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Review Article

Advanced Studies and Applications on Animal Models of Acne

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Abstract

Acne is a common chronic skin condition characterized by inflammation of the hair follicles and sebaceous glands, severely affecting patients‘ appearance and psychological well-being. Suitable animal models are fundamental for investigating the pathogenesis of acne and developing therapeutic strategies. This paper summarizes recent advancements in acne animal model research, exploring the construction methods of commonly used models, their advantages and limitations, and their applications in studying the pathogenesis of acne, screening drugs, and evaluating therapeutic efficacy. Additionally, recommendations for improving the design of animal models are provided to advance the field of acne research further. This review aims to offer guidance for acne vaccine research and the development of anti-inflammatory and antimicrobial drugs.

Keywords: Acne; *Propionibacterium acnes*; Animal models

Introduction

Acne is a prevalent chronic skin condition that primarily affects patients‘ appearance and psychological well-being, accompanied by inflammation of the hair follicles and sebaceous glands. In recent years, the number of acne patients worldwide has surpassed 640 million, with an overall prevalence rate of 20.5%. However, studies have shown that over 95% of individuals experience acne to varying degrees; among them, adolescents and young adults (ages 16-24) have the highest prevalence, reaching 28.3% [1]. Acne primarily occurs on the face and manifests as non-inflammatory lesions such as papules, pustules, nodules, and cysts. Its aetiology includes excessive sebum secretion, abnormal keratinization of the hair follicle and sebaceous duct, proliferation of *Propionibacterium acnes* (*P. acnes*), and inflammatory responses [2,3]. Despite the availability of various treatment options, the complex pathophysiological mechanisms of acne remain incompletely understood, and treatment outcomes vary between individuals, requiring further investigation. Animal models play a crucial role in studying skin diseases as they can simulate human physiological and pathological characteristics. Animal models not only facilitate in-depth exploration of the pathogenesis of acne but also enable the evaluation of therapeutic and preventive strategies, providing strong support for clinical applications.

This review summarizes recent advancements in acne animal models, discussing the application of different animal models in the study of acne pathophysiology, drug screening, and efficacy evaluation. By analyzing the construction methods and advantages and limitations of commonly used animal models, this review aims to provide a theoretical basis for acne re-search and clinical treatment and to offer suggestions for improving animal model design, thereby advancing the field of acne research.

The Mechanism of Acne Development

The pathogenesis of acne involves the interplay of various host factors, including dysbiosis of the follicular sebaceous microbiome, androgen stimulation of sebaceous glands, and cellular immune responses. The process begins with the formation of hyperkeratotic plugs, composed of keratinocytes, located in the lower part of the follicular infundibulum. With the accumulation of keratin and sebum, microcomedones gradually transform into closed comedones. As the follicular opening expands, open comedones are formed, appearing dark due to the presence of melanin and oxidized lipids. The proliferation of *Propionibacterium acnes* and its suppression of the cellular immune response further promote the development of inflammatory papules and pustules. Eventually, the rupture of the hair follicle releases bacteria, keratin, and pro-inflammatory lipids into the dermis, triggering inflammation and the formation of nodules [4,5].

Androgens (such as dihydrotestosterone) regulate sebaceous gland activity and promote sebum secretion by binding to androgen receptors in sebocytes, affecting multiple pathophysiological factors and thereby contributing to the formation of both non-inflammatory and inflammatory acne lesions [6]. Excess sebum provides a favourable environment for bacterial growth and facilitates the colonization of *Propionibacterium acnes*. Additionally, fatty acids in sebum accelerate the differentiation of keratinocytes and induce epidermal barrier dysfunction associated with acne formation. The proliferation of *Propionibacterium acnes* and other inflammatory mediators within the follicular sebaceous unit (such as defensins and cytokines) trigger inflammatory mechanisms, further promoting the development of acne lesions.

Unhealthy dietary habits have been identified as potential contributors to the development and severity of acne. Research suggests that whey protein in milk is associated with an increased risk of acne [7,8]. Additionally, alcohol exacerbates acne by elevating testosterone levels, promoting inflammatory responses, and facilitating the growth of Propionibacterium acnes, a key bacterium involved in acne pathogenesis [9]. Furthermore, there may be a significant association between obesity and acne vulgaris. Obesity has been linked to the development of acne, and adopting a low Glycaemic Index (GI) diet may help reduce acne severity. However, the impact of weight loss on acne improvement requires further investigation [10].

Types of Animal Models for Acne Research and Their Evaluation Criteria

Due to the differences in sebaceous glands, hair follicles, skin microbiota, and immune-inflammatory responses among various animal species, using different animals for ac-ne research can lead to diverse modelling results. Commonly used animal species for acne models include rabbits, rats, mice, guinea pigs, hairless mice, golden hamsters, Mexican hair-less dogs, miniature pigs, and rhesus monkeys. For instance, rhesus monkeys are primates with skin structures, physiological conditions, and immune responses similar to humans. However, their use in acne modelling is more expensive [11]. Miniature pigs share similar skin structures with humans, and their skin metabolism of 5-aminolevulinic acid mirrors that of humans [12]. Acne formation in Mexican hairless dogs resembles that of humans, but their acne develops spontaneously without the need for external stimulation [13]. Golden hamsters are sensitive to androgens, which can effectively influence sebaceous glands and hair follicles, making them a suitable acne model; however, they are not ideal for studying infection, inflammatory responses, or immune responses [14]. Hairless mice can develop acne lesions similar to human blackheads and have comparable physiological and histological features, but they do not exhibit secondary inflammation [15-17]. Guinea pig skin can develop inflammatory papules, and by intradermally injecting a suspension of human keratinocytes, an effective guinea pig acne model can be established [18]. Rat models are characterized by indicators such as ear redness, epidermal thickening, inflammation, excessive keratin secretion, and the accumulation of subcutaneous sebum and triglycerides (TG). Viaminate drug ameliorates rat acne model induced by *Propionibacterium acnes* by inhibiting keratinocyte proliferation and inflammatory response [19]. The most frequently used animal models for acne are mice and rabbits (Figure 1).

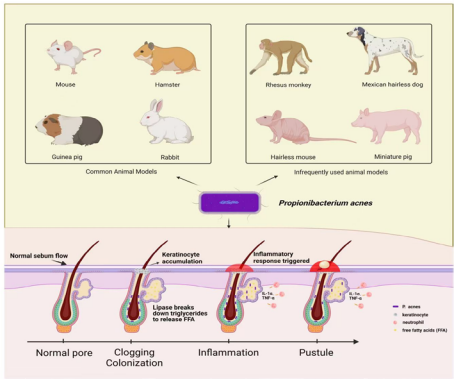

Figure 1: Acne animal models and pathogenesis.

Commonly used: Mice, guinea pigs, hamsters, rabbits (for studying *P. acnes*-induced inflammatory mechanisms); **Less utilized:** Rhesus monkeys, Mexican hairless dogs, hairless mice, miniature pigs. **Key pathogenesis:** Follicular hyperkeratosis → *P. acnes* proliferation → Immune cell recruitment → Inflammatory cascade. Figure created with Biorender (Biorender.com).

The skin structure of mice closely resembles that of humans, featuring a high density of hair follicles and widespread sebaceous gland distribution, which makes it an ideal model for investigating the pathogenesis and inflammatory processes of acne. Moreover, the skin‘s thin nature facilitates minimally invasive procedures. Two primary methods are commonly employed for establishing acne models in mice. The first involves the application of chemical substances to induce acne-like lesions, such as croton oil (a potent irritant) [20], carrageenan (a polysaccharide) [21], 2,4-dinitrochlorobenzene (a chemical irritant) [22], and oestrogen (a hormonal agent) [23]. These chemicals are typically applied daily to the ear pinna of the mice, provoking an inflammatory and immune response, thus establishing an acne model. The second method uses *Propionibacterium acnes* bacterial suspension, which is administered via intradermal injection into the dorsal skin of male mice at a concentration of 106-108 CFU/mL, followed by a 14-day observation period. During this time, clinical, pathological, and immunological assessments are conducted to evaluate the acne-like responses [24-27].

Rabbit skin is thicker, with larger and moderately dense hair follicles, making it an ideal model for studying complex skin pathophysiological processes, particularly in the fields of immunology and sebaceous gland function. Three primary methods are used to establish an acne model in rabbits. The first method involves the application of chemical agents alone. Chemicals, such as oleic acid [18,28], coal tar [29,30], tetradecane [31], squalene peroxide [32], and isopropyl myristate [31], are applied to the ear

of the rabbit daily for 14 days to induce an inflammatory response, thereby creating a rabbit ear acne model. The second method utilizes bacterial suspension alone, in which *Propionibacterium acnes* or Staphylococcus epidermidis suspension is injected into the inner ear of the rabbit, and lipid substances are applied to simulate the pore blockage seen in human acne. This model is induced by daily or alternate-day intradermal injections of *Propionibacterium acnes* suspension (1×10^8 CFU/mL, 30-100 μL) into the right ear [33]. The third method combines both chemical agents and *Propionibacterium acnes* for induction. Chemical agents simulate the surface sebum found in humans, and 0.5 mL of coal tar is applied daily for 14 consecutive days to the area near the ear canal opening on the inner side of the rabbit's right ear, while alternate-day injections of *Propionibacterium acnes* suspension are administered. This approach establishes a rabbit ear acne model [34].

In the establishment of the acne model, evaluation parameters typically include clinical assessment, pathological features, and immune response markers. Clinical assessment mainly focuses on the clinical presentation of acne, such as the type, number, distribution, severity of lesions, and the extent of skin inflammation. Pathological features generally involve the observation of skin tissue sections, evaluating follicular occlusion, sebaceous gland hypertrophy, local inflammatory responses, alterations in keratinocyte differentiation, bacterial burden, and *Propionibacterium acnes* colonization, among other pathological characteristics. Immune response markers include the assessment of inflammatory factors (e.g., proinflammatory cytokines TNF-α, IL-1β, IL-6, IL-8), immune cell infiltration (such as T cells and macrophages), and molecules related to immune tolerance or activation. These parameters collectively assist in the comprehensive evaluation of the acne model establishment and its simulation of acne's pathological mechanisms.

Current methods for constructing acne animal models face several challenges, particularly with chemical induction, which can adversely affect the stability and reproducibility of the models. For instance, the use of specific chemical agents, such as aldehyde compounds, may impact model reproducibility due to individual variations or changes in experimental conditions. As a result, improving the induction protocol to enhance model quality has become a primary focus of research. Possible optimization strategies include the combined use of multiple induction factors, such as hormonal treatments and bacterial infections, or employing gene editing technologies to develop specific models for studying the pathogenesis of acne. Furthermore, researchers are exploring more physiologically relevant induction methods, such as modulating the skin's microbiome or immune response, to more accurately reflect the underlying pathological processes of acne, thereby improving both the model's stability and its clinical applicability.

Application of Animal Models in Research

Application of Animal Models to Evaluate Potential Therapeutic Strategies

Animal models play a crucial role in evaluating potential therapeutic methods. They allow the simulation of human diseases, the validation of treatment effects, and the assessment of safety, efficacy, and side effects, providing critical preclinical data for drug development and clinical trials. These models help optimize treatment strategies, reduce clinical risks, and accelerate the research and development process. Various therapeutic agents have been studied using animal models for acne treatment, including plant extracts (e.g., thymol, rosmarinic acid, and other terpenoids and phenolic compounds), antimicrobial peptides (e.g., CEN1HC-Br, BLP-7), medium-chain fatty acids (e.g., decanoic acid, lauric acid), alkaloids (e.g., tetrahydroindolizidine alkaloids), synthetic drugs (e.g., adapalene), surfactants and lipids (e.g., surfactant oil gel), and other aromatic and phenolic compounds (e.g., quercetin, glycyrrhizin flavonoids). These agents are primarily utilized for antioxidant, antibacterial, and anti-inflammatory treatments and have also been explored in the context of monoclonal antibody and bacteriophage therapies.

Anti-inflammatory Drugs

The surfactant-oil gel significantly alleviates inflammatory acne vulgaris induced by *Cutibacterium acnes* in mice, improving symptoms such as epidermal swelling, erythema, and thickening while also reducing bacterial colony counts. Its mechanisms include reducing inflammation and oxidative stress and inhibiting the TLR-mediated activation of the NF-κB pathway, thus suppressing the inflammatory response [35].

The study employed a *Cutibacterium acnes* mouse model to evaluate the anti-inflammatory effects of *D. crepidatum* (DCE) and tetrahydroindoline alkaloid (HCA). The results demonstrated that HCA significantly reduced erythema and swelling in the mouse ear, decreased the expression of pro-inflammatory cytokines IL-1β and IL-8, and that *D. crepidatum* and its active ingredient HCA exert a protective effect against acne-related inflammation [36].

The Kyoto rhino Krh/krh rat is a well-established acne model induced by ethylnitrosourea and carrying the hairless gene. The study assessed the therapeutic effects of adapalene in this model. Twelve-week-old rats were treated with either adapalene or vehicle, six times a week for 12 weeks. The results showed that adapalene significantly reduced the open comedo area, lipid production, and increased epidermal thickness while promoting the production of IL-10 and IL-12a cytokines. The study suggests that adapalene effectively alleviates acne by regulating lipid metabolism and cytokine production [37].

Ethanol oregano extract (EOE) significantly inhibited Propionibacterium acnes-induced skin inflammation, with efficacy evaluated by assessing ear thickness and biopsy weight in mice [38]. Intradermal injection of ethanol rosemary extract (ERE) notably alleviated ear swelling and granulomatous inflammation induced by *Propionibacterium acnes* [39]. The total phenolic compound extract from bitter melon leaves (TPE) effectively reduced Propionibacterium acnes-induced ear inflammation in mice. In an 8-week-old male ICR mouse model, TPE was injected into the left ear (treated with *Propionibacterium acnes*) and the right ear (PBS control) for comparison. The results demonstrated that TPE significantly alleviated ear swelling and micro abscess formation [35]. Additionally, Banana Peel Extract (MBPE) exhibited strong anti-inflammatory effects by inhibiting nodule formation, bacterial growth, and the production of pro-inflammatory cytokines, including IL-1α, IFN-γ, TNF-α, and IL-8 in rats [40]. Quercetin, a polyphenolic antioxidant, significantly reduced ear erythema, swelling, granulomatous reactions, and inflammatory cell accumulation in *Propionibacterium acnes*-induced mice. This suggests that quercetin could serve as a potential treatment for *Propionibacterium acnes*-induced skin inflammation, with potential applications in both pharmaceuticals and cosmetics [41]. In another study, the anti-acne effects of all-trans retinoic acid and Nobiletin ex-tract were compared in hamsters. After 15 days of topical treatment, both 2% Nobiletin extract and 0.2% all-trans retinoic acid significantly reduced the size of sebaceous glands and decreased triglyceride (TG) levels on the skin surface, suggesting that Nobiletin extract could be an effective anti-acne agent [42]. In a separate experiment, acne was induced in rats. Topical application of liquorice flavonoid gel for 14 days reduced hyperkeratosis, inhibited the inflammatory response, and decreased the expression of IL-8 and TNF-α in both serum and skin, suggesting that liquorice flavonoids exert anti-acne effects by modulating the skin microbiome and metabolic balance [43]. Finally, liquorice chalcone A was shown to inhibit ASC speck formation and mitochondrial Reactive Oxygen Species (ROS) production induced by Propionibacterium acnes. Topical application of liquorice chalcone A reduced ear skin inflammation in mice and lowered caspase-1 activity and IL-1β production in the ear. As an NLRP3 inflammasome inhibitor, liquorice chalcone A effectively modulated Propionibacterium acnes-induced skin inflammation [44].

Anti-inflammatory and antimicrobial agents

Lauric acid, a medium-chain fatty acid, demonstrates notable bactericidal properties. Studies have indicated that both intradermal injection and topical application of lauric acid effectively reduce the colonization of *Propionibacterium acnes* in mouse ears and alleviate ear swelling and granulomatous inflammation induced by the bacterium. Compared to capric acid, lauric acid exhibits more potent antimicrobial activity against *Propionibacterium acnes*, and both compounds reduce ear swelling and the formation of micro abscesses in mice [45,46].

The antimicrobial peptide CEN1HC-Br exhibits bactericidal effects against Propionibacterium acnes. It exerts anti-inflammatory actions by downregulating TLR2 and inhibiting the expression of pro-inflammatory cytokines, including IL-8, TNF-α, and MMP-2, thereby reducing ear oedema in rats [47]. In a rat model of ear oedema, the antimicrobial peptide BLP-7 significantly inhibited *Propionibacterium acnes*-induced skin inflammation, reducing ear thickness by 54.21% compared to the negative control group, highlighting its anti-acne and anti-inflammatory properties [48]. In a rat model of ear oedema, the antimicrobial peptide BLP-7 significantly inhibited *Propionibacterium acnes*-induced skin inflammation, reducing ear thickness by 54.21% compared to the negative control group, highlighting its anti-acne and anti-inflammatory properties [49].

A heat-inactivated *Propionibacterium acnes* vaccine administered intranasally to mice successfully induced specific antibodies, providing protective immunity against Propionibacterium acnes and promoting the resolution of ear inflammation. The generated antibodies effectively neutralized cytotoxicity and reduced the production of the pro-inflammatory cytokine IL-8 in sebocytes [50]. Currently, two monoclonal antibody therapies targeting IL-1α and IL-17A are undergoing clinical trials to evaluate their effectiveness in treating moderate to severe acne vulgaris [51,52].

Phage therapy is an emerging treatment for acne that targets explicitly pathogenic bacteria, avoiding damage to beneficial bacteria. This specificity helps mitigate the side effects associated with traditional acne therapies [53]. In a study, 38 female ICR mice, aged 8 weeks, were subcutaneously injected with one of eight newly isolated phage strains or physiological saline (control group) on their backs, followed by the application of artificial sebum to the injection sites for two consecutive days. On day 3, the phage-treated group developed inflammatory acne lesions, while the control group exhibited only mild skin elevation. Researchers photo-graphed the lesions and assessed their diameter, height, and scabbing daily. On day 10, the mice were euthanized for tissue biopsy and histopathological examination. Bacterial and phage counts in the lesion sites were determined using colony-forming units (CFU) and Plaque-Forming Units (PFU), respectively. Results demonstrated that phage treatment significantly reduced bacterial load and inflammation at the lesion sites [54].

Potential preventive strategies for the application of animal models in research

Acne vaccines induce the immune system to generate specific antibodies [50], neutralize the cytotoxic effects of *Propionibacterium acnes*, and reduce the release of pro-inflammatory factors, thus preventing the onset and progression of acne. Compared to traditional drug therapies, acne vaccines offer more durable and specific therapeutic effects. Acne animal models play a crucial role in vaccine development and testing, as they can replicate the inflammatory response seen in human acne, assess immune activation, antibody production, and the ability

to neutralize bacterial toxicity, providing scientific evidence for the safety and efficacy of the vaccine. For instance, candidate vaccines include those targeting toxin factors such as CAMP factor immunotherapy antibodies, sialidase, hyaluronidase, and antimicrobial peptides.

Toxin factors

The currently available *Cutibacterium acnes* vaccine can prevent acne but does not offer therapeutic effects nor neutralize its virulence factors. To address this limitation, researchers have developed an immunotherapeutic antibody targeting the CAMP factor of *Cutibacterium acnes*. The CAMP factor was encapsulated in radish leaves using agrobacterium-mediated infiltration technology, followed by nasal immunization in mice, successfully inducing neutralizing antibodies, which significantly alleviated the inflammatory response caused by *Cutibacterium acnes*. The neutralization of the CAMP factor effectively suppressed bacterial growth at the infection site without disrupting bacteria in other areas. The study suggests that the CAMP factor is a promising new target for the treatment of *Cutibacterium acnes*-related diseases [55].

Bacterial sialidase

A vaccine designed to target inflammatory acne caused by *Propionibacterium acnes* consists of sialidase anchored to the cell wall of *Propionibacterium acnes* or inactivated *Propionibacterium acnes*. Studies indicate that this vaccine induces protective immunity in ICR mice and reduces the elevation of specific cytokines induced by *Propionibacterium acnes*. Mice immunized with sialidase produce detectable antibodies that can effectively neutralize the cytotoxic effects associated with *Propionibacterium acnes*-induced interleukin-8 (IL-8) in sebocytes. Furthermore, these mice show evidence of protective immunity, as demonstrated by reduced ear swelling and a decrease in the release of the pro-inflammatory macrophage inflammatory protein-2 (MIP-2) [56].

Hyaluronidase

The hyaluronidase variants HylA and HylB of *Propionibacterium acnes* are closely associated with acne and health conditions. In the mouse acne model, after anaesthesia with isoflurane vapor, *Propionibacterium acnes* bacterial suspension was intradermally injected into 8-week-old female mice, and a synthetic sebum analog was applied daily. After 24 or 48 hours of infection, disease severity was assessed, and the mice were sacrificed. Skin lesions were harvested and homogenized, and Colony-Forming Units (CFU) were quantified on Brain Heart Infusion (BHI) agar plates. HylA exerts a potent pro-inflammatory effect, while HylB demonstrates anti-inflammatory properties. HylB is linked to health by mitigating inflammation through the degradation of Hyaluronic Acid (HA) into HA disaccharides, whereas HylA generates large HA fragments that activate the TLR2-dependent inflammatory response. Substituting the serine near the catalytic site of HylA with glycine enhances its enzymatic activity, resulting in an HA degradation pattern intermediate between that of HylA and HylB. Selective targeting of HylA with peptide vaccines or inhibitors can alleviate pathological changes associated with acne [57].

Antimicrobial Peptides

Cathelicidins are a class of multifunctional antimicrobial peptides involved in innate immune responses. Cathelicidin-BF exhibits potent antimicrobial activity against *Cutibacterium acnes* and also demonstrates significant bactericidal effects against other microorganisms such as *Staphylococcus epidermidis*. In the murine skin colonization model, *Cutibacterium acnes* was cultured to the exponential phase in BHI broth. The bacterial cells were then washed and resuspended in a sodium chloride solution. Following this, 1×10^7 CFU/20 ml of the bacterial suspension was intradermally injected into the left ear of Kunming mice. In contrast, the same volume of sodium chloride solution was injected into the right ear as a control. A placebo gel, antimicrobial peptide-BF gel, or 0.2% clindamycin gel was applied to the ear, and the area was sealed with dressings and tape. After 24 hours, ear thickness changes were measured. The left ear was excised, the gel was removed, and the ear was homogenized. Following homogenization, the bacterial count was determined by CFU enumeration. The homogenate was incubated anaerobically at 37°C for 72 hours, and bacterial counts were recorded. The Cathelicidin-BF gel was shown to alleviate swelling and granulomatous inflammation in the ear induced by *Cutibacterium acnes*, confirming its anti-inflammatory properties [58].

Recent Advances in Animal Models for Acne Research

Zebrafish Model in Acne Research

Zebrafish, with its simple skin structure and ease of observation and manipulation, has emerged as an ideal model for studying skin development and dermatological diseases. The well-established gene editing techniques in zebrafish make it a valuable tool for investigating the functional roles of genes associated with acne. UP256 is a widely used drug for acne treatment and may also offer therapeutic potential for conditions related to excessive skin pigmentation. Using the zebrafish model, researchers can quantify melanin levels to assess the efficacy of UP256 in such conditions [59].

SKH-hr1 Hairless Mouse Model

Hairless mice, caused by a mutation in the Hr gene on chromosome 14, exhibit a lack of significant hair growth while retaining sebaceous glands and hair follicles, making them ideal for long-term monitoring of skin changes. A comparative analysis was performed using clinical evaluations, histopathological examinations, photographic documentation, biophysical measurements, and blood analyses. The results show that SKH-hr1 mice are particularly suit-able for acne treatment and prevention research [60]. This study evaluated the effectiveness of anti-acne drugs by comparing untreated mice with those treated with established effective therapies, with a specific focus on their impact

on the early stages of acne lesions and the recurrence of acne after treatment. Despite the advantages of the mouse model, limitations exist, including the potential for improper injection techniques and variations in skin thickness, which may affect the comparability of results. Future studies should extend the experimental duration and provide a comprehensive assessment of the spontaneous healing process in these models.

Novel Techniques for Acne Assessment

The novel acne evaluation techniques include the following categories: 3D image analysis, which effectively assesses lesion parameters and serves as a key tool for evaluating acne severity and guiding the selection of treatment methods; the VISIA-CR skin analysis system (a skin UV spectral imaging device), which rapidly captures high-definition images and evaluates changes in acne through multi-angle polarized light; and the RBX-red technology, which uses orthogonal polarized imaging to detect haemoglobin levels, reflecting vascular alterations and the degree of inflammation [61].

Conclusions and Future Directions

Acne animal models are pivotal in understanding the underlying pathological mechanisms, evaluating treatment strategies, and advancing new drug development. Although existing models, such as those involving mice, rats, rabbits, and pigs, each have their distinct advantages and limitations, they vary in their ability to replicate the complex pathological processes observed in human acne. Despite these differences, animal models continue to be indispensable tools for screening potential therapies and assessing their efficacy, particularly in studies involving the microbiome, immune response, and skin barrier function. Such models are expected to be central to future research in these fields. These studies not only enhance our understanding of acne pathogenesis but also offer critical insights for developing novel therapeutic strategies.

For the successful translation of findings from acne animal models to clinical applications, the transition from animal studies to clinical trials must be expedited while addressing technical, ethical, and regulatory challenges. From a technical standpoint, it is essential that animal models accurately reflect the diverse pathological features of human acne, supported by the development of efficient, reproducible experimental protocols. Ethically, the principle of the 3Rs (Replacement, Reduction, and Refinement) should guide the use of animals in research, emphasizing alternatives to animal testing, minimizing animal usage, and reducing suffering. On the regulatory front, there is a need to standardize animal research data and streamline clinical trial design. Additionally, fostering a robust connection between animal models and clinical research, through a feedback loop, allows researchers to refine model design based on clinical observations, ensuring that animal study results translate into actionable insights for clinical treatment. These strategies will accelerate the clinical implementation of novel acne therapies, contribute to the advancement of precision medicine, and enhance the real-world impact of animal model research in acne prevention and treatment.

Future research should prioritize the development of more comprehensive and accurate animal models that closely mimic the pathophysiology of human acne. This endeavour requires a multifaceted approach, considering factors such as the structure and function of the hair follicle-sebaceous gland unit, the colonization of *Propionibacterium acnes*, immune responses, and androgen regulation. Combining various modelling techniques may offer a more representative simulation of human acne. With advancements in gene editing, tissue engineering, and stem cell technologies, the creation of more humanized animal models is now feasible. For instance, gene editing can be used to develop models with hair follicle-sebaceous gland units that closely resemble those found in humans. At the same time, tissue engineering allows the generation of three-dimensional skin models to simulate human skin‘s physiological conditions. Additionally, stem cell technologies can be employed to generate hair follicle-sebaceous gland cells, repair skin tissue, and optimize the pathological characteristics of these models. Moreover, integrating multi-omics approaches (such as genomics, transcriptomics, proteomics, and metabolomics) provides powerful tools to deepen our understanding of acne‘s pathogenesis. By analyzing the genetic, transcriptomic, proteomic, and metabolic changes in animal models, researchers can identify potential biomarkers and therapeutic targets, laying the groundwork for personalized acne treatments. Given the genetic and clinical variability in acne patients, the establishment of individualized animal models based on specific patient data will provide valuable insights for tailored drug development and therapeutic interventions, ultimately enhancing the precision and efficacy of acne treatment.

Conclusion

In conclusion, while significant progress has been made in the development of acne animal models, numerous challenges remain. Through ongoing innovation and refinement, the creation of more ideal models will lay the foundation for a deeper understanding of acne pathogenesis and the development of effective prevention and treatment strategies.

Author Contributions

Conception, Z.W. and J.G.; Methodology, Z.W. and J.G.; Software (searching for sources), T.L.; Verification (source), Z.W. and J.G.; Formal analysis, Z.W. and J.G.; Writing-original draft preparation, T.L.; Writing-review and editing, T.L., Z.W., and J.G.; Supervision, Z.W. and J.G. All authors have read and agreed to the published version of the manuscript.

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