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Antimicrobial properties of mesenchymal stem cells: prospects for application against antibiotic-resistant infections



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ABSTRACT

The growing antimicrobial resistance challenges the existing healthcare system, leading to the emergence of severe and chronic bacterial infections that are resistant to standard antibiotic therapy. In this regard, the search for alternative therapeutic approaches is attracting attention, among which mesenchymal stem cells (MSCs) and their derivatives are considered a promising biological tool due to their combination of direct antimicrobial action, immunomodulatory effects, and the ability to regulate tissue regeneration.

THE PURPOSE of this review is to systematize current data on the antibacterial, antiviral, and antifungal properties of MSCs, analyze the mechanisms of their action, and evaluate the possibilities of using cell therapy to overcome antibiotic resistance.

METHODS. The paper analyzed publications in recent years available in PubMed, Scopus, and Web of Science databases. The literature search was performed using the key terms "mesenchymal stem cells," "antimicrobial properties," "antibacterial properties," "antimicrobial peptides," "antibiotic resistance," "antifungal properties," and "antiviral properties" in various combinations, using inclusion/exclusion criteria to select relevant works.

RESULTS. The review of the literature indicates that MSCs of various origins produce antimicrobial peptides, including LL-37, β -defensins, and lipocalin-2, which are capable of directly inhibiting the growth of Gram-positive and Gram-negative bacteria. MSCs extracellular vesicles, which contain microRNAs, proteins, and peptides that modulate bacterial virulence, disrupt biofilm structure, and enhance antibiotic activity, play a significant role. The immunomodulatory properties of MSCs are realized through the polarization of macrophages towards anti-inflammatory M2 cells, the suppression of pro-inflammatory cytokine secretion, and the enhancement of phagocytosis. The antiviral effects of MSCs include the regulation of interferon production, the expression of antiviral genes, and the reduction of cytokine storm intensity, which is essential in virus-induced lesions, such as COVID-19. The antifungal properties of MSCs are manifested through activation of the cellular component of innate immunity.

CONCLUSION. The analyzed data from scientific sources indicate that MSCs possess a multicomponent antimicrobial potential and can be considered a basis for new therapeutic strategies in the treatment of antibiotic-resistant and virus-associated infections, as well as fungal diseases. Further research should focus on standardizing MSC cultivation methods, determining effective dosages, and refining therapeutic protocols.

KEY WORDS: mesenchymal stem cells; antimicrobial peptides; immunomodulation; antibiofilm activity; antiviral effect; regenerative medicine

Antibiotic resistance is rapidly becoming one of the most serious global public health threats of the 21st century, as an increasing number of bacterial strains are losing their sensitivity to commonly used antibacterial drugs. The rising incidence of infections caused by multidrug-resistant strains of microorganisms complicates the treatment of both acute and chronic infectious processes. It leads to a significant increase in hospitalizations, mortality, and economic costs [1]. Infections associated with the formation of microbial biofilms are complicated to treat, as in

this state the bacteria demonstrate tenfold higher resistance to antibiotics and immune system effectors [2]. Chronic diseases of bacterial etiology, such as osteomyelitis, skin and soft tissue infections, chronic respiratory infections, and inflammatory diseases of the oral cavity, are primarily associated with the ability of bacteria to form biofilms and evade immune system control [3-6]. Traditional antibiotic treatment plans in such cases often prove to be insufficiently effective, which necessitates the development of new biologically oriented approaches [7, 8].

At the current stage of development in experimental and clinical medicine, mesenchymal stem cells (MSCs) and their derivatives are attracting considerable attention due to their combination of regenerative [9-11], anti-inflammatory [12, 13], immunomodulatory [14, 15], and anti-apoptotic properties [16]. In addition, new data are emerging on the antimicrobial effects of MSCs. The therapeutic potential of MSCs in combating infectious processes was analyzed by Sharma et al. [17]. The authors emphasized that MSCs not only suppress bacterial proliferation but also modulate excessive immune responses, stimulate tissue regeneration, and maintain homeostasis in areas of inflammation [17]. The antimicrobial effect of MSCs is manifested paracrinally, due to the bactericidal components of their secretome [18, 19]. Data from modern experimental studies indicate that MSCs from various tissue sources (bone marrow, adipose tissue, placenta, umbilical cord, dental pulp) can significantly reduce the viability of pathogenic microorganisms, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* [20], and also exhibit a synergistic effect in combination with low doses of antibiotics [21].

MSC extracellular vesicles, particularly exosomes, are of great interest as potential natural nanotransport systems for intercellular communication, as they play a role in delivering antimicrobial peptides to infection sites [22, 23]. A significant advantage of exosomes is the minimization of risks in clinical use, compared to cell therapy, when certain types of stem cells can exhibit immunogenic [24, 12], teratogenic, or tumorigenic effects [25, 26].

Given the available data, an important task arises - to study in more detail the mechanisms of antimicrobial action of MSCs both in laboratory conditions and in models of living organisms, to investigate the effect of MSCs on the formation and destruction of bacterial biofilms, and, as a result, to enhance the antimicrobial efficacy of MSCs. In the clinical setting, MSCs are currently being investigated in over 80 clinical trials. In particular, the treatment of sepsis and infections caused by multidrug-resistant strains highlights their potential as an adjunctive therapy.

THE PURPOSE of this review is to systematize current experimental and clinical scientific data on the antimicrobial properties of MSCs, analyze the mechanisms of their interaction with bacteria, viruses, fungi, and immune cells of the human body, and evaluate the possibilities of using cell therapy to overcome antibiotic resistance.

RESEARCH METHODOLOGY

To write this manuscript, a search of scientific literature was conducted in the international scientometric databases Scopus, Web of Science Core Collection, and PubMed/MEDLINE, which focused on the antibacterial, antibiofilm, and immunomodulatory properties of MSCs, as well as the antifungal and antiviral effects of these cells associated with the secretion of antimicrobial peptides and extracellular vesicles. The authors followed the PRISMA flow chart principles (**Fig.1**) for writing the manuscript, ensuring a transparent and structured approach to selecting and analyzing scientific papers. To form search queries, MeSH terms and their combinations in arbitrary form were used for the following keywords: *mesenchymal stem cells OR MSCs; antimicrobial OR antibacterial OR anti-biofilm; LL-37 OR cathelicidin OR defensins OR lipocalin-2; exosomes OR extracellular vesicles; biofilm OR antibiotic resistance; sepsis; infection; antifungal properties; antiviral properties*. This study considered works published between 2020 and 2025, using the aforementioned keywords.

Inclusion criteria: (i) full-text journal articles written in English, papers should have addressed the antibacterial, antiviral, antifungal, antibiofilm and immunomodulatory properties of MSCs (ii) scientific papers published in 2020 or later. **Exclusion criteria:** (i) case reports; (ii) conference papers; (iii) materials published before 2020; (iv) randomized controlled trials; (v) editorials, short communications, errata.

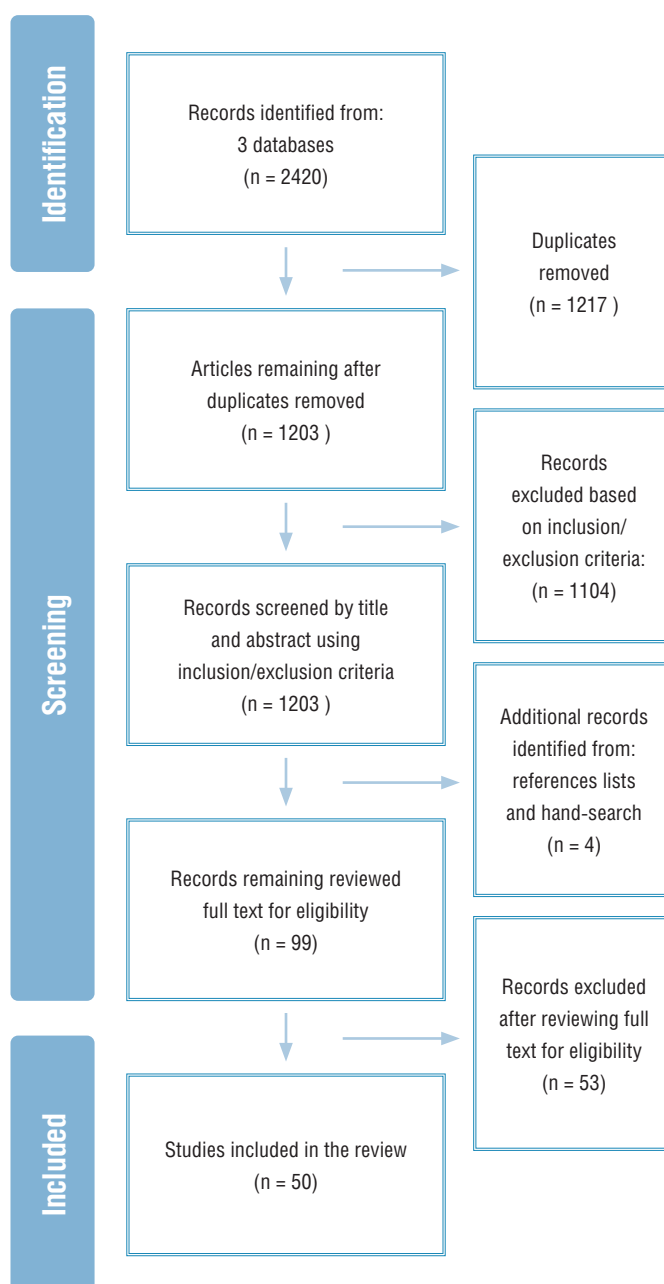


Fig. 1. PRISMA flow-chart of inclusion/exclusion criteria.

A total of 2420 publications were identified. After removing duplicates, 1203 articles remained. Eligible studies were distributed equally among the co-authors for critical review of articles by title and abstract. The co-authors reviewed the abstracts of 1203 records to determine whether they met the inclusion and exclusion criteria. As a result, 1104 publications were discarded, leaving 99 publications for full-text review. The selected materials included both research and review articles. All selected records were again distributed equally among the authors for full-text review. At this stage, 53 articles were excluded after analysis based on the inclusion/exclusion criteria. When reviewing the remaining articles and familiarizing the authors with their references, four additional publications were selected (three articles published before 2020, as the authors considered the information in them to be essential to the research topic, and one publication in Ukrainian, which concerned biofilm-forming strains). The procedure is shown in Figure 1 of the PRISMA flowchart. (**Fig. 1**).

RESULTS AND DISCUSSION

Antibiotic resistance as a global health challenge.

According to the WHO, antimicrobial resistance continued to worsen in 2025. More than 40 % of countries report high rates of resistance to clinically significant pathogens [27]. One in six bacterial infections worldwide has become resistant to standard antibiotics. The highest rates are recorded in Southeast Asia and the Eastern Mediterranean, where one in three infections is caused by antibiotic-resistant strains of microorganisms. On the African continent, some types of infectious disease pathogens demonstrate resistance to antibacterial drugs in more than 70 % of cases [27]. The rise of multidrug-resistant bacterial strains is reducing the effectiveness of conventional antibacterial therapies and making it difficult to treat both acute and chronic infections [28-30]. The consequences include increased mortality, prolonged hospitalization, increased healthcare costs, and limited effective therapeutic options. The global increase in antibiotic resistance poses a significant threat, reducing the effectiveness of commonly used antibiotics against common bacterial infections [31, 32].

Bacterial diseases are a group of infectious diseases resulting from the colonization and multiplication of pathogenic bacteria in human tissues, leading to disruption of physiological homeostasis, an inflammatory response, toxicosis, and, in severe cases, sepsis, multiple organ failure, and death [33]. The problem is particularly acute in bacterial diseases accompanied by the formation of biofilms, as this condition provides microorganisms with significantly higher resistance to antibiotics and immune system effectors. Biofilm creates a stable microenvironment and promotes the recurrence of inflammatory processes, which significantly complicates the treatment of chronic infections. Data obtained by Kryvtsova et al. show that biofilm-forming strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* have considerably increased resistance to ampicillin, tetracycline, macrolides, and cephalosporins compared to their planktonic forms, which remain sensitive to most of these drugs [34]. Traditional approaches to treating infectious diseases are increasingly demonstrating the need for revision and updating, with an emphasis on developing more effective modern therapeutic strategies. In this regard, MSCs, which possess both immunomodulatory and regenerative potential, as well as antibacterial action, are of particular interest.

Mesenchymal stem cells: characteristics and biological properties.

MSCs are undifferentiated multipotent cells derived from the mesenchyme, the embryonic connective tissue, and have a great potential for tissue and organ regeneration. In the adult human body, they are located in the stroma of the bone marrow and other anatomical niches, including adipose tissue, dental pulp, umbilical cord, placenta, and menstrual fluid [35]. Each population of MSCs differs morphologically, in the expression of markers, and in the ability to undergo specific differentiation pathways *in vitro* into different types of mesodermal cells, such as chondroblasts, osteoblasts, and adipocytes [36, 37]. Such differences underscore the need to select a specific population of MSCs to address specific therapeutic issues.

Bone marrow-derived MSCs (BM-MSCs) are the most studied population, widely used both in regenerative medicine and in studies of antibacterial activity [38]. MSCs isolated from bone marrow are primarily localized near sinusoids, where they support hematopoietic stem cells and provide optimal conditions for their proliferation. BM-MSCs are characterized by the stable secretion of antimicrobial molecules, including LL-37, lipocalin-2, and β -defensins, which give a pronounced direct antibacterial effect. Their exosomes also contain both antimicrobial peptides (AMPs) and regulatory microRNAs, in particular those that affect macrophage polarization and suppress the secretion of pro-inflammatory cytokines TNF- α and IL-6 [38]. However, a significant limitation of these cells is the invasive method of collection, as well as age-related changes that reduce their functional potential.

Adipose tissue-derived MSCs (ADSCs) demonstrate a high yield of cells and a large number of exosomes containing AMPs and molecules capable of modulating the neutrophil response [39]. ADSCs are characterized by increased levels of LL-37 and β -defensins, which enhance their activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms. ADSCs are also effective in inducing the transition of macrophages to the M2 phenotype. However, their properties may vary depending on the donor status; in particular, obesity reduces the secretory activity and antimicrobial potential of these cells.

Umbilical cord-derived MSCs (UC-MSCs) and placental MSCs (PMSCs) are characterized by high proliferative capacity. They are relatively "young" phenotype and produce significant amounts of lipocalin-2, while LL-37 secretion from these cells is stable but lower compared to ADSCs. UC-MSCs and PMSCs exhibit the highest exosome yield among all MSC types, and their vesicles are rich in regulatory microRNAs and factors that inhibit pathogen virulence [40,41]. PMSCs, according to published data, have the most potent "innate" antibacterial profile, making them particularly promising in models of resistant infections [40].

Dental pulp stem cells (DPSC) and periodontal ligament cells (PDLSCs), including immature permanent stem cells from the apical papilla (SCAP), belong to oral MSC populations and are characterized by active secretion of β -defensins and moderate levels of LL-37. DPSC and PDLSC have antibacterial activity mainly against oral pathogens (*Porphyromonas gingivalis*, *Fusobacterium nucleatum*), while there is less data on their systemic action. The ease of access and minimal invasiveness of collection make these cells promising for local therapies of infections in the oral cavity, although their antibacterial potential requires further investigation [42].

Antimicrobial mechanisms of action of MSCs.

The antimicrobial activity of MSCs is primarily due to the secretion of AMPs: β -defensins, cathelicidin LL-37, and lipocalin-2, which directly inhibit the growth of pathogens by blocking their survival mechanisms.

AMPs are evolutionarily conserved, genetically encoded small effector molecules (10–150 amino acids). They are found in all living organisms, from prokaryotes to humans [42]. Such molecules are usually positively charged, which enables them to interact with the negatively charged bacterial membranes. The destruction of pathogens, mediated by antimicrobial peptides, occurs by disrupting membrane integrity, inhibiting protein, DNA, or RNA synthesis, and interacting with specific intracellular targets [43]. Additionally, AMPs are potent chemoattractants that can recruit antigen-presenting cells, thereby contributing to the emergence of an acquired immune response.

The antimicrobial peptide LL-37 (human cathelicidin) is one of the main antimicrobial factors produced by MSCs [44]. It is a cationic amphipathic peptide that exhibits a broad spectrum of antibacterial activity, several immunomodulatory effects, anticancer activity, as well as chemotactic and proangiogenic properties. Its molecular mechanism of action is based on electrostatic interactions with negatively charged components of bacterial membranes. In Gram-negative bacteria, such targets include lipopolysaccharides, whereas in Gram-positive bacteria, lipoteichoic acid and other anionic components of the cell wall are involved [45]. As a result of such interactions, LL-37 binds to the surface of the bacterial membrane, changes its electrostatic characteristics and disrupts the integrity of the lipid bilayer. The peptide is incorporated into the membrane with the formation of pores, which causes the release of intracellular contents, loss of osmotic balance and death of the microorganism. These data are complemented by the results of a study by Yagi H et al., which found that human MSCs effectively inhibit the growth of *Staphylococcus aureus* *in vitro*. Stimulation of MSCs with $1,25(\text{OH})_2\text{D}_3$ enhances the expression of the antimicrobial peptide LL-37 and, accordingly, increases their bactericidal activity. At the same time, blockade of the vitamin D receptor attenuates this effect, confirming the role of LL-37 in the antibacterial mechanisms of MSCs [46]. Comune et al. demonstrated that both the soluble form of LL-37 and LL-37 immobilized on nanoparticles retain high

bactericidal activity even in serum and exhibit proangiogenic properties [19]. In addition, LL-37 inhibits bacterial intercellular communication, thereby reducing the ability of pathogens to coordinate the synthesis of virulence factors and form biofilms, which are a primary element of anti-

biotic resistance. LL-37 also activates the FPRL-1 receptor and stimulates the production of VEGF, promoting angiogenesis and tissue regeneration (Fig. 2).

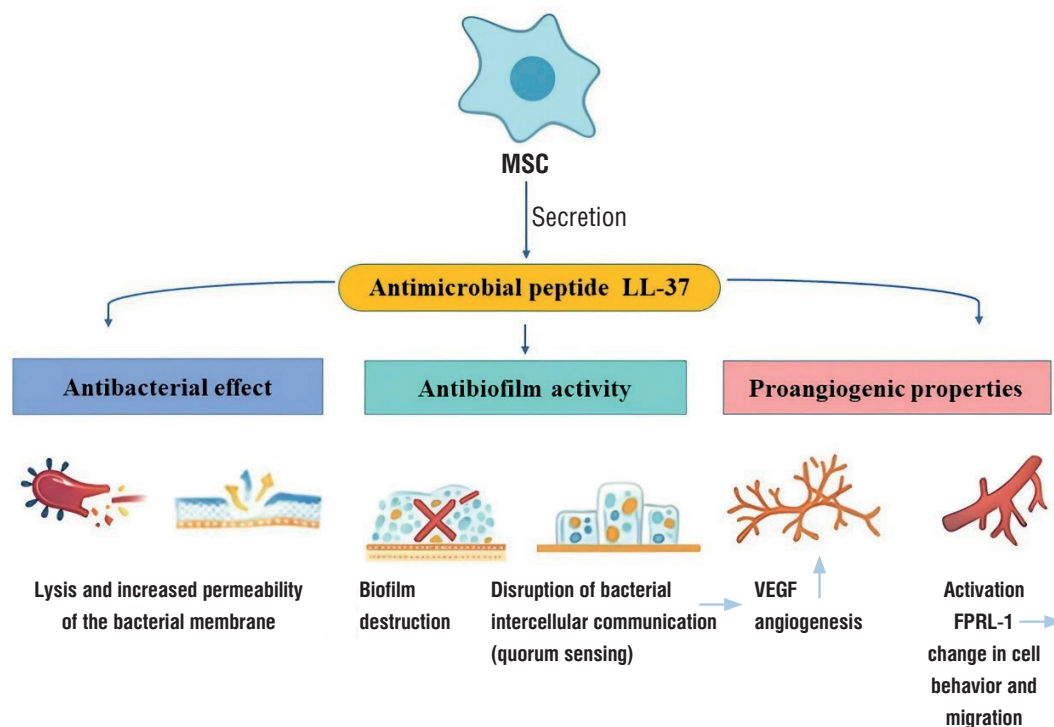


Fig. 2. The role of LL-37 in the antibacterial and angiogenic mechanisms of MSCs.

Defensins produced by MSCs constitute another important class of antimicrobial peptides. These molecules are classified as α -defensins, β -defensins, or θ -defensins, depending on their cellular origin, gene structure, and the relationship of cysteine residues in their sequence [44, 47]. These peptides perform important functions in the innate and adaptive immune systems, providing protection against bacterial and viral pathogens, promoting wound healing, modulating cytokine and chemokine expression, stimulating histamine release, and enhancing antibody production [48]. Defensins β (hBD 1, hBD 2, hBD 3) are human antibacterial peptides expressed by MSCs. With the exception of hBD 1, their expression is induced by proinflammatory signals or microorganisms. hBD 1 and hBD 2 are predominantly active against Gram-negative bacteria, while hBD 3 has a broad spectrum of antibacterial activity [48]. This makes the regulation and targeted use of defensins, for example for wound or infection treatment, especially in conditions of reduced production of these peptides, a promising therapeutic approach.

Hepcidin is another natural human protective peptide synthesized by erythrocytes and bone marrow cells, but MSCs can stimulate its production through paracrine effects. This antibacterial factor exerts a regulatory effect on the amount of iron in the body and also has a broad spectrum of antimicrobial activity against fungal species and bacteria, including *Escherichia coli*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and group *B streptococci* [49]. Hepcidins, like cathelicidin and defensins, can destroy bacterial membranes, inhibit the growth of pathogens, and enhance the effectiveness of antibiotics when used in combination. Hypoferremia mediated by this antibacterial factor can perform a protective function in the host organism, limiting the availability of iron for pathogenic strains and, accordingly, inhibiting the growth rate. The increased bactericidal activity of MSC hepcidins in an acidic environment makes them promising for the development of new drugs targeting the treatment of bacterial infections in tissues with low pH levels.

Lipocalin-2 (LCN2) is a critical antibacterial component that affects critical metal-dependent metabolic pathways in bacteria. These include mechanisms for the capture and use of metals, primarily iron, which is an indispensable element for bacterial growth, DNA synthesis, enzyme activity, and the construction of energy chains. The primary method by which bacteria obtain iron is through the use of siderophore systems. They involve the secretion of siderophores that bind iron in the host organism and ensure its further transport into the bacterial cell [50].

LCN2 intercepts bacterial siderophores (e.g., enterochelin in *Escherichia coli*), blocking the access of microorganisms to iron. This leads to inhibition of their metabolism, replication, and virulence. Since iron is a significant factor in the existence of pathogens, the impact on metal-dependent systems is considered one of the most effective strategies for natural antibacterial defense [51].

The combination of the effects of LL-37, β -defensins, hepcidin, and LCN2 on bacterial membrane structures, biochemical processes, and metal-dependent systems forms an antimicrobial multilevel impact of MSCs. It is important that these mechanisms affect the basic life processes of bacteria, so the development of resistance to them is significantly more complex than in the case of classical antibiotics, which often act through interaction with individual enzymes or specific structures.

Immunomodulating properties of MSCs.

Numerous studies indicate that MSCs might be vital in the body's initial reaction to pathogens, serving as an essential part of innate immunity. It has been established that these cells express Toll-like receptors, which recognize conserved bacterial-associated molecular patterns [52]. Activation of TLRs causes a change in the phenotype of MSCs and a reorganization of their secretory profile, which affects the activity of the primary effector cells of innate immunity - macrophages, neutrophils, and dendritic cells [53, 54]. One of the critical consequences of such

activation is the ability of MSCs to regulate the intensity of the inflammatory reaction: they reduce the production of pro-inflammatory cytokines, in particular TNF- α , IL-1 β , and IL-6, and at the same time enhance the functional activity of phagocytes, contributing to a more effective elimination of pathogens [13, 14]. It is known that MSCs induce the polarization of macrophages towards the M2 anti-inflammatory phenotype, thereby limiting the development of a cytokine storm, contributing to the restoration of homeostasis, and reducing systemic tissue damage during the infectious process [55, 56].

In addition to stimulating macrophages, MSCs also enhance the activity of neutrophils, which are not only capable of phagocytosing microbial pathogens but also of forming extracellular traps and regulating inflammation [57, 58]. The immunomodulatory effect of MSCs is not limited to bacterial infections, but is also evident in conditions of viral and fungal diseases. It is known that MSCs can enhance the production of type I interferons, induce the expression of antiviral genes, produce microRNAs that disrupt viral replication, and also reduce the excessive

pro-inflammatory response that occurs in the pathogenesis of many viral infections [57]. Clinical trial data from patients with severe COVID-19 indicate that MSC administration is associated with a decrease in IL-6 and TNF- α levels. Along with a reduction in tissue-injury markers, supporting the immunomodulatory potential of these cells [59, 60].

It has been established that the antifungal effect of MSCs is mediated by the secretion of M-CSF (macrophage colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor), which stimulate the formation of monocytes/macrophages, support their survival, and enhance their phagocytic activity [18].

Therefore, MSCs exhibit a pronounced immunomodulatory property, which is achieved through the secretion of biologically active molecules that regulate the formation and activation of immune cells. **Figure 3** shows the main mechanisms of the antimicrobial and immunomodulatory effects of MSCs, which are mediated through the production of their derivatives (exosomes).

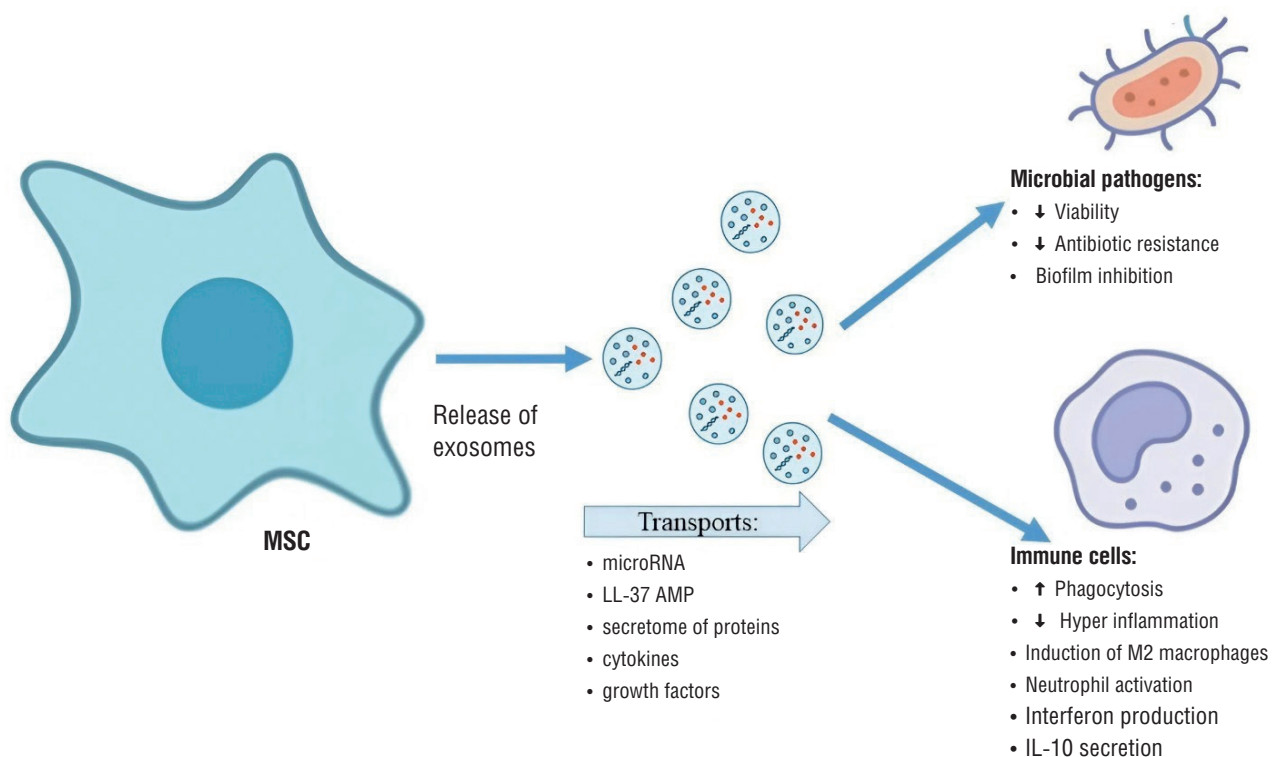


Fig. 3. Mechanisms of antimicrobial and immunomodulatory action of MSCs.

Synergism of MSCs with antibiotics.

The antimicrobial properties of MSCs are manifested not only in a direct bactericidal effect, but also through synergistic interactions with antibiotics [61]. Studies by Esfandiary et al. indicate that methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* remain the leading pathogens of nosocomial infections and sepsis, and their increasing resistance to antibiotics necessitates the need for new biologically oriented strategies, particularly the use of preconditioned MSCs. Pretreatment of these cells with low concentrations of antibiotics (e.g., linezolid, vancomycin, meropenem, or cephalosporins) in the range of 1-2 $\mu\text{g}/\text{mL}$ can significantly enhance their antimicrobial activity. This is manifested by an increase in bacteriostatic and bactericidal effects, as well as an increase in the expression of antimicrobial peptides [62].

According to Winkler & Mao, the combination of MSCs with antibiotics in a single carrier provides a pronounced synergistic effect. GelMA

microparticles, which simultaneously transport cells and antibacterial molecules, significantly reduce the bacterial load and destroy biofilms more effectively than the separate use of MSCs or antibiotics [63].

Comparison of antibacterial and immunomodulating properties of MSCs of different origin.

MSCs derived from different tissues share common basic characteristics and a general spectrum of antibacterial properties; however, their secretory profile, number of exosomes, and efficacy in modulating the immune response can vary significantly depending on their source of origin [64]. This is due to the age, physiological, and biochemical characteristics of the tissue from which the MSCs are isolated, as well as the different activities of genes responsible for the synthesis of antimicrobial peptides and regulatory molecules (**Table 1**).

Table 1. Comparison of antibacterial and immunomodulatory properties of different types of MSCs [37–42].

Steps	AMP	Exosomes (EVs) (quantity, efficiency)	Antibiofilm effect	Immunomodulation (M1→M2, cytokines)	Advantages	Limitation
BM-MSCs (bone marrow)	High LL-37 expression; stable LCN2 secretion; moderate β -defensins	Medium-yield EVs; contain AMPs and miRNAs that regulate macrophages	Well-confirmed <i>in vitro</i> effect against <i>S. aureus</i>	Marked reduction of TNF- α , IL-6; M2 activation	Best studied type; strong immunoregulatory properties	Invasive cell harvesting; donor age affects quality
ADSCs (adipose tissue)	High levels of LL-37, β -defensins; good antibacterial activity	High yield of EVs; effective in modulating neutrophils	Powerful inhibition of biofilms (especially <i>P. aeruginosa</i>)	Strong immunomodulation, rapid M1 → M2 switching	Easy to pick, large number of cells	Variability between donors (obesity → weaker MSCs)
UC-MSCs (cord blood/ Wharton's jelly)	Good secretion of LCN2, moderate LL-37; young cells → higher potential	Highest yield of EVs; rich in regulatory miRNAs	Effective against gram-negative pathogens	Significant reduction in pro-inflammatory cytokines	Non-invasive collection; low immunogenicity	Limited access; dependence on cord blood banks
PMSCs (placenta)	Good secretion of LL-37, β -defensins and LCN2; characteristic distinct innate antibacterial profile	Very high yield of EVs; exosomes contain regulatory miRNAs, AMPs, and factors that reduce bacterial virulence	Effective against gram-positive and gram-negative bacteria; promising in inhibiting biofilms	Powerful immunoregulation: pronounced suppression of pro-inflammatory cytokines, induction of M2 macrophages	Non-invasive collection; young cell age; high secretory activity even compared to UC-MSC	Dependence on the availability of placental material
DPSCs (dental pulp)	Marked secretion of β -defensins; potentially high LL-37	Medium-yield EVs active against oral pathogens	Promising against oral biofilms	Modulate local immune responses in oral tissues	Easy access during tooth extraction	Less data on systemic antibacterial activity
PDLSCs / SCAP (periodontal ligament / apical papillae)	Data are limited; secretion of AMPs is moderate	EVs may affect perio-dontitis pathogens	Possible destruction of <i>P. gingivalis</i> and <i>F. nucleatum</i> biofilms	Regenerative and immunomodulatory effects in the periodontium	Most relevant for the treatment of perio-dontitis	Limited studies on antibacterial properties

Analysis of the data presented in the table reveals that different types of MSCs retain a basic set of antibacterial and immunomodulatory properties; however, the intensity and spectrum of their action depend on the origin of the cells. Perinatal MSCs (UC-MSCs and PMSCs) generally show greater secretory activity and more pronounced immunomodulatory effects than adult MSC sources (BM-MSCs and ADSCs). In contrast, adult populations tend to deliver a more consistent, though at times less robust, antimicrobial response.

Role of MSCs in modulation of systemic infections.

Sharma et al. discuss the broader therapeutic role of MSCs in infectious conditions, noting that these cells can limit bacterial growth; moderate exaggerated immune responses, supports tissue repair, and maintains local homeostasis at sites of inflammation [17].

Clinical studies have demonstrated the effectiveness of using MSCs in treating severe conditions, such as sepsis. According to Alp et al., MSC therapy demonstrates a high level of safety in patients with sepsis, although the question of clinical efficacy requires further study [65]. A general analysis by Yang et al. confirms that MSCs can reduce signs of organ dysfunction in sepsis due to their cytokine-regulating and antibacterial mechanisms [66].

In vitro experimental studies demonstrate that not only MSCs, but also conditioned medium enriched with their secretions, obtained without additional stimulation, is capable of inhibiting the growth of both gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria, providing a decrease in colony-forming units by 1.4–2 logarithmic units [61].

The effect of MSCs on the formation of bacterial biofilms is essential. Studies by Jiang et al. demonstrated the ability of MSCs and their extracellular vesicles to suppress bacterial load and regulate the inflammatory process [67]. MSCs inhibit bacterial adhesion to surfaces, prevent the formation of new biofilms, dissolve existing *S. aureus* biofilms, and enhance the antimicrobial activity of neutrophils and macrophages [61]. Bagheri-Josheghani et al. confirmed the antibacterial potential of MSCs, in which the conditioned medium of MSCs encapsulated in chitosan nanostructures exhibited pronounced antibacterial and antibiofilm activity both *in vitro* and *in vivo*. The resulting composite significantly reduced the bacterial load and destroyed biofilms more effectively than the individual components, which indicates a synergistic effect between the MSC secretome and the nanomaterial [68]. The available data confirm the promising use of MSCs in the therapy of chronic infections accompanied by biofilm formation (Fig. 4).

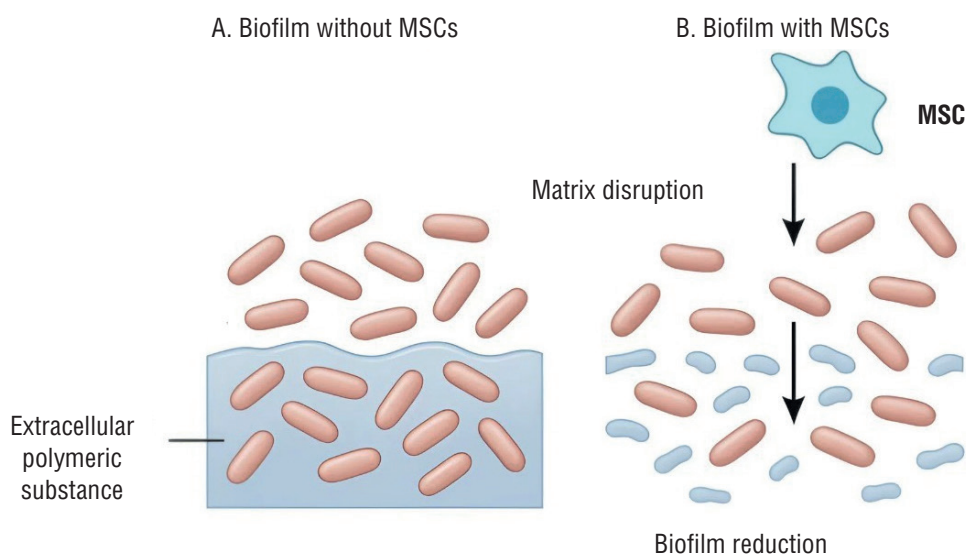


Fig. 4. Effect of MSCs on biofilms.

Figure 4 illustrates a schematic comparison of the bacterial biofilm structure in the absence of MSC exposure (panel A) and after the action of MSC factors (panel B). In panel B, arrows indicate matrix destabilization and a decrease in the total mass of the biofilm. After exposure to MSCs, the destruction of the extracellular matrix and a reduction in the density of bacterial clusters are observed.

Numerous preclinical studies have confirmed that the use of MSCs or their secretome reduces bacterial load, improves tissue healing, and reduces inflammation [69]. In an animal model of *E. coli*-induced pneumonia, MSC transplantation was accompanied by a decrease in the number of bacteria in the lungs and bronchoalveolar tree [58].

Role of MSCs in regulation of virus-induced immune response.

Although most studies on the antimicrobial effects of MSCs have focused on antibacterial activity, a growing body of evidence suggests their antiviral potential, which is primarily mediated through immunomodulatory mechanisms. For example, in a model of lethal HSV-1 infection, the administration of MSCs increased survival by enhancing IFN- γ production and reducing the levels of IL-6 and TNF- α [17]. MSCs have also been shown to inhibit the proliferation of HTLV-1-infected T cells by secreting IDO and PGE2, which reduce viral gene expression [17]. The antiviral effect of MSCs depends on the type of pathogen: for example, BM-MSC conditioned medium effectively reduced HSV-1 replication, but did not show similar activity against dengue and enterovirus [17]. During the COVID-19 pandemic, significant data have been accumulated on the use of MSCs and their exosomes to reduce cytokine storms [70]. An analysis of 33 clinical trials showed the potential efficacy of the therapy in controlling the hyperinflammatory response and improving the condition of critically ill patients [71], which is consistent with the findings of other authors on the critical role of the immunoregulatory properties of MSCs in virus-induced lesions, including acute lung injury and myocarditis [72, 73].

Antifungal potential of MSCs.

In addition to the described antibacterial and antiviral properties of stem cells, there are currently some works devoted to the antifungal activity of MSCs. Among the numerous fungal pathogens, *Candida albicans* attracts the greatest attention from researchers. This is an opportunistic microorganism capable of forming biofilms on various tissues and organs, and due to the suppression of the host immune system, it causes severe systemic infectious lesions. Ghasemian describes, in his review, individual populations of MSCs primed by TLR4 and IL-17+, which have an immunostimulatory effect and, as a result, exhibit high antifungal efficacy [74].

The promise of MSC-mediated approaches as an adjunctive strategy for treating candidal infections was demonstrated by Bicer et al. [75]. Candidiasis, especially in patients with immunodeficiency states or on immunosuppressive therapy, is associated with a high mortality rate, which can reach about 40%. MSCs derived from palatine adipose tissue (PAT-MSC) and cultured in a 3D biomaterial (CM-PAT-MSC-3D) using nanofibrillar cellulose were tested against *C. albicans* strains ATCC 10231 and ATCC MYA 2876 using an *in vitro* antifungal activity assay. The combination of PAT-MSC and CM-PAT-MSC-3D significantly inhibited fungal growth: at an inoculum of 500 CFU, the inhibition level was 99.75 % for *C. albicans* ATCC 10231 and 99.91 % for ATCC MYA-2876. It was also shown that LL-37 expression was significantly increased in PAT-MSC cultures in both 2D and 3D formats, with 3D conditions further enhancing LL-37 gene transcription. This suggests that LL-37 may play a role not only in antibacterial but also in antifungal effects. In contrast, the expression of other antimicrobial peptides, hepcidin, lipocalin, surfactant protein D, and β -defensin-2, was not detected [75].

Prospects for further research on the anti-microbial activity of MSCs.

As can be seen from the reviewed literature, many researchers have noted the positive effect of MSCs on controlling bacterial, viral, or fungal infections; however, there is significant variability in the results obtained due to the diversity of pathology modeling protocols and methods for assessing antimicrobial activity [76].

Currently, several important limitations must be considered before the clinical application of MSCs. Most studies have been conducted outside living organisms or in experimental animal models, and the diversity of MSC sources and cultivation protocols creates heterogeneity of results.

Due to these limitations, the results cannot be directly extrapolated to humans. Therefore, unified approaches to conducting studies, clear justification of doses, and proven cultivation conditions are necessary to achieve the most pronounced and yet safe therapeutic effect.

Future research should be directed at how MSCs exert their antimicrobial effects and evaluate their performance in both preclinical and clinical settings, as well as refine combination regimens that pair MSC-based approaches with antibiotics. Such an approach may increase the effectiveness of therapy for bacterial infections, reduce the likelihood of resistance formation, and expand clinical opportunities in the management of persistent and chronic diseases.

CONCLUSION

The antibacterial properties of mesenchymal stem cells provide a multifactorial mechanism of action, including a direct bactericidal effect through the secretion of antimicrobial peptides (cathelicidin, defensins, hepcidins), stimulation of innate immunity, and increased effectiveness of antibiotics. The obtained data substantiate the feasibility of using MSCs as a promising component of modern therapeutic strategies in the treatment of bacterial infections caused by antibiotic-resistant strains, as well as in infections with a biofilm component. MSCs have been shown to limit biofilm formation, enhance the activity of macrophages and neutrophils, and modulate inflammatory response features that could help control bacterial burden more effectively and reduce tissue injury.

The additional antiviral, antifungal, and immunoregulatory properties of MSCs expand the possibilities of their use in infectious lesions of mixed etiology.

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Антимікробні властивості мезенхімальних стовбурових клітин та перспективи їх застосування проти антибіотикорезистентних інфекцій



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РЕЗЮМЕ

Зростаюча антимікробна резистентність кидає виклик існуючій системі охорони здоров'я, зумовлюючи появу важких та хронічних бактеріальних інфекцій, стійких до стандартної антибіотикотерапії. У зв'язку з цим привертає увагу пошук альтернативних терапевтичних підходів, серед яких мезенхімальні стовбурові клітини (МСК) та їхні похідні розглядаються як перспективний біологічний інструмент завдяки поєднанню прямої антимікробної дії, імуномодуючим ефектам та здатності регулювати тканинну регенерацію.

МЕТОЮ огляду є систематизація сучасних даних щодо антибактеріальних протівірусних, і протигрибкових властивостей МСК, аналіз механізмів їхньої дії та оцінка можливостей застосування клітинної терапії у подоланні антибіотикорезистентності.

МАТЕРІАЛИ І МЕТОДИ. У роботі проаналізовано публікації за останні роки, доступні в базах PubMed, Scopus і Web of Science. Пошук літератури здійснювався за ключовими термінами "mesenchymal stem cells", "antimicrobial properties", "antibacterial properties", "antimicrobial peptides", "antibiotic resistance", "antifungal properties", "antiviral properties" в різних комбінаціях, із використанням критеріїв включення/виключення, щоб вибрати релевантні роботи.

РЕЗУЛЬТАТИ. Аналіз літератури вказує, що МСК різного походження продукують антимікробні пептиди, зокрема LL-37, β -дефензини та ліпокалін-2, що здатні безпосередньо пригнічувати ріст грампозитивних і грамнегативних бактерій. Значну роль відіграють позаклітинні везикули МСК, які містять мікроРНК, білки та пептиди, що модулюють бактеріальну вірулентність, порушують структуру біоплівки та посилюють активність антибіотиків. Імуномодуючі властивості МСК реалізуються через поляризацію макрофагів у напрямку протизапальних M2 клітин, пригнічення виділення прозапальних цитокінів і посилення фагоцитозу. Протівірусні ефекти МСК включають регуляцію продукції інтерферонів, експресію антивірусних генів і зменшення інтенсивності цитокінового шторму, що має значення при вірус-індукованих ураженнях, включно з COVID-19. Протигрибкові властивості МСК, проявляються через активацію клітинної ланки вродженого імунітету.

ВИСНОВКИ. Проаналізовані дані наукових джерел свідчать, що МСК мають багатокомпонентний антимікробний потенціал і можуть розглядатися як основа для нових терапевтичних стратегій у лікуванні антибіотикорезистентних та вірус-асоційованих інфекцій, чи грибових захворювань. Подальші дослідження мають бути спрямовані на стандартизацію методик культивування МСК, підбір ефективних дозувань та оптимізацію терапевтичних протоколів.

КЛЮЧОВІ СЛОВА: мезенхімальні стовбурові клітини; антимікробні пептиди; антибіоплівкова дія; протівірусний ефект; імуномодуляція, регенеративна медицина