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Review article

Comparative study of mouse models of atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic, recurrent inflammatory disease. Animal models are important for studying disease mechanisms and identifying new therapeutic agents. However, owing to AD heterogeneity and complexity, there is currently no mouse model that can fully simulate human AD. We searched experimental articles published between 2017 and 2021 to identify the most suitable AD mouse model. We summarized and compared 614 articles, including details on mouse strains, sex, age, irritants, modeling cycles, and spontaneous mouse models. BALB/c mice (45.3 %) were the most commonly used. Generally, 4–8-week-old mice were used, and 44 irritants were identified. The most common irritant was 2,4-dinitrochlorobenzene (DNCB), followed by *Dermatophagoides farinae* mite antigen extract (DfE). The modeling period was generally 21–30 days. There is no perfect AD animal model, and we suggest selecting the most suitable AD model based on previous research or using two or more models to meet experimental requirements. When exploring allergies and T cell differentiation, it is recommended to use DNCB and DfE separately or in combination to stimulate BALB/c mice and NC/Nga mice for constructing AD models. If researchers want to explore the differentiation of Th17 and Th2 cells, the use of flaky tail mice is recommended. If researchers want to conduct research from the perspective of transcriptomics, it is recommended to increase the construction of IL-23 injected mice.

1. Introduction

Atopic dermatitis (AD) is a complex and highly heterogeneous skin inflammatory disease that affects up to 25 % of children and 2–3% of adults [1,2]. Clinically, the disease is characterized by erythema, xerosis, edema, erosions/excoriations, oozing and crusting, and lichenification; however, these symptoms vary according to patient age and disease severity [2,3]. Individuals with AD are at an increased risk of food allergies, allergic rhinitis, asthma, and a wide range of health and psychosocial outcomes [4,5]. The chronic, recurrent, pruritus of the disease; economic burden; and the involvement of the whole family in the treatment process severely affect quality of life [6]. AD has a complex and multifactorial pathogenesis involving a strong genetic predisposition, immunological and environmental factors, and microbial dysbiosis, which lead to a dysfunctional epidermal barrier and dysregulation of the immune system [7]. Additionally, research is difficult because of the number of synergistic factors that influence the disease. Previous studies

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have shown that type 2 immune cytokines play important roles in chemokine production, skin barrier dysfunction, and AD pathogenesis [8–10]. However, the pathogenesis of AD is not exclusively explained by Th2 immunity, and there is increasing evidence that AD involves multiple immune pathways [11–13]. Chronic AD is associated with the recruitment of Th1, Th22, and Th17 cell subsets, resulting in epidermal thickening and abnormal keratinocyte proliferation [8]. Multiple factors, including the filaggrin (*FLG*) gene, neuroinflammation, altered lipid composition, and microbial imbalance, can contribute to the development of AD. Therefore, it is difficult to fully present the pathogenesis, inflammation level, and clinical features of AD in an animal model. As an important tool for human disease research, animal models are an important cornerstone to promote the development of medicine. In particular, model construction in mice is straightforward, and mice have high availability and low cost and are widely used. To better study AD, researchers have developed various mouse models, including (1) using epithelial sensitive antigens and haptens to enhance the AD model caused by skin sensitization, (2) genetic engineering of mouse AD models, and (3) spontaneous AD mouse models [14]. Although there are many different ways to stimulate AD in mouse models, none of them can fully demonstrate all the characteristics of clinical AD. Many researchers believe that using antigens to stimulate mouse skin to create an AD model is similar to models of contact dermatitis and cannot be used to obtain a reasonable AD animal model. This study aimed to summarize and objectively review experimental articles on AD in mice published between 2017 and 2021 and recommend the most suitable AD model for future experimental research.

2. Results

2.1. Mouse strains commonly used in animal models of AD

We generated statistics for AD mouse model strains from 614 original articles. If two animal strains were used in one study, we calculated one animal strain to be 0.5. As shown in Table 1, the most commonly used mouse strain from 2017 to 2021 was BALB/c, used in a total of 276.5 (45.3 %) studies. Nc/Nga mice were the next most commonly used, with a total of 151.5 (24.7 %) articles. Other mice, including hairless C57BL/6 and Swiss mice, were less frequently used. Genetically engineered mice were used in 13 % of studies. The proportion of BALB/c and Nc/Nga mice was 69.8 %, indicating that BALB/c and Nc/Nga mice are the most commonly used AD mouse models. More than three mouse strains were used to construct the models in three studies, which required a separate statistical analysis.

2.2. Age and sex analysis of AD mouse models

Fig. 1A and B summarize the age and sex data of the mouse models; if there were two instances of mouse age and sex in the same study, these were counted as 0.5. There were no articles with three instances. Most experimental researchers chose 6–8-week-old mice; according to our data, 74.2 % of the studies used 4–8-week-old mice, and the usage rate of mice >8 weeks old was 8.4 %. In terms of sex, the proportions were similar, at 35.8 % for males and 43.4 % for females. Additionally, we found that approximately 13–17 % of the articles did not clearly state the age and sex of mice, but some studies provided the weight of mice.

2.3. Analysis of irritants for AD

There were 44 irritants in the AD mouse models in the 614 studies (Table 2). A total of 23 irritants appeared ≤5 times, including trimellitic anhydride (5), HR-AD diet (low zinc/magnesium diet, 4.5), *Dermatophagoides farinae* mite antigen extract (DfE) + Staphylococcal enterotoxin B (SEB) (4), *Aspergillus fumigatus* (*Af*, 4), DfE + 1-fluoro-2,4-dinitrobenzene (DNFB) (3), house dust mite (HDM) + *Staphylococcus aureus*/SEB (*S. Aureus*/SEB) (3), oxazolone (OX) + 2,4-dinitrochlorobenzene (DNCB) (3), ovalbumin (OVA) + SEB + calcipotriol (2), *S. Aureus*/SEB (2), picryl chloride (2), O-tetrade-canoylphorbol-13-acetate (2), anti-dinitrophenyl (DNP)-IgE antibody (1.5), toluene diisocyanate (1), particulate matter (PM2.5) + DNCB (1), DNFB + fluorescein isothiocyanate (FITC) (1), *Myobia musculi* (1), OVA + dibutyl phthalate (1), OVA + *S. aureus* (1), PM2.5 (1), OVA + HDM (1), OX + DNFB (1), salt-soluble wheat protein (1), and

Table 1
Mouse strains and number of articles.

Mouse strain	Count	Percent
BALB/c mice	276.5	45.0 %
NC/Nga mice	151.5	24.7 %
SKH-1 hairless mice (hr/hr)	42	6.8 %
C57BL/6 mice	37	6.0 %
ICR (CD-1) mice[a]	8.5	2.9 %
Kunming mice[a]	6	
Swiss Webster mice	3	
CF-1 mice	1.5	0.2 %
Genetically engineered mice	80	13.0 %
More than three types of mice	4	1.3 %
Not specified	4	
Total	614	

[a] ICR and Kunming mice are derived from Swiss mice.

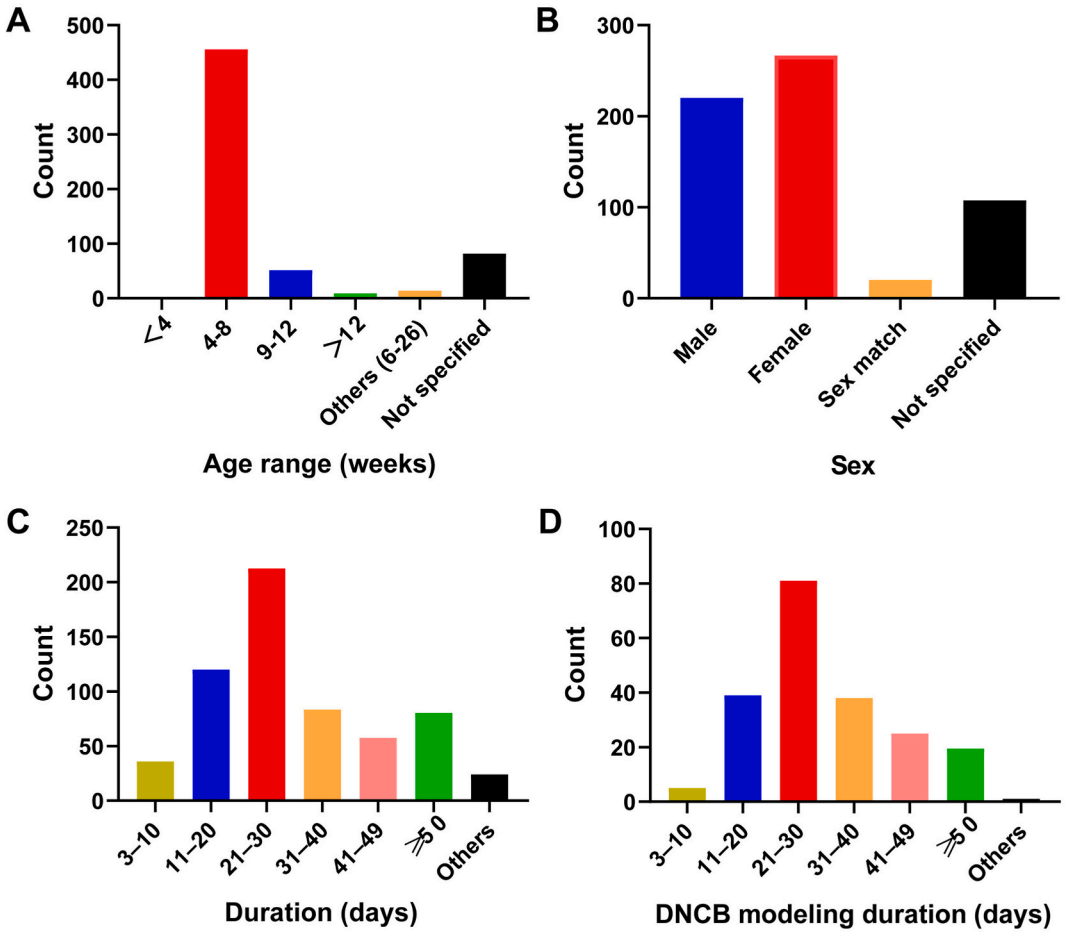

Fig. 1. Age range, sex, and modeling duration of the mouse models. (A) Age range statistics of the mouse models. (B) Sex statistics of the mouse models. (C) Modeling duration of the mouse models. (D) Modeling duration of the DNCB mouse models.

Table 2
Irritants used in mouse models.

Irritants	Count	Percent
2,4-Dinitrochlorobenzene (DNCB)	208.5	34.0 %
House dust mite (HDM)/*Dermatophagoides farinae* mite antigen extract (DfE)/*Dermatophagoides farinae Biostir*® AD (Dfb)	81	13.2 %
1-fluoro-2,4-dinitrobenzene	52.5	8.6 %
Ovalbumin	51.5	8.4 %
Oxazolone	42	6.8 %
Calcipotriol	32	5.2 %
Spontaneous	26	4.2 %
HDM/DfE/Dfb/Biostir® AD + DNCB	25	4.1 %
2,4,6-trinitrochlorobenzene	13	2.1 %
Phthalic anhydride	9.5	1.5 %
Fluorescein isothiocyanate	8	1.3 %
More than three types of mice	6	/
Used five times or less	47	
Not specified	12	
Total	614	

OVA + DNCB (1). The main stimuli used were DNCB, HDM, DNFB, and OVA. Among these, DNCB was the most commonly used (34.0 %). The second most common was dust mite stimulation; however, this was less than half that in studies using DNCB. These were followed by DNFB, OVA, OX, calcipotriol, spontaneous models, HDM + DNCB, and 2, 4, 6-trinitrochlorobenzene (TNCB). The usage frequency of phthalic anhydride and FITC was low, accounting for only approximately 1.3–1.5 % of studies.

2.4. Concentrations of DNCB used in mouse models

As shown in Table 3, 59.2 % of the studies used 1 % DNCB during the sensitization period and 0.2–0.5 % DNCB during the challenge period. During the challenge period, the most commonly administered concentrations of DNCB were 0.2 % and 0.5 %. More than 8 % of the articles used 2 % DNCB for sensitization. Sixteen studies used lower concentrations of DNCB during the sensitization period (0.5 %) and higher concentrations of DNCB (1 %) during the challenge period. A concentration of 0.1 % was administered to all hairless mice during the challenge period. This may be because hairless mice lack hair protection and require lower DNCB concentrations to avoid serious skin irritation, which may affect animal ethics.

2.5. Mouse modeling duration

The modeling period is crucial for the progress of experimental research. As shown in Figs. 1C and 34.6 % of the studies selected a modeling duration of 21–30 days. However, owing to the chronic recurrent nature of AD, 13.1 % of the studies had a modeling period of >50 days. More than 67 % of the articles had an experimental period of 11–40 days. We collected data on the modeling duration for DNCB (Fig. 1D). These results were similar to those in Fig. 1C, where 38.8 % of the DNCB stimulation models had a duration of 21–30 days. There were relatively few studies conducted for <10 days and >50 days.

2.6. Articles with three or more modeling methods

As shown in Table 4, nine articles used >3 mouse modeling methods; therefore, we have listed them separately for analysis. Some studies aimed to distinguish between acute and chronic dermatitis, whereas others used multiple models for pharmacodynamic and mechanistic comparisons.

2.7. Analysis of commonly used spontaneous mouse models

A spontaneous mouse model refers to the ability to spontaneously produce AD-like skin lesions under specific pathogen-free (SPF) or conventional conditions, which is more consistent with clinical AD characteristics than other models. Table 5 summarizes the characteristics, duration, and application of commonly used spontaneous mouse models, including NC/Nga, flaky tail, IL-4 transgenic (Tg), TSLP Tg, and IL-33 Tg mice. NC/Nga mice develop AD-like skin lesions under conventional conditions, whereas other spontaneous models can develop dermatitis under SPF conditions. Except for TSLP Tg mice, the modeling period of the other spontaneous models was at least 5 weeks or even 11 weeks, and individual differences were significant. We calculated that between 2017 and 2021, only 10 studies used the spontaneous model of NC/Nga mice, with even fewer studies using Tg mice (data not shown).

3. Discussion

An appropriate animal model should facilitate the development of new therapeutics, analysis of pathogenic mechanisms and target validation, evaluation of drug candidates, and identification of disease subtypes requiring differential treatment [24,25]. However, owing to the heterogeneity and complexity of AD, there is currently no mouse model that can fully simulate human AD. Herein, we searched for literature on mouse models of AD between 2017 and 2021 and identified 44 modeling methods across 614 articles. Inevitably, there are some limitations to this study. The literature included in our study may not be exhaustive. Our study investigated data from the Web of Science exclusively; data from other significant search engines such as PubMed and Embase were excluded. This study focused on analyzing commonly used and readily accessible animal models, without considering certain mouse models carrying inactivated mutations, which are more suitable for studying single-target validation pathways. Genetically engineered mouse models with altered expression of AD-related genes fail to mimic the complexity of human AD and the broader dysregulation of signaling pathways.

Unlike other disease models, the AD mouse model does not have a relatively unified standard in terms of mouse strains, irritants,

Table 3
Concentrations of 2,4-dinitrochlorobenzene (DNCB) used in modeling.

Concentration of DNCB		Count	Percent
Sensitization	Challenge		
1 %	0.2 %	43	20.6 %
1 %	0.5 %	43	20.6 %
1 %	0.4 %	18.5	8.9 %
0.5 %	1 %	16	7.7 %
1 %	0.3 %	15	7.2 %
2 %	0.5 %	9	4.3 %
1 %	0.1 %	11[a]	5.3 %
2 %	0.2 %	8	3.8 %
1 %	0.2–0.5 %	123.5	59.2 %

[a] All mice were hairless.

Table 4
Analysis of three or more modeling methods.

Articles	Mouse strains	Age and sex	Irritants	Concentration	Duration	Application
Travis P. Barr et al. [15]	flaky tail (filaggrin-deficient) mice	Male, 8–12-week-old	Dust mite extract	2.5 mg/mL	56 d	Chronic models
	CF-1 mice	Male, 8–12-week-old	DNFB	Sensitization: 1 % Challenge: 0.1 %	42 d	
			OX	1 %	2 d	Acute model
Ayaka Kitamura et al. [16]	BALB/c mice	Female, 6–7-week-old	DNFB	0.15 %	35 d, 42 d, 49 d, 37 d	To develop a protocol that involves less animal distress
Hyun Jung Park et al. [17]	NC/Nga mice	Female	1 % DNCB; 0.7 g/kg toluene; formaldehyde; SLS or SLES; 16.6 mg/kg DP, TP, or DF		21 d	To find an appropriate model for testing of sensitivity to environmental allergens
	BALB/c mice	Female, 8-week-old	Experiment 1: 1 % DNCB; 2 % TDI; 1 % HDI; 20 % TMA Experiment 2: Phase 1: 20 % TMA (BALB/c) Phase 2: 1 % DNCB; 0.7 g/kg toluene; formaldehyde; SLS, or SLES; or 16.6 mg/kg DP, TP, or DF		42 d	
Atsuo Tanimoto et al. [18][a]	BALB/c mice	Female	DNFB	0.15 %	29 d	Chronic dermatitis, comparison of drug efficacy.
	C57BL/6 mice	Female	Recombinant mouse TSLP	0.5 μg	11 d	
			Recombinant mouse IL-23	0.25 μg	13 d	
	Nc/Nga mice	Female	Mite extract	5 μg	19 d	
Yong Hyun Jang et al. [19]	BALB/c mice TLR1$^{-/-}$, TLR2$^{-/-}$, TLR6$^{-/-}$ mice	/	DfE	10 mg/mL	42 d	To investigate whether DfE mediates innate immune activation through specific TLRs
David A. Ewald et al. [20]	NC/Nga	Male, 10-week-old	Mite	/	/	To evaluate the transcriptomic profiles of six common murine models
	flaky tail	Female, 26-week-old	Spontaneous	/	23 weeks	IL-23-injected mouse model, which has been traditionally considered to resemble psoriasis.
	Flg mutated	Female, 26-week-old	Spontaneous	/	/	
	C57BL/6	Female, 15-week-old	OVA	0.1 %	50 d	
		Female, 6-week-old	Recombinant murine IL-23	3 μg/100 μL	7 d	
	BALB/c mice	Female, ~10-week-old	OX	Sensitization: 5 % Challenge: 0.1 %	22–25 d	
Min Ho Kim et al. [21]	NC/Nga mice	Female, 4-week-old	HDM ointment	130 mg	17 d	To ascertain whether the increase in ILC3s is strain- or allergen-specific, containing no mature B and T lymphocytes.
	C57BL/6 mice, Rag1−/− mice	/	MC903	45 μM	16 d	
			OX	Sensitization: 3 % Challenge: 0.6 %	16 d	
			HDM ointment	130 mg	17 d	
Yoon-Hwan Kim et al. [22]	NC/Nga mice	Female, 8-week-old	HDM	100 mg	28 d	Compare each model's immunological patterns
			TNCB	2 %	14 d	
				Sensitization: 2 % Challenge: 0.2 %	56 d	
Monika D. Scuron et al. [23]	BALB/c mice	Female	TSLP	3 μg/20 μL	9 d	Acute model
			FITC	0.5 %	35 d	Chronic model
	IL-33 transgenic mice	5-week-old	Spontaneous	/	>7–10 weeks	Spontaneous model

DF, *Dermatophagoides farinae;* DfE, *D. farinae* mite antigen extract; DNCB, 2,4-dinitrochlorobenzene; DNFB, 1-fluoro-2,4-dinitrobenzene; DP, *Dermatophagoides pteronyssinus*; FITC, fluorescein isothiocyanate; HDI, hexamethylene diisocyanate; HDM, house dust mite; IL, interleukin; MC903, calcipotriol; OVA, ovalbumin; OX, oxazolone; SLES, sodium lauryl ether sulfate; SLS sodium laureth sulfate; TDI toluene diisocyanate; TLR, toll-like receptor; TMA, trimellitic anhydride; TNCB, 2, 4, 6-trinitrochlorobenzene; TSLP, thymic stromal lymphopoietin; TP, *Tyrophagus putrescentiae*.

[a] The description of duration in the article does not match the figure. The data used in this study were based on this figure.

Table 5
Common spontaneous mouse models.

Spontaneous model	Characteristic	Duration	Application
NC/Nga mice	Inbred mouse strain; spontaneously develop AD-like skin lesions under conventional conditions and closely mimic human AD	>6 weeks	Used as an appropriate model to study the spontaneous model similar to the pathophysiology seen in patients with AD
Flaky tail (gene symbol ft, *ft/ft*)	A frameshift mutation in the filaggrin (Flg^{ft}) gene; develop spontaneous dermatitis under SPF conditions	Phase 1: From 3 days after birth to 4 weeks. Phase 2: From 8 weeks of age with a constant increase in clinical severity	Used as an appropriate model to study early AD onset associated with profilaggrin deficiency
IL-4 Tg mice	Spontaneously develop chronic pruritic inflammatory skin lesions under SPF conditions	>80 days	For studying the pathogenesis of AD involving IL-4
TSLP Tg mice	Develop eczematous-like changes under SPF conditions	2–5 weeks	For studying the pathogenesis of AD from subclinical onset to final disease phenotype
IL-33 Tg mice	Spontaneously develop AD-like eczema under SPF conditions	>5–10 weeks	For studying the pathogenesis of AD involving IL-33

AD, atopic dermatitis; IL, interleukin; SPF, specific pathogen-free; Tg, transgenic; TSLP, thymic stromal lymphopoietin.

modeling period, or definition of acute and chronic dermatitis. Flaky tail mice show selective Th17 activation and lack Th2 activation, which is a hallmark of the AD immune response [20,26,27]. According to transcriptome analysis data, compared to NC/Nga,flaky tail, FLG-mutated, OXA-challenged, and OVA-challenged mice, IL-23-injected mice showed the largest overlap with human AD skin lesions [20]. Although IL-23-injected mice have been found to have AD-like skin lesions, they are traditionally used for psoriasis modeling [28]. When studying transcriptomics alone, IL-23-injected mice should be considered. The spontaneous model of NC/Nga mice, which is widely recognized as highly consistent with the clinical characteristics of AD, has a low usage rate owing to the long and unstable modeling period, which brings many uncertainties to scientific research [14,29,30]. According to our data, the most commonly used mouse strain is BALB/c, followed by NC/Nga. This finding may also be related to funding and accessibility. NC/Nga mice clearly show the diverse immune polarizations seen in human AD, including innate, Th1, Th2, and Th17 pathways, which might be useful for the investigation of the complex cytokine interactions, but not the barrier aberrations of patients with AD [20]. OVA may not be an effective stimulant, as some articles have reported that applying OVA to the intact skin of BALB/c, NC/Nga, or C57BL/6 mice is less likely to induce sensitization and lesion development [31–34].

Many researchers believe that the AD mouse model constructed with hapten stimulators is similar to the contact dermatitis model and cannot be used as a classic model for AD. For preclinical efficacy studies, animal models of AD should exhibit good stability and reproducibility in the onset and severity of skin lesions. Therefore, inducible models are generally preferred over spontaneous models. According to our data, among the 614 articles, 34 % of AD mice were stimulated using DNCB and 13.2 % using DfE. The other two haptens, DNFB and TNCB, together accounted for 45 % of the studies. A review of the literature revealed that although AD and contact skin are not the same in clinical practice, the description of mouse skin lesions and the commonly used expression of inflammatory factors were similar [35–41]. After repeated application of hapten stimulation in mice, a shift in immune response from Th1 to Th2 was observed, accompanied by changes in important AD markers, such as IgE [42]. The immune response induced by hapten may also be influenced by the selected mouse strain. For instance, one study has found that the T cell subsets in FITC-induced skin lesions are mainly $CD4^+$ cells in BALB/c mice and $CD8^+$ cells in NC/Nga mice [43].

In recent years, new skin models have been introduced. Researchers have established a humanized mouse model for acute AD; however, the important factors of human AD pathological biology and treatment response have not been recorded in this animal model [44]. Additionally, some studies have focused on genotypic AD-like 3D skin equivalents, which can analyze skin diseases in a way that closely resembles *in vivo* conditions [45].

Altogether, no single murine model fully captures all aspects of human AD skin, and the standardization of AD mouse models and the development of new mouse models require more in-depth research. The stability and repeatability of OVA and spontaneous models are not as reliable as those of hapten models. For research focusing on the mechanisms of diverse immune polarization, NC/Nga mice should be the first choice. If the focus is on Th17 pathways or early AD onset, flaky tail mice should be selected. DNCB, the most commonly used stimulant, is sufficient for certain studies, but using two or more models would yield richer and more accurate results. When exploring allergies and T cell differentiation, DNCB and Dfe are best used separately or jointly to stimulate BALB/c and NC/Nga mice to construct respective AD models. To study Th17 and Th2 cell differentiation, researchers should not only use a hapten model but also incorporate flaky tail mice. For transcriptomic studies, it is advised to include IL-23-injected mice.

4. Materials and methods

4.1. Eligibility criteria and selection of studies

The inclusion and exclusion criteria for studies of interest were pre-determined before conducting the literature search, which included experimental articles on AD in mice as follows: “atopic dermatitis mice skin” [All Fields]. All AD-related articles, including those focused on itching and contact dermatitis but not specifically defined as AD, were included to achieve maximum rigor in the data

summarized herein. The search was conducted on the Web of Science from 2017 to 2021 to enable the inclusion of all original articles, which were limited to those published in English, for complete reading. The bibliographies of relevant articles were also searched for potentially eligible studies.

Two authors independently confirmed the search strategies and screened the studies. Subsequently, the two authors excluded articles that did not meet the criteria. Divergent viewpoints were resolved through discussions or by a third party. The search query resulted in 1710 non-duplicate results on the Web of Science. Of these, 253 articles were excluded because they were based on an unoriginal article. An additional 842 articles were excluded based on a language other than English, not defined as AD (e.g., itch, contact dermatitis, and allergic inflammation in mice), 3-dimensional skin modeling, and not including a mouse model. Finally, 614 articles were analyzed (Data availability, supplemental information).

4.2. Data extraction

Qualitative and quantitative information regarding the associations of interest was extracted from the included publications.

CRediT authorship contribution statement

Siqi Ye: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Lian Zhu:** Investigation, Data curation. **Tao Ruan:** Formal analysis, Data curation. **Jinjing Jia:** Investigation, Formal analysis. **Xiumei Mo:** Project administration, Formal analysis. **Fenggen Yan:** Investigation, Formal analysis. **Junfeng Liu:** Methodology, Formal analysis. **Yu Zhang:** Formal analysis. **Dacan Chen:** Writing – review & editing, Funding acquisition.

Data availability statement

The datasets are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2025.e41989.

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