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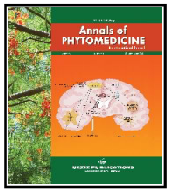

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Antiallergic activity of leaves of *Hibiscus mutabilis* L. in mast cell mediated allergy model

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Abstract

Mast cell-mediated allergic reactions are involved in numerous allergy disorders, including asthma, sinusitis and allergic rhinitis. When mast cells are stimulated, they degranulate and releasing various mediators like inflammatory cytokines and histamines. In this study, we evaluate the effect of ethanolic extract of *Hibiscus mutabilis* L. on a mast cell-mediated allergy models. The protective efficacy of an ethanolic extract of *H. mutabilis* against compound 48/80 induced degranulation of mast cell was carried out. Compound 48/80 induced histamine release from blood along with nitric oxide levels of rat peritoneal fluid, serum and Broncho alveolar fluid were calculated. The ethanolic extract of *H. mutabilis* showed inhibitory effects on mast cell degranulation and further, it showed significant protection against histamine release from blood along with nitric oxide levels of serum, Broncho alveolar fluid and rat peritoneal fluid was activated by compound 48/80. Hence, our report showed that an ethanolic extract of leaves of *H. mutabilis* inhibits mast cell-derived allergic reactions.

1. Introduction

Allergic diseases, which include allergic asthma, drug allergy, food allergy, allergic rhinitis, allergic atopic eczema/dermatitis syndrome, *etc*., are a collection of widespread conditions thought to be mediated by immunoglobulin (Ig) E. These illnesses affect the people of all ages in nations around the globe. Over the past few years, allergies have become more common. It is currently one of the major illness of the twenty-first century and affects between 30 to 40% of the global population. Allergens are environmental antigens that trigger allergic reactions by activating the immune system. The majority of allergens reacting with IgE and IgG antibody are proteins, frequently with carbohydrate side chains, though they can also be pure carbohydrates or other low molecular weight compounds (Daya Chothani and Patel, 2020). Epithelial and mucosal tissues all across the body contain mast cells. Mast cells can be seen in the thoracic and peritoneal cavities of rodents (Da Silva *et al*., 2014; Prasad Konduri *et al*., 2022). Mast cells are important players in allergic reactions, and their activation may be all that is required to cause tissue edema and microvascular leakage to develop quickly in sensitized subjects exposed to allergens. Histamine, proteoglycans, neutral proteinases, prostaglandin D2, leukotriene C4, and some cytokines are among the powerful mediators of allergic inflammation that are mostly found in mast cells (Xie and He, 2005). Histamine and inflammatory mediators like proteases, prostaglandins and various pro-inflammatory and chemotactic cytokines, are released during the process of degranulation, which is triggered by mast cell activation (Kalesnikoff and Galli, 2008). Eosinophils and lymphocytes, among other cells, enter the body and become activated in response to allergic reactions (Metcalfe *et al*., 1997). Stimulants that are not immunologicals such as basic chemicals, neuropeptides, complement elements, and specific medications can also cause mast cell degranulation (Oskeritizian *et al*., 2005). Polymers of basic amino acids and compound 48/80 are two of the most effective mast cell stimulators that cause degranulation (Ennis *et al*., 1980). Many antiallergic medications have been shown to inhibit histamine release by directly modifying the ion-gating mechanism, preventing calcium from entering the cytosol from the outside environment (Foreman *et al*., 1977).

The World Health Organization (WHO) has acknowledged herbal medicine as a crucial component of India and China's primary healthcare systems. India, which is rightfully referred to as the "Botanical garden of the Globe," is possibly the largest producer of medicinal plants in the entire globe. There are few economically significant medicinal herbs that are not harvested or grown in this nation. Herbal medicines have been used in some capacity by indigenous medical systems including Ayurveda, Siddha, and Unani for thousands of years. India has made significant advancements in process technology, agro technology, standardization, quality control, research and development since gaining independence in 1947. Several herbs have been used for the treatment and prevention of asthma since the dawn of time, but systematic investigations that pinpoint every potential mechanism of action of each and every herbal antiasthmatic medication are still absent (Urvisha *et al*., 2015). Herbal medicines have a number of benefits, including minimal or no adverse effects, low cost, and the ability to be used for long period of time (Malik *et al*., 2020; Sri Bharathi *et al*., 2021).

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H. mutabilis, also known as Cotton Rosemallow or Changeable Rose, is a big, bushy shrub in the Malvaceae family (The Wealth of India, 2001; Kirtikar and Vasu, 1991). It is a Chinese traditional medicine frequently utilised to treat swellings and skin diseases (Valkenburg, and Bunyapraphatsara 2001). The plant contains rutin, quercetin, sterol-glucosides, lupinus, luteus, gibberellin and cyanidin (Duke and Ayensu, 1985). The presence of cyanidin, anthocyanidin found in flowers, causes the pink basal blotch on the petals of *H. mutabilis* (Fukui *et al*., 1971). Its leaves, in particular, are utilised in medicine as an antidote, anodyne, refrigerant and expectorant, Rutin (quercetin-3-rutinoside) is a major bioactive flavonoid glycoside found in the leaves of this medicinal plant (Yao *et al*., 2003). Rutin efficiently inhibited the expression of inflammatory mediators and controlled NF-B signaling, demonstrating its efficacy as a potential treatment for allergic asthma (Hong-yan *et al.,* 2017).The plant is reported to possess hepatoprotective activity, anti-inflammatory, antimitotic activity, antifilarial activity, anticancer, analgesic activity and CNS depressant activity (Jiangning *et al*., 2014; Raut *et al*., 2014; Subhash *et al*., 2014; Prasanta *et al*., 2012; Dipak and Thange Trupti, 2022; Ghogare *et al*., 2007; Bhalke *et al*., 2008). Regarding the *H. mutabilis's* ayurvedic usage and documented activity, it is proposed to examine its antiallergic potential using several experimental models.

2. Materials and Methods

2.1 Chemicals

Griess reagent, toluidine blue, RPMI-1640 (Ponmani and Co, Coimbatore), Compound 48/80, (Sigma-Aldrich), and all other reagents and chemicals utilised were analytical grade.

2.2 Plant material

2.2.1 Collection of plant material and authentication

In the present study, *H. mutabilis* was obtained from the outskirts of Coorg, Karnataka, India during the month of October 2022. The plant was identified and authenticated by Agricultural University, Coimbatore, India (BSI/SRC/5/23/2022/Tech/523).

2.2.2 Preparation of plant extract

H. mutabilis leaves were collected, cleaned, and dried in the shade to remove extra moisture. The dried powder of leaves was extracted in Soxhlet with a 70:30 ethanol: water hydroalcoholic mixture in a continuous heat extraction in a Soxhlet apparatus. The solvent was collected using a distillation assembly after the extraction, and the extracts were concentrated. For the experiment, the extracts were kept in an airtight container.

2.3 Preliminary phytochemical screening

The chemical substance such as alkaloids, flavonoids, terpeniods, tannins and aldehydes in ethanolic extract was determined using the conventional process and chemical tests (Treas and Evans, 1989).

2.4 Animals

Albino Wistar rats (200-250 g) were obtained from the Nandha College of Pharmacy's animal house in Erode, Tamil Nadu. The Animals were kept in regular settings (25°C, 50-55% relative humidity) for 12 h of darkness and 12 h of night, respectively. Food and water were easily accessible to the animals. According to CPCSEA guidelines, the study was only carried out after receiving approval from the Institutional Animal Ethical Committee (Proposal No: NCP/IAEC/2022-23/02).

2.5 Acute toxicity study

The OECD 423 guidelines were followed for conducting the acute toxicity investigation. Female Swiss Albino mice (18-20 g) received a single dosage of extract at 2000 mg/kg, and they were watched for 14 days. After 14 days, there were no evidence of toxicity or death, indicating that 2000 mg/kg of the extracts were safe for future testing (Jonsson *et al*., 2013). Among these, 400 mg/kg and 200 mg/kg, were chosen for the current investigation.

2.6 Mast cell stabilizing activity

The animals (Albino Wistar rats) were separated into five groups (n=6). Five days before the mast cell collection, rats were given daily doses of Ketotifen (1 mg/kg, p.o) and ethanolic extracts of *H. mutabilis* (200 and 400 mg/kg). The animals were treated with 10 ml of sterile saline after being administered with anesthetic ether to make it unconscious. The peritoneal fluid was removed after a light massage and placed in a test tube with RPMI-1640 (pH 7.2-7.4). Mast cells are centrifuged at low speed (400-500 rpm) in three times, removing the supernatant after each wash and adding the pellet of mast cells to the medium. Compound 48/80 (1µg/ml) was incubated with mast cells from the control and treatment groups at 37°C for ten minutes. Toluidine blue (0.1%) is utilised to stain the mast cells. After incubation, using a high-power microscope, the percentage of defence against degranulation was measured (45x). The percentage of protection against degranulations was determined (Singh *et al*., 1998; Chandrashekhar *et al*., 2011).

2.7 Determination of blood histamine release

Rats were given daily treatments with Ketotifen at doses of 1 mg/kg, p.o and ethanolic extracts of *H. mutabilis* at doses of 400 and 200 mg/kg to five days before blood was drawn. The blood was drawn from the rats by cardiac punctured after they had been given anesthetic ether. The blood samples were then treated with compound 48/80 (1 µg/ml), and perchloric acid was added to promote cell destruction, which resulted in histamine production, before being centrifuged at 400 rpm for 5 min at 4°C. By using the o-phthalaldehyde spectrofluorimetric technique, the histamine content was identified (Shore *et al*., 1959).

2.8 Determination of serum nitric oxide level

Rats were administered the standard medication (Ketotifen) at a dose of 1 mg/kg and the *H. mutabilis* ethanolic extract at doses of 400 and 200 mg/kg daily for 5 days before to the blood collection. The rats were given anaesthetic ether anaesthesia before having blood drawn from their cardiac punctured, centrifuged at 500 rpm for 5 min, and then incubated for 15 min at 37°C with an equal volume of serum and Griess reagent (pH 2). The control and extract-treated groups had been incubated with compound 48/80 (1 µg/ml), the normal group's sample was incubated with saline solution, and the absorbance at 546 nm was measured, at the end of the incubation period (Mc cauley *et al*., 2005; Ganapathy *et al*., 2010).

2.9 Determination of rat peritoneal fluid nitric oxide

As mentioned before (Section 2.6), the peritoneal fluid was collected during the mast cell stabilization activity. 40 µl of glycine buffer,

Griess reagent (pH 2) and an equal volume of peritoneal fluid were added. After 15 min of incubation at 37°C, the mixture was centrifuged, and the supernatant was used to calculate the absorbance. Compound 48/80 (1 µg/ml) was incubated with the control and test groups for 15 min at 37°C, and the absorbance was then measured at 546 nm. The sample from the normal group was incubated with saline solution (Mc cauley *et al*., 2005).

2.10 Broncho alveolar (BAL) fluid nitric oxide level

The BAL fluid was removed, centrifuged, and then equal amount of an acidic Griess reagent (pH 2) was added. The control and treated groups were each incubated with compound 48/80 (1 µg/ml), and 40 µl of glycine buffer for 15 min at 37°C. The absorbance was then measured at 546 nm (Mc cauley *et al*., 2005).

2.11 Statistical analysis

All of the data is presented as mean ± SEM. The significance of the mean differences between control and treated animals for various parameters was evaluated using one-way analysis of variance (ANOVA). The threshold for significance is $p<0.05$.

3. Results

3.1 Preliminary phytochemical screening

Preliminary phytochemical study of leaves extract of *H. mutabilis* proved the presence of flavonoids, terpeniods, alkaloids, tannins, and aldehydes through phytochemical analysis.

3.2 Effect of ethanolic extract of *H. mutabilis* on degranulation of mast cell

That was considerable ($p<0.001$) defence from degranulation of mast cell caused by compound 48/80. The standard (Ketotifen) group demonstrated 68.12% protection, while the treated groups at doses of 200 and 400 mg/kg showed 45.78% and 59.34% protection from degranulation of mast cell, respectively. Figure 1 summarizes the findings.

3.3 Effect of *H. mutabilis* extract on compound 48/80 induced on blood histamine release

When compared to the normal group, the control group rats had significantly ($p<0.001$) higher histamine release in the blood. Contrarily, treatment with an ethanolic extract of *H. mutabilis* significantly ($p<0.05$ to $p<0.001$) decreased the blood's histamine levels as compared to the control group. Table 2 summarizes the outcomes.

3.4 Effect of *H. mutabilis* extract on compound 48/80 induced serum, BAL fluid, and peritoneal fluid nitric oxide levels

When compared to the normal group, the control group had significantly ($p<0.001$) higher release of nitric oxide from serum, BAL fluid and peritoneal fluid. When compared to the control group, ketotifen and test group which is treated with ethanolic extract of *H. mutabilis* resulted in significantly lower serum level ($p<0.05$ to $p<0.001$), Broncho alveolar fluid ($p<0.001$) and peritoneal fluid nitric oxide ($p<0.01$ to $p<0.001$) and Table 3 summarizes the findings.

Table 1: Effect of ethanolic extract of *H. mutabilis* on mast cell degranulation

Treatment	Dose	% Protection from mast cell degranulation
Normal control (normal saline)	1 ml/kg	78.67 ± 2.342
Negative control	-	37.45 ± 2.213
Standard (Ketotifen)	1 mg/kg	68.12 ± 1.453***
EHM-1	200 mg/kg	45.78 ± 2.231**
EHM-2	400 mg/kg	59.34 ± 1.75***

values are expressed as a mean ± SEM, n=5, $p<0.001$ as compared with normal group (student's t -test). *$p<0.05$, **$p<0.01$, ***$p<0.001$ as compared to the control group. One way analysis of variance (ANOVA) method. EHM- ethanolic extract of *H. mutabilis*.

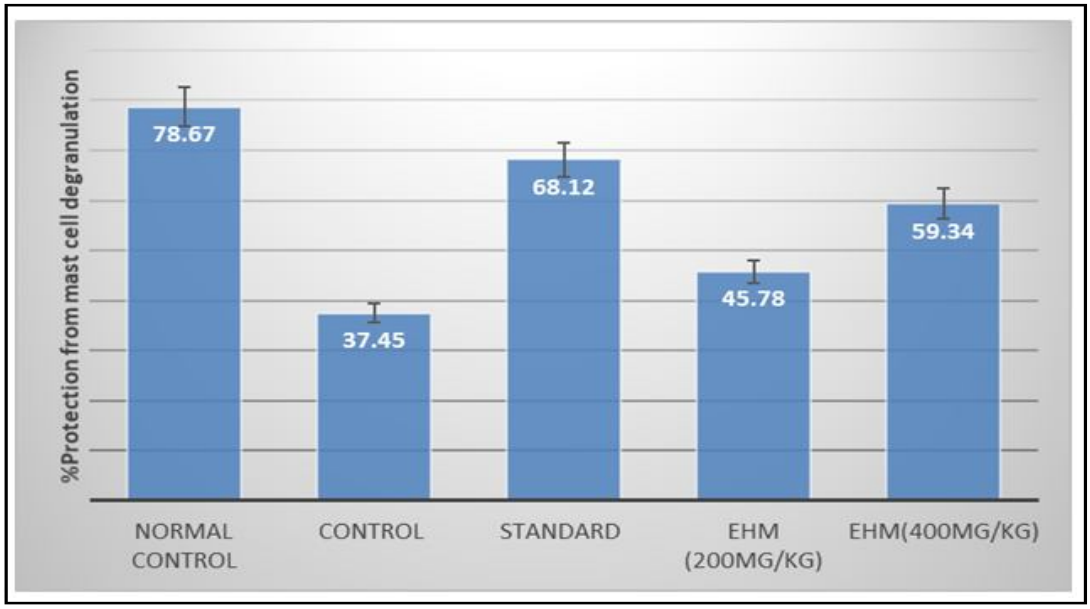

Figure 1: Effect of ethanolic extract of *H.mutabilis* on percentage protection from mast cell degranulation.

Table 2: Effect of *H. mutabilis* extract on compound 48/80 induced blood histamine release

Treatment	Dose	Blood histamine content (µg/ml)
Normal control (normal saline)	1 ml/kg	0.031 ± 0.06
Negative control	—-	0.140 ± 0.051
Standard (Ketotifen)	1 mg/kg	0.044 ± 0.012***
EHM-1	200 mg/kg	0.082 ± 0.043**
EHM-2	400 mg/kg	0.051 ± 0.018***

values are expressed as a mean ± SEM, n=5, $p<0.001$ as compared with normal group (student's t -test). *$p<0.05$, ** $p<0.01$, ***$p<0.001$ as compared to the control group. One way analysis of variance (ANOVA) method. EHM- ethanolic extract of *H. mutabilis.*

Table 3: Effect of *H. mutabilis* extract on compound 48/80 induced serum, rat peritoneal fluid and broncho alveolar fluid nitric oxide levels

Treatment	Dose	Serum nitric oxide	BAL nitric oxide	RPF nitric oxide
Normal control (normal saline)	1 ml/kg	4.102 ± 0.1607	9.751 ± 0.652	2.182 ± 0.172
Negative control	-	9.352 ± 1.056	14.92 ± 2.436	4.733 ± 0.423
Standard (Ketotifen)	1 mg/kg	3.820 ± 0.142***	5.336 ± 0.324***	2.218 ± 0.136***
EHM-1	200 mg/kg	5.535 ± 0.543*	8.318 ± 1.122*	3.233 ± 0.283**
EHM-2	400 mg/kg	4.138 ± 0.323***	5.834 ± 0.765***	2.458 ± 0.203***

values are expressed as a mean ± SEM, n=5, $p<0.001$ as compared with normal group (student's t -test). *$p<0.05$, ** $p<0.01$, ***$p<0.001$ as compared to the control group. One way analysis of variance (ANOVA) method. EHM-ethanolic extract of *H. mutabilis*.

4. Discussion

H. mutabilis is a Chinese traditional medicine frequently utilized to treat swellings and skin infections (Valkenburg and Bunyapraphatsara, 2001). In China, traditional Chinese medicine has a long history of clinical use spanning thousands of years and has grown in importance in the maintenance of health and the treatment of disease (Lalitha *et al*., 2022). The therapeutic applications and alleged health benefits of *H. mutabilis* are employed in traditional cultures, although there is minimal scientific data to back up these statements. The current research has proven that *H. mutabilis* has potent antiallergic capabilities.

H. mutabilis prevented a systemic allergic response caused by compound 48/80. With just five days of therapy, we saw a considerable reduction in the discharge of allergy mediator's levels in blood histamine, rat peritoneal, serum, and broncho alveolar fluid as well as a significant defence against the degranulation of mast cell. Mast cells, with the release of various mediators and cytokines, play a significant part in the case of severe allergic reactions. Mast cells play a main role in the case of severe allergic reactions by releasing a variety of mediators and cytokines. Due to its capacity to trigger mast cell degranulation, the synthetic chemical compound 48/80 has also been utilised as a direct and practical reagent to investigate the mechanism of anaphylaxis (Ennis *et al*., 1980). Several studies have demonstrated that compound 48/80 stimulation starts the signal transduction pathway's activation, which causes histamine to be released (Amir and English, 1991).

H. mutabilis was shown flavonoids, terpeniods, tannins, alkaloids and aldehydes through phytochemical analysis. Rutin was said to have antihistaminic, antiallergic, and mast cell stabilizing properties (Hong-yan *et al.,* 2017). Many flavonoids reported to have smooth muscle relaxing and bronchodilator properties (Hazekamp *et al*., 2001). Flavonoids are a broad class of naturally occurring aromatic chemicals that are found in the majority of plants.(Sri Bhuvaneswari *et al*., 2022). Flavonoids from *H. mutabilis*, such as quercetin, rutin and luteolin, have been shown to decrease basophil histamine release and neutrophil beta glucuronidase production, which results in antiallergic action (Pathak *et al.,* 1991). Moreover, these flavonoids prevented the release of histamine brought on by compound 48/80 (Bellant, 1971). Mast cells are important part in a number of physiological processes including homostasis and disease. The enzyme nitric oxide synthase (NOS) produces nitric oxide, a diatomic radical that is hazardous to living things. Various mast cell processes, including as degranulation, adhesion, leukotriene synthesis and early mediator release are influenced by NO (Ganapathy *et al*., 2010). The inducible version of NOS-2 produces NO at relatively sustained and high levels during allergic immunological and inflammatory situations (Coleman, 2002) Nitric oxide may produce free radicals, causing tissue damage, lymphocyte infiltration, and inflammatory responses. Levels of nitric oxide in blood, rat peritoneal fluids, and broncho alveolar fluids were significantly ($p<0.05$ to $p<0.001$) inhibited by an ethanolic extract of *H. mutabilis.*

5. Conclusion

Rutin (quercetin-3-rutinoside) is a major bioactive flavonoid glycoside found in the leaves of this medicinal plant. Rutin efficiently inhibited the expression of inflammatory mediators and controlled NF-B signaling, demonstrating its efficacy as a potential treatment for allergic asthma. Hence, flavonoids may be responsible for antiallergic properties. The ethanolic extract of leaves of *H. mutabilis* exhibits antiallergic properties and also potential to stabilize mast cells. These findings may be useful in treatment of allergic condition, although further study is required to specify the mechanism of action, bioactivity determination, *etc*., which contribute antiallergic activity.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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