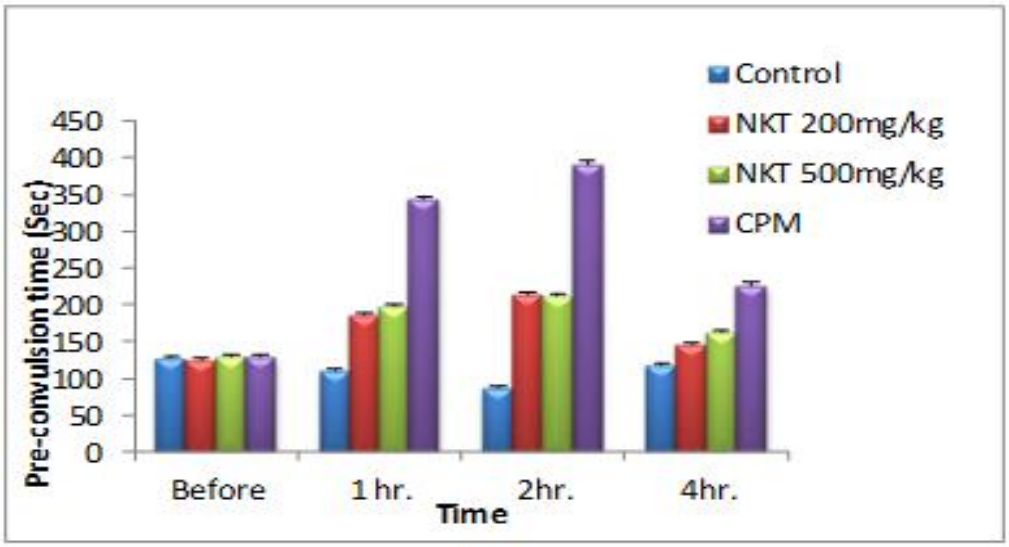

Figure-2: Effect of *Naauruvi Kuzhithylam* on histamine induced bronchoconstriction in Guinea pigs.

Histamine can induce bronchoconstriction and bronchial hypersensitivity which is a common feature of asthma. The presence of histamine H1 sensitive excitatory receptors and acetylcholine muscarinic receptors in the airway smooth muscle of man and animals have been established.[12] In the present study, guinea pigs were used because among the various animal models, guinea pig model resembles the human allergic pathology especially in terms of release of mediators histamine and leukotrienes that are responsible for bronchoconstriction in a manner similar to that of humans. Another similarity between the guinea pig model and asthmatic patients is that enhanced bronchoconstriction that occurs in both species following sensitization, in response to β-adrenergic antagonists.[13,14]

Table 1: Percent protection of *Naauruvi Kuzhithylam* against histamine induced bronchoconstriction in Guinea pig.

Groups	Treatment and Dose	% Protection		
		1 hr.	2hr.	4hr.
Test 1	*NKT 250mg/kg*	40.82	59.92	19.56
Test 2	*NKT 500mg/kg*	44.51	59.24	27.42
Standard	CPM 2mg/kg	67.98	78.10	48.06

In the present invivo pharmacological study .the results of *Naauruvi Kuzhithylam* suggested that the percentage protection of *Naauruvi Kuzhithylam*-250mg/kg and 500mg/kg was 59.92 and 59.24% respectively at 2nd hour whereas the standard drug showed 78.10% of protection (Fig-2 & Table-1). Hence it is effective in reducing the symptoms of bronchial asthma (Suvasa irumal) also to improve the lung function parameters of asthmatic subjects.

CONCLUSION

The results of present study suggested that the study drug *NKT* showed antagonism against histamine at 100µg/ml and also protected the Guinea pigs against histamine-induced bronchospasm. Hence *Naauruvi Kuzhi thylam* (*NKT*) that is used traditionally in the traditionally in the management of asthma (Suvasa irumal) was pharmacologically tested and justified. Further preclinical studies on phytoconstituents responsible for antiasthmatic action and target mechanism of action at molecular levels need to be scientifically explored.

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