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ORIGINAL ARTICLE **OPEN ACCESS**

Mast Cell Stabilizing and Anti-Inflammatory Activity of Leaves of *Calotropis gigantea*

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ABSTRACT
Calotropis gigantea Linn, an extensively cultivated Asclepiadaceae plant, is believed to possess a number of medicinal properties. It reportedly has a lengthy history of use as a traditional treatment for a variety of illnesses. Studies have been done on the anti-diabetic properties of calotropis leaves. Using petroleum ether, chloroform, ethanol & water, extracts of C. gigantea leaves were made, and their anti-asthmatic effects were assessed. Using in vivo models, the current study evaluates the effects of Calotropis gigantea leaf extract. Chlorpheniramine (CPM) and Dexamethasone were used as the reference drugs. The study demonstrates that the leaves of Calotropis gigantea have anti-asthmatic properties. The research found that the Calotropis gigantea pet ether extract is advantageous for asthma patients.
Keywords: *Calotropis gigantea, anti-asthmatic, activity*

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INTRODUCTION

The word "asthma" in today's English language originates from the Greek for "breathless" [1]. Asthma, a chronic inflammatory disease, is caused by antigen sensitization or a genetic predisposition to airway inflammation. Asthma is characterized by bronchial hyperreactivity, enhanced mucus production & remodelling & airway congestion. These symptoms are all brought on by the immune system's infiltration into the lungs, which causes inflammation [2]. Dendrites from neurons, T lymphocytes, mast cells, eosinophils, & neutrophils are some of the key cells involved in the inflammatory process that causes asthma. Asthma prevalence in school-aged children has increased by 75%, and there are an estimated 15–20 million asthmatics in India alone, according to mortality data from wealthy nations. The rate varies between 0.1 and 0.8 per 10,000 people aged 5-34. Symptomatic relief is the primary requirement for asthma attack management. In India, a variety of traditional medical systems, including Ayurveda, Unani, & Siddha, list numerous herbs for the treatment of asthma. Laticiferous shrubs of the genus Calotropis are indigenous to Asia and Africa. Calotropis gigantea R. (purple or red-flowered or "arka") and Calotropis pricera R. (white-flowered or "alarka") are its two species. Found in region of Punjab, India, Ceylon, Singapore, the Malay Peninsula, and southern China [3] and in regions south of the Himalayas. The Asclepiadaceae family, which include the milky shrub Calotropis gigantea (crown flower), also known as madar in Hindi, is widespread in India. It is regarded as a crucial plant for the therapy of asthma in both Ayurvedic & Unani medication. In Ayurvedic medicine, the entire dried plant is used as a tonic, expectorant, depurative & antihelminthic. The leaves can be used to treat intermittent fever, arthralgia, paralysis, and edema. The leaves are bitter, astringent, stomachic, anthelmintic & tonic, among other medical qualities. Calotropis gigantea has been found to contain proteases, 3-methyl butanoates of amyrin [4], flavonol glycosides, calotropis stigmasterol & sitosterol, cardenolides, pregnanone & more. The whole Calotropis gigantean (Asclepiadaceae) plant can be found throughout India up to an altitude of 900 metres, which includes the Andaman Islands [5, 6]. An additional typical place is referred to as mudar. The immature leaves are rectangular and broad, with a coriaceous base and a sharp or occasionally rounded tip. They have a glaucous green tint and measure between 6 and 20 centimeters in length and 3 to 8 centimeters in breadth. This has a length of 0.5 to 2 cm [7,8]. The fruits are single or in pairs, and they can range in length from 7 to 10 centimeters. They are also turgid and recovered. The 2.5 to 3.2 centimeter long, broadly ovate, brown, flattened seeds have a white tuft of silky hair on the apex and are covered in brown pigment.

Pedunculate corymbs at the axillary nodes have lilac, pale pink, or purple flowers, as well as occasionally light greenish-yellow or white blooms [9]. The unscented flowers have reflexed, spreading corolla lobes. Flowers are visible throughout the year, but in central India, November through March are the busiest months for blossoming.

MATERIAL AND METHODS

Plant material

The leaves of Calotropis gigantea were taken from the dry parts of Nashik districts in Maharashtra, India. They were then authenticated at the Department of Botany, HPT (Arts) & RYK (Science) College Road, Nashik, for taxonomic identification. The leaves from the plant were taken off, dried, and ground into a coarse powder.

Preparation Of Plant Extract

The gathered Calotropis gigantea leaves were procured and brought to the laboratory and washed thoroughly with running water to remove dirt and other extraneous matter. They were then rinsed with distilled water and shed dried prior to being ground into powder to yield between 500g to 1 kg of powder for each sample. Leaves were reduced to small pieces and dried in the shade. The dried leaves were further reduced to a powdered state through grinding. By passing powdered plant components through a screen (sieve), fine powder was separated from coarse powder, and coarse powder was stored in airtight, well-labeled containers until use. Approximately 1 kilogramme of powdered material was extracted with petroleum ether (60-800), chloroform, ethanol & distilled water.

Experimental Animals

Albino mice (25–30 g), Wistar rats (150–170 g) & guinea pigs (350–400 g) were preserved in polypropylene cages at a temp. of 22±20 °C & under a 12-hr day/night cycle. The animals received a healthy diet & access to fresh water throughout the experiment, the animals received a healthy diet and access to fresh water. The Sir Dr. M. S. Gosavi College of Pharmaceutical Education & Research, Gokhale Education Society, Nashik, Maharashtra, institutional animal ethical committee accepted the study's methods.

Acute Toxicity Study

According to OECD guideline 425, the acute toxicity of test extracts was assessed employing the up-and-down method & a body weight limit of 2,000 mg/kg.

Antiasthmatic Activity

Effect of Test Extracts on Mast Cell Degranulation's

Calotropis gigantea leaves were tested on mice in 10 groups, including control groups of six mice each. Three days' worth of intraperitoneal medication was administered. The placebo group received 5 ml/kg of 1% tween-80 in their body weight. The control group got sodium chromoglycate (50 mg/kg), while the experimental groups received plant extracts (100 & 150 mg/kg). On day four, an intraperitoneal injection of 0.9% saline solution (10 ml/kg body weight) was given to each mouse. After massaging the peritoneum, the fluid was extracted and placed in a test tube with L-Glutamine, 25 mM Hepes buffer without sodium bicarbonate, & 10 ml of buffer medium from the RPMI-1640 (pH 7.2–7.3). The fluid was centrifuged at a speed of 400–500 RPM. In the same buffer media, mast cells were twice pelleted before being centrifuged to eliminate the supernatant. Cell suspensions from treated and untreated mice were incubated at 37 0C for 10 minutes after being challenged with 100 g/ml of egg albumin. Toludine blue 1% was used to stain the cell suspension for viewing under a microscope. Over numerous distinct visual regions, 100 cells were counted. Mast cell degranulation bursts rather than whole cells were observed [18]. Determine the total number of degranulated mast cells.

Effect of Test Extracts on Passive Cutaneous Anaphylaxis

Rats were given 100 mg of egg albumin as an adjuvant and 12 mg of $Al(OH)^3$ subcutaneously on days 1, 3, & 5 to induce sensitization. Animals were bled on day 10 to obtain antiserum, which was kept at -20 °C. There were six rodents in each of the ten groups of rats. On the shaved backs of rats, one millilitre of homologous antiserum was injected. The control group received intraperitoneal administration of 5 ml/kg of body weight of 1% tween-80 after 24 hours. The control groups got test extracts (100 & 150 mg/kg, body weight) while the experimental groups received intraperitoneal sodium chromoglycate (50 mg/kg, body weight). Each group got a 0.5 ml injection of a solution containing 0.5% Evan blue & 1% egg albumin (1:1) after 30 minutes. 30 minutes after injecting blue dye, the leakage area was calculated as the diameter of the blue spots in mm^2 [18-21].

Carageenan Induces Paw Edema

In this investigation, 20 groups of six rats each were used. The control group got intraperitoneal injections of saline solution (1% tween-80) at a dosage of 5 ml/kg of body wt. Dexamethasone was supplied intraperitoneally to the control group at a dosage of 50 mg/kg, whereas extracts were given to the test

group at dosages of 100 & 150 mg/kg of body wt. 30 minutes after treatment, 0.1 cc of 1% (w/v) carrageenan was administered into the hind paw of each group. Paw volume was determined using an Ugo Basile 4140 plethysmometer at 1, 2 & 3 hours after carrageenan injection [22–24].

Effect of Test Extracts on Histamine Induced Contraction of Goat Tracheal Chain

A butcher was paid for goat trachea. The trachea was cut into rings, which were then utilized to make a necklace. 30 ml of Kreb's solution were added to a 370.5 °C air bath that included the trachea. The 400 mg load was allowed to mix with the suspended tracheal chain for 45 minutes. The organ bath was added with Kreb's solution every 15 minutes. Histamine-induced constriction responses were seen in the existence and absence of test extracts in Krebs solution at concentrations that varied from 2.5 to 25 g/ml. The extent to which goat trachea that had been constricted with histamine relaxed in the presence of test extracts was investigated [25-26].

RESULT AND DISCUSSION

The goal of this investigation was to examine the anti-asthmatic activity of various Calotropis gigantea leaf extracts.

Mast Cell Degranulation

Table 1: Effect of Leaves test extracts on mast cell Degranulation

Treatments	Dosage (i.p.) mg/kg	Number of Degranulated Mast Cells (Mean ± SEM)	% Protection of mast cells
Control (1% Tween-80)	5 ml/kg	72.43±1.54**	-
PECGL	100	29.52±1.25**	39.42**
	150	30.31±1.32**	31.54**
CCGL	100	63.67±1.53	20.43
	150	66.32±1.79	21.62
EECGL	100	62.43±1.63	19.44
	150	68.13±1.02	18.34
AECGL	100	64.72±1.06	21.03
	150	61.05±1.32	25.53
Sodium chromoglycate	50	26.73±1.43**	61.59**

n = six in each group. **P<0.05 significant compared with control group

This extract significantly inhibited mast cell degranulation compared to control group [Table 1].

Mast cells are considered to play a role in the emergence of asthma, an inflammatory disease [39]. Histamine, leukotrienes, & prostaglandins are some of the mediators released by degranulating mast cells that contribute to type-I allergies in asthma [40–42]. Mast cells are in charge of producing and secreting a variety of cytokines, such as interleukin (IL)-4, IL-5, & IL-13, which control the generation of IgE & the progression of eosinophilic inflammation [43]. Basic FGF-2, one of the profibrogenic cytokines that mast cells make and secrete, is involved in the pathophysiology of asthma.

Mast cell degranulation was highest in the 1% tween-80-treated control group of mice (72.43±1.54) at a dosage of 5 ml/kg body weight. Nevertheless, following intraperitoneal delivery of sodium chromoglycate, a widely used medication, mast cell degranulation was inhibited by 26.73 ± 1.43 percentage points in comparison to the placebo group.

Mast cell degranulation was decreased by 69.52±1.25 and 67.31±1.33 after intraperitoneal injection of PECGL at dosages of 100 & 150 mg/kg, respectively (P<0.05). Table 5 & Figure 5 illustrate how test extracts affected degranulated mast cells.

Passive Cutaneous Anaphylaxis

Table 2: Effect of leaves test extracts on passive cutaneous anaphylaxis

Treatments	Dosage (i.p.)	Area of blue dye leakage (mm^2) (Mean ± SEM)	% Inhibition
Control (1% Tween-80)	5 ml/kg	46.32±1.56**	-
PECGL	100	15.03±1.24**	67.73
	150	17.93±1.39**	68.17
CCGL	100	33.63±1.73	50.53
	150	34.74±1.83	52.32
EECGL	100	22.74±1.02	66.27
	150	26.74±0.4	64.52
AECGL	100	28.03±1.64	57.56
	150	30.16±1.43	52.57
Sodium chromoglycate	50	7.38±0.152 **	87.42

n = six in each group. **P<0.05 significant compared with control group

This extract significantly inhibited passive cutaneous anaphylaxis compared to control group [Table 2]. Histamine & pro-inflammatory cytokines are produced during an anaphylactic reaction, a potentially lethal condition [44]. A passive cutaneous anaphylaxis reaction can be triggered by a number of substances, including egg albumin & anti-IgE.

Capillary dilatation, which permits blood fluids to leak out into the skin's intercellular spaces, is the cause of passive cutaneous anaphylaxis, which shows up as a blue patch. When a specific IgE receptor (FcεRI) aggregates on the surface of mast cells in response to a matching antigen, passive cutaneous anaphylaxis results [45]. This release of mediators increases vascular permeability and causes dye leakage [46].

The area of blue dye leakage, which peaked at 46.32±1.56 mm2 in the PCA control group administered 1% tween-80 at a dosage of 5 ml/kg body weight, was considerably ($P<0.05$) reduced by intraperitoneal administration of sodium chromoglycate at a dosage of 50 mg/kg body weight.

After intraperitoneal injection of PECGL at dosages of 100 & 150 mg/kg in comparison to the control group, the area of blue dye leakage was significantly ($P<0.05$) reduced (Table 2).

Carrageenan Induced Paw Edema

Table 3: Effect of leaves test extracts on carrageenan induced paw edema

Treatments	Dosage (i.p)	Paw volume (ml) Mean ± SEM			% Inhibition of paw edema		
		1 hr	2hr	3hr	1 hr	2hr	3hr
Control (1% Tween-80)		**0.54±0.01****	**0.63±0.02****	**0.64±0.04****	**-**	**-**	**-**
PECGL	100	0.25±0.03**	0.34±0.02**	0.35±0.04**	21.84	35.64	36.26
	150	0.26±0.01**	0.36±0.01**	0.37±0.02**	22.84	27.54	32.82
CCGL	100	0.42±0.02	0.48±0.01	0.58±0.01	33.68	36.78	38.85
	150	0.43±0.01	0.51±0.01	0.61±0.01	32.03	37.45	36.62
EECGL	100	0.39±0.42	0.41±0.03	0.52±0.04	25.46	27.46	39.21
	150	0.46±0.40	0.53±0.04	0.54±0.05	36.48	38.43	39.72
AECGL	100	0.41±0.08	0.47±0.01	0.45±0.01	30.84	33.36	27.57
	150	0.45±0.05	0.49±0.01	0.48±0.02	31.53	26.63	28.72
Sodium chromoglycate	50	0.22±0.02**	0.32±0.03**	0.31±0.02**	18.43	27.54	20.54

n = six in each group. **P<0.05 significant compared with control group

This extract significantly inhibited carrageenan induced paw edema compared to other extracts [Table 3]. The development of asthma is significantly influenced by airway inflammation. The primary goal of treating asthma is to lessen or stop the inflammatory response that causes airway remodeling, temporary obstruction of the airways, and bronchial hyperresponsiveness. A precise therapy target has, regrettably, not yet been found due to the complexity of the condition. It will be possible to develop more logical medications for the treatment of the condition by aiming to recognize the functions of inflammatory cellular components in asthma. During the initial stage of carrageenan-induced paw edema, mast cells release inflammatory mediators associated with asthma, including as histamine & serotonin [47, 48]. Rats with carrageenan-induced paw edema received dosages of 100 & 150 mg/kg of test extracts intraperitoneally. After giving carrageenan injections to rats, scientists used a plethismometer to measure the edema in their paws after 1, 2 & 3 hours. Maximum paw edema swelling in the control group was 0.54±0.01, 0.63±0.02, and 0.64±0.04 at 1, 2 & 3 hrs after carrageenan injection, respectively. While rat paw edema at 1, 2 & 3 hrs after carrageenan injection was significantly (P0.05) decreased by dexamethasone therapy at 50 mg/kg body weight, the numbers were 0.22±0.02, 0.32±0.03, and 0.31±0.02, correspondingly.

Compared to the control group, PECGL-treated rats had significantly less paw edema 1, 2 & 3 hours after carrageenan injection when given dosages of 100 & 150 mg/kg, body weight. But at the end of 1, 2, and 3 h following carrageenan treatment, PECGL decreased paw volume by 0.25±0.03, 0.34±0.02, and 0.35±0.04 at a dosage of 100 mg/kg, body weight, and by 0.15±0.01, 0.27±0.01, and 0.21±0.02 at a dosage of 150 mg/kg. The initial stage of carrageenan-induced paw edema is marked by the production of histamine, serotonin & other proinflammatory mediators liable for asthma [47, 48].

At 1, 2 & 3 hrs after receiving a carrageenan injection, control rats displayed the highest increase in paw edema swelling, with values of 0.54±0.01, 0.63±0.02, & 0.64±0.04. At 1, 2, & 3 hrs after the carrageenan injection, the impact of dexamethasone at 50 mg/kg on the rat paw edoema were statistically significant ($P<0.05$) for declines of 0.22±0.03, 0.38±0.03, & 0.31±0.02, correspondingly, in comparison to the control group. In this experimental work, 100 mg/kg & 150 mg/kg of PECGL demonstrate statistical significance. 0.25±0.03, 0.34±0.02, 0.29±0.04 and 0.15±0.01, 0.27±0.01, 0.21±0.02 were measured at 1, 2 & 3 h, as indicated in table 3.

Effect of Test Extracts on Goat Tracheal Chain

Table 4: Effect of leaves test extracts on goat tracheal chain

SN	Conc. of Histamine (µg/ml)	Conc. of extracts (µg/ml)	Height of response(mm) Mean ± SEM				% Relaxation of goat trachea			
			PECGL	CCGL	EECGL	AECGL	PECGL	CCGL	EECGL	AECGL
	0.5	-	36.64 ± 1.37	30.83±1.74	38.17±1.84	31.667±1.64	-	-	-	-
	0.5	2.5	34.75±0.96	27.34±0.58	36.43±0.64	29.64±0.75	1.94	17.54	1.37	12.64
	0.5	5.0	20-.62±0.83	23.65±0.57	24.14±0.43	22.54±0.58	31.83	9.69	25.00	29.18
	0.5	10.0	18.64±0.45	21.86±0.75	19.75±0.66	21.48±0.49	41.56	30.65	40.04	30.04
	0.5	20.0	16.75±0.94	18.54±0.74	15.85 0.83	18.75±0.54	48.74	41.65	43.76	41.17
	0.5	25.0	15.64±1.54 **	16.86±0.65 **	12.33± 0.88 **	16.96±0.43 **	52.65	47.97	60.22	48.72
	0.5	-	27.86±0.77	30.75±0.55	29.49±0.53	30.84±0.88	-	-	-	-

****P<0.05 significant compared with control group**

This extract significantly inhibited goat tracheal chain compared to control group [Table 4].

In the current investigation, it was discovered that all test extracts at a concentration of 25g/ml significantly (P<0.05) relaxed the histamine-precontracted goat trachea. Histamine-contracted goat trachea exhibited dosage-dependent relaxations in response to test extracts.

At a concentration of 25 g/ml, the % relaxations of histamine-induced goat trachea by PECGL, CCGL, EECGL, and AECGL were 52.65, 47.97, 60.22, and 48.72 correspondingly. In this experiment, PECGL was reported to have greater relaxing effects on histamine-induced goat trachea than other test extracts.

CONCLUSION

Steroids, also known as glucocorticoids, are the classes of medication that are utilised the most frequently in the management and treatment of persistent asthmatic disorders. Calotropis gigantea is a plant that has a great deal of untapped potential and can be helpful in treating a wide variety of ailments. Even though Calotropis gigantea has a number of potential uses in medicine, there is an urgent requirement to investigate its therapeutic potential on a molecular level with the assistance of a number of different biotechnological instruments and methods. According to the findings of this study, leaves of CG possesses an anti-asthmatic action, which raises the possibility that it could one day be used as a viable medicinal medication in the treatment of asthma.

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