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# Microbial Dysbiosis and Immune–Barrier Interactions in Atopic Dermatitis: A Review

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ABSTRACT

Atopic dermatitis (AD) is a multifactorial inflammatory skin disease characterised by immune dysregulation, skin barrier dysfunction, and microbial imbalance, which collectively contribute to a substantial global health burden. Epidemiological evidence shows increasing prevalence worldwide, with pronounced rises in urbanised Asian populations and early childhood. Advances in molecular and multi-omics approaches have transformed skin microbiome research, revealing consistent patterns of reduced microbial diversity and dominance of *Staphylococcus aureus*, alongside complex interactions with protective commensals such as *Staphylococcus epidermidis*. These microbial shifts exacerbate type 2 immune responses and barrier disruption, establishing a self-perpetuating cycle of chronic inflammation. Advances in molecular and multi-omics approaches have enhanced understanding of AD heterogeneity, linking genetic factors, skin barrier impairment, and immune–microbiome interactions to disease pathogenesis. This review summarises current insights into the role of the microbiome in AD, emphasising host–microbe interactions, geographic and ethnic differences, and novel therapeutic opportunities targeting microbial modulation. Future progress requires harmonised, multicentre, longitudinal studies that integrate immunological, genetic, microbial, and barrier-related data to unravel AD complexity. Such approaches will enable precision medicine strategies and robust evaluation of novel interventions, addressing a critical need for effective and tailored therapies across diverse populations.

## INTRODUCTION

Atopic dermatitis (AD), also known as eczema, is a complex inflammatory skin disorder characterized by several interrelated pathophysiological mechanisms, including impaired skin barrier function, immune dysregulation, and altered microbial diversity (Sroka-Tomaszewska & Trzeciak, 2021). AD causes severe

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itching and recurrent eczematous lesions (Weidinger & Novak, 2016). Symptoms of AD vary in intensity, scope, and duration over time. AD symptoms vary in intensity, scope, and duration, and significantly impact quality of life. Individuals with AD may experience comorbidities and exhibit diverse responses to treatment (Chovatiya & Silverberg, 2022).

Globally, AD prevalence has increased, particularly in Asian populations and urban areas (Cheng et al., 2021). While high-income regions experience the greatest burden, variation in prevalence rates (0.96% to 22.6% in Asian children and 1.2% to 17.1% in European adults) highlights the geographical and ethnic differences (Bylund et al., 2020). The Asia Pacific region has seen a recent increase in AD prevalence. For instance, in China, the prevalence varies, with estimates ranging from 5-10% in urban areas (Gu et al., 2023). In South Korea, reports indicate prevalence rates of 10-20% among children, while Malaysia shows a prevalence of about 13.8%, particularly in children, with higher rates observed in urban areas (Hadi et al., 2021). Genetic polymorphisms associated with AD are shared among Asian populations globally but rare in other ethnic groups (Cheng et al., 2021). This highlights the need for a better understanding of (Suaini et al., 2020). These findings emphasize the importance of considering ethnic differences in clinical and immuno-phenotypes in future AD research and treatment development.

The pathogenesis of AD involves immune system signalling disruption, skin barrier dysfunction, and increased *Staphylococcus aureus* bacteria on the skin (Edslev et al., 2020). These factors create a self-perpetuating cycle of inflammation and skin damage (Bjerre et al., 2021). While AD's aetiology is multifactorial, recent studies increasingly highlight the role of the skin microbiome in disease pathogenesis (Demessant-Flavigny et al., 2023; Yang et al., 2020). Microbial dysbiosis, characterized by reduced bacterial diversity and a shift towards pathogenic bacteria, further exacerbates inflammation and skin damage by disrupting host–microbe homeostasis (Bjerre et al., 2021; Hrestak et al., 2022). Dysbiosis promotes aberrant immune activation, such as increased Th2-skewed responses and impaired antimicrobial peptide production, thereby linking microbiome imbalance to immune dysregulation in AD (Blicharz et al., 2021; Fyhrquist et al., 2023) .

This review examines the complex epidemiology and pathophysiology of AD, with a focus on the role of the skin microbiome in disease progression. Special emphasis is placed on genetic, environmental, and microbial factors. By analysing recent findings, this review highlights the critical role of microbial communities in shaping disease onset, severity, and response to therapy as well as the need for personalized AD management through microbiome-targeted therapies.

## PATHOGENESIS OF AD

The complex pathogenesis of AD results from genetic predispositions, and environmental and immunological factors (Pareek et al., 2024). It involves an interplay of impaired epidermal barrier, immune dysregulation, and alterations in the skin microbiome (Patrick et al., 2021; Sroka-Tomaszewska & Trzeciak, 2021). These interconnected factors create a vicious cycle that bolsters inflammation of AD, barrier dysfunction, and increased susceptibility to environmental triggers.

### Immune Dysregulation in AD

One of the primary defects of AD is characterized by dysregulated immune responses (Patrick et al., 2021). The pathogenesis involves complex interactions between innate and adaptive immunity, with keratinocytes playing a crucial role in triggering downstream immune responses (Ong, 2022). AD is primarily marked by Th2-skewed immune response, with involvement of Th1, Th17, and Th22 pathways (Rothenberg-Lausell et al., 2024). Key cytokines implicated in AD include IL-4, IL-13, and IL-31, which contribute to immune abnormalities and pruritus (Dubin et al., 2021). It drives both acute and chronic phases of the disease. In the acute phase, the immune response is driven by Th2 cytokines, notably IL-4, IL-5, and IL-13 (Alsabbagh & Ismaeel, 2022; Duca et al., 2021). These cytokines disrupt keratinocyte

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differentiation by inhibiting the expression of proteins like filaggrin, compromising the skin barrier integrity (Beck et al., 2022; Howell et al., 2007). In addition, these cytokines, particularly IL-4 and IL-13 downregulate the antimicrobial peptide (AMP) levels, which leads to increased vulnerability of the skin to secondary skin infections (Duca et al., 2021).

While Th2 cytokines dominate, there is evidence supporting the involvement of Th1 and Th17 cytokines in AD pathogenesis (Alsabbagh & Ismaeel, 2022; Ong, 2022). As the disease transitions to its chronic phase, the immune response evolves to involve Th1, Th2/Th22, and Th17 cells (Duca et al., 2021). Recent research by Tsoi et al. (2020) demonstrates that the alterations associated with the shift from non-lesional to acute, and then to chronic inflammation in AD are primarily quantitative rather than qualitative with augmentation of Th2, Th1, Th17, and IL36 responses in the chronic phase of the disease. Th17 cells produce IL-17, a potent pro-inflammatory cytokine that contributes to neutrophilic inflammation and amplifies the inflammatory cascade (T. Liu et al., 2020; Ruiz de Morales et al., 2020). This cytokine not only fosters an inflammatory environment but also disrupts the skin barrier, making it more susceptible to allergens and pathogens (Ruiz de Morales et al., 2020). The IL-36 family of cytokines (including proinflammatory IL-36α, IL-36β, and IL-36γ) has emerged as significant contributors to chronic inflammation in AD (Ahmad et al., 2024). These cytokines, primarily expressed in barrier tissues like the skin keratinocytes, signal through the IL-36R heterodimer, activating inflammatory pathways (Ahmad et al., 2024). IL-36 cytokines play a crucial role in communication between the epidermis and the immune system, influencing both innate and adaptive responses (Ahmad et al., 2024).

**Interaction Between Skin Microbiome and Immune Pathways**

The skin of individuals with AD is frequently colonized by *S. aureus*, which can be present in up to 90% of lesional and non-lesional skin (Ogonowska et al., 2021). This colonization highlights the dynamic interplay between the skin microbiota and the immune system, as the microbiota interacts with epithelial and immune cells to maintain barrier integrity and functional immunity (Kobayashi & Imanishi, 2021). The relationship between the microbiome and immune pathways of AD is bidirectional (Wrześniewska et al., 2024). Immune dysregulation in AD fosters an environment conducive to microbial dysbiosis, while this dysbiosis can further drive inflammation by activating immune responses. For instance, S. aureus superantigens stimulate dendritic and T cells, amplifying Th2 and Th17 responses (Clowry et al., 2024). This dysbiosis correlates with elevated levels of pro-inflammatory cytokines, including IL-4, IL-33, and thymic stromal lymphopoietin (TSLP) (Amar et al., 2022).

TSLP, an epithelial-derived cytokine primarily expressed by keratinocytes, plays a crucial role in initiating and amplifying Th2-type immune responses (Luo et al., 2023). It acts on dendritic cells, promoting their maturation and the subsequent activation of naive T cells towards a Th2 phenotype. Elevated levels of TSLP are often observed in patients with AD, particularly in areas of skin barrier disruption. Notably, TSLP contributes to the inflammatory milieu by promoting the secretion of other cytokines, such as IL-4 and IL-13, while also enhancing the skin's susceptibility to microbial colonization, particularly by S. aureus. Moreover, TSLP, along with IL-33 and IL-25, triggers the production of type 2 cytokines, including IL-4, IL-13, and IL-5 (Nakajima et al., 2021; Ong, 2022). These cytokines, primarily produced by Th2 cells, significantly contribute to the characteristic features of AD (Nakajima et al., 2021). Additionally, IL-31, another type 2 cytokine, induces pruritus by acting on sensory neurons (Takahashi et al., 2023). TSLP's immunomodulatory activity extends beyond Th2 responses, influencing Th17 responses, skin fibrosis, epidermal hyperplasia, and angiogenesis (Wang & Zuo, 2021).

The immune response in AD is dominated by type 2 T-helper cells, leading to increased expression of IL-4, IL-5, and IL-13 (Çetinarslan et al., 2023). The IL-4/IL-13 axis is particularly important for driving the inflammation characteristic of AD (Pappa et al., 2022). Epithelial cells produce alarmins like TSLP, IL-33, and IL-25, which activate group 2 innate lymphoid cells (ILC2s) and promote type 2 immune reactions (Kobayashi & Imanishi, 2021). The JAK-STAT signalling pathway modulates

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multiple immune axes involved in AD, including the transduction of Th2 cytokines and regulation of the epidermal barrier (Huang et al., 2022).

Recent studies using spatial and single-cell transcriptomics have revealed unique cellular interactions in AD lesions, including crosstalk between activated fibroblasts, M2 macrophages, dendritic cells, and T cells (Mitamura et al., 2023). The innate immune system plays a crucial role in AD, with various cell types and pattern recognition receptors contributing to the inflammatory response through cytokine production, including TNF-α (Pan et al., 2024; Yamaguchi et al., 2023). TNF-α promotes the expression of adhesion molecules on endothelial cells, facilitating the recruitment of inflammatory cells to the skin, and enhances the production of other pro-inflammatory cytokines, creating a cascade effect that amplifies inflammation (Fania et al., 2022; Jang et al., 2021).

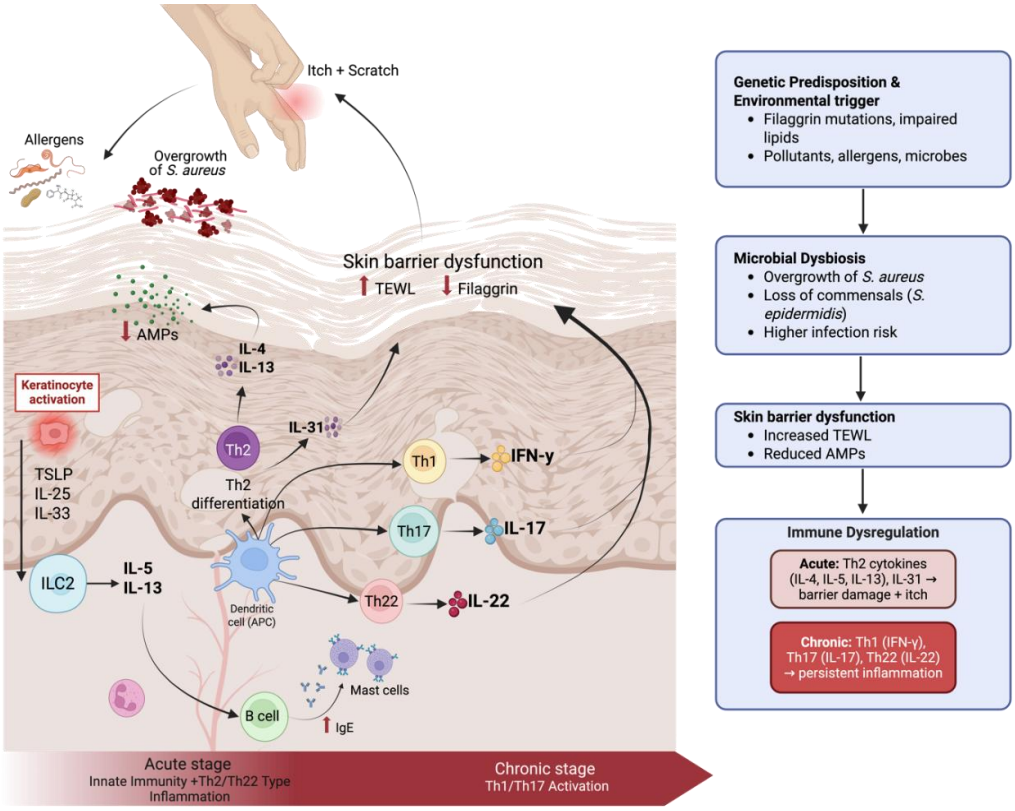


**Fig. 1.** Interplay of skin barrier dysfunction, microbial dysbiosis, and immune dysregulation in AD

## THE SKIN MICROBIOME AND AD

The skin is the body's largest organ and also serves as a primary defence barrier against various environmental insults (Harris-Tryon & Grice, 2022). The skin microbiome, an intricate ecosystem of microorganisms, plays a pivotal role in maintaining skin health (Harris-Tryon & Grice, 2022). One of its core functions is to shield us from pathogenic microorganisms, such as S. epidermidis(Nørreslet et al., 2022). It achieves these goals by sheer aggressiveness which is competing for resources and places to adhere to the body by producing antimicrobial peptides and modulating tensions in the local immune response. These activities prevent infections that try to take hold while maintaining a dynamic state of

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equilibrium in community type with other populations of microbes on your skin's surface. Furthermore, the skin microbiome also affects the skin barrier (Harris-Tryon & Grice, 2022). Certain bacteria on the skin, like S. epidermidis, produce compounds that prompt the body to generate moisturizing proteins and lipids essential for maintaining the skin's softness and protective qualities, especially in demanding environmental conditions. Also, the skin microbiome educates and modulates immune responses by inducing tolerance to commensals like Streptococci sp., balancing survival and pathogen defence (Zheng et al., 2020).

Several factors influence not only the composition but also the balance of skin microbiota. These include genetics, age, and gender, as well as extrinsic factors like environmental exposure, lifestyle, and skincare practices (Moskovicz et al., 2020; Skowron et al., 2021). Genetic predispositions can influence which kinds of microbes will thrive on the skin (Skowron et al., 2021). Genetic differences mean that some people have more types of microorganisms than others. Variations in immune system genes can affect how human skin responds to microbial colonization and infection. The skin microbiome goes through many changes in one's life. The skin microbiome begins to form at birth and is influenced by several factors (Townsend & Kalan, 2023). These include how the baby is delivered, the mother's microbiota, any antibiotic treatments, hygiene practices, nutritional deficiencies, living conditions, contact with animals or pets, and overall environmental exposure (Santiago-Rodriguez et al., 2023). At first children are colonized by their mother’s bacteria when they leave the womb, but then as a child grows its skin changes (Ronan et al., 2021).

Moreover, different hormones secreted by men and women can affect the properties of their skin, such as sebum production. This in turn affects what microorganisms will grow there (Chu et al., 2021). Skin microbiota can be enriched by the environment, such as climate, pollution, and UV radiation. For example, a kind of UV light reduces the diversity of skin bacteria. This leads to dysbiosis in skin. The skin microbiome is profoundly affected by everyday practices such as diet, hygiene, and the use of skincare products (Skowron et al., 2021). For example, frequent use of antibiotics or antiseptics and harsh cleansing products can upset microbial balance, leading to skin diseases.

According to Skowron et al. (2021), the skin's healthy microbiome is composed of bacteria, fungi, viruses, and mites. The bacteria of the most well-studied component, include genera like Staphylococcus, Corynebacterium, Cutibacterium and Micrococcus. Each of these genera plays specific roles in ensuring skin health and homeostasis. Both commensal and pathogenic species belong to Staphylococcus. S. epidermidis, a commensal bacterium, emits antimicrobial peptides to inhibit the colonization of pathogenic species such as S. aureus. Nevertheless, an overpopulation of pathogenic Staphylococcus species can result in skin infections and worsen some diseases (Koh et al., 2022). Corynebacterium sp. which is sweat-fat decomposing bacteria, are involved in the sweat and sebum disassembly process, they give the skin its smell and keep it in a stable state of balance. They also participate in modulating nearby immune responses. A largely sebum-associated bacterium, Cutibacterium sp. produces lipases that degrade sebum to help maintain skin health (Mayslich et al., 2021). However, it can also contribute to an outbreak of acne. Micrococcus sp., while of greatly less note, is known to be found in the natural skin flora and helps to increase the diversity as well as balancing out its overall microbiome (Panthee et al., 2022). Understanding healthy microbiota functions sets a foundation for identifying disruptions contributes to AD pathogenesis.

## Skin Dysbiosis: Characterization of AD-Associated Skin

AD is associated with alterations in the skin microbiota, a condition known as microbial dysbiosis (Mazur et al., 2023). Microbial diversity in healthy skin, involving *Staphylococcus, Corynebacterium*, and *Cutibacterium*, is key to homeostasis and pathogen defence (Skowron et al., 2021). However, in AD patients, this complex community is profoundly disrupted. According to Koh et al. (2022), those with AD often have reduced counts of protective skin commensals, resulting in a fragile population that struggles to safeguard the barrier and avoid inflammation.

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**Table 3**: Evidence on Skin Microbiome Alterations in AD Patients

| Studies | Study Design | Country | Sample Size | Key findings | Methodology | Limitations |
|---|---|---|---|---|---|---|
| **Bjerre et al. (2021)** | Case-control study | Denmark | 15 | Dysbiosis in AD involves low bacterial diversity and elevated *Staphylococcus* spp. | Shotgun metagenomics | Small sample size and lack of investigation into microbiota interactions (bacteria, fungi, viruses) in AD. |
| **Suwarsa et al. (2021b)** | Pilot study | Indonesia | 16 | *S. aureus* was prevalent in moderate AD with reduced microbial diversity compared to mild AD and healthy controls | 16s rRNA gene sequencing | Potential lack of generalizability due to the small sample size |
| **Khadka et al. (2021)** | Randomized-control trial | Mexico | 42 | Elevated relative abundances of *S. aureus* in patients were associated with the severity of AD and a decrease in apparent alpha diversity. | 16S rRNA gene sequencing | Small sample size limits treatment comparison power; non-standardized emollient and corticosteroid use; uncharacterized host factors; lack of blinding may introduce bias. |
| **Edslev et al. (2021)** | Cross-sectiona study | Denmark | 184 | Staphylococcal communities on skin are associated with AD severity, with increased *S. aureus*, *S. capitis,* and *S. lugdunensis*, and decreased *S. hominis,* correlated with disease severity. | 16S rRNA and tuf amplicon sequencing | Inconsistent sampling locations and treatments may have influenced results; 16S rRNA qPCR estimates may be affected by copy number variations. |
| **Fonfara et al. (2024)** | Longitudinal cohort study | Germany | 50 | Elevated proinflammatory biomarkers and altered skin microbiome precede paediatric AD onset | Luminex and 16S amplicon sequencing | Small sample size; lack of follow-up samples for severity analysis; limited to volar forearm samples, affecting generalizability. |
| **Rauer et al. (2023)** | Cohort study | USA | 48 | *S. aureus* dominated the skin microbiome in 79% of AD samples, 49% in lesional and 28% in non-lesional sample | 16S rRNA gene sequencing | Small sample size limits generalizability; insufficient representation of diverse populations may affect findings. |

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|---|---|---|---|---|---|---|
| **Li et al. (2024)** | Case-control study | China | 100 | Children with AD showed reduced microbiota diversity and downregulated metabolic pathways | 16S rRNA gene sequencing | Collecting samples at a single time point may not capture the variability of microbiota across different conditions or time periods |
| **Olesen et al. (2022)** | Longitudinal cohort study | Denmark | 38 | Infants with AD had less rich and slower maturing skin microbiomes than healthy infants. | 16S rRNA gene sequencing | Small sample size; variation in lesion location and treatments may skew results; healthy infants 4 months younger may affect age-related observations. |
| **Huang et al. (2024)** | Observational study | China | 36 | AD patients exhibited reduced bacterial species richness and evenness, a significant increase in Staphylococcus abundance, with gender-based differences observed only in healthy individuals. | 16S rRNA gene sequencing | Small sample size, and sampling limited to the elbow fossa excluding microbiota variations at other AD-affected sites. |
| **Yang et al. (2024)** | Observational study | China | 172 | The AD group showed reduced microbiota diversity, with increased Staphylococcus dominance correlating negatively with other genera and consistent across age groups. | 16S rRNA gene sequencing | Statistical power may be compromised by subgroup analysis, and the correlational nature of the analysis restricts the ability to infer causation. |
| **Rapin et al. (2023)** | Observational study | Norway a Sweden | 346 | Distinct temporal variations in skin bacterial composition were observed in the first year of life, influenced by age and delivery mode, which significantly affected microbiome colonization at birth. | 16S rRNA gene amplicon sequencing | The reliance on parental questionnaires may introduce bias, and sampling from only the lateral upper arm could fail to capture the full diversity of the skin microbiome across different body sites. |

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The balance between members of the skin microbial communities and the immune system plays a pivotal role in guarding against cutaneous disorders (Zhou et al., 2020). The balance of the skin microbiome can be disrupted by internal factors leading to dysbiosis (Smythe & Wilkinson, 2023). The development and exacerbation of AD have been associated with skin dysbiosis (Y. Liu et al., 2020). As reviewed by Kim and Kim (2019), individuals with AD exhibit lower gut microbiome diversity, lower presence of beneficial species like *Bifidobacterium*, and increased harmful bacteria species. Specifically, AD is primarily attributed to a decrease in microbial diversity and an increased presence of *S. aureus* on the skin.

AD patients during acute phases, reduced bacterial diversity coupled with *S. aureus* domination creates an environment conducive to inflammation exacerbation due to impaired skin barrier function (Fölster-Holst, 2022). Moreover, the skin microbiome in patients with AD shows deviations in species composition, leading to contamination by opportunistic pathogens. These pathogens can cause progression of the disease and provoke the development of secondary pyogenic skin infection (Chernushevich et al., 2023).

Microbial communities on the skin comprising various organisms play critical roles in maintaining proper immune function (Hrestak et al., 2022). Disruption of this cutaneous microbiome balance can lead to immune system dysregulation and contribute to inflammatory skin conditions like AD. Interestingly, the percentage of exacerbation in patients correlates with overrepresentation in *S. aureus* (Olisova et al., 2021). Additional research on the impact of skin microbiome on AD might reveal treatment approaches focusing on re-establishing a balance withing the skin microbial community.

**Abundance and Virulence Factor of Key Bacteria**

*S. aureus,* an opportunistic gram-positive bacterium, is frequently present, on the skin of humans, and is thought to play a significant role in the severity of AD (Chung et al., 2022; Funmilola Abidemi, 2018). De Pessemier et al. (2021) reported that *S. aureus* is more prevalent on the skin of individuals with AD compared to healthy controls. The altered immunological responses and inflammatory reactions seen in AD have also been linked to skin microbiome dysbiosis, which increases *S. aureus* colonization (Hrestak et al., 2022).

In addition to *S. aureus*, the role of *S. epidermidis*, a commensal bacterium on the skin, has also been studied in the context of AD severity. *S. epidermidis* is a common inhabitant of the human skin microbiota and is generally considered beneficial, as it can inhibit the growth of pathogenic bacteria such as *S. aureus* (Severn & Horswill, 2023). However, recent findings suggest that the interaction between *S. epidermidis* and AD severity is intricate (Landemaine et al., 2023). Williams et al. (2020) noted that certain strains of *S. epidermidis* can synthesize serine protease inhibitors that impair the skin barrier function and promote inflammation, potentially contributing to the pathogenesis of AD. Moreover, Byrd et al. (2017) reported increased AD severity was associated with overgrowth of specific *S. epidermidis* strains, potentially due to their ability to stimulate the production of pro-inflammatory cytokines. The initial phase of AD begins with the impairment of the skin barrier leading to inflammation of the skin and the onset of reactions as highlighted by Kim and Leung (2018). The skin barrier dysfunction and changes allow foreign antigens and pathogens to bypass the innate immune system's first line of defence (Chung et al., 2022). Both *S. aureus* and *S. epidermidis* can further compromise the already weakened skin barrier, worsening the condition of AD patients (Fölster-Holst, 2022; Severn & Horswill, 2023).

Poh et al. (2022) reported that as the abundance of *S. aureus* increases on the skin of individuals with AD, the severity of the condition also increases. Additionally, they observed the expression of various virulence factors at AD skin sites. The bacterium's virulence factors can enhance its survival and trigger inflammation, contributing to the pathogenesis of atopic diseases (Chung et al., 2022). The colonization of *S. aureus* dysbiotic strains of *S. epidermidis* may play a crucial role in perpetuating skin inflammation through the stimulation of Th2 cells and the release of various cytokines and chemokines (De Pessemier et al., 2021; Iwamoto et al., 2017). Immune dysregulation in AD caused by altered skin

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microbiome is associated with an imbalance in immunity involving Th1, Th2, and Treg cells, which results in alterations in Th1- and Th2-mediated immune responses and IgE-mediated hypersensitivity (Yang et al., 2020). These cells release various cytokines and chemokines, promoting inflammation and attracting more immune cells to the affected skin.

**Skin Microbiome Research**

The study of skin microbiota has evolved significantly from traditional culture-based methods to advanced molecular techniques over the past decades. Historically, the study of skin microbiota primarily relied on culture-based methods. In these approaches, microbial cells collected from specific skin sites are cultivated in suitable media to identify particular species or pathogens (Santiago-Rodriguez et al., 2023). However, this approach had significant limitations, particularly in underestimating microbial diversity, as not all skin microbes are recoverable through cultivation (Santiago-Rodriguez et al., 2023). This inherent bias limits the understanding of the full spectrum of skin microbiota and their ecological interactions.

As research progressed, the field had a transformative shift towards advanced molecular techniques (Figure 4). Modern research has now primarily emphasized culture-independent methods, particularly high-throughput sequencing technologies (Ruuskanen et al., 2022). Techniques such as amplicon sequencing and untargeted metagenomics have emerged as powerful tools for overcoming the constraints of culture-based methodologies. Recent developments in metagenomic and multi-omic approaches have provided deeper insights into the structural and functional capacities of microbial communities, as well as their intricate associations with various skin disorders (Chen et al., 2023; Ruuskanen et al., 2022). For example, the introduction of molecular techniques, particularly polymerase chain reaction (PCR) and next-generation sequencing (NGS) technologies, has revolutionized the study of skin microbiomes. These methodologies has helped researchers to identify, quantify, and profile gene expression patterns in skin disorders (Gabriel et al., 2024) According to Hodkinson and Grice (2015), NGS facilitates the study of previously unculturable microbes, allowing deeper insights into microbial communities that were inaccessible.

In addition, the implementation of 16S ribosomal RNA (rRNA) sequencing has facilitated a more comprehensive analysis of the skin microbiome, revealing not only microbial diversity but also its correlations with conditions such as AD (Suwarsa et al., 2021). Such technologies have enhanced the accuracy of diagnoses, enabled personalised treatment approaches, and improved patient outcomes (Jinks et al., 2024). However, the transition to molecular techniques does not happen easily. Biases can still be introduced during various stages of the research process, including sample collection, nucleic acid extraction, amplification, and data analysis. For instance, the choice of extraction methods may preferentially enrich certain bacterial groups, skewing the results. Consequently, understanding these technical nuances and implementing rigorous quality control measures is essential for ensuring the reliability and reproducibility of findings.

Furthermore, the integration of bioinformatics tools has become increasingly crucial in managing and analysing the vast datasets generated by sequencing technologies (Cabello-Aguilar et al., 2023). Bioinformatics have been applied to various area, including comparative genomics, transcriptomic, and microbiome analysis (Uesaka et al., 2022). These tools enable precise characterizations of microbial communities and their functional potential, facilitating a more nuanced understanding of the dynamic relationships between skin microbiota and host health. The evaluation of skin microbiota and endophenotypes in AD necessitates a multifaceted approach due to the disease's heterogeneity, encompassing various isolation and assessment methodologies. Sampling methods and biophysical parameter measurements are crucial for correlating microbial flora with skin conditions (Perugini et al., 2023). Researchers emphasize the importance of standardized protocols and consideration of factors like study design, sampling techniques, and data analysis to ensure high-quality microbiome research (Kong et al., 2017).

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The initial step in microbiota evaluation involves the effective isolation of microbial DNA from skin samples. Common techniques include swabbing, tape stripping, and punch biopsies, each offering distinct advantages. Swabbing is minimally invasive and allows for the collection of surface microbiota, while tape stripping provides a means to sample the stratum corneum, offering insights into the microbial communities residing at the skin's surface (Barber & Boiko, 2022; Ogai et al., 2018; Yélamos et al., 2022). Punch biopsies, although more invasive, yield deeper samples that can reveal the diversity of the microbiome in the epidermal and dermal layers (Sfriso et al., 2020). Following collection, microbial DNA can be extracted using various kits designed for high yield and purity, which is critical for subsequent analyses.

Various methods for studying the skin microbiota have been developed, including culture-dependent and culture-independent approaches such as 16S rRNA sequencing and metagenomic shotgun sequencing (Grogan et al., 2019). Recent studies have developed optimized methods for extracting high-quality DNA suitable for shotgun metagenomic sequencing, overcoming challenges associated with low bacterial biomass on the skin (Serghiou et al., 2023). Researchers have also established protocols to correlate skin microbiota composition with biophysical parameters, providing insights into microbial influences on skin health(Perugini et al., 2023). These advancements contribute to a more comprehensive understanding of skin microbiota and its applications in various fields.

## FUTURE RECOMMENDATIONS AND CONCLUDING REMARKS

Existing literature highlights the intricate relationship between the skin microbiota and AD, focusing on shifts in microbial diversity and the dominance of *S. aureus* in AD-affected skin (Hrestak et al., 2022). Studies consistently report a decrease in microbial diversity coupled with a rise in pathogenic bacteria, particularly *S. aureus*, which exacerbates inflammation and barrier dysfunction in AD (Ogonowska et al., 2021). While protective commensals like *S. epidermidis* are typically reduced, their role in modulating disease outcomes remains multifaceted. Investigations also underscore the significance of skin endophenotypic variations, especially in Asian populations, in shaping disease severity and treatment responses.

Despite significant advances, variations in sampling methods, study designs, and microbiome characterization approaches complicate the synthesis of findings. The lack of standardized protocols poses challenges to reproducibility and comparability across studies. This limitation is particularly critical for clinical trials, as consistent methodologies are essential to evaluate treatment effectiveness rigorously. Standardization not only strengthens trial outcomes but also facilitates inclusion in systemic review and meta-analyses, thereby generating high-level evidence for the usefulness of microbiome-targeted interventions. Research gaps remain evident in several areas. Limited studies address how geographic and ethnic differences, particularly in Southeast Asian populations, influence skin microbiota profiles and endophenotypic variations. Distinct endophenotypes among Asian subtypes of AD, highlight the disease's complexity and calls for tailored treatment approaches (Rothenberg-Lausell et al., 2024). While the involvement of *S. aureus* and *S. epidermidis* is well-documented, the role of strain-specific differences, especially in *S. epidermidis*, in either mitigating or exacerbating AD remains underexplored. Moreover, most studies are cross-sectional, limiting insight into the temporal dynamics of microbial shifts and their correlation with disease progression or treatment response.

Future research should employ longitudinal, and multicentre studies with harmonized methodologies, integrating host genetics, lipidomics, immune responses, and microbiome analyses to unravel the complex interplay driving AD pathogenesis (Park et al., 2021; Pessôa et al., 2023) Standardized approaches will also enhance the comparability of results across different populations and interventions. Furthermore, while probiotics, prebiotics, and bacteriophage therapies show potential to restore microbial balance, evidence for their efficacy and long-term safety remains limited, particularly in non-Western populations. Future research should also investigate the mechanisms underlying these therapies to optimize treatment strategies. Addressing these gaps can pave the way for personalized

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therapeutic strategies that account for microbial and host-specific factors, ultimately improving outcomes for diverse AD populations. By incorporating a broader range of environmental influences and exploring the mechanisms of potential therapies, future studies can provide a more comprehensive understanding of AD and enhance treatment efficacy.

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## CONFLICT OF INTEREST STATEMENT

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare the absence of conflicting interests with the funders.

## AUTHORS' CONTRIBUTIONS

NAMN and NNYS was responsible for the method ology, investigation, data curation, formal analysis, visualization, and writing the original draft of the manuscript. LSM and KR provided critical review and edited the manuscript whereas MFI super vised the overall project, providing critical review and editing of the manuscript, validating the findings, and overseeing the project administration. All authors have read and agreed to the published version of the manuscript

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