INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH AND ANALYSIS

ISSN(print): 2643-9840, ISSN(online): 2643-9875

Volume 09 Issue 01 January 2026

DOI: 10.47191/ijmra/v9-i1-40, Impact Factor: 8.266

Page No. 288-293

Therapeutic Potential of Umbilical Cord-Derived Mesenchymal Stem Cell (UC-MSC) Secretome in the Control of Antibiotic-Resistant Bacterial Infections

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ABSTRACT: Antimicrobial resistance represents one of the major challenges in the control of bacterial infections and has driven the development of alternative therapeutic strategies beyond conventional antibiotics. In this context, the secretome derived from umbilical cord–derived mesenchymal stem cells (UC-MSCs) has emerged as a promising biologically based approach. The UC-MSC secretome is a complex mixture of bioactive molecules, including proteins, antimicrobial peptides, lipids, microRNAs, and extracellular vesicles or exosomes, which play roles in modulating microorganisms, immune responses, and tissue repair. Numerous experimental studies have demonstrated that the UC-MSC secretome exhibits antibacterial activity against both Gram-positive and Gram-negative pathogens, either as conditioned medium or as exosomes formulated within biomaterial systems such as hydrogels, liquid bandages, and functional scaffolds. In addition to reducing bacterial burden and inhibiting biofilm formation, this approach also supports wound healing by enhancing angiogenesis, epithelialization, and restoration of the tissue microenvironment. The therapeutic effects of the UC-MSC secretome are not solely attributable to direct bactericidal activity but are also mediated by its interconnected immunomodulatory and regenerative properties. Although available preclinical evidence consistently indicates therapeutic potential, variability in secretome production methods, exosome isolation techniques, and biomaterial formulations remains a major challenge for result interpretation and reproducibility. Therefore, further mechanistic studies and protocol standardization are required to support the development of UC-MSC secretome–based therapies as safe and effective adjuvant treatments for bacterial infection control.

KEYWORDS: antibacterial activity, biofilm, antimicrobial resistance, UC-MSC secretome

I. INTRODUCTION

Antimicrobial resistance (AMR) has developed into one of the most serious public health challenges globally over the past few decades. The prevalence of infections caused by antibiotic-resistant pathogenic bacteria has increased significantly worldwide. An analysis of the global burden of antimicrobial resistance in 2019 estimated that approximately 1.27 million deaths were directly attributable to antibiotic-resistant bacterial infections, and the total contribution of resistance to global mortality reached nearly 5 million deaths across various regions of the world.[1] Pathogens such as Escherichia coli, methicillin-resistant Staphylococcus aureus, carbapenem-resistant Klebsiella pneumoniae, and Acinetobacter baumannii are frequently reported to exhibit high levels of resistance to major classes of antibiotics, including cephalosporins, fluoroquinolones, and carbapenems.[2]

The increase in resistance has resulted in higher morbidity rates, prolonged hospital stays, increased treatment costs, and failure of conventional antibiotic therapies, thereby imposing a substantial economic and social burden on healthcare systems in many countries.[3] The complexity of bacterial resistance itself includes the production of antibiotic-degrading enzymes, alterations in molecular targets, enhanced efflux systems, and biofilm formation, which collectively further limit the effectiveness of conventional antimicrobial therapies. These conditions emphasize the urgency of developing alternative therapeutic strategies that not only focus on bacterial eradication but are also capable of modulating host immune responses and supporting tissue repair processes.[4,5]

One innovative approach that has attracted increasing attention in recent years is the utilization of secretome produced by mesenchymal stem cells (MSCs), particularly those derived from the umbilical cord (umbilical cord-derived MSCs/UC-MSCs). The secretome is a collection of bioactive factors secreted by cells, including cytokines, chemokines, growth factors, antimicrobial

peptides, microRNAs, and extracellular vesicles, which collectively play roles in immunomodulatory, anti-inflammatory, regenerative, and antimicrobial activities.[6,7] Umbilical cord-derived mesenchymal stem cells (UC-MSCs) possess several important advantages compared to other stem cell sources. Unlike embryonic stem cells, which face ethical barriers and risks of teratoma formation, UC-MSCs are derived from tissue discarded after childbirth, making their collection non-invasive and ethically acceptable. Compared to adult MSCs such as bone marrow-derived MSCs, UC-MSCs exhibit higher proliferative capacity, better growth stability, and gene expression profiles that more closely resemble embryonic cells. These advantages allow for the acquisition of large numbers of cells following in vitro expansion.[6]

Clinically, UC-MSCs can be used for both autologous and allogeneic therapies. In autologous applications, these cells have potential for regenerative or anti-inflammatory therapy in neonatal conditions, whereas for allogeneic use, UC-MSCs can be expanded and stored in cell banks. Nevertheless, the health status of the neonatal donor must first be ensured through genetic or chromosomal screening. Overall, the ease of isolation and high expansion capacity make UC-MSCs a highly promising source of MSCs for various clinical applications.[8,9]

A number of experimental studies have demonstrated that UC-MSC secretome exhibits antibacterial activity against various pathogenic bacteria, including antibiotic-resistant strains. These effects are primarily attributed to the presence of antimicrobial peptides, immunomodulatory cytokines, and extracellular vesicles carrying microRNAs and regulatory proteins, which together can reduce bacterial viability and inhibit biofilm formation. The secretome also modulates immune responses and supports tissue repair, thereby providing dual therapeutic benefits.[10]

The integration of secretome with biomaterials such as hydrogels or polymer scaffolds has been shown to enhance the stability, local retention, and controlled release of bioactive factors.[11] This approach has demonstrated promising results in wound and soft tissue infection models, with reductions in bacterial burden and accelerated healing.[12] However, variations in secretome production methods and heterogeneity among research models remain challenges for data consistency.

Although experimental evidence regarding the antibacterial potential of UC-MSC secretome continues to grow, these findings remain scattered across various studies with diverse designs, secretome production methods, and infection models.[10, 11, 12, 13] To date, there have been limited literature reviews that specifically and systematically summarize experimental evidence related to the antibacterial activity of UC-MSC secretome and the factors influencing its effectiveness. The objective of this article is to comprehensively review experimental evidence regarding the therapeutic potential of UC-MSC secretome in controlling bacterial infections, with a focus on antibacterial activity, mechanisms of action, and formulation strategies that support translational applications. This review is expected to provide an integrated understanding, identify existing research gaps, and serve as a foundation for the development of alternative therapies to address the challenge of antimicrobial resistance.

Antibacterial Activity and Therapeutic Approaches Based on UC-MSC Secretome

Overall, UC-MSC secretome demonstrates consistent antibacterial activity. UC-MSC conditioned medium has been shown to inhibit the growth of Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae, including after undergoing physical processes such as nebulization, although certain components such as LL-37 were reduced. Exosome-based formulations, such as liquid band-aids and thermosensitive hydrogels, exhibited bacterial inhibition as well as accelerated wound healing characterized by increased angiogenesis and epithelialization without showing toxicity in animal models. The use of more complex biomaterials, such as gallium/chitosan/silk sponges or MXene-based photothermal hydrogels, enhanced exosome retention and effectiveness, providing strong antibacterial activity, including biofilm reduction and bacterial membrane damage.[14]

Variations in effectiveness were observed between Gram-positive and Gram-negative bacteria, with responses generally being more consistent against S. aureus. Nevertheless, several exosome formulations, particularly sprayable hydrogels and photothermal hybrids, demonstrated significant activity against more resistant Gram-negative bacteria. Heterogeneity in secretome isolation methods, differences in conditioning duration, and variations in biomaterial types also influenced outcomes across studies, indicating the need for protocol standardization to improve research reproducibility.[15]

There is also evidence that UC-MSC secretome provides benefits beyond the context of cutaneous wounds, as demonstrated in an intrauterine study in horses reporting improvement of the uterine environment and indications of reduced microbial burden. This finding confirms that the antibacterial effects of UC-MSC secretome are not solely direct in nature but are also mediated by inflammation modulation and tissue repair[16] (Table 1).

Table 1. Comparison of Therapeutic Approaches Based on UC-MSC Secretome and Exosomes Against Various Bacterial Pathogens

No	Title & Authors	Product & Model	Pathogen & Method	Main Outcome
1	Nebulized MSC-CM Retains Antibacterial Properties[14]	UC-MSC CM; nebulized; in vitro	E. coli, K. pneumoniae, S. aureus; CFU, OD	Antibacterial activity retained after nebulization; significant CFU reduction.
2	Liquid Band-Aid with UC-MSC Exosomes[15]	Exosome UC-MSC; hydrogel; in vitro/in vivo	E. coli, S. aureus; zone inhibition + wound assay	Increased bacterial inhibition; faster wound healing.
3	Dual-Functional Ga/Chitosan/Silk Sponge with Exosomes[17]	Exosome sponge; in vitro/in vivo	Gram+ & Gram–; antibacterial & biofilm assays	Strong antibacterial activity; biofilm reduction; enhanced tissue regeneration.
4	Sprayable Hydrogel Containing UC-MSC Exosomes[18]	Exo@AMCN hydrogel; in vivo	S. aureus, E. coli	Broad antibacterial effects; increased angiogenesis and epithelialization.
5	Exosome–MXene Photothermal Hydrogel[19]	Exosome hydrogel + MXene; photothermal	Gram+ & Gram– skin bacteria	Strong bactericidal effects via photothermal mechanisms.
6	Thermosensitive Hydrogel Loaded with HUCMSC-C [20]	CM-hydrogel; in vitro/in vivo	S. aureus, E. coli	Inhibited bacterial growth; accelerated wound healing.
7	WJ-MSC CM Improves Uterine Microenvironment[16]	WJ-MSC CM; intrauterine; in vivo	Clinical Gram+ & Gram– isolates	Reduced bacterial burden; improved uterine environment; increased pregnancy rate.

Overall, the synthesis of seven studies indicates that UC-MSC secretome represents a strong candidate as an adjuvant therapy in the control of bacterial infections. This secretome not only exhibits direct antibacterial activity but also supports tissue regeneration, reduces inflammation, and improves the wound microenvironment. Although the results are promising, the majority of evidence still originates from preclinical studies, therefore, further investigations are required to evaluate safety, dominant mechanisms, consistency of effects, and potential for clinical translation

Antibacterial Mechanisms of UC-MSC Secretome

Various studies indicate that the antibacterial activity of UC-MSC secretome is multimodal in nature and does not rely on a single component. UC-MSC secretome contains proteins, antimicrobial peptides, bioactive lipids, and microRNAs that collectively can suppress bacterial growth.[13,21] Direct mechanisms occur through disruption of membrane integrity, inhibition of bacterial cellular metabolism, or interference with essential bacterial functions. Several studies have reported the presence of antimicrobial components such as the cathelicidin LL-37 and lipocalin-2, although the stability of LL-37 may decrease after exposure to certain physical processes such as nebulization, making the antibacterial effect more likely to originate from a combination of other more stable active molecules.[14] In addition, the presence of antiprotease proteins such as alpha-1 antitrypsin in the extracellular fraction also plays a role in reducing tissue damage caused by inflammation, thereby creating an environment more conducive to the healing process.[7]

Extracellular vesicles, including exosomes, are key components because they function as carriers of these various bioactive molecules and provide stability as well as targeted delivery to infected tissues.[6] UC-MSC secretome also demonstrates indirect effects through modulation of the host immune response by reducing local inflammation, enhancing phagocytosis, and accelerating tissue regeneration through increased angiogenesis and epithelial cell proliferation.[10,18] This combination of direct and indirect mechanisms explains how several secretome formulations are able to reduce bacterial burden while simultaneously accelerating wound healing in preclinical models.[15,17,19]

Variations in Secretome Preparation and Experimental Approaches

Analysis of existing studies indicates that variations in secretome preparation methods greatly influence the composition and biological potency of the final product.[6,13] The source of UC-MSCs may originate from Wharton's jelly or other segments of the umbilical cord, and differences in tissue origin can affect the molecular profile of the secretome.[8,9] Culture conditions, such as conditioning duration, serum-free media, or the presence of specific stimulatory factors, can result in variations in protein levels

and extracellular vesicle content.[13] Differences in isolation methods, such as differential ultracentrifugation, membrane filtration, or commercial kits, also contribute to variations in particle size, EV concentration, and bioactive cargo.[6,7]

Similar heterogeneity is observed in antibacterial testing methods. Some studies employ zone of inhibition measurements, while others use CFU reduction, MIC values, or antibiofilm analyses [12]. In vivo models also vary widely, ranging from acute wounds and diabetic wounds to animal uterine models. Secretome formulations introduce additional variability; thermosensitive hydrogels, gallium/chitosan/silk sponges[17], sprayable system[18] or combinations with MXene-based photothermal materials[19] result in different release profiles and cargo stability. This methodological diversity poses challenges in comparing outcomes across studies but also reflects a range of innovative approaches with potential for clinical development.[11,20]

Differences in Responses Among Bacteria

The analyzed studies indicate that Gram-positive bacteria, particularly Staphylococcus aureus, including resistant strains such as MRSA, tend to exhibit more consistent responses to UC-MSC secretome.[12,13] Gram-negative bacteria such as E. coli, K. pneumoniae, and P. aeruginosa still demonstrate reduced growth under certain secretome formulations, but the magnitude of the response is more variable, likely due to differences in outer membrane structure as well as resistance mechanisms such as efflux pumps.[5]

In in vivo models, UC-MSC secretome interventions are able to reduce bacterial burden while simultaneously improving wound healing parameters such as epithelialization and angiogenesis.[15,17–19] These findings confirm the dual effects of secretome, which not only inhibit pathogens but also modulate the microenvironment to support tissue recovery. Veterinary studies on intrauterine infusion of WJ-MSC conditioned medium further extend the evidence that UC-MSC secretome can provide indirect antibacterial benefits in different biological systems through inflammation modulation, although not all studies report quantitative bacterial measurements.[16,22] Due to heterogeneity in models and methodologies, interpretations regarding the spectrum of activity among bacteria must be made cautiously, and more definitive conclusions require further studies with more uniform designs.[23]

Translational Opportunities and Therapeutic Implications

The consistency of preclinical data regarding the antibacterial activity and pro-regenerative properties of UC-MSC secretome presents substantial opportunities for the development of adjuvant or alternative therapies for bacterial infections, particularly in cases of chronic wounds and antibiotic-resistant skin infections.[13,21] Biomaterial formulations such as thermosensitive hydrogels,[11,20] antimicrobial sponges,[17] or photothermal systems[19] enable more effective local delivery of secretome and prolong the release of bioactive molecules. The ability to prime UC-MSCs prior to secretome collection also provides the potential to enhance the content of specific antimicrobial factors within the secretome.[14]

Nevertheless, clinical implementation requires careful attention to several critical aspects, including the standardization of secretome production procedures, the establishment of quality parameters such as EV concentration or protein profiles, and long-term safety assessments related to immunogenicity.[6,24,25] Additional research is required to determine dose–response relationships, dominant molecular mechanisms involved in antibacterial activity, and the potential combination of secretome with conventional antibiotics to reduce dosage and the risk of resistance.[4,5] Collaboration among biomedical researchers, clinical microbiologists, and biomaterial developers is essential to design effective and safe formulations for progression toward evaluation in human clinical trials.[26,27]

II. CONCLUSION

This review confirms that UC-MSC secretome possesses promising therapeutic potential in the control of bacterial infections through a combination of direct antibacterial activity, antibiofilm capacity, modulation of inflammatory responses, and support of tissue regeneration. Various biomaterial formulations further emphasize the capacity for local application of the secretome, while cell priming strategies open opportunities to enhance the loading of active molecular components. Nevertheless, significant challenges remain, particularly related to variability in production methods and the lack of clinical evidence. Further studies focusing on protocol standardization, characterization of active components, clinically relevant biofilm assays, and translational testing in representative animal models and early-phase clinical trials are critically needed to realize the potential of UC-MSC secretome as a novel antimicrobial therapeutic modality.

ACKNOWLEDGEMENT

The authors would like to express their gratitude to the Doctoral Program (PhD) in Biomedical Science, YARSI University, for academic support in the preparation of this review. Appreciation is also extended to fellow researchers who provided scientific input and to parties who facilitated access to the files and data of the studies analyzed.

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