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Experimental *in- vivo* animal models for asthma/ allergic asthma: importance and documented parameters- A review

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ABSTRACT

Allergies are related to foods, drugs, synthetic materials, diseases, a person's immunity, and other factors, and they cause major morbidity and socioeconomic consequences. Asthma is among the most widespread respiratory conditions in the world, affecting 6.4 million children in the United States and 350 million individuals globally; within the next 30 years, 400 million individuals are estimated to be affected. The European Union has the greatest mortality rate and the largest yearly costs at 72.2 billion euros. Allergic respiratory disorders can lead to serious, life-threatening illnesses like anaphylaxis. According to epidemiological research, these disorders and their clinical effects are currently affecting people all over the world in all age groups. As a result, people all around the world are looking for new therapies and medications with minimal or no side effects. Therefore, to conduct more research trials, scientists need an *in vivo* animal model and data obtained from previously published study findings. Understanding the clinical features of asthma makes it possible for us to better comprehend the pathophysiology of allergic illnesses in animals, which then enables us to apply some of this knowledge to humans. To achieve the goal of this review study, a literature search was conducted using PubMed ® (US National Library of Medicine, USA), Google Scholar, and Hilary. which is to give evidence-based recommendations for various animal models. The study covered the years 2000 through 2023. To widen the scope of this research area, information on about five animal models were gathered. Here, discusses the use of mice, rats, guinea pigs, dogs, and sheep as asthma animal models in earlier studies, and documented parameters were gathered.

Keywords: Allergy, Animal models, Asthma, Experimental *in- vivo* models, Animal models for AHR.

INTRODUCTION

The prevalence of allergy disorders appears to be rising, allergy are associated with foods, medications, synthetic materials, diseases, a person's immunity, etc.; and they cause significant morbidity and socioeconomic costs. Individualized immunity varies depending on several variables, such as genetic background, age, general health, and prior exposure to pathogens. Individual immunity is greatly influenced by genetic variations. A human leukocyte antigen (HLA) system, which participates in delivering antigens to immune cells, is one of many genes and genetic variants that studies have found to affect immunological responses. Differences in immune system performance and vulnerability to infections are influenced by genetic variation [1]. A person's immune system changes during their lifespan. Infants and elderly individuals are more vulnerable to infections because their immune systems are less effective. Immunosenescence, or the aging of the immune system, is caused by changes in immune cell populations and a fall in reactivity [2]. An individual's immune system can be strongly impacted by their general health, which includes elements like nutrition, physical fitness, and chronic illnesses. A strong immune response is supported by adequate nutrition, regular exercise, and a healthy lifestyle. On the other hand, ailments including chronic illnesses, obesity, and malnutrition can impair immunity, leaving people more prone to infections [3]. Individual immunity is also influenced by environmental factors, immunological memory, and previous exposure [4].

Allergic diseases are a major global health concern. Based on these findings, the epidemic of the twenty-first century has been identified as an allergic disorder [5]. Around 350 million people currently suffer from asthma worldwide, with 6.4 million children in the USA. Asthma is one of the most prevalent respiratory disorders [6] with an anticipated increase to 400 million during the following 30 years. It has the greatest mortality rate and the biggest yearly expenditures in the EU (72.2 billion euros) [7]. Although anaphylaxis and life-compromising conditions are induced by several factors [8], allergic diseases majorly contribute to it [9]. According to data from Europe, anaphylaxis affects between 1.5 and 7.9 people per 100,000 annually, with an estimated 0.3% of the population at risk [10]. Additionally, one in three thousand hospital patients in the US had an anaphylactic reaction [10]. In an Italian investigation from 2004 to 2016, 392 deaths from definite anaphylaxis and 220 deaths from potential

anaphylaxis were recorded. The general rate of mortality for definite anaphylaxis was 0.51 per million per year [11]. Different Asian nations have different asthma prevalence rates. Asthma prevalence among adults was reported to be 2.2% in a study from China, for instance [12]. Asia-Pacific was in the middle of the pack globally for the adolescent group in terms of reported current rhinoconjunctivitis symptoms. However, Hong Kong and Bangkok have some of the highest prevalence rates ever observed. Asia-Pacific, which is the third-highest region globally, has a reasonably high frequency of rhinoconjunctivitis in the age range of 6-7 years [13]. The prevalence of asthma appears to have peaked or reached a plateau in countries with high prevalence, however, it is currently increasing in many Asian cities. Singapore, Seoul, and Hong Kong have lower incidences of asthma than the UK and Australia despite their considerable urbanization [13]. Asthma and rhino conjunctivitis appeared more common in industrialized nations including Korea, Japan, Hong Kong, and Singapore, which is consistent with the trends of allergic illnesses worldwide [13].

epidemiological findings suggest a worldwide population of different age groups was currently suffering from these conditions and their clinical outcomes [14]. Hence the world population is seeking new medications and therapeutics findings with no or fewer adverse effects. Researchers, therefore, need an *in vivo* animal model to carry out their studies, as well as information gathered from published research findings, to undertake more research trials. It is crucial for the creation of novel medications and comprehending the clinical characteristics of asthma helps us learn more about the pathophysiology of allergic disorders in animals, which then allows us to apply some of this knowledge to humans. As the objective of this review article, is to provide evidence-based recommendations for these animal models, a literature search was done using Hinary (WHO, Switzerland), Google Scholar, and PubMed® (US National Library of Medicine, USA). studies published between the date 2000 and the date 2023 were included. About five animal models were documented to broaden this research field. The characteristics of each model were compared and documented to provide documented parameters about animal models, such as relative merits and limitations, importance, immunological characteristics, pathological features, and advantages and disadvantages. Here, it is discussed how sheep, dogs, guinea pigs, mice, and rats were used as asthma animal models in early studies, along with the established parameters.

Allergic asthma

Elevated levels of immunoglobulin (Ig) E antibody, which directly attaches to mast cells and starts the release of histamine and other mediators upon re-contact with allergen from sources, are typically associated with type 1 hypersensitivity reactions. There are numerous allergies there, including molds, animal feces, mites, pollens (from primarily entomophilous plants), and various foods [15]. Type I, Type II, Type III, and Type IV hypersensitivity reactions are the four traditional classifications for traditional classifications [16]. The signs and symptoms of allergies are caused by type I hypersensitivity reactions, or occasionally type IV reactions. Numerous people experience allergic reactions, which range in severity from moderate to severe and often result in death. which take place in inappropriate body places and occasionally change depending on the circumstances affecting interpersonal variability [17], but a typical respiratory allergy is associated with asthma. Immunoglobulin E (IgE)-mediated mast cell and basophil degranulation, also known as type I hypersensitivity, is the release of antibodies against the antigen by mast cells and basophils. This causes mast cells to degranulate, releasing histamine and other inflammatory mediators as a result [17]. Asthma caused by allergies can be a symptom of this hypersensitivity.

Numerous cells and cellular components are involved in the chronic inflammatory condition of the airways known as asthma. Chronic inflammation contributes to the hyperresponsiveness of the airways, which results in recurrent attacks of coughing, wheezing, shortness of breath, and chest tightness. Airway inflammation, airway obstruction that is at least partially reversible, and airway hyperresponsiveness (AHR) are the three characteristics that distinguish asthma [18]. Numerous stimuli, such as Allergan's challenge of actively or passively sensitized laboratory animals, might cause AHR. AHR may also be inherent, as it happens on its own. However, the AHR mechanism is still unknown [18]. some literature believed AHR was generally due to the changes in airway smooth muscle (ASM) Properties [18], as well as due to the post-receptor mechanisms, which lead to hyperresponsiveness. not only changes in contractile protein or signaling can induce increased smooth muscle contraction and lead to AHR. and as well as the mechanical impedances to airways also cause AHR. AHR is caused by a number of distinct mechanisms in various disease states. therefore, to get a better understanding of their mechanisms, Animal models are extremely useful. in allergic situations, airway inflammation can be seen. When an allergen causes it to become activated, it produces an eosinophilic component. The cytokines and chemokines linked to the Th2 cytokines frequently cause eosinophilia. Dendritic cells present antigens to OVA-specific T lymphocytes, primarily CD4+ cells. It is in charge of Th2 cells' secretion of interleukins (IL- 4, IL- 5, IL- 13) [18,19]. The presence of ozone and other non-allergic stimuli are accompanied by neutrophilic inflammation. T cells' contributions to these reactions have not been well investigated.

Around 300 million people globally, across all age categories, suffer from asthma, and its prevalence is rising. According to estimates, 180,000 people die each year from asthma-related causes or 18 fatalities per million people [19]. All age groups worldwide are experiencing a sharp rise in the prevalence of allergic airway illness. According to reports, in recent decades the frequency in children has reached over 30% in various nations and has reached over 10% in some adult populations [20]. Although there are various classification systems for allergies, when it comes to IgE-associated allergic disorders, clinical manifestations might range from minor symptoms to potentially fatal events, [21] such as food allergies, allergic rhinitis, allergic asthma, skin allergies, etc.[21]. An estimated 300 million people worldwide experience these respiratory diseases [21]. There are more than 300 million sufferers of allergic asthma globally, including 25 million Americans and 6.4 million children in the USA [6], which sometimes gives rise to life-threatening anaphylaxis-like conditions as well [22], Between 0.7% and 23.5% of the general Asian population is thought to suffer from asthma [23]. The frequency of asthma in children aged 6-7 from various Asian nations ranged from 1.2% in Taiwan to 31.5% in Indonesia [13,25]. The Phase III International Study of Asthma and Allergies in Childhood (ISAAC) found that the prevalence of asthma and allergies varied from 0.8 to 14.9% in children aged 6-7 and from 1.4 to 39.7% in children aged 13–14 around the world. This illness is very common in Asia, with prevalence rates ranging from 27% in South Korea to 32% in the United Arab Emirates [25]. In Asia, allergy illnesses will become more common during the next 20 years as a result of the region's rapid economic growth and urbanization [26]. other than these diseases, many diseases follow an allergic reaction [21]. The prevalence of these

diseases has significantly impacted the lives of those who suffer from them in communities around the world, which has resulted in a decline in the quality of life that is tied to one's health [5].

In order to assess a potential drug to treat allergic asthma, researchers are investigating treatment options. It is also clear that study into the immunobiological processes driving respiratory tract sensitivity and research into the creation of alternative assays for evaluating potentially allergenic substances are both extremely effective. As a result, this review will concentrate on the *in vivo* animal models that have been employed in earlier research to assess potential anti-allergic asthma treatment options [28,29].

Various purposes for including an animal model of asthma

There is a large variety of asthma models in different animals, and they are using a variety of techniques for research. Animal models of asthma can be used to study the pathophysiology of the condition and test possible pharmacological treatments. Depending on the type of animal used (Figure 1) and the technique used to induce the disease, the findings may be applicable to individuals with asthma [30,31].

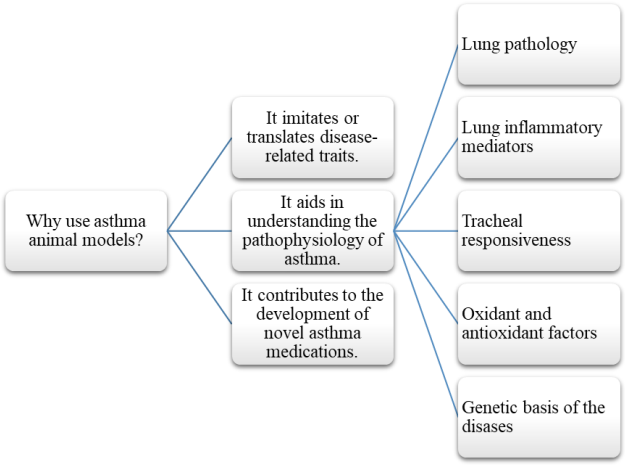

Figure 1: Various purposes of including an animal model of asthma

***In vivo* models to assess respiratory asthma/ allergic asthma**

Although *in vivo* models have not received formal validation, there has been significant investment in the previous few decades in the development of techniques to discover different kinds of respiratory sensitizers. Additional animal research could be helpful in analyzing the processes behind *in vivo* respiratory sensitization and elucidating their mechanistic details [31].

A useful tool that enables investigations to be carried out in a setting with an intact immune and respiratory system is the use of animal models and *in vivo* experiments. These models demonstrated the significance of T Helper type 2-driven allergic reactions in the development of asthma and are useful for identifying possible therapeutic targets for allergic pathways. Although several medications have been demonstrated to be somewhat effective in animal models of asthma, human asthmatics have seen less therapeutic benefit from them. Several factors, including the animal species used and the technique employed to induce asthma, may be responsible for this.

As research in this field continues to increase, understanding this area will aid in the discovery of viable pharmacological therapy for allergic asthma/asthma. As a result, this study focuses on *in vivo* models that can be used to assess allergic asthma.

The data is summarized in Table 1. In this section, we examine previous studies that used mice, rats, guinea pigs, dogs, and sheep as asthma animal models. The importance of animal models in the research of respiratory asthma, the immunological point of view, the conclusion of the experiment, the advantages and disadvantages of each animal model, the pathophysiology of these animals, and key points to remember when handling them are discussed.

Selection of animal models for respiratory allergic asthma research

Research goals, as well as laboratory restrictions such as the housing of large or unusual animals, are taken into account while choosing an experimental model. Before using new medicines on humans, the final phase of validation should be conducted on large animals with ethical and societal difficulties like dogs and sheep. Most of the time, small animal models like rats, mice, or guinea pigs will be sufficient to evaluate the immune system, food, or other factors in allergic asthma inflammation at the histological level, offering adequate statistical significance and pre-clinical relevance [20,33].

METHODOLOGY

As the purpose of this review article, is to deliver evidence-based recommendations regarding Experimental *In-vivo* animal models that can be used for asthma/ allergic asthma, Importance, and documented parameters, A literature search was done using Hinary (WHO, Switzerland), Google Scholar, and PubMed® (US National Library of Medicine, USA) using the following keywords, “animal models”, “asthma”, “allergy”, “experimental *in-vivo* models”, “animal models for AHR”. Research findings released between 2000 and 2023 were incorporated. About five animal models were documented to broaden this research field. The characteristics of each model were compared and documented to provide documented parameters about animal models, such as relative merits and limitations, importance, immunological characteristics, pathological features, and advantages and disadvantages. Here, discusses the use of mice, rats, guinea pigs, dogs, and sheep as asthma animal models in earlier studies, and documented parameters were introduced in Table 1.

RESULTS

The literature was searched to find out the documented parameters of experimental *In vivo* animal models for asthma, their importance, immunological basis, outcomes that can be observed due to response to an allergy, benefits, and drawbacks of each animal model, documented pathological features of each animal model, and valuable considerations that researchers have to consider about the animal model are introduced as a table. These all details were introduced according to the previously published literature and their documented parameters. Therefore, this review must be unbelievably valuable who conducted their studies related to allergic airway diseases, asthma, hyperresponsiveness, etc.

According to epidemiological statistics, the global population of various age groups is currently suffering from respiratory allergy diseases and associated clinical effects. As a result, the global population is looking for novel treatments and therapeutics that have no or few side effects [82]. To conduct additional research

Table 1: Experimental *In vivo* animal model for allergic asthma and documented parameters

In-Vivo Model	Importance	Immunological point of view	Outcome	Advantage	Disadvantage	Pathology	Valuable consideration	References
01. Mice	- Considering that a thorough understanding of their genetics exists, the most common species for mimicking allergy responses in the airway; commercially available, reasonably priced mouse-specific probes for assessing allergic reactions.; sensitized to the number of antigens including ovalbumin (OVA).	- Resulting in a marked Th2-type reactivity with antigen-specific IgE levels in the lungs.	- Eosinophilia and airway responsiveness to bronchoconstrictor substances.	- There are significant differences across strains in Th2 response, antigen-specific IgE, eosinophilia, and the airway's receptivity to broncho-constricting drugs. This variation in strains for a particular antigen can be highlighted as a benefit of using mice as asthma model organisms. It enables the discovery of the genetic and cellular pathways behind airway responsiveness and inflammation. -Can use mice models for understanding the development of asthmatic phenotype. - crucial for determining the Cytokines and mediators involved in the allergic response. -allergen inhalation of a mouse model of asthma has developed airway remodeling, which is more typical of human asthma. - Models for sensitization and chronic exposure to HDM (House Dust Mite) extract via the respiratory route have demonstrated that it is possible to cause a pathology that is similar to human asthma. These models demonstrate a promising field of study for	- Therapies that were noticed to be effective in mouse models of asthma have not been efficacious in human clinical trials. - The patterns of mediators produced by mast cells differ between mice and rodents in general. Serotonin, which does not play a function in human asthma, is released by rodent mast cells. Such considerations must be made when extending results from animal models to individuals. -Lack of response to allergen exposure after sensitization. -Sometimes showed tolerance to allergens. - There is no evidence of spontaneous airway hyperresponsiveness. - Musculature of the airway is limited. -Lung anatomical differences - Histamine does not affect them. -Absences of a chronic model	-The plethora of mechanisms evident in mice as an asthma model. However, several issues are debated. -Histology is sometimes shown as allergic alveolitis, due to inflammatory response levels in the mice.	-Inflammatory response level is dependent on the dose of antigen used. - In mouse asthma models, mice eosinophils rarely degranulate, whereas human eosinophils routinely degranulate. - Physiologically airway hyperresponsiveness give outcome as early-phase reaction(EPR) and late-phase reactions(LPR). This has been proved by utilizing allergens and sensitization approaches.	[20] [29] [32-46]

				using mice as an asthma model. - The main anaphylactic antibody is IgE. - There are several immunological reagents available. - Multiple inbred strains. - Short gestational periods make breeding simple. both small and inexpensively priced.				
02. Rats	- Rats are widely used as models of allergic airway illness. - Because they are frequently affordable, it is possible to undertake extensive research on a variety of outcomes. - Due to the quick development of genetic technology, overtaken in recent years. - There were various rat strains, with Brown Norway (BN) being the most widely used. The responses to sensitization and challenge varied greatly amongst different strains, according to the literature.	- Rats often have a Th2-dominated response following sensitization and challenge, which is characterized by eosinophilia and antigen-specific IgE. - Using adaptive transfer techniques, the involvement of T cells has been directly shown. -With the support of their T helper 2 cytokines (IL 4, IL 5, and IL 13), CD4+ and CD8+ T cells are both activated in response to allergen exposure in the sensitized	-Eosinophilia - IgE that is specific to an antigen -Allergen-induced airway constriction -Allergen-induced airway hyperresponsiveness	- Due to its bigger size than mice, which enables the measurement of the traditional features of allergic airway disorders, the rat model represents a substantial advantage over mice. due to an increase in the amount of serum and BAL fluid that can be acquired, such as airway and systemic indicators. - Large size and increased anesthetic stability can be introduced as advantages that enable the evaluation of physiological outcomes such as airway hyperresponsiveness and acute reaction to allergen inhalation. - Understanding and manipulating rat genetics will enable for deeper investigation of allergic processes in asthma rat models. - They are easily sensitized to a variety of neoantigens,	- Specific probes for evaluating allergic consequences are not widely accessible. - Reagents for investigations in rats are limited in comparison to mice, however, their availability has expanded in recent years. - As a significant criticism of rat models of asthma, it was demonstrated that the development of tolerance with increasing allergen avoids the development of chronic allergic reactions and related lung structural and functional abnormalities in asthmatics. Some, however, believe that tolerance development is vital in understanding allergy disorders. -Sensitization requires allergen injections.		- The extent of response in these immunological and inflammatory markers is significantly depending on the strain employed. - The study found that BN rats exhibit a more prominent IgE and inflammatory response to challenge after sensitization than other strains. -Rats have been shown increased responses to nonspecific	[18][20] [29] [36][47-57]

		rat respectively.		including OVA, HDM extracts, and Ascaris antigens. - According to the literature, BN rats provide an opportunity to examine the mechanisms underlying the asthmatic phenotype, and, like the mouse, this was accomplished through genetics and septic immunology. It is the fundamental benefit of utilizing rats as an asthma model. - Because there is a link between acute response, antigen inhalation, and nonspecific AHR (Airway hyperresponsiveness) in human beings, rats demonstrated that they can create an EPR, LPR, and AHR. - As a result, they have a major advantage over mice as a connection between immunological events, acute physiological responses to allergen inhalation, and the development of non-specific AHR. - The major anaphylactic antibody, IgE, causes long-lasting airway reactions.	- Adjuvants are required for sensitization. - There is a scarcity of species-specific immunological reagents.		Broncho constricting agents and acute response to allergen inhalation. - Acute response in BN rats revealed both EPR and LPR, with peaks at 6-8 hours. -Rats are used as a slandered method to test the efficiency and toxicity of new drugs before proceeding with clinical trials. - Antigen-tolerant rats have revealed the relevance of a subpopulation of T cells known as T regulatory cells (Treg) in suppressing all ergy reactions.	
03. Guinea pigs	- A historically significant animal model of allergic airway reactions.	-IgG1 appears to be important in allergy responses in	-Eosinophilia -Increased airway responsiveness	-Guinea pigs are quickly challenged and sensitized. - A good airway disease model.	-More expensive than mice and rats. - Specific probes for evaluating allergic	- A study indicated that, except for serotonin,	- To see if isolated guinea pig airways are a	[20][29, 30] [33] [36] [58-66]

	- The most popular animal model and test method for contact hypersensitivity to proteins and chemical irritants. - used as a "screening" model for testing asthma medications and for the development of medicines like corticosteroids and β receptor agonists. - Guinea pigs can be used as the perfect model to study the physiological anomalies of human asthmatics since they have well-defined EPR and LPR to allergen sensitization. - In such a situation, irritants rather than the typical "atopic asthmatics" reactions are responsible for guinea pigs' airways. - Their strong nature of sensitivity—which is known to be fatal in rare cases—to chemical irritants is known as their acute response. - Guinea pigs are frequently pretreated with antihistamines to moderate the response to manipulate this as a	guinea pigs. -Repeated exposure to the allergen causes the development of tolerance in guinea pigs. - They have an elevated baseline amount of eosinophils. This may impact the outcomes of long-term experiments.		-It has natural AHR - They exhibit excellent pharmacological reactions in the lungs. - They developed both early and late-phase asthmatic reactions. - Guinea pigs are used as a rodent model for asthma because they are easily provoked to react and are radially sensitized to OVA. - Ressmeyer et al. also discovered a disparity in the leukotriene pathway response of the guinea pigs, with a comparable response to the direct agonist LTD4, but a weak response to montelukast, which is known to be an efficient antagonist of this route in humans. - Guinea pigs are useful as models of immediate hypersensitivity to irritants because they have pharmacological properties similar to humans. However, when applying these ideas to the human lung, caution must be employed. -They have a large body size; due to that, it is helpful to measure the outcome parameters easily. The lung is the primary target of anaphylaxis -cholinergic agonist response -Eosinophils and neutrophils	consequences are not widely accessible. -They have axon reflexes. -Reagents for experiments are not easily available. -We have limited genetic knowledge about guinea pigs. -Tolerance can be developed after repeated exposure to the allergen. - Guinea pigs are restricted for mechanistic research, particularly those involving genetics, due to a scarcity of bred strains and a scarcity of guinea pig-specific reagents. - A study found that the reaction of Leukotrienes differed between guinea pigs and humans, implying a change in the mechanism of action. - when we directly extrapolate the results of airway allergic responses in guinea pigs to humans, we have to consider the Pre-treatments that are required to make the guinea pigs a workable model. -The main anaphylactic antibody is IgG1. -Shortage of inbred strains - Only a few species-	which caused bronchoconstriction in guinea pigs but not humans, precision-cut lung slices showed greater agreement between, the pharmacological responses of guinea pigs and human airways than that seen in rodents. -Additionally, postmortem bronchoconstriction in guinea pigs was observed, which requires pre-treatment with capsaicin or isoproterenol in experiments involving post-mortem manipulation of the airway. This condition is thought to be caused by the local release of	good representation of human airways, their response to pharmacological agonists has been directly compared with that of humans. - According to Sa's study, when methacholine, histamine, and allergen sensitization were introduced into the airways of guinea pigs and humans, they both responded similarly.	

	model for occupational asthma.			are the main components of pulmonary inflammation.	specific reagents are available.	substance P into the airways.		
04. Dogs	- For many years, dogs have been utilized as asthma models. - Respiratory mechanics are typically evaluated under anesthesia, however, they can also be tested in conscious dogs. - Interestingly, some dog breeds have spontaneous and hereditary nonspecific airway hyperactivity, which is substantially more reactive to methacholine and citric acid than mongrel dogs. - As part of the lung function testing, flow volume loops were used, the forced oscillation technique allowed assessment of bronchoconstriction in healthy histamine challenge dogs, barometric whole-body plethysmography (BWBP) can be performed in conscious or lightly sedated dogs and allows quantification of airway reactivity and head out plethysmography	- Dogs are an ideal allergy model because they have a predisposition to produce allergic responses to antigens that are clinically important to atopic humans. This allergy represents a superficial reaction in the form of dermatitis or conjunctivitis, rather than asthma-like conditions. - The development of certain eosinophilia in the airways as a result of allergens has been demonstrated. However, this inflammation does not result in a rise in the airways' responsiveness. -Several dog	- Elevated IgE -Eosinophilia - Response of the airways to the allergen and to histamine itself - The possible effect of ultrafine carbon particle exposure before challenge exposure has been studied in ragweed-sensitized dogs. Even though drug exposure increased the number of neutrophils in the BALF, the immunological allergic response remained unchanged.	- More recent models have taken advantage of dogs' tendency to develop allergies by selectively breeding male and female dogs with high IgE titers. -Half of the offspring inherit elevated levels of IgE which has been linked to the inheritance of atopy in humans. - Sensitization to ragweed can be achieved through a series of intraperitoneal and subcutaneous injections. -They showed natural susceptibility to an allergen - Atopy is easily developed. - Eosinophils are naturally occurring in the airway. - The onset of long-term alterations in pulmonary function - Gas exchange and ventilation-perfusion ratios have been studied in *Ascaris suum* dogs after bronchoprovocation with an allergen, methacholine, or histamine. - Hyperventilation and "Ski asthma" can be studied with dogs.	- It is extremely labor-intensive and costly, but it may be particularly valuable in discovering mechanisms of illness, particularly those related to long-term changes in lung function. -High cost - They have wider airways (almost no bronchoconstriction) - Reagents are difficult to obtain	-They have a monopodial branching system of trachea bronchial airways. - Morphological changes in the respiratory tract of dogs were assessed by bronchial biopsies and chest radiographs. -Computed tomography is used as a promising tool for the assessment of bronchial wall thickening and airway narrowing.	- In comparison to other models, this is the first to exhibit sustained AHR after the challenge, with an increase in responsiveness reported up to 5 months after the third challenge. - Lower airway illnesses in dogs that occur naturally include neutrophilic chronic bronchitis in elderly animals and eosinophilic bronchopenumopathy in young dogs. - Even though dogs poorly suffer from lower airway illnesses and share few symptoms of asthma, they	[30][33] [67-76]

	allows measurement of airway resistance and FRC (Functional Residual Capacity).	models display the hallmarks of atopic asthma, including IgE, Eosinophilia, acute physiological constriction in response to allergen inhalation, and AHR.					have been employed in asthma studies due to their lung function.	
5. Sheep	-As a dog, sheep are sensitized to *A. suum.* - Natural diversity exists within sheep that mount an allergic physiological response to an inhaled allergen; this pattern of variance is similar to that seen in humans. -Naturally inclined to viral and bacterial respiratory diseases. - Respiratory mechanics, inductance plethysmography, and head-out plethysmography can all be used to assess sensitization in conscious animals. -Bronchoscopy and BALF can be used to investigate the increased inflammatory cell influx into the airways. (eosinophils, N=neutrophils, and	- In sheep, the reaction to challenge is characterized by an influx of inflammatory cells such as eosinophils and neutrophils entering the airway. - This reaction shows a pattern of mediators similar to human asthmatics, specifically the leukotriene LTE4. -bronchial inflammatory cell infiltration and nonspecific airway hyperreactivity occur within hours of allergen exposure.	-Eosinophilia -Neutrophilia	- Natural allergy susceptibility -Immediate physiological responses to inhaled allergen -Nonspecific AHR -Long-term AHR after challenge (Similar to human asthma) -In Broncho constrictive responses, this model can demonstrate both immediate physiological responses to an inhaled allergen, such as the EPR, LPR, and nonspecific AHR. Of responders, some had single responses, an EPR, and 30-50% had dual responses, an EPR and LPR, which is similar to the level of variation between human asthmatics. -It has been demonstrated that only those sheep that develop an LPR have AHR 24h after challenge, which is also similar to asthmatics. - The allergic sheep is an interesting model for lengthy	-Extremely labor-intensive and expensive - Platelet factor antagonists affect the late-phase allergic reaction in sheep but not humans. - There were some differences between the responses in this model and those in humans, with early interest in platelet-activating factors being one example. Drugs that functioned through this system and were beneficial in modulating lung allergy reactions in sheep were shown to be ineffective in humans. - There were not many studies on airway remodeling, a characteristic of chronic asthma, in this species, which could be linked to a reluctance to sacrifice animals due to the high	-Remodeling has been poorly investigated. -However, the house dust mite model shows that after six months of recurrent allergen exposure, bronchial epithelial hyperplasia, collagen deposition, bronchial smooth muscle expansion, and the appearance of mast cells in alveolar septa occur.	- This model and asthma share notable similarities in medication efficacy, with cromolyn and corticosteroids being successful treatments for allergic airway response in sheep.	[30][33] [36] [68] [77-81]

	macrophages)			and repeated experiments because there is no need to anesthetize the animals. - The sheep provides an opportunity to examine mucociliary clearance because of its size, and treatment trials contrasting the impact of bronchodilators on lung function and mucociliary clearance have been carried out.	cost of doing so. - When it was discovered that platelet factor antagonists could control the late phase allergic response in sheep but poor in humans, it was clear that there was a significant difference between sheep asthma and human asthma.			

researchers will require *in vivo* animal models as well as information obtained from published research findings. Understanding the clinical aspects of asthma helps us understand more about the pathogenesis of allergic illnesses in animals, which allows us to apply some of this knowledge to people [82].

An important method for examining the pathophysiology, mechanisms, and medications intended to treat allergic asthma is through the use of animal models. Information regarding allergy illnesses can be learned by using animal models [82]. In this review, we have mainly introduced documented parameters regarding previously used experimental *In vivo* animal models for allergic asthma/asthma, and documented parameters, such as each animal model and its importance, immunological basis, outcomes that can be observed due to response to an allergy, benefits, and drawbacks of each animal model, documented pathological features of each animal model, and valuable considerations that researchers have to consider about the animal model are introduced [19].

Asthma can be modeled using a variety of animals, but the most popular models are rodents (inbred mice and rats) and guinea pigs. These animals have the advantages of being simple to handle and inexpensive when compared to other models. More recently, species-specific probes have been developed, allowing for the conduct of in-depth mechanistic studies [83]. However, there are several problems with current animal models of asthma, including the differences between these species' immunology and anatomy and those of humans, the need for adjuvants during sensitization, the acute nature of the primary response, and the use of adult animals as the main disease model [83]. Although some of these concerns might be addressed by larger animals like sheep and dogs, their biology is different from that of humans, they are also quite expensive, and there aren't many probes that can be added to these species [84].

The creation of novel medicines and improvements to existing therapies are made possible by having access to an appropriate model, in addition to providing a helpful framework for understanding disease. Importantly, medical professionals and veterinarians working together might enhance the best animal model, create novel species medicines, create feature research using the animal models, and can be archive some relevant aims [85]. As an example, the identification of mast cell receptor antagonists, the mapping of anaphylaxis checkpoints, the identification of allergen nature in various diseases, and the mapping of Th2 responses in allergic diseases. In order to discover an appropriate animal model, researchers need to understand animal models and the parameters that are related to them. By using these animal models, activation techniques and medications that can treat specific organs will be created that are safer, better, and more long-lasting. At the very least, all animals should be kept in allergen- and pathogen-free environments that follow the criteria for laboratory animals. Additionally, all animal procedures should be approved by an ethics committee [33].

Understanding the origin and development of the illness in humans requires experimental models of respiratory asthma. Before beginning clinical trials with new biomaterials and treatments, the use of animal models in research on pulmonary allergic asthma is a critical step [36]. To demonstrate the safety and effectiveness of new biomaterials or treatments for pulmonary allergic asthma, experimental animals' anatomy, physiology, and pathogenicity should be as similar to patients' as possible [86]. mice are the most popular species utilized to mimic allergy reactions in the airways, due to the knowledge of their genetic makeup; commercially available, reasonably priced mouse-specific probes for evaluating allergy outcomes; and sensitivity to several antigens, such as ovalbumin. In mice, the amount of antigen-specific IgE produced a specific Th2-type response in the lungs. Like mice, rats are frequently inexpensive, making them useful as models of allergic airway illness. This makes it possible to undertake extensive investigations on numerous outcomes. The T helper 2 cytokines (IL 4, IL 5, and IL 13) in sensitized rats stimulate both CD4+ and CD8+ T cells when the rat is exposed to an allergen. Guinea pigs are commonly used in drug testing for asthma as well as the development of drugs such as receptor agonists and corticosteroids as a "screening" model [58]. IgG1 appears to be crucial for allergic reactions in guinea pigs, and repeated exposure to the allergen results in tolerance development. Since dogs naturally tend to have allergic reactions to antigens that are clinically significant to atopic humans, they are an appropriate model for allergies and have been used for many years as asthma models [67]. Sheep that mount an allergic physiologic response to an inhaled allergen is naturally diverse; this pattern of variation is similar to that seen in humans [68]. The main limitation of these larger animals was found to be extremely labor-consuming and expensive. Aside from these huge animal models, smaller, less expensive species including guinea pigs, mice, and rats have been proposed. Guinea pigs continue to be excellent models for immunological research. More systematic use of these small animal models appears to be necessary for future study, particularly in surgical settings.

CONCLUSION

Global populations across various age groups are currently experiencing a rise in respiratory allergy diseases, prompting a search for innovative treatments with minimal side effects. To conduct further research, scientists emphasize the need for *in vivo* animal models and insights from existing research. Asthma can be modeled using a variety of animals, but the most popular models are rodents (inbred mice and rats) and guinea pigs. These animals have the advantages of being simple to handle and inexpensive when compared to other models. More recently, species-specific probes have been developed, allowing for the conduct of in-depth mechanistic studies. However, there are several problems with current animal models of asthma, including the differences between these species' immunology and anatomy and those of humans, the need for adjuvants during sensitization, the acute nature of the primary response, and the use of adult animals as the main disease model. Although some of these concerns might be addressed by larger animals like sheep and dogs, their biology is different from that of humans, they are also quite expensive, and there aren't many probes that can be added to these species.

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Author contributions

H.D.T. Madhuranga conceptualized and drafted the manuscript, and, he was a major contributor to editing. Prof. C.N.R.A. Alles Substantively reviewed the draft and conceptualized the manuscript. All respective authors read and approved the final manuscript document.

Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

AHR - Airway Hyperresponsiveness
ASM - Airway Smooth Muscle
BAL - Bronchoalveolar Lavage
BN - Brown Norway
BWBP - Barometric Whole-Body Plethysmography
CD4 - Cluster of Differentiation 4
EPR - Early-Phase Reaction
EU - European Union
FRC - Functional Residual Capacity
HLA - Human Leukocyte Antigen
HDM - House Dust Mite
Ig (E) – Immunoglobulin (E)
IgG - Immunoglobulin G
IL- interleukin
ISAAC - International Study of Asthma and Allergies in Childhood
LPR - Late-Phase Reactions
LTD4 - The leukotriene D4
OVA – Ovalbumin
Th2 - Type 2 T helper
Treg - T regulatory cells
UK - the United Kingdom
USA – United States of America
WHO – World Health Organization

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