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BEYOND PATHOGENICITY: BIOACTIVE COMPOUNDS AND ANTIMICROBIAL POTENTIAL OF *Staphylococcus epidermidis*

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Aim. To review the antimicrobial potential of *Staphylococcus epidermidis*, particularly its bacteriocins and antimicrobial peptides (AMPs), and to highlight their possible applications in human health, food preservation, aquaculture, and other industrial sectors.

Methods. A literature-based review approach was adopted to analyze existing studies on *S. epidermidis* — derived antimicrobial compounds. Published research focusing on bacteriocins, AMPs, pathogen inhibition, strain safety, and potential applications across healthcare and non-healthcare sectors was examined.

Results. Studies indicate that *S. epidermidis* produces potent antimicrobial compounds, including bacteriocins and AMPs, which exhibit strong pathogen-specific activity. These compounds demonstrate inhibitory effects against several pathogens, notably methicillin-resistant *Staphylococcus aureus* (MRSA), and show promise in managing skin infections, chronic wounds, and biofilm-associated infections. Although the bacterium is widely present in natural environments, its potential applications in food preservation and aquaculture remain underexplored. Furthermore, the dual nature of *S. epidermidis* as both a beneficial commensal and an opportunistic pathogen has limited its broader utilization. However, recent advances in strain selection and genetic studies have identified non-virulent strains, such as *S. epidermidis* YTPW-4, which lack major pathogenic traits and may be suitable for safe biotechnological applications.

Conclusions. *S. epidermidis*–derived bacteriocins and AMPs represent promising antimicrobial agents with potential applications beyond healthcare, including sustainable food systems, aquaculture, and precision medicine. However, comprehensive safety assessments and further research are necessary to harness their therapeutic and industrial potential fully.

Keywords: *Staphylococcus aureus*, antimicrobial peptides (AMPs), antibiotics, bacteriocins, neoplasia, acne.

The global reliance on broad-spectrum antibiotics, coupled with their widespread use in sectors such as clinical and agricultural settings, is the reason for the emergence of antibiotic-resistant pathogens. These resistant pathogens complicate the treatment of common infections, extending illness duration and contributing to a rise in morbidity and mortality [1]. Resistance development is further exacerbated by the high production costs and inherent risks of developing new antibiotics, resulting in significant limitations

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in effective treatment options. If current trends continue, predictions indicate that by 2050, effective antibiotics may become scarce for treating infections, particularly those caused by Gram-negative bacteria—pathogens which are presently a primary concern due to their complex resistance mechanisms [2–3].

To counter these growing challenges, public health authorities are advocating judicious antibiotic use to curb the development of resistance and limit the presence of antibiotic residues in the food supply [4–6]. Consequently, research has turned towards alternative strategies, with particular emphasis on bacteriocins and/ or bacteriocin-like inhibitory substances (BLIS). These naturally occurring peptides, produced by various bacterial strains, have drawn significant attention as they offer new solutions for combating even antibiotic-resistant pathogens through unique mechanisms [7–9]. Furthermore, bacteriocins/ BLIS are typically considered safe, non-toxic to eukaryotic cells, and are inactivated by digestive proteases [10]. In the food industry, bacteriocins have long been explored for use as effective preservatives [11]. Beyond their role in food preservation, bacteriocins are also being explored for their potential to treat and prevent infections in plants [12], animals [13], and humans [14].

But it is a fact that the majority of current bacteriocin research largely overlooks the immense diversity of bacteriocins/ BLIS produced by diverse bacterial genera. Staphylococcal bacteriocins, produced by *Staphylococcus* species, are prime examples of bacteriocins that have received comparatively little research attention [7]. This limited research attention is surprising given that studies estimate that approximately 99% of bacterial species synthesize at least one bacteriocin, highlighting their evolutionary significance in microbial competition and defense [15]. Besides, *the Staphylococcu*s genus is widespread in nature, found in diverse environments, including soil, air, water, dust, and various foods, such as meat, cheese, and raw milk [16–18]. Thus, the genus offers significant potential for the discovery of novel bacteriocins, particularly from strains like *Staphylococcus epidermidis*, which is abundant and known to produce a variety of these antimicrobial compounds [19–21]. Despite its ubiquity and potential, *S. epidermidis* remains under-researched in this context. Among the staphylococcins characterized from *S. epidermidis* are notably Epidermin, Pep5, Epilancin K7, Epicidin 280, Epilancin 15X, Epicidin 280, and Nukacin IVK-45. These staphylococci are distinguished by their unique structures and mechanisms of action, which make them effective antimicrobial agents. However, data on their practical applications remain limited [14, 22–26].

Thus, expanding research into staphylococcins, particularly those produced by *S. epidermidis*, could yield bacteriocins with unique properties that are beneficial for food preservation, healthcare, and the development of new antimicrobial therapies. In the context of escalating antibiotic resistance, exploring the diverse and underutilized bacteriocins beyond those produced by lactic acid bacteria represents a promising frontier for future research and biotechnological advancement. This review provides an in-depth overview of the current research landscape on antimicrobials derived from *S. epidermidis*, their potential applications, and the challenges inherent in leveraging these potent antimicrobial peptides for medical and industrial applications.

Bacteriocins in microbial defence: tools for selective bacterial control and targeted therapy

Microbes in their natural environments often inhabit polymicrobial communities, sharing ecological niches where space and resources are constrained [27–28]. To navigate these competitive conditions, microbes have evolved diverse strategies for competition and communication, mediated by various chemical secretions and signaling mechanisms, enabling them to survive and coexist with other strains and their surrounding ecosystem [29].

Antimicrobial peptides (AMPs), including Bacteriocins are prime examples of such chemical secretions. Whereas AMPs are natural antimicrobial agents produced by various organisms, Bacteriocins are a specific type of ribosomally synthesized small AMPs produced by several bacteria, forming a diverse group of antimicrobial compounds that confer a competitive advantage by targeting specific bacterial strains within a shared ecological niche [26, 30]. Thus Bacteriocins and other AMPs play a crucial role in maintaining bacterial fitness and regulating microbial populations within specific environments [31]. As part of a “bacterial warfare” strategy, many commensal bacteria inhibit the growth and colonization of invasive pathogens by producing AMPs, including bacteriocins,

thereby providing a competitive advantage to the producer strains [32].

Recent research has elucidated the significance of bacteriocins/ BLIS, produced by bacteria, as potential novel antimicrobials, especially amid the rise of antibiotic-resistant pathogens. It is estimated that approximately 99% of bacterial species produce at least one bacteriocin, indicating their widespread natural occurrence and evolutionary role in microbial competition and defense [15]. This prevalence, along with their potent activity against various pathogens, positions bacteriocins/ BLIS as significant candidates in the ongoing search for alternative antimicrobial agents.

Bacteriocins/BLIS offer several advantages over traditional antibiotics, positioning them as promising candidates in the search for novel antimicrobials, as summarized in Table 1.

Thus, bacteriocins/BLIS are valuable for various commercial sectors, such as food preservation, and therapies, such as nisin used in processed cheese to prevent spoilage, and show promise in treating peptic ulcers. They also have applications in women's health as spermicides, in skincare to control acne-causing bacteria, and in oral care to prevent bad breath. Additionally, bacteriocins have potential in cancer therapy due to their ability to induce apoptosis in tumor cells and to promote plant growth when applied to crops [43].

Unveiling the multifaceted potential applications of antimicrobials of *Staphylococcus epidermidis*

S. epidermidis is a bacterium that constitutes a significant part of the normal human Skin and mucosal microbiota [Table 2] [44]. Beyond human-associated environments, *S. epidermidis* has been isolated from non-human sources, mainly from marine sponges [21] and various fish species (Table 2) [46–48]. Its presence across such diverse environments highlights its adaptability and potential significance. Further details on the microbiological and biochemical characteristics of *S. epidermidis* are summarized in Table 2.

Table 1. **Comparative Advantages of Bacteriocins/BLIS Over Conventional Antibiotics**

Property	Description
Narrow Spectrum of Activity [33]	Bacteriocins/BLIS generally exhibit a narrow spectrum of activity, enabling them to target specific bacterial species while minimizing disruption to the host's overall microbiota, reducing the risk of dysbiosis-linked inflammatory and metabolic disorders. This selectivity is crucial for applications where maintaining microbiota balance is essential for health.
Reduced Risk of Resistance Development [11, 34–38]	The specificity of bacteriocins/BLIS is thought to exert less selective pressure on antimicrobial resistance than traditional broad-spectrum antibiotics. This specificity, coupled with the immunity mechanisms present in bacteriocin-producing strains, further reduces the likelihood of resistance emergence. Immunity genes, often co-located with bacteriocin structural genes, confer resistance in producer strains, thereby limiting the development and spread of resistance among target bacteria.
Efficacy Against Quiescent Cells [39–40]	Unlike some conventional antibiotics that primarily target actively dividing cells, many bacteriocins are effective against both quiescent and actively dividing bacterial cells. This characteristic allows bacteriocins to target dormant bacterial populations, which are often associated with chronic and recurrent infections resistant to conventional treatments.
Amenability to Bioengineering [35, 41]	Bacteriocins, as ribosomally synthesized peptides, can be engineered to improve their functional properties, such as potency, solubility and stability, thereby enhancing their clinical applicability, and stability in diverse environments.
High Potency [35, 41]	Exhibits antimicrobial activity at nanomolar concentrations, ensuring effective pathogen inhibition with minimal disruption to the microbiota and minimal environmental impact.
Safety Profile [33]	Bacteriocins/BLIS are generally recognized as safe due to their low toxicity to eukaryotic cells and their susceptibility to digestive proteases, which reduces their impact on the gastrointestinal microbiota. Although this susceptibility may restrict their application to injectable or topical administration, it also ensures that bacteriocins are metabolized in a way that minimizes disruption to the host's natural microbiota—an advantageous characteristic for preserving microbiota-associated health benefits.

Table 2. **Overview of *Staphylococcus epidermidis* Characteristics**

Category	Feature	Characteristics
Ecology & Medical Relevance	Type [44]	Coagulase-negative, Gram-positive bacterium
	Human-associated Locations [20, 44, 45]	Predominant in the Skin and mucosal surfaces. It is widespread in areas of the body, such as the nasal passages and regions prone to perspiration, such as the armpits and back, where warm, moist conditions favor its growth. Additionally, *S. epidermidis* is linked to foot odor due to its production of enzymes that degrade leucine in sweat, leading to the formation of isovaleric acid.
	Availability at diverse locations [21, 46–48]	Found in marine sponges and fish like tilapia, gilthead sea bream (*Sparus aurata*), carp (*Cyprinus carpio*), and catfish (*Silurus glanis*)
Metabolism	Anaerobic Utilization of Glucose [44]	Yes, but does not produce coagulase or ferment mannitol
	Acid Production (Aerobic) [44]	Positive for: Fructose, Maltose, Sucrose, Glycerol
Colony Characteristics	Size [21, 44]	Pin-headed/Very small
	Type [21, 44]	Round
	Color [21, 44]	Opaque
	Shape [21, 44]	Convex
Morphological Characteristics	Shape [21, 44]	Cocci
Physiological Characteristics	Motility [21, 44]	–
Biochemical Characteristic[21, 44]	Gram's Staining	+
	Oxidase	–
	Catalase	+
	Sugar utilization (oxidative/fermentative)	Fermentative
	Methyl Red	–
	Voges-Proskauer	+
	Indole	–
	H_2S Production	+
	Urease	+
	Nitrate Reductase	+
	β-Galactosidase	+
Biotechnological Potential	Lipase Enzyme Activity [44]	Produces esters (geranyl, medium-chain, unsaturated esters)
	Bacteriocins Produced [22–24, 52–58]	Epidermin, Pep5, Epilancin K7, Epilancin 15X, Epicidin 280 and Nukacin IVK-45

Although ubiquitous in nature, human-derived *S. epidermidis* is recognized for its role in host defense, producing AMPs, including bacteriocins, that inhibit pathogenic bacteria in skin infections and even in skin neoplasms [49–51]. Basically, *S. epidermidis* strains produce bacteriocins (details in Table 2) that belong to the lantibiotic class, as per bacteriocin classifications, and are characterized by the presence of unique amino

acids such as lanthionine, β-methyllanthionine, and dehydrated amino acids [59–61]. Most lantibiotics induce bacterial cell lysis and death through membrane potential-dependent permeabilization or the formation of transmembrane pores [62–64] (details in Fig. 1). For example, Epidermin, Pep5, and bacteriocins produced by *S. epidermidis* bind to negatively charged lipoteichoic acids, triggering autolysis of the target cell by releasing and activating cell wall-hydrolyzing enzymes [62]. This defensive capability of *S. epidermidis* underscores its potential as a therapeutic agent, not only protecting against infections but also offering alternative approaches to antibiotics. The key antimicrobial actions of *S. epidermidis-derived* bacteriocins and AMPs against pathogenic bacteria are described in detail below.

Bacteriocins and AMPs from *Staphylococcus epidermidis*: Targeted Approach to Combat Staphylococcus aureus-Induced Skin Diseases

The human Skin is home to a vast, complex, and dynamic microbial ecosystem. Billions of bacteria colonize various areas of the Skin, thriving due to the body's constant exposure to the external environment. The skin microbiome acts as a natural barrier and plays a crucial role in immune defense; however, disruptions in its balance can lead to skin infections and contribute to various dermatological conditions. Common skin infections and chronic inflammatory conditions, such as atopic dermatitis, eczema, acne, and infections in burn wounds, are frequently associated with pathogens such as *Propionibacterium acnes*, *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Corynebacterium* species [65].

Among the diverse bacterial species associated with skin infections, *S. aureus* is particularly significant. It is a common opportunistic pathogen implicated in both community-acquired and hospital-acquired infections [66–67]. *S. aureus* infections range from minor and self-limiting skin issues to severe, potentially life-threatening conditions, including Skin and soft tissue infections, osteomyelitis, meningitis, urinary tract infections, mastitis, and septicemia [68–70]. Furthermore, *S. aureus* is a notable cause of biofilm-associated infections and food poisoning. In hospitals, it is a leading cause of nosocomial infections, responsible for 30% of infectious endocarditis cases and the second most common cause of hospital-

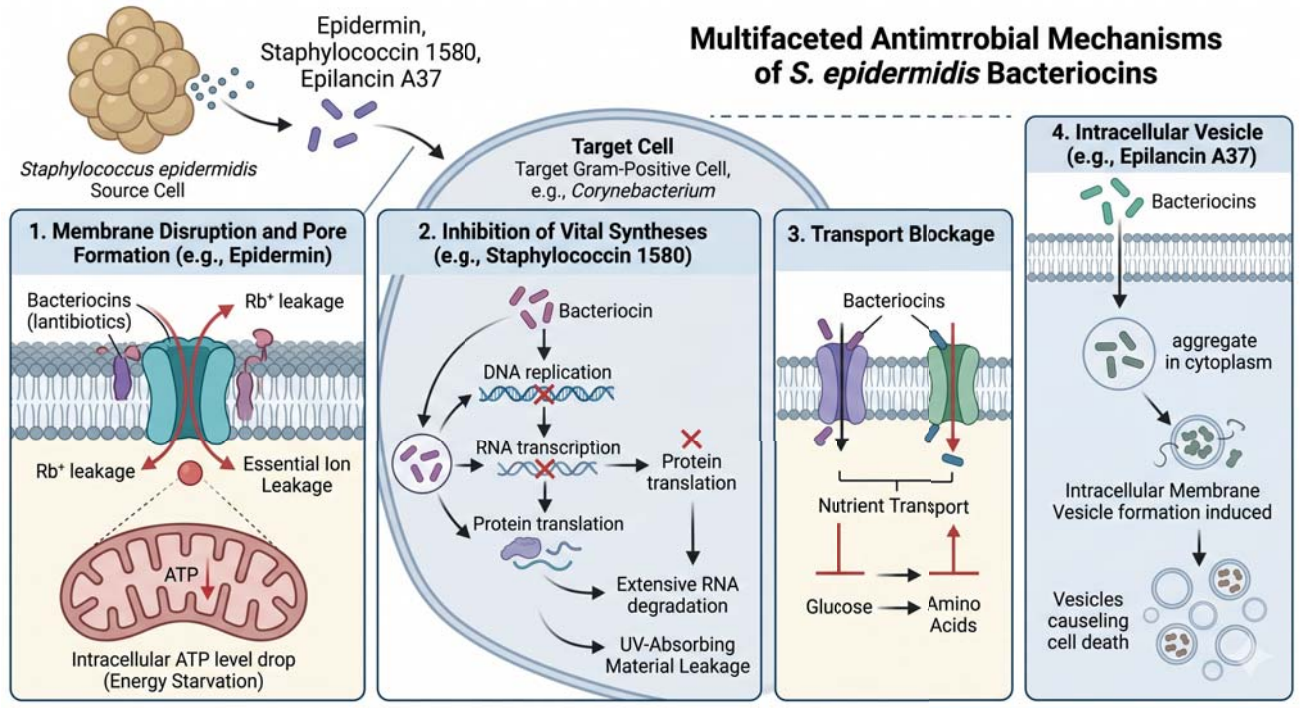

Fig. 1. **Generalized schematic representation of the mechanisms of action of *Staphylococcus epidermidis* bacteriocins and other bioactive compounds**

acquired pneumonia [71–74]. Even if nasal Skin is compromised by cuts, abrasions, or other forms of injury, these bacteria can enter the wound site and cause infection [75].

Another significant clinical concern regarding *S. aureus* is the elevation of methicillin-resistant *S. aureus* (MRSA) strains [76]. These MRSA strains, resistant to multiple antibiotics, have spread globally, posing severe challenges in healthcare settings [76]. This resistance is particularly relevant in infections associated with atopic dermatitis (AD), a chronic inflammatory skin condition marked by dry, itchy, eczematous patches [77]. During AD flare-ups, *S. aureus* plays a critical role by disturbing the skin microbiome and exacerbating inflammation. It produces phenol-soluble modulins (PSMs), such as δ-toxin, which compromise the skin barrier and activate dermal mast cells, promoting further inflammation [78–81].

Traditional antibiotic treatments for *S. aureus* are increasingly inadequate in controlling *S. aureus* populations without negatively affecting beneficial skin microbiota [82]. The overuse of antibiotics has also led to increased antibiotic resistance [83], underscoring the need for precision therapies that target specific pathogens without disrupting commensal microbes. In this context, *S. epidermidis*, a benign skin colonizer, can inhibit pathogenic bacteria and prevent infections through competitive exclusion, producing AMPs including bacteriocins [51, 84–85]. This competitive advantage enables *S. epidermidis* to play a protective role in maintaining skin homeostasis and reducing the risk of pathogenic colonization. *S. epidermidis* produces Phenol-Soluble Modulins (PSMs) (PSMg and PSMd) that selectively kill pathogenic bacteria, including *S. aureus* and group A *Streptococcus* (GAS) [84–86]. Additionally, these substances can modulate the host's immune response by diminishing inflammation after injury, supporting the development of cutaneous T cells, and enhancing the expression of host AMPs such as cathelicidins and β-defensins [87–94].

One promising line of research involves isolating bacteriocins from *S. epidermidis*. For instance, a thermostable cytoplasmic bacteriocin from *S. epidermidis* has been shown to selectively target *S. aureus* and MRSA strains, providing a pathogen-specific treatment option for AD. Because the depletion of specific AMP-producing strains in AD patients has been noted, leading to reduced natural defenses against *S. aureus* colonization [51]. This discovery has sparked interest in microbiome-targeted therapies, which aim to restore these beneficial microbial populations. Clinical trials have shown that reintroducing AMP-producing *S. epidermidis* strains can help reduce *S. aureus* levels on the Skin of AD patients, thereby mitigating the severity of AD symptoms.

Additionally, the bacteria itself has been shown to exhibit inhibitory effects against MRSA strains, underscoring their potential in nasal decolonization strategies [95]. In this study, they demonstrated that administering a probiotic effectively prevents MRSA colonization of the nose. Specifically, intranasal administration of an *S. epidermidis* strain resulted in a significant reduction in MRSA colonization within two days. Translationally, this approach could serve as a preventative measure during acute MRSA outbreaks. These findings emphasize viable alternatives to traditional antibiotics, addressing the critical challenge of antibiotic resistance in *S. aureus* and other pathogenic bacteria.

Staphylococcus species also produce a range of other secretory-AMPs (sAMPs) alongside bacteriocins, and several of these non-bacteriocin AMPs show promise as therapeutic agents for *S. aureus* infections. Esp is a serine protease produced by some *S. epidermidis* strains [96]. It was noted that the presence of certain *S. epidermidis* strains within the nasal cavity appeared to influence *S. aureus* nasal colonization. The Cell Free Supernatants (CFS) of these strains inhibited *S. aureus* in vitro, leading to the purification and identification of Esp. Application of purified Esp or Esp-producing *S. epidermidis* to the nasal cavities containing *S. aureus* eliminated *S. aureus* colonization. Esp is also effective against *S. aureus* biofilms, cleaving autolysin-derived murein hydrolases [97] and preventing the release of DNA, a structural component of *S. aureus* biofilm extracellular matrices [98–99]. Esp also targets *S. aureus* surface proteins, disrupting host-pathogen interactions [100], allowing Esp to be active against biofilm-forming *S. aureus* cells. This suggests Esp could be a very promising antimicrobial agent.

Innovative Therapeutic Approaches for Managing Chronic Wound Infections using antimicrobials of *Staphylococcus epidermidis*

Chronic wounds are particularly vulnerable to infections involving diverse bacterial communities, commonly comprising species such as *Staphylococcus*, *Pseudomonas*, *Peptoniphilus*, *Enterobacter*, *Stenotrophomonas*, *Finegoldia*, and *Serratia* [101] These pathogens often form resilient biofilms, which intensify tissue damage, impede wound healing, and complicate treatment options (Fig. 2). Addressing such infections requires innovative therapies, particularly those that target pathogens without disrupting beneficial skin flora.

Recent studies *have shown that S. epidermidis is* a promising probiotic for treating skin infections. Research by [102] identified a specific strain, *S. epidermidis* Y73, which produces bacteriocins without forming biofilms. This unique strain has shown potential in wound healing when incorporated into cellulosic pads. These pads preserved bacterial viability for up to 20 weeks and, when applied to wounds in infected rabbits, significantly accelerated healing compared with control treatments. This finding underscores *S. epidermidis* Y73 as a promising candidate for therapeutic wound care (Fig. 2). Moreover, synergistic antibacterial strategies have shown promise in combating complex wound pathogens. A recent study evaluated the combined effect of epidermin, a bacteriocin produced by *S. epidermidis,* and staphylolysin (LasA), a protease from *P. aeruginosa*, against key wound pathogens [103]. The agar well diffusion assay revealed that while epidermin and LasA each displayed antibacterial effects independently, their combined application significantly enhanced inhibitory activity across all tested pathogens, particularly clinical isolates. This synergy suggests that an epidermin-LasA combination could provide an effective alternative therapy, specifically for wound and burn infections where biofilm-forming pathogens are prevalent.

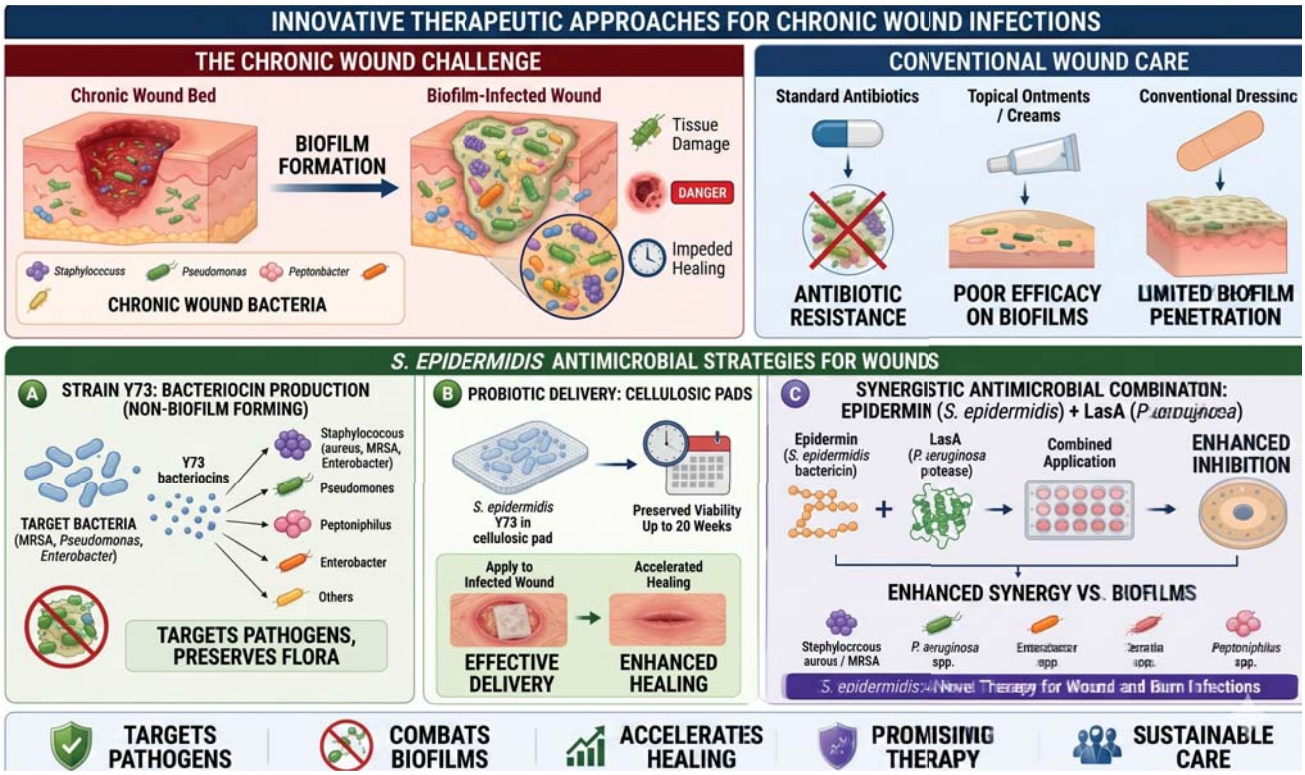

Fig. 2. **Innovative Therapeutic Approaches for Managing Chronic Wound Infections using *Staphylococcus epidermidis***

The diagram illustrates the transition from the challenges of chronic wound management to novel probiotic-based solutions.

The Role of *Staphylococcus epidermidis* in Modulating Acne Pathogenesis

In healthy Skin, *Cutibacterium acnes* contributes positively to the microbiota of the pilosebaceous unit, maintaining a balanced environment. However, during puberty, *C. acnes* may over-colonize these units, leading to reduced microbial diversity and dysbiosis, often resulting in acne [104–107] [Fig. 3]. Topical acne treatments commonly include retinoids (e.g., adapalene, tretinoin) that mitigate inflammation by modulating *C. acnes* -triggered innate immune responses [108–111] [Fig. 3]. While benzoyl peroxide remains effective, the frequent use of topical antibiotics like erythromycin and clindamycin has led to antibiotic resistance in *C. acnes* within 4–6 weeks of monotherapy [112–114]. Systemic antibiotics are associated with less resistance but can disrupt gut microbiota [114–116]. In this context, *S. epidermidis* has shown potential to control *C. acnes*-induced dysbiosis, offering a possible means to reduce acne severity [107, 117]. In antagonism assays, certain *S. epidermidis* strains, namely strains FS1 and 14.1.R1, displayed antimicrobial activity against *C. Acnes* [118]. Research has further indicated that *S. epidermidis* can suppress *Cutibacterium acnes* growth by producing succinic acid, a fatty acid fermentation product [107, 118–120] (Detail in Figure 3). Staphylococcal lipoteichoic acid (LTA) from *S. epidermidis* has been linked to the induction of miR-143 in keratinocytes, which helps control inflammation, thereby supporting skin homeostasis and mitigating the inflammatory response induced by *C. acnes* [120]. These findings highlight the beneficial role of *S. epidermidis* in maintaining skin balance and suggest its potential application as a probiotic for skin health, beyond its bacteriocin production.

Potential Role of *Staphylococcus epidermidis* Bacteriocins in Managing Veterinary Diseases

Bovine mastitis, an infection of cow udders, is a major trouble for the dairy industry, leading to economic losses from milk rejection, decreased milk quality, premature cow culling, drug costs, veterinary expenses, and additional labor for farmers [121–123]. *S. aureus* and *Streptococcus* spp. are the primary bacterial pathogens responsible for this disease [124]. Current treatments yield inconsistent results, particularly against *S. aureus*, which often

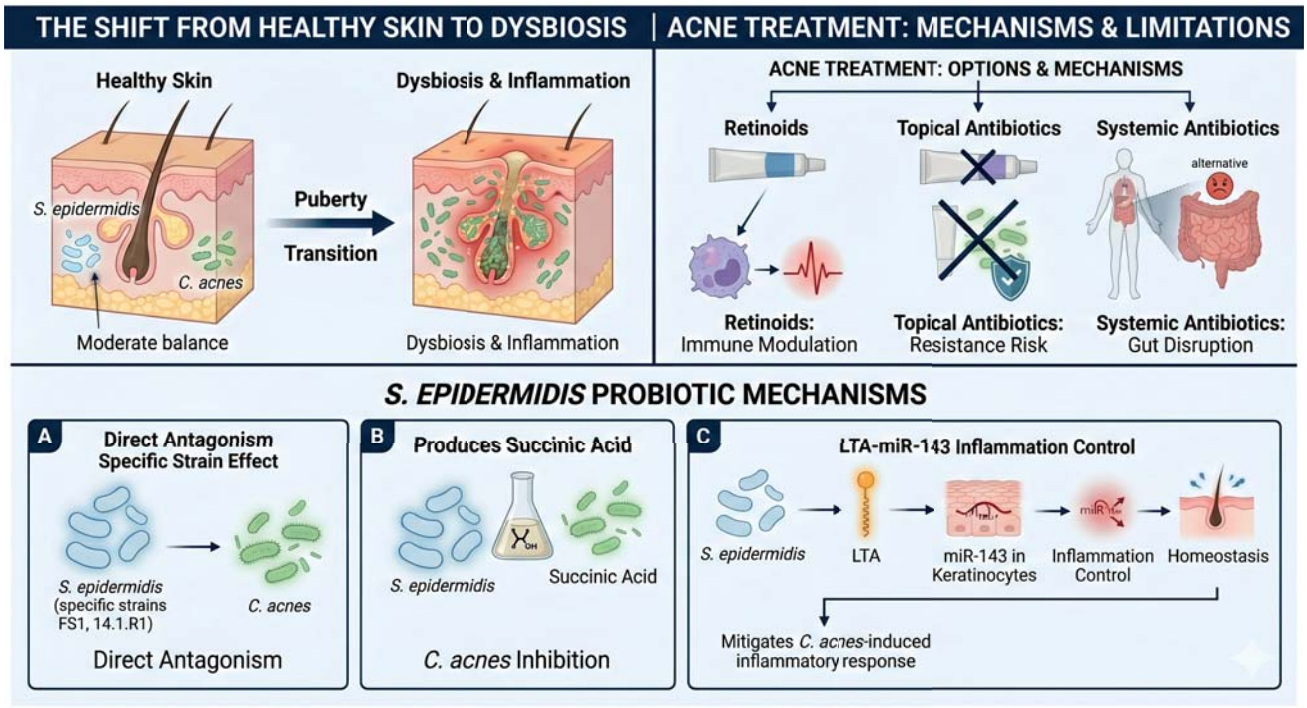

Fig. 3. **Pathogenesis of acne, treatment limitations, and the probiotic mechanisms of *S. epidermidis***

causes chronic infections and substantial economic impact [123–125].

Bacteriocins produced by *S. epidermidis* have shown promise as potential therapeutic agents for the treatment and prevention of mastitis, addressing a critical need, as only a limited number of bacteriocins have demonstrated effectiveness against mastitis-causing pathogens. In a study assessing the inhibitory effects of *S. epidermidis*-derived staphylococcins (Pep5, epidermin, epilancin K7, and epicidin 280), the activity was tested against 165 strains of *S. aureus* and 74 strains of *Streptococcus agalactiae* isolated from cows with mastitis [7]. The results indicated that epidermin effectively inhibited over 85% of the strains tested. The remaining staphylococci showed limited efficacy, inhibiting fewer than 48% of the pathogens tested. These findings suggest that epidermin could serve as a non-antibiotic alternative for managing mastitis, effectively targeting both staphylococcal and streptococcal pathogens associated with the disease.

Potential of *Staphylococcus epidermidis* in Food Fermentation

Many *Staphylococcal* strains, including *Staphylococcus botulinum, Staphylococcus equi, Staphylococcus succinum,* and *Staphylococcus xylosus*, constitute a significant proportion of the intrinsic bacteria found in naturally fermented food products and are frequently used as starter cultures in fermentation [126–127]. Similarly, *Staphylococcus* sp. SK1-1-5, isolated by [127], has been employed as a starter culture to enhance the quality and aroma of fish sauce. Additionally, various coagulase-negative *Staphylococcal* (CoNS) strains are utilized in the food industry for their exceptional functional properties. However, *S. epidermidis* has limited or, more likely, nil applications in food production, with the notable exception of its role in Chinese Baijiu production. Baijiu, a traditional Chinese spirit, is produced using *Daqu* — a saccharifying and fermenting agent derived from wheat, barley, and peas through natural inoculation and microbial fermentation [128]. The microbial diversity in *Daqu* plays a critical role in shaping Baijiu's flavor, particularly in *Nongxiangxing* (strong-flavor) varieties.

A recent study isolated a strain of *S. epidermidis* (YTPW-4) from *Daqu*, highlighting its potential in Baijiu fermentation [128]. This strain exhibited high esterase activity, facilitating the production of ethyl caproate, a key flavor compound in Baijiu, achieving levels of 583.09 mg/100 mL. It also enhanced the synthesis of other important flavor compounds, including propyl-3-methylbutyrate, hexanoic acid, and ethyl acetate, during laboratory-scale fermentation. Furthermore, *S. epidermidis* YTPW-4 demonstrated remarkable resilience, maintaining viability at pH 3.5 and in 8% ethanol, conditions typical of Baijiu fermentation. These findings suggest that *S. epidermidis* could serve as a viable starter culture not only for Baijiu production but also for other foods, significantly enhancing the flavor profile and sensory attributes, offering an innovative approach to improving overall quality.

Skin Neoplasms and the Role of *Staphylococcus epidermidis* in Cancer Defence

Skin neoplasms, known as abnormal growths of skin cells, can be benign or malignant. Malignant neoplasms are cancerous and capable of invading surrounding tissues and spreading throughout the body via metastasis, forming secondary tumors in other organs. Recent research has uncovered a remarkable property of *S. epidermidis* in combating malignancies. Certain strains of *S. epidermidis* produce 6-N-hydroxyaminopurine (6-HAP), a molecule that inhibits DNA polymerase activity, a critical enzyme for DNA replication. In laboratory studies, 6-HAP selectively inhibited the proliferation of tumor cell lines without affecting normal primary keratinocytes [50]. Resistance to 6-HAP was associated with the expression of mitochondrial amidoxime-reducing components, enzymes absent in cells sensitive to the compound. These findings indicate that 6-HAP exerts a targeted effect, selectively suppressing tumor cells while sparing healthy skin cells. The efficacy of 6-HAP was further validated in animal models [50]. Intravenous administration of 6-HAP in mice suppressed the growth of B16F10 melanoma without causing systemic toxicity, suggesting a favorable safety profile. Additionally, colonization of mice with a *S. epidermidis* strain capable of producing 6-HAP significantly reduced the incidence of ultraviolet-induced skin tumors. This finding highlights a potential role for *S. epidermidis* in providing protective effects against skin cancers.

Interestingly, 6-HAP-producing *S. epidermidis* strains have been identified in the skin microbiomes of multiple healthy individuals, suggesting that their presence may naturally confer protection against certain types of skin cancer [50]. This discovery underscores the skin microbiome's role in maintaining host defense mechanisms and opens new avenues for exploring microbiome-based therapies for cancer prevention and treatment.

Expanding the potential of *Staphylococcus epidermidis*: balancing promise and challenges

Despite its widespread presence across various environments, such as human Skin, marine sponges, and fish, the applications of *S. epidermidis* or its antimicrobial agents remain largely restricted. Research primarily focuses on its potential to combat human skin pathogens, particularly for treating skin infections and inhibiting *S. aureus*, leaving its broader applications underexplored. For instance, while certain *S. epidermidis* strains, such as *S. epidermidis* YTPW-4, have shown potential to enhance flavor profiles in fermented products like Chinese Baijiu, their use as biopreservatives or antimicrobial agents in the food industry remains limited. Similarly, despite frequent isolation from fish microbiota, its role and potential application in aquaculture as an antimicrobial agent-producing fish intestinal colonizer have not been studied. These gaps are surprising given their potential to contribute to sustainable practices in these fields.

A significant challenge with *S. epidermidis* lies in its dual role as both a beneficial commensal and an opportunistic pathogen. It is a leading cause of infections associated with indwelling medical devices, such as intravenous catheters and central venous catheters [129–130]. These infections often result from contamination during device insertion, with *Staphylococcus epidermidis* forming biofilms on medical equipment. These biofilms are notoriously difficult to treat, posing a serious risk of systemic infections and complicating their application in clinical settings. Moreover, its pathogenic potential extends to aquaculture, where it has been identified as a causative agent of fish diseases in regions such as Japan, Taiwan, and Greece [46]. Such findings highlight the need for a better understanding of its pathogenic mechanisms before considering it for use in fish health management. Toxicity studies involving *S. epidermidis* or its antimicrobial agents could offer a viable solution; however, a significant limitation remains the lack of comprehensive safety evaluations, particularly those utilizing animal models, to thoroughly assess the toxicity and virulence of *S. epidermidis*. Although certain strains, such as *S. epidermidis* YTPW-4, have been found to lack key virulence factors, including hemolytic, enterotoxin, decarboxylase, and coagulase genes, phenotypic tests have confirmed their safety [128]. These findings are limited to a small number of studies. Broader and more rigorous assessments, including long-term toxicity and immunological impacts, are essential before advocating its widespread application in food, healthcare, or aquaculture. A more effective approach to minimize the risk of pathogenicity associated with *Staphylococcus epidermidis* is to use purified bacteriocins rather than administering the whole bacterial strain, as is commonly practiced in probiotic applications. This strategy enables targeted antimicrobial activity while minimizing potential complications associated with live bacteria, thereby improving safety and effectiveness in practical applications.

Overall, while *S. epidermidis* exhibits promising antimicrobial properties and potential applications across multiple industries, its dual identity as a commensal and pathogen, combined with limited research beyond human health, constrains its broader utility. However, it must be noted that, despite *P. aeruginosa*'s pathogenic reputation, its bacteriocins are actively being explored for diverse applications [131–133]. They are used to combat bacterial infections, including those caused by *P. aeruginosa* [132, 133]. Additionally, these bacteriocins are being investigated for their utility as antimicrobial agents in food preservation, in various biotechnological fields, and in bioremediation to degrade environmental pollutants [131–133]. *S. epidermidis* is not as classically pathogenic as *P. aeruginosa*. If bacteriocins from *P. aeruginosa* — a well-known pathogen — can be explored and applied successfully, there is no reason why those from *S. epidermidis* should not be considered. Future research focused on safety assessments and the exploration of potential applications in food preservation, aquaculture, and therapeutic

interventions could be key to unlocking its full potential while addressing any associated risks.

Conclusions

S. epidermidis represents an underutilized resource in the search for innovative antimicrobial solutions. Its production of bacteriocins and AMPs highlights its potential as a targeted agent against resistant pathogens, such as *S. aureus* and MRSA. While significant progress has been made in using these compounds to treat skin infections and biofilm-related complications, broader applications in food preservation, aquaculture, and healthcare remain largely untapped. Addressing challenges associated with *S. epidermidis's* dual nature — as both a commensal and an opportunistic pathogen— will require rigorous strain selection, safety evaluations, and genetic profiling to mitigate risks.

The discovery of non-virulent strains, such as *S. epidermidis* YTPW-4, that lack key pathogenic factors marks a step forward toward ensuring safe and effective applications. Further exploration of these strains could show promise not only for human health but also for improving food quality and promoting sustainable aquaculture practices. To unlock the full potential of *S. epidermidis*, future research must focus on optimizing its antimicrobial properties, ensuring safety through comprehensive studies, and exploring its utility across diverse sectors. By leveraging S. epidermidis's antimicrobial capabilities, we can develop sustainable alternatives to conventional antibiotics to address the growing crisis of antibiotic resistance.

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Authors' Contribution

Arnab Chatterjee — conceptualization, writing — original draft, review, and editing; Kauik Mondal — provided supervision support; Sutapa Sanyal — supervision, guidance, and critical review of the manuscript.

Declaration

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Competing Interests

The authors declare no competing interests.

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Ethics and Consent to Participate declarations

Not applicable

Consent for Publication

Not applicable. This article does not contain any individual person's data in any form.

Data availability

Not applicable. No new data were generated or analyzed in this study, as it is a review of existing literature. All referenced data are available in the cited publications.

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АНТИМІКРОБНИЙ ПОТЕНЦІАЛ ТА БІОАКТИВНІ СПОЛУКИ *Staphylococcus epidermidis*: ЗА МЕЖАМИ ПАТОГЕННОСТІ

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Мета. Оцінити антимікробний потенціал *Staphylococcus epidermidis*, зокрема його бактеріоцинів і антимікробних пептидів (AMPs), а також висвітлити можливості їх застосування у сфері охорони здоров'я, харчовій промисловості, аквакультурі та інших галузях.

Методи. Проведено огляд наукової літератури з аналізом опублікованих досліджень, присвячених антимікробним сполукам, що продукуються *S. epidermidis*. Розглядалися роботи, пов'язані з бактеріоцинами, антимікробними пептидами, пригніченням патогенів, безпечністю штамів та потенційним застосуванням в медичних і немедичних секторах.

Результати. Дослідження показують, що *S. epidermidis* продукує потужні антимікробні сполуки, зокрема бактеріоцини та антимікробні пептиди, які демонструють виражену специфічну активність проти патогенів. Ці сполуки ефективні проти ряду збудників, у тому числі метицилін-резистентний *Staphylococcus aureus* (MRSA), і мають потенціал у лікуванні шкірних інфекцій, хронічних ран та інфекцій, пов'язаних із біоплівками. Незважаючи на широке поширення цього мікроорганізму в природі, його можливе застосування у харчовій промисловості та аквакультурі залишається недостатньо дослідженим. Крім того, подвійна роль *S. epidermidis* як корисного коменсала та опортуністичного патогена обмежує його ширше використання. Однак сучасні досягнення у відборі штамів і генетичних дослідженнях дозволили ідентифікувати невірулентні штами, такі як *S. epidermidis* YTPW-4, які не мають основних патогенних властивостей і можуть бути безпечними для біотехнологічного застосування.

Висновки. Бактеріоцини та антимікробні пептиди, продукувані *S. epidermidis*, є перспективними антимікробними агентами з потенційним застосуванням не лише у медицині, але й у сталих харчових системах, аквакультурі та прецизійній медицині. Однак для повного використання їх терапевтичного та промислового потенціалу необхідні всебічні дослідження безпеки та подальші наукові розробки.

Ключові слова: *Staphylococcus aureus*, антимікробні пептиди (AMPs), антибіотики, бактеріоцини, неоплазія, акне.

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