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Future Acne Therapy MSC Secretome as an Antimicrobial Agent: Literature Review

Monica Indiasti Putri[1*], Marlina[1], Ikhwan Resmala Sudji[1]
[1]**Biotechnology**, Graduate School, Universitas Andalas, Padang, Indonesia;

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*Corresponding Author:
Monica Indiasti Putri,
Universitas Andalas,
Padang,
Indonesia;
Email:
indiastiputrimonica@gmail.com

Abstract: Acne vulgaris is a chronic inflammatory skin condition influenced by excess sebum production, bacterial colonization, and host immune responses. Microorganisms, particularly *Cutibacterium acnes* and *Staphylococcus aureus*, play a key role in acne pathogenesis and contribute to persistent inflammation. With increasing antibiotic resistance, innovative therapeutic approaches that are effective, safe, and immunomodulatory are urgently required. This literature review aims to evaluate the role of adipose-derived mesenchymal stem cell (ADMSC) secretome in inhibiting acne-causing bacteria. The review was conducted using databases including ResearchGate, PubMed, Google Scholar, and ScienceDirect, using keywords such as secretome, MSC secretome, antibacterial, *C. acnes*, *S. aureus*, and acne vulgaris. A total of 13 relevant research articles were identified. The ADMSC secretome contains antimicrobial peptides (e.g., LL-37), cytokines, growth factors, and extracellular vesicles that can disrupt bacterial membranes, enhance phagocytosis, and inhibit biofilm formation. Several studies demonstrate strong inhibitory effects against *S. aureus*, including resistant strains, while data on *C. acnes* remains limited but still supports its therapeutic relevance.

Keywords: ADMSC secretome, LL-37, antimicrobial, *Cutibacterium acnes, Staphylococcus aureus*

Pendahuluan

Acne vulgaris (AV) is a globally prevalent chronic inflammatory skin disorder that affects adolescents and young adults, exerting substantial impact on psychological well-being and quality of life (Mastrofrancesco, A., et al. 2025; Layton, A. M. 2025). As a dermatological condition, AV encompasses various clinical manifestations such as comedones, papules, pustules, and nodules that may progress to long-term complications including persistent hyperpigmentation and permanent scarring. These broad clinical implications highlight the complexity of the disease and its relevance to both biomedical research and public health (Żmuda, B., et al. 2024).

Scientifically, AV is understood as a multifactorial condition driven by interconnected biological processes, including excessive sebum production, follicular hyperkeratinization, microbial colonization, and dysregulated inflammatory responses. Among the microbial populations involved, Cutibacterium acnes and Staphylococcus aureus have emerged as key contributors, not only through their ability to proliferate within pilosebaceous units but also through their role in initiating and sustaining inflammatory cascades. These mechanisms underscore the importance of both microbial and immunological factors in the pathogenesis of AV (Jędrowiak, M., & Michalski, K. 2022).

Despite the availability of numerous therapeutic options ranging from topical agents to systemic antibiotics and isotretinoin clinical management of AV continues to face substantial limitations) (Wang, J., et al. 2024; Maguire, G. 2019). Longterm antibiotic use contributes to growing concerns of antimicrobial resistance, while systemic treatments can lead to adverse effects requiring vigilant monitoring. Moreover,

current therapies often lack regenerative capacity and fail to effectively modulate the inflammatory microenvironment, resulting in suboptimal clinical outcomes and persistent risk of scarring. These therapeutic gaps highlight an urgent need for innovative and effective strategies (Salgado, E., et al. 2024).

In recent years, biomedical research has advanced toward the development of cell-free therapeutic modalities, particularly secretome-based interventions derived from mesenchymal stem cells (MSCs). Secretome from adipose-derived MSCs (ADMSCs) contains an array of bioactive molecules including antimicrobial peptides, cytokines, growth factors, and extracellular vesicles capable of modulating inflammation, inhibiting microbial growth, and promoting tissue regeneration (Vasam & Bohara., 2023). This emerging approach represents a promising alternative to conventional therapies and demonstrates potential in addressing the complex pathogenesis of AV.

Therefore, this study aims to review and synthesize the latest scientific evidence regarding the therapeutic potential of ADMSC secretome in acne vulgaris (Jaiswal et al., 2024). It specifically evaluates its antibacterial mechanisms against acne-associated microorganisms, its immunomodulatory effects, and its regenerative capabilities. Furthermore, the study outlines current challenges and future research directions, emphasizing the clinical relevance and urgency of developing innovative cell-free therapies for acne management.

Bahan dan Metode

The search was conducted in the latest scientific publication database (2020–2025) for the keywords: “secretome”, “mesenchymal stem cell secretome”, ‘antibacterial’, “Cutibacterium acnes”, “Staphylococcus aureus”, “acne vulgaris”. In vitro laboratory articles, preclinical studies, and systematic reviews were prioritized.

Hasil dan Pembahasan

This literature review found 13 articles that met the criteria. Table 1 summarizes studies on the use of ADMSC secretome for acne treatment.

Tabel 1. Literature Review of ADMSC Secretome Studies on Bacterial Infections Relevant to Acne (2021–2025)

Studies / autors	Result
Castro Ramos A., dkk. (2024) - Frontiers in Microbiology	MSC and secretome exhibit in vitro/in vivo antibacterial activity against various bacteria; consistent evidence but different effector components across studies highlight the need for standardization.
Giannasi C., dkk. (2024) - Biology (MDPI)	AD-MSC secretome rich in cytokines, growth factors, EVs/miRNA; immunomodulatory & antibacterial potential; suitable for dermatological applications with formulation optimization
Shaaban F., dkk. (2025) - Stem Cell Res Ther	The ADMSC secretome exhibits large inhibition zones and measurable MIC; 96% of Staphylococcus isolates are sensitive; supporting the antibacterial potential of ADMSC against S. aureus.
Kudinov V.A., dkk. (2021) - Pharmaceuticals (MDPI)	Placenta MSC secretome-based gel reduces bacteria (including S. aureus) and accelerates wound healing; promising translational evidence for topical formulations.
Wu X., dkk. (2022) - Frontiers in Microbiology	MSC exosomes (secretome components) are capable of delivering antibacterial molecules and modulating immunity; therapeutic potential for microbial infections
Ali L., dkk. (2025) - FASEB / PMC	Preclinical evidence supports the antibacterial potential of secretome; need for control studies, dose-response studies, and identification of active components (e.g., LL-37).
Rajesh A., dkk. (2024) - Review (ScienceDirect)	Secretome enhances innate defense function (phagocyte activation) and can reduce bacterial load; supports a non-antibiotic approach.
Dubus et al., (2020)	Providing updates on the role of C. acnes strains/phylotypes in inflammation and acne pathogenesis; emphasizing the need for target-specific therapies.

Pahar et al., (2020)	LL-37 is produced by many cells (including MSCs); multifunctional: antimicrobial, immunomodulatory; a candidate antibacterial mediator secretome.
Bhattacharjya S., dkk. (2024) - Biosci/Biomolecules (MDPI)	An integrative review of LL-37; explaining its membranolytic action and inflammatory modulation — supporting the role of LL-37 in the MSC secretome effector.
Zriek, F 2021)- Review	Describing the methods of production, concentration, standardization, and therapeutic application is essential for the clinical translation of topical secretome.
Da Silva K., dkk. (2025) - PMC review	Critical analysis of secretome differences between cell sources; implications for selecting ADMSCs in skin/acne applications
Hamann T., dkk. (2025) - Microorganisms (MDPI)	Demonstrating intraspecies diversity of C. acnes; meaning that antibacterial agents need to be tested against different phylotypes for clinical relevance.

1. Antimicrobial Mechanism of ADMSC Secretome

The secretome of MSCs derived from adipose tissue is a mixture of various paracrine factors secreted by cells: antimicrobial peptides (AMPs), cytokines, growth factors, extracellular vesicles (EVs), and microRNAs (Ramos, A. C., et al. 2024). Some key aspects of the mechanism are:

a). Antimicrobial peptide LL-37: Many studies show that MSCs produce LL-37 (human cathelicidin), which has direct activity against bacteria through membrane damage and immune system modulation. For example, a systematic review showed that in 8 of 31 studies on MSC antibacterial activity, LL-37 was the main mediator of the antibacterial effect (Giannasi, C., et al. 2024). However, LL-37 is not the only mediator; other factors such as defensin-2, HGF, and IL-8 have also been reported to be involved.

b). Modulation of host immune response: Secretome can activate M1 macrophages, enhance phagocytosis, stimulate neutrophils, and strengthen bacterial clearance by the innate immune system. For example, in a review by Giannasi et al., ADMSC secretome contains factors such as IFN-γ, TNF, and CSF2 that promote immune responses and can strengthen antibacterial action (Ramos, A. C., et al. 2024).

c). Indirect/synergistic antibacterial properties of components: In vitro studies show that ADMSC-conditioned media can inhibit bacterial growth even when LL-37 has decreased, indicating that there is synergy between various mediators in the secretome. Example: hADSC-conditioned media remains effective even when LL-37 decreases after bacterial exposure (Shaaban, F., et al. 2025).

d). Anti-biofilm effects & inhibition of microbial colonization: Although there have not been many specific studies on C. acnes, the MSC literature shows that secretome/EV can interfere with bacterial biofilm formation, which is highly relevant to acne because C. acnes and S. aureus also form biofilms in follicles and skin lesions (Giannasi, C., et al. 2024).

Thus, the ADMSC secretome-based therapeutic approach has two synergistic pathways: direct (antimicrobial via peptides such as LL-37) and indirect (immune modulation & biofilm disruption). This makes it an attractive strategy for acne therapy, which involves microbes and inflammation.

2. In Vitro/In Vivo Evidence Against Bacteria and Acne Relevance

a). ADMSC Secretome vs Staphylococcus aureus

A study by Shaaban et al. (2025) tested the secretome of ADMSC against 73 clinical isolates of Staphylococcus, including MRSA. Results: significant inhibition (>70%) and inhibition zones up to 32 mm against S. aureus ATCC. [12] This indicates a clear antibacterial capacity against Gram-positive bacteria, which are also commonly found in acne lesions.

b). ADMSC Secretome vs Cutibacterium acnes

Although specific MIC secretome tests against C. acnes have not been widely published (research gap), systematic reviews show that most MSC antibacterial studies are still against S. aureus, E. coli, and Pseudomonas, with very limited testing against C. Acnes (Giannasi, C., et al. 2024).

From an acne perspective, since C. acnes is the dominant bacterium, direct MIC secretome testing of ADMSC against C. acnes is crucial.

3. Relevance to Acne
Acne involves colonization of C. acnes in the sebaceous follicles and an inflammatory response. S. aureus can appear as a secondary microbe and worsen the condition. Because the ADMSC secretome can inhibit both types of bacteria and modulate inflammation, its translation into acne therapy is logical. This approach is able to address both microbes and inflammation at the same time—superior to antibiotics, which only target bacteria and carry the risk of resistance.

4. Challenges & Issues in Clinical Translation
Although the potential is very promising, there are several challenges and important issues that need to be considered:
a). Variability of cell sources and secretome profiles: A review by Ramos et al. highlights that different MSC sources (bone marrow, umbilical cord, adipose tissue) produce different secretome profiles, and most studies still use BM-MSCs (Ramos, A. C., et al. 2024). For skin/acne applications, ADMSCs are an easily accessible option, but their antibacterial profile must be specifically validated.

b). Standardization and dosage: Secretome production (culture conditions, concentration, purification methods) varies greatly. Trigo et al. (2025) emphasize the importance of optimization and standardization so that therapies can be replicated and clinically tested (Wu, X., et al. 2022).

c). Identification of active components: Although LL-37 has been widely reported, several studies show that bacterial inhibition persists even when LL-37 levels have decreased—indicating that other components are also involved ((Shaaban, F., et al. 2025). For regulatory and safety risks, it is important to know which factors are primary.

d). Testing against C. acnes and biofilm: Since acne specifically involves C. acnes, research evaluating the secretome of ADMSCs against this bacterium, including follicular biofilm models, is urgently needed. Without it, translation to acne will lack strong evidence.

e). Topical formulations and applications: For acne therapy, topical formulations or local injections are more relevant than systemic ones. Studies such as Kudinov et al. (2021) show that MSC secretome gel can be used on infected wounds, but specific studies on skin/acne are still very limited (Ali, L., et al. 2025).

f). Safety and regulation: Since secretomes are biological products, issues of contamination, immunity, and clinical regulation must be considered. This is especially true for cosmetic/dermatological applications.

Kesimpulan

The therapeutic approach based on ADMSC secretome as an antimicrobial agent for acne shows great potential, especially due to its dual antibacterial and immunomodulatory effects. LL-37 emerges as an important mediator, but the synergy of several mediators in the secretome is key. Although evidence against S. aureus is quite good, evidence against C. acnes is still limited, which is a crucial gap in research. For clinical translation, standardization, appropriate formulation, and safety testing are important next steps.

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