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PRECLINICAL SCREENING MODELS FOR ANTIHISTAMINIC ACTIVITY: AN OVERVIEW

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ABSTRACT: Antihistamines appear to be the mainstay in allergic reaction treatment. Allergy is rooted in the primary rejection reaction of parasites in which histamine derived from mast cells generates an immediate aggressive environment, and eosinophils are recruited for killing. Antihistamines are medicinal products used to treat allergic rhinitis, conjunctivitis, urticaria, cold and flu, tachyphylaxis, motion sickness, and acute allergic reactions. A vast number of animals can be used for this activity, with rodents (inbred mice and rats) and guinea-pigs being the most common models, which are easy to maintain and relatively economical compared to other available models. Therefore, animal models used in asthma are greatly useful in antihistaminic studies because they promise new insights into human allergic symptoms. The available *in-vivo* and *in-vitro* models are used to investigate the mechanism of action of drugs with antihistaminic activity. This work aims to bring all the different *in-vivo* animal models and *in-vitro* techniques together for conducting antihistaminic activity research.

INTRODUCTION: Asthma is a widespread and persistent airway inflammatory disorder [1]. It is a disorder in which bronchial tubes lead to coughing, tightness of the chest, and difficulty breathing. Histamine is synthesized by the L-histidine decarboxylase enzyme from L-histidine and stored in granules of mast cells and basophils [1]. Histamine play an important role in autoimmune pathology and its mechanism, as well as in autoimmune allergic, malignant, and inflammatory disease pathogenesis, such as chronic urticarial, atopic dermatitis, auto-immune myocardium, multiple sclerosis, experi-mental autoimmune encephalomyelitis, allergic rhinitis, acute anaphylaxis, asthma, atherosclerosis, multiple sclerosis, and malignant melanoma respectively [2, 3]. Histamine has a significant role in allergic ailments such as urticaria and rhinitis [4]. Antihistaminic drugs can control histamine release and have the ability to prevent the degranulation of mast cells. The H1-receptor antagonist such as hydroxyzine, promethazine, diphenhydramine, *etc*. is believed to be used in treating asthma [4]. Antihistaminic drugs are bound on the histamine receptor present on the cell surface. There are 4 types of receptors present in every cell such as H1, H2, H3, and H4. Drugs classified as antihistamines in the first generation are also referred to as classical antihistamines.

Histamine contributes to bronchial wall oedema due to vascular permeability, encouraging bronchial smooth muscle contraction mediated by H1 receptor and stimulating the parasympathetic system [4]. A noteworthy helpful class of medications used to treat various hypersensitive conditions such as rhinitis, urticaria, roughage fever and even asthma is structured by antihistamines (H1) [5, 6]. Histamine H1 receptor antagonists (antihistamines) have become one of the most widely used drugs for unfavorably susceptible issues since their disclosure and early improvement

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during the 1940s [7]. More established original antihistamines show a highly restrictive fondness for H1 receptors. Still, a large number of these drugs show partiality restriction for various cell receptor classes, such as muscarinic cholinergic subtypes (M1M5) [8]. As moderately more precise histamine H1 receptor antagonist than the initial operators, second-age antihistamines were developed more up to this stage, with some degree of restricting midway interfered effects, such as sedation. Nonetheless, as with histamine H1 receptors in the cerebrum, some of the fresher antihistamines are certainly officially ideal for muscarinic receptors [9]. Another characteristic of the more developed antihistamines is that they enter the mind and bind to central nervous system cell receptors, causing sedation and impaired psychomotor execution. Old-style antihistamines are related to the symptoms of localized infections [10].

Ayurveda has reported several drugs from plant sources used to treat bronchial asthma, autoimmune diseases, and allergic disorders. Another characteristic of the more developed antihistamines is that they enter the brain and bind to the central nervous system (CNS) cell receptors, causing sedation and impaired psychomotor execution. The antihistamines of the old style are related to signs of localized infection. Histamine is the most important inflammatory mediators; it induces allergic reaction symptoms, most of which include extreme inflammation mediated by H1 histamine [11–13].

Models for Screening of Antihistaminic Activity:

***In-vitro* Techniques /Tissue Model:**

1. Isolated goat trachea chain preparation.
2. Isolated guinea pig trachea chain preparation.
3. Guinea pig ileum tissue preparation.
4. Rat/mice ileum tissue preparation.

***In-vivo* Model / Animal Model:**

1. Histamine-induced bronchoconstriction in guinea pigs/mice/rats.
2. Passive paw anaphylaxis in rats/guinea pig/mice.
3. Milk-induced leukocytosis in mice.
4. Milk-induced eosinophilia in mice.
5. Clonidine-induced catalepsy in mice.
6. Haloperidol-induced catalepsy in mice.

***In-vitro* Techniques /Tissue Model:**

Isolated Goat Trachea Chain Preparation: Isolated tracheal tissue from the adult goat was acquired shortly after the animals were slaughtered. The trachea has been cut into separate parts and joined to form a chain sequentially, and the trachea fragments were collected and suspended in a bath containing Kreb's solution that was aerated and held at 37±0.5 °C continuously. One end of the tracheal muscle was attached to an S-shaped aerator and the other attached to isotonic frontal writing lever to Kymograph sheet on a revolving drum. The tissue was allowed to equilibrate in the organ bath for 45 min under a load of 0.5 r. A dose-response curve for histamine in-plane Kreb's solution and in a solution containing drug extract was recorded at variant molar concentrations. For recording the DRC of histamine in the absence and presence of drug extract, a graph of the percentage of the maximal contractile response on the ordinate and negative logarithm of different molar concentrations of histamine on abscissa was plotted [14–20].

Isolated Guinea Pig Trachea Chain Preparation: Isolated tracheal tissue from the guinea pig was acquired shortly after the animals were slaughtered. The trachea has been cut into separate parts and joined to form a chain sequentially. The trachea fragments were collected and suspended in a bath containing Kreb's solution that was aerated and held at 37±0.5 °C continuously. One end of the tracheal muscle was attached to an S-shaped aerator and the other attached to isotonic frontal writing lever to Kymograph sheet on a revolving drum. The tissue was allowed to equilibrate in an organ bath for 45 min under a load of 0.5r. A dose-response curve for histamine in-plane kerb’s solution and in a solution containing drug extract was recorded at variant molar concentrations. For recording the DRC of histamine in the absence and presence of drug extract, a graph of the percentage of the maximal contractile response on the ordinate and negative

logarithm of different molar concentrations of histamine on abscissa was plotted [21–23].

Guinea Pig / Rabbit Ileum Tissue Preparation: Overnight fasted guinea pigs of either sex weighing 400-600 r were sacrificed using stunned by head-blow and ileum was mounted in an organ bath containing Tyrode solution, which was continuously aerated and maintained at 37 ± 0.5 °C. The ileal segment was attached to the transducer (FDT10-A) and the other attached to an isotonic frontal writing lever to rotating smoked drum. The resting tension was adjusted to a load of 0.5r. The 30 min period was given to stabilize the tissue, and a drug tissue contact time of 1 min was maintained. The dose-response curve (DRC) of histamine was retaken after adding different extract doses. The percentage of maximum contractile response on the ordinate and negative logarithm of histamine molar abscissa concentration was graphed. The dose-response curve of histamine should be reported with and without drug extract [24, 25, 26, 27].

Rat / Mice Ileum Tissue Preparation: The rat/mice that were fasted overnight were sacrificed. The ileum was put in an organ bath with Tyrode solution, which was continuously aerated and maintained at 37±0.5 °C. The ileal segment was attached to the transducer (FDT10-A) and the other attached to an isotonic frontal writing lever to rotate the smoked drum. The resting tension was adjusted to a load of 0.5r. The 30 min time period was given to stabilize the tissue, and a drug tissue contact time of 1 min was maintained. The dose-response curve (DRC) of histamine was retaken after adding different doses of the extract. The percentage of maximum contractile response on the ordinate and negative logarithm of histamine molar abscissa concentration was graphed. The dose-response curve of histamine should be reported with and without drug extract [28, 29, 30, 31].

***In-vivo* Model / Animal Model:**

Histamine-Induced Bronchoconstriction in Guinea Pigs / Mice/Rats: Animals were split into eight groups (n=6), the control group provided distilled water, and a single extract dose was offered to other groups (75, 150, 200, 300, 600, and 1200 mg/kg PO). Chlorpheniramine maleate (2 mg/kg) serves as a positive control. Each animal was pre and post medication treatment and was kept within the histamine chamber and subjected to 0.2% histamine aerosol. The PCT cycle was measured from the time of initiation to the beginning of dyspnea, leading to pre-convulsive dyspnea within a minute. For each dose and positive control, the percentage of protection offered by PCT drugs was determined. By using the formula below, the percentage of protection was determined.

$$\text{Percentage protection} = (1 - T1/T2) \times 100$$

Where T1 = PCT average before test drug administration and T2 = PCT average after test drug administration [25, 1, 32, 33].

Passive Paw Anaphylaxis in Rats / Guinea Pig/ Mice: On days 1, 3, and 5, animals got subcutaneously 100 mcg of egg white. Blood was gathered from the retro-orbital plexus and centrifuged to isolate serum on the 10th day of sensitization. It was entitled to clot the gathered blood, and at 1500 rpm the serum was divided by centrifugation. Animals in eight groups (n=6) were divided. The saline solution got by the control group, and other groups were given a singular concentrate portion of 85 mg/kg, 175 mg/kg, 250 mg/kg, 350 mg/kg, 700 mg/kg, and 1400 mg/kg PO Dexamethasone (0.27 mg/kg PO) was utilized as a standard. Animals were sensitized with serum into the left hind paw before medication therapy. The right hind paw got the same normal saline solution quantity. The animals were challenged with 10 mcg of egg white in 0.1 ml of normal saline solution. 1-h post-administration of the study drug and the paw expansion was assessed using a plethysmometer. The amount of oedema restraint was calculated after 24 h in order to use the below equation [34, 35].

$$\text{Inhibition rate} = [1 - (T/C)]\ 100$$

T – Average relative difference in paw volume (test group). C – Average relative difference in paw volume (control group).

Milk-induced Leukocytosis in Mice: Mice (Swiss Albino) with weight 20-25 gm were split into six categories containing six mice. Blood samples were obtained using pentobarbital sodium (IP), using RO (retro-orbital) vein under sedation. The animals belonging to the group I received orally distilled

water (10 ml/kg). Group II received boiled and cooled milk [4 ml/kg, subcutaneously (SC)].

Group 3 received standard as dexamethasone. Group 4 to group 6 received extract doses in low, moderate, and high doses. Except for the normal control group, all these classes were infused with boiled and cooled milk of a dose 4-ml/kg SC after 1 hr. of drug treatment.

The details of the grouping of animals and injection schedule for this study are given in **Table 1.**

The difference between total leukocyte counts was conducted and calculated in each group before test compound administration and 24 h after milk infusion [36–40].

Milk-induced Eosinophilia in Mice: Mice (Swiss Albino) with weight 20-25 gm were split into six categories containing six mice. Blood samples were obtained using pentobarbital sodium (IP), using RO (retro-orbital) vein under sedation. The animals belonging to the group I received orally distilled water (10 ml/kg). Group II received boiled and cooled milk [4 ml/kg, subcutaneously (SC)]. Group 3 received standard as dexamethasone. Group 4 to group 6 received extract doses in low, moderate, and high doses. Except for the normal control group, all these classes were infused with boiled and cooled milk of a dose 4 ml/kg SC after 1 h. of drug treatment. The details of the grouping of animals and injection schedule for this study are given in **Table 1.** The difference between total eosinophil counts was conducted and calculated in each group before test compound administration and 24 h after milk infusion [39].

TABLE 1: ANIMAL GROUPING FOR MILK-INDUCED LEUKOCYTOSIS AND EOSINOPHILIA STUDY

Group	Test substance	Dose	Albino mice per group
1	Normal saline	10 ml/kg	6
2	Milk	4 ml/kg	6
3	Dexamethasone (Standard) + Milk	mg/kg	6
4	Extract (Low dose) + Milk	mg/kg	6
5	Extract (Medium dose) + Milk	mg/kg	6
6	Extract (High dose) + Milk	mg/kg	6
	Total animals required		36

Clonidine-induced Catalepsy in Mice: Mice (Swiss albino) with weight 20-25 gm were split into five categories containing six mice. The normal control group received the saline; the standard group received chlorpheniramine maleate (10mg/kg IP). The other three groups received a low, medium, and high dose of the drug extract. After 1 h, Clonidine (1 mg/kg SC) was injected to all the groups who had already received the standard saline dose of drug extract. The catalepsy period was determined by using bar test at 0 min, 15 min, 30min, 60min, 90 min, 120min, 150 min, 180 min [34-44]. The details of the grouping of animals and injection schedule for this study are given in **Table 2.**

TABLE 2: ANIMAL GROUPING FOR CLONIDINE-INDUCED CATALEPSY STUDY

Group	Test substance	Dose as required	Albino mice per group
1	Normal saline + Clonidine	1 ml/kg	6
2	Chlorpheniramine maleate (Standard) + Clonidine	10 mg/kg	6
3	Extract (Low dose) + Clonidine	mg/kg	6
4	Extract (Medium dose) + Clonidine	mg/kg	6
5	Extract (High dose) + Clonidine	mg/kg	6
	Total animals required		30

Haloperidol - Induced Catalepsy in Mice: Mice (Swiss albino) with weight 20-25 gm were split into five categories containing six mice. The normal control group received the saline; the standard group received chlorpheniramine maleate (10mg/kg IP). The other three groups received a low, medium, and high dose of the drug extract. After 1 h, haloperidol (1 mg/kg SC) was injected into all the groups who had already received the standard saline dose of drug extract. The catalepsy period was determined by using bar test at 0 min,

15 min, 30min, 60min, 90 min, 120min, 150 min, 180 min [45, 46, 47].

The details of the grouping of animals and injection schedule for this study are given in **Table 3.**

TABLE 3: ANIMAL GROUPING FOR HALOPERIDOL-INDUCED CATALEPSY STUDY

Group	Test substance	Dose as required	Albino mice per group
1	Normal saline + Haloperidol	1 ml/kg	6
2	Chlorpheniramine maleate (Standard) + Haloperidol	10 mg/kg	6
3	Extract (Low dose) + Haloperidol	mg/kg	6
4	Extract (Medium dose) + Haloperidol	mg/kg	6
5	Extract (High dose) + Haloperidol	mg/kg	6
	Total animals required		30

Bar Test Scoring: The bar test was used to calculate catalepsy. In this test, the animal's front paws were alternatively located on the horizontal bar 3 cm above the base and 5 cm parallel to it. It was observed when the mice removed their front paw from the counter.

Step 1: The mice were removed and put on the table from the house cage. If the mice did not move when touched or moved back gently, a value of 0.5 was assigned.

Step 2: The mice's front paws were alternatively put on a 3 cm long bar. A value of 0.5 was applied to the step 1 value for each paw if within 15 sec the mice failed to correct the posture.

Step 3: Alternatively, the front paws of the mice were positioned on a 5 cm long bar; if the mice did not correct the posture within 15 sec, a value of 1 was applied to the value of Step 1 and 2 on each paw.

Formula for the Estimation of Cataleptic Value: Total value = 0.5 + [0.5 × time (in c) of front right paw on 3 cm long bar] + [0.5 × time (in c) of front left paw on 3 cm long bar] + [1 × time (in c) of front right paw on 5 cm long bar] + [1 × time (in c) of front left paw on 5 cm long bar].

Tissue Preparation: The animals were dieted overnight with free exposure to water before 1 day of the commencement of the research. The animals were humanly sacrificed by ether under sedation. Around 1 cm from the ileocaecal junction, surgical removal of a 3 cm section of the ileum was carried out. The transverse tissue sheet had been removed, as illustrated earlier. Nearly 1.5 cm long strips were put in 5 ml of organ water containing 95% O_2 and 5% CO_2 in the Krebs-Henseleit arrangement and kept at 37 °C. With the aid of two tight loops, the tissue was fixed. At one end of the prepared tracheal chain, the s-shaped aerator pipe was connected, and to another end, isotonic frontal writing lever was attached. Before the procedures began, the tissue strips were balanced for 45 min under resting stress of 1 g. The tissue responses, *i.e.*, the dose-response curve of histamine, were traced on kymographic paper.

CONCLUSION: In this review, we have discussed *in-vivo* models and *in-vitro* techniques used in antihistaminic research. These animal models have similar characteristics and features similar to humans. The animal models and in vitro techniques are essential for developing a new drug to treat allergic disorders, asthma, *etc*. Each model is an essential tool for investigating the extract's effect on different elements of histamine-related consequences such as asthma, bronchoconstriction, eosinophilia, and inflammation-related allergic disorders and mechanism of action of drug with antihistaminic activity. More animal models, software, and advanced techniques have to be developed to advance asthma research.

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