# Antibiofilm Activities of Bacteria from the Skin Microbiome Against Staphylococcus epidermis

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**Abstract.** The skin microbiome is a diverse community of microorganisms living on the skin surface. Some microbiome bacteria may produce antibiofilm compounds, and thus play a role in defending against infectious bacteria. Bacteria cultures were isolated from the foreheads and retroarticular creases of 50 Malaysian females (ages 20-65) and investigated for the ability to inhibit biofilm formation in *Staphylococcus epidermidis* at the attachment, maturation, and dispersion stages. Results demonstrated that skin microbiome bacteria can inhibit biofilm formation, primarily by preventing attachment and dispersion. This research underscores the potential of using these antibiofilm properties as probiotics to bolster the skin's natural defenses.

**Keywords:** Antibiofilm properties, Probiotics, Skin Microbiome; *S. epidermidis*.

## 1.0 Introduction

The human skin, our largest organ, is a complex ecosystem hosting a diverse community of microorganisms collectively referred to as the skin microbiome [1]. This microbiome includes bacteria, fungi, viruses, and archaea, with prominent genera like *Staphylococcus, Corynebacterium*, and *Propionibacterium* [2]. These microorganisms form symbiotic relationships with the host, actively contributing to skin health, immunity, and protection against pathogens. Various regions of the skin, such as sebaceous, moist, and dry areas, house distinct microbial communities shaped by factors like pH, moisture, and sebum production [3]. Beyond passive colonization, the skin microbiome actively guards and shapes the skin's microenvironment, playing a pivotal role in preventing pathogenic colonization and proliferation.

Biofilms are organized microbial communities encased in self-produced extracellular matrices, present unique challenges due to their enhanced resistance to antimicrobial agents and host immune responses [4]. Biofilm formation initiates with planktonic microorganisms attaching to surfaces, followed by extracellular polymeric substance (EPS) matrix formation [5]. These biofilms, composed of bacteria, fungi,

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algae, and protozoa, are notorious for their role in chronic infections, such as those associated with medical devices [6]. They also impact industries like food processing and water treatment, where they can lead to equipment corrosion and reduced efficiency [5].

Understanding mechanisms to inhibit biofilm formation and disrupt established biofilms is crucial in managing biofilm- related skin infections, a common healthcare concern. Pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*, known for forming biofilms on skin and medical devices, pose challenges due to their resistance to antibiotics. Chronic wounds, including diabetic ulcers and pressure sores, often harbor biofilms, contributing to delayed healing and increased infection risk [7]. Biofilm-related skin infections frequently recur, necessitating repeated treatments and prolonged healing times [8].

Numerous strategies have been explored to prevent or disrupt biofilm formation, including the use of antimicrobial agents, EPS-degrading enzymes, and quorum-sensing inhibitors. Biofilms also have potential applications in bioremediation, wastewater treatment, and biocatalysts [9]. Thus, understanding biofilm formation, composition, and control mechanisms opens doors to innovative solutions in various fields. Antibiofilm compounds offer potential therapeutic options for managing biofilm-associated skin infections, with the aim of improving treatment outcomes. Effective antibiofilm strategies tailored to skin infections require collaborative efforts among microbiologists, dermatologists, and material scientists [10].

This review explores the antibiofilm potential of the skin microbiome, focusing on its effectiveness against biofilm-positive strains of Staphylococcus epidermidis (ATCC34958) and biofilm-negative controls (ATCC12228). We will assess attachment inhibition, maturation, and biofilm disruption mechanisms to shed light on this critical aspect of skin health.

## 2.0 Literature Review

### 2.1 Skin Microbiome

The skin microbiome, consisting of bacteria, fungi, viruses, and archaea, has been extensively studied with advances in sequencing technologies [2]. Among the skin microbiome's constituents, bacteria, particularly genera like *Staphylococcus, Propionibacterium, Corynebacterium, and Cutibacterium*, play a prominent role [1]. These commensal microbes form a protective barrier by competing for nutrients and space, reducing the risk of pathogenic invasion [2]. Moreover, the skin microbiome interacts with the host immune system, influencing both innate and adaptive immunity, crucial for maintaining immune homeostasis and preventing chronic inflammatory skin conditions [11]. The skin microbiome contributes to skin health by aiding wound healing, maintaining pH balance, and producing antimicrobial peptides, while dysbiosis has been linked to skin disorders like acne, eczema, and psoriasis [12]. Factors like age, genetics, environment, and hygiene practices shape the skin microbiome's composition.

Microbiome-based therapies, such as probiotics and topical prebiotics, are emerging for skin disorder treatments. Additionally, microbiome-targeted skincare products are gaining traction.

## 2.2 Bacteria Commonly Found in the Skin Microbiome

*Staphylococcus epidermidis*, a coagulase-negative staphylococcus, is a prevalent skin bacterium known for inhibiting pathogenic growth. Under normal conditions, it coexists harmlessly with the host but can become opportunistic in compromised skin defenses, partly due to its biofilm-forming capabilities. Biofilm-forming *S. epidermidis* strains are associated with skin infections like acne and folliculitis, posing a challenge in skin health [12].

*Cutibacterium acnes* is a gram-positive bacterium found in sebaceous skin areas. It contributes to acne development and plays a role in skin homeostasis and immune responses [13]. Various Corynebacterium species are common on the skin and may have immunomodulatory effects. Streptococcus species, found on the skin, can be both beneficial commensals and opportunistic pathogens [14]. Micrococcus species, particularly Micrococcus luteus, contribute to skin resilience and protection against environmental factors [15]. Other members of The *Cutibacterium* genus, besides *C. acnes*, are involved in skin disorders and sebum breakdown [16].

## 2.3 Bacterial Biofilm

Bacterial biofilms form through stages, starting with initial attachment, microcolony formation, matrix production, and mature biofilm development [6]. Biofilm-associated microbes exhibit distinct phenotypes compared to planktonic counterparts. They are implicated in healthcare-associated infections like *Pseudomonas aeruginosa* biofilms in cystic fibrosis patients' lungs and oral diseases related to dental plaque [17]. Recent research reveals the presence and significance of bacterial biofilms in the skin microbiome. These biofilms, consisting of various species, including *S. epidermidis* and *Propionibacterium C. acnes*, contribute to skin health by acting as protective barriers against pathogens and influencing immune responses [2, 12]. Dysbiosis in skin bacterial biofilms is associated with skin disorders like acne and atopic dermatitis [12].

## 2.4 Characteristics of Bacterial Biofilm

Bacterial biofilms are diverse, often comprising multiple species with distinct roles and functions within the biofilm structure [5]. They feature an extracellular matrix composed of polysaccharides, proteins, and DNA, providing structural stability, protection, and a nutrient-rich environment [6]. Initial bacterial adhesion to surfaces is mediated by factors like pili and flagella. Biofilms exhibit notable antibiotic resistance due to the extracellular matrix and altered gene expression [18]. They display spatial

and temporal heterogeneity, impacting bacterial activity and gene expression patterns. Biofilms are linked to chronic infections, including those involving medical implants and wounds.

### 2.5 Formation of Biofilm

Biofilm formation initiates with initial bacterial attachment to a surface, mediated by weak forces like van der Waals interactions and electrostatic forces. Subsequently, bacteria undergo irreversible attachment, firmly anchoring themselves through adhesins and surface structures. Microcolonies form, serving as the building blocks of mature biofilms, with densely packed cells encased in a protective extracellular matrix [4]. Matrix production is a critical stage, providing stability and protection. As biofilm development progresses, microcolonies expand and merge into mature biofilms, exhibiting increased resistance to environmental stresses and antimicrobial agents. Some biofilms disperse, releasing planktonic bacteria to colonize new surfaces and continue the biofilm life cycle [19].

### 2.6 Antibiofilm Compounds

Enzymatic disruption of biofilms shows promise, with DNase and dispersin B degrading extracellular DNA and polysaccharides within the biofilm matrix [19]. Various small molecules with antibiofilm properties have been identified, including quorum-sensing inhibitors, cranberry extracts rich in phenolic compounds, and synthetic molecules [20, 21]. Metal and metal oxide nanoparticles, such as silver and zinc oxide nanoparticles, exert antibiofilm activity by damaging the biofilm matrix and affecting microbial adhesion. Antimicrobial peptides (AMPs), like LL-37, disrupt biofilm matrix, prevent adhesion, and target microbial cells. Phage therapy is explored to target specific biofilm-forming bacteria by penetrating the biofilm and lysing bacterial cells [22].

## 3.0 Methodology

### 3.1 Ethics approval

Ethical approval was granted by the Researched Ethics Committee of Universiti Teknologi MARA.

### 3.2 Sample collection

Skin microbiome samples were obtained from 50 healthy Malaysian mother-daughter pairs, aged between 20-65 years. Swabs were used to collect samples from the forehead (Fh) and retroarticular crease (Ra) of each participant. Exclusion criteria included self-reported antibiotic treatment (oral or systemic) within 6 months before enrolment, observable dermatologic diseases, and significant comorbidities, including

HIV and other immunocompromised states. Subjects were instructed to avoid hand sanitizers and antimicrobial soaps and skincare products for one day before the sample collection appointment. Subjects are also instructed not to shower for 12 hours before the sample collection appointment.

### 3.3 Skin Swabs

Skin bacteria were collected by the swabbing method [3]. A 4.4 × 4.4-cm square on the forehead (Fh) and retroarticular crease (Ra) skin area were swabbed gently with a cotton swab (Cutaneous swabs, Epicentre, USA) that was soaked with moistened in 0.9% sodium chloride with 0.1% Tween-20 in a Z-stroke manner. Subsequently, the bacteria from the swab were evenly spread onto DeMan-Rogosa-Sharpe Medium (MRS) agar, Mannitol Salt Agar (MSA), and Tryptose Soy Agar (TSA) plates.

### 3.4 Isolation skin bacteria

The bacteria collected from the swab were cultured on DeMan-Rogosa-Sharpe Medium (MRS) agar, Mannitol Salt Agar (MSA), and Tryptose Soy Agar (TSA) plates and incubated at 37°C for three days. Then, single colony was selected and purified on the primary isolation agar and was incubated at 30°C for 4 days. the purified colonies were then cultured in 96 deep well plates containing Tryptose Soy Broth (TSB).

### 3.5 Preparation of Sterile Conditioned Medium (SCM)

Pure colony-cultured in 96 deep well plates containing TSB and incubated for 24 hours at 37°C was perform before prepare the SCM and test for antibiofilm activity. After incubation, the cells were pelleted by centrifugation, and the spent medium from each culture was recovered and filtered-steriled using a syringe filter with a pore size of 0.45 um. The resultant SCM samples were used for screening of antibiofilm activities.

### 3.6 Antibiofilm assay

The biofilm inhibition assay was performed at three different stages of biofilm formation: attachment, maturation, and dispersion. The positive control used was the biofilm-forming bacteria *S. epidermidis* ATCC35984, while the negative control was the non-biofilm-forming strain *S. epidermidis* ATCC12228. The bacteria cultures were prepared by first growing them overnight at 37°C in TSB supplemented with 1% glucose (STSB), then diluting in fresh STSB at 1:100 and growing until they reach the mid-log phase. The cultures' turbidity was adjusted to 0.08 - 0.13 at OD 570, which is equivalent to 1 X 108 CFU/ml.

For the antibiofilm attachment assay, about 100 µl of the prepared *S. epidermidis* ATCC35984 culture was dispensed into the wells of a microtiter plate. A volume of 50 µl of cell free medium was mixed with the bacteria cultures, except for the control wells, which receive 50 µl of diluted TSB at 1:10 instead. The plate was incubated at 37°C for 4 hours to allow bacteria cells to attach to the well surface and initiate formation of a biofilm. The contents were then discarded, and the plate was carefully washed with 300 µL of PBS and fixed in 150 µL of methanol for 20 minutes. The methanol was then discarded, and the microtiter plate was left inverted to air dry. Following that, the adherent biofilm layer was stained for 15 minutes with 150 µL of 1% crystal violet. The excess stain was then gently washed away with tap water before being air-dried and resolubilized in 150 µL of ethanol for 30 minutes. The optical density of the resolubilized dye was measured at a wavelength of 570 nm.

For the antibiofilm maturation assay, 100 µl of the *S. epidermidis* ATCC35984 culture was added into the wells of the microtiter plate and incubating it at 37°C for one hour to allow cells to attach to the well surface. Following that, except for the controls, 50 µl of cell free medium secretion was added to the wells and incubated at 37°C for 24 hours. The amount of biofilm formed was then measured as described in the antibiofilm attachment assay above.

For the antibiofilm dispersion assay,100 µl of the biofilm former *S. epidermidis* culture was incubated at 37°C for 24 hours to allow biofilm formation and maturation. Then, 50 µl of cell free medium was added, and the incubation is continued at 37°C for 24 hours. Following that, the biofilm formation of *S. epidermidis* cells was evaluated in the same manner as described in the antibiofilm attachment assay above. The amounts of biofilm formed by the positive control *S. epidermidis* ATCC35984 and the negative control *S. epidermidis* ATCC12228 were taken to represent 100% and 0% biofilm formation, respectively. The percentage of antibiofilm activity was then calculated using the formula shown below.

$$100 - [\frac{(S - N)}{(P - N)} \times 100\%] \quad (1)$$

whereby:
S = OD570 of *S. epidermidis ATCC35984* + cell free medium (test samples)
N = OD570 of *S. epidermidis ATCC12228* + 0.1 M PB (negative control)
P = OD570 of *S. epidermidis ATCC35984* + 0.1 M PB (positive control)

The percentage of antibiofilm between 1 and 50 percent was considered low activity, 51 percent to 90 percent was considered moderate, and more than 90 percent was considered high antibiofilm activity. All positive samples were retested twice in triplicates, and only selected as an antibiofilm producer if a high antibiofilm activity was reproduced in all three tests.

# 4.0 Findings

## 4.1 Antibiofilm assays

A total of 112 swab samples were collected, yielding 960 bacterial isolates, which were then subjected to three different antibiofilm assays. These assays aimed to assess biofilm attachment, maturation, and dispersion. The objective was to investigate whether commensal skin microbes could inhibit the growth and activity of *S. epidermidis* ATCC 35984 biofilms. The results are presented in Table 1 below.

At the attachment of biofilms, Samples HD1, HD2, ED2, ED3, HM2, HM3, and all EM2 samples demonstrate substantial antibiofilm activity with over 90% inhibition. In contrast, Sample HM1 exhibits negligible antibiofilm activity. These findings highlight that skin microbiome samples exhibit significant inhibitory effects on the attachment of *S. epidermidis* ATCC34958 to surfaces. However, most samples do not display significant antibiofilm activity at the maturation stage. Only samples ED2 (4A), EM2 (3H), and HM1 (2B) exhibit a moderate level of antibiofilm activity. None of the samples demonstrate any antibiofilm activities at the maturation stage of biofilm formation.

The findings suggest that commensal bacteria naturally present on healthy skin may strengthen the host's defenses by producing molecules that inhibit biofilm formation by *S. epidermidis* ATCC 35984. Among the 960 bacterial isolates, only 52 isolates from both the forehead (Fh) and retroarticular crease (Ra) demonstrated inhibitory activity against *S. epidermidis* ATCC 35984 biofilms. Remarkably, 98% of these isolates (51 out of 52) could prevent the attachment of *S. epidermidis* ATCC35984 to surfaces. In contrast, only 4% (2 out of 52) could hinder the dispersion of S. *epidermidis* ATCC 35984 biofilms. Notably, none of the isolated bacteria exhibited the ability to disrupt the maturation of the biofilm. Furthermore, the results indicated that 79% (41 out of 52) of the isolated bacteria originated from the retroarticular crease (Ra), while only 21% (11 out of 52) were derived from the forehead (Fh) area. Considering the inhibitory activity data presented in **Table 4.1**, it is noteworthy that only one isolate, obtained from the retroarticular crease (Ra) and identified as ED2, displayed significant inhibitory effects in both attachment and dispersion assays against S. *epidermidis* ATCC35984. This isolated bacterium will undergo identification through Sanger gene sequencing.

**Table 1.** The inhibitory activity of skin microbiome against *S. epidermis* ATCC35984.

| Samples No. | Antibiofilm Activity | | | | | |
|---|---|---|---|---|---|---|
| Samples | Attachment | Dispersion | Maturation | Attachment | Dispersion | Maturation |
| HD1 | 1H | | | +++ | - | - |
| HD1 | 5H | | | +++ | - | - |

| | | | | | |
|---|---|---|---|---|---|
| HD2 | 2C | | +++ | - | - |
| HD2 | 7B | | +++ | - | - |
| HD2 | 8C | | +++ | - | - |
| HM1 | | 2B | - | ++ | - |
| HM2 | 8D | | +++ | - | - |
| HM2 | 12B | | +++ | - | - |
| HM3 | 1C | | +++ | - | - |
| HM3 | 1H | | +++ | - | - |
| HM3 | 7D | | +++ | - | - |
| ED2 | 4A | 3H | +++ | ++ | - |
| ED2 | 6E | | +++ | - | - |
| ED2 | 8B | | +++ | - | - |
| ED2 | 12D | | +++ | - | - |
| ED2 | 12E | | +++ | - | - |
| ED3 | 4G | | +++ | - | - |
| ED3 | 7A | | +++ | - | - |
| EM2 | 12A | | +++ | - | - |
| EM2 | 1E | | +++ | - | - |
| EM2 | 2C | | +++ | - | - |
| EM2 | 2G | | +++ | - | - |
| EM2 | 2E | | +++ | - | - |
| EM2 | 3A | | +++ | - | - |
| EM2 | 3B | | +++ | - | - |
| EM2 | 3C | | +++ | - | - |
| EM2 | 3G | | +++ | - | - |
| EM2 | 4C | | +++ | - | - |
| EM2 | 4D | | +++ | - | - |
| EM2 | 4E | | +++ | - | - |
| EM2 | 4F | | +++ | - | - |
| EM2 | 5B | | +++ | - | - |
| EM2 | 5C | | +++ | - | - |
| EM2 | 5D | | +++ | - | - |
| EM2 | 5E | | +++ | - | - |
| EM2 | 5H | | +++ | - | - |
| EM2 | 6A | | +++ | - | - |
| EM2 | 6D | | +++ | - | - |
| EM2 | 6E | | +++ | - | - |
| EM2 | 6F | | +++ | - | - |
| EM2 | 6G | | +++ | - | - |
| EM2 | 7B | | +++ | - | - |
| EM2 | 7C | | +++ | - | - |
| EM2 | 7D | | +++ | - | - |
| EM2 | 8A | | +++ | - | - |
| EM2 | 8B | | +++ | - | - |
| EM2 | 8D | | +++ | - | - |
| EM2 | 8F | | +++ | - | - |
| EM2 | 9B | | +++ | - | - |
| EM2 | 9C | | +++ | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| EM2 | 9D | | | +++ | - | - |
| EM2 | 9F | | | +++ | - | - |
| Total:52 | 51/52 | 2/52 | 0/52 | | | |

Note: +++ = strong, >90% inhibition; ++ = medium, 71 to 90% inhibition; + weak, 50 to 70% inhibition; and - = no activity, <50% inhibition.

In summary, most samples exhibit strong antibiofilm activity in terms of attachment, while few, such as samples ED2 (4A), EM2 (3H), and HM1 (2B), display moderate activity in dispersion. HM1 (2B) also demonstrates moderate activity in maturation. The table provides a preliminary overview of antibiofilm properties of these samples across various conditions. To gain a deeper understanding of these antibiofilm activities and their potential applications, further analysis and experiments are warranted.

## 5.0 Discussion

The skin microbiome's ability to hinder the attachment of *S. epidermidis* ATCC34958 is a promising discovery, indicating that skin commensals may compete for attachment sites or produce antibiofilm compounds that deter pathogenic attachment. This aligns with prior research on skin microbiota safeguarding against pathogenic colonization [1]. The skin microbiome's capacity to disrupt established biofilms is a significant finding since these are notoriously difficult to eliminate. It suggests that some skin microbiome components may offer a novel approach to treating biofilm-related infections, consistent with earlier studies emphasizing biofilm dispersion inhibition in infection control [19]. The skin microbiome constituents' disruption of biofilm maturation underscores their potential to interfere with the coordinated processes needed for biofilm development, ultimately preventing robust biofilm formation. The results indicate that most samples show no activity (-) in maturation inhibition, suggesting that skin microbiome bacteria are less effective in preventing biofilm maturation. This finding might imply that they are more effective at preventing initial attachment and dispersion rather than inhibiting existing biofilm maturation. The antibiofilm properties of the skin microbiome have promising clinical implications, potentially leading to the development of probiotics or topical treatments that harness the skin microbiome's natural defense mechanisms.

## 6.0 Conclusion& Recommendations

The study's findings highlight the potential of skin microbiome bacteria in inhibiting *S. epidermidis* biofilm formation, especially in terms of attachment and dispersion inhibition. However, further research is necessary to pinpoint the specific bacterial strains responsible for this inhibitory effect and to gain a deeper understanding of how they hinder biofilm maturation. Additional research is required to identify the

specific skin microbiome components responsible for the observed antibiofilm properties and to uncover the underlying mechanisms. Clinical trials should also be carried out to assess the feasibility of using skin microbiome-based treatments for preventing and treating biofilm-related skin infections. While some research has explored the skin microbiome's capacity to combat biofilms, a comprehensive investigation that covers various aspects of biofilm inhibition and disruption is warranted.

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