DEVELOPMENT OF NEXT-GENERATION DRUGS AGAINST ANTIMICROBIAL RESISTANCE: MODERN STRATEGIES AND FUTURE PROSPECTS

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Abstract. Antimicrobial resistance (AMR) is one of the major global challenges that reduces the effectiveness of existing medicines in the treatment of infectious diseases and poses a serious threat to modern medicine. In particular, the spread of multidrug-resistant bacteria requires not only the development of new antibacterial drugs but also the creation of innovative strategies aimed at improving the efficacy of existing therapeutic agents. This article analyzes the major mechanisms of bacterial antimicrobial resistance, the identification of new molecular targets, the development of antibacterial compounds belonging to new chemical classes, antibiotic re-engineering, antimicrobial peptides, bacteriophage therapy, anti-virulence approaches, antibiofilm strategies, and combination therapy. The priority directions for the development of new medicines were also assessed based on the World Health Organization's 2024 Bacterial Priority Pathogens List and data from the 2025 antibacterial clinical and preclinical pipeline. The literature review demonstrated that an effective pharmaceutical strategy against AMR should not be limited to the discovery of new antibiotics but should also encompass the development of agents with novel mechanisms of action, non-traditional biological therapeutics, drug combinations, and targeted drug-delivery technologies.

Keywords: antimicrobial resistance, antibiotic resistance, next-generation antibiotics, antimicrobial peptides, bacteriophage therapy, biofilm, anti-virulence therapy, antibiotic re-engineering, drug delivery.

Introduction. Antimicrobial resistance refers to the ability of microorganisms to develop resistance to the effects of antimicrobial agents used to control or eliminate them. Although AMR is a broad concept encompassing bacteria, viruses, fungi, and parasites, the issue of developing new antibacterial drugs is particularly important because bacterial resistance has created serious treatment challenges in modern clinical practice [4]. A large-scale study assessing the global burden of bacterial AMR estimated that in 2019, bacterial resistance was associated with 4.95 million deaths, while 1.27 million deaths were directly attributable to AMR. The study included data from 204 countries and territories and covered 23 pathogens and 88 pathogen–drug combinations [1,4]. A subsequent Global Burden of Disease 2021 analysis examined the burden of bacterial AMR from 1990 to 2021 and modeled possible scenarios through 2050. These findings indicate that antimicrobial resistance may continue to represent a major epidemiological challenge over the coming decades [2]. The increasing burden of AMR, together with the need for new therapeutic agents, highlights the insufficient expansion of the antibacterial research and development pipeline. A review published in Nature Medicine in 2024 emphasized that the antibiotic development pipeline is not expanding at a rate commensurate with the global burden of resistant infections and that significant

economic challenges affect antibiotic research and development [2,3]. In its 2024 Bacterial Priority Pathogens List, the World Health Organization grouped 24 bacterial pathogens into 15 families and classified them into critical, high, and medium priority categories. The critical-priority group includes carbapenem-resistant *Acinetobacter baumannii*, third-generation cephalosporin-resistant or carbapenem-resistant *Enterobacterales*, and rifampicin-resistant *Mycobacterium tuberculosis* [4]. Therefore, one of the major objectives of pharmaceutical research is to develop drugs with novel mechanisms of action against resistant microorganisms while also creating technologies capable of restoring or enhancing the activity of existing therapeutic agents.

Molecular basis of antibacterial resistance. Understanding the mechanisms by which bacteria protect themselves against antimicrobial agents is essential for the development of new antibacterial drugs. Bacterial resistance can arise through genetic mutations or through the acquisition of resistance determinants from other microorganisms. The horizontal transfer of resistance determinants contributes to the rapid dissemination of resistance within bacterial populations [5,6]. Bacteria can neutralize antibacterial agents through several mechanisms. These include enzymatic degradation or modification of the drug, reduced cellular uptake, active efflux of the drug from the cell, and modification of the molecular target of the antimicrobial agent [6]. In Gram-negative bacteria, changes in the outer membrane and porins can affect the entry of drug molecules into the cell. Activation of efflux pumps can prevent the achievement of effective intracellular drug concentrations. In addition, enzymes such as β-lactamases can inactivate β-lactam antibiotics, thereby limiting therapeutic options [4,6]. The diversity of these mechanisms demonstrates the need for multiple complementary approaches in drug development. A new therapeutic agent should either be less susceptible to existing resistance mechanisms or target a biological process within the bacterial cell that has not been adequately exploited by current therapies.

Identification of novel molecular targets and new antibacterial classes. A substantial proportion of conventional antibiotic discovery has relied on previously characterized biological targets and chemical scaffolds. However, the rapid development of resistance has highlighted the limitations of existing molecular platforms. Consequently, an important direction in drug discovery is the identification of biological processes that are essential for bacterial survival but have been less extensively targeted by currently available antibiotics [7]. Genomics and structural biology have expanded the ability to identify bacterial proteins as potential drug targets. Proteomics and metabolomics additionally enable systematic investigation of bacterial responses to antimicrobial exposure. Potential targets identified through these technologies can subsequently be developed into drug candidates through small-molecule screening and structural optimization. The WHO 2025 analysis emphasizes novel targets, novel mechanisms of action, novel chemical classes, and the absence of known cross-resistance when assessing the innovativeness of antibacterial agents [5]. However, the identification of a novel molecular target alone does not guarantee the clinical success of a drug. In addition to antibacterial activity, a drug candidate must be evaluated for selectivity, toxicological safety, pharmacokinetic and pharmacodynamic properties, and its ability to reach the site of infection.

Antibiotic re-engineering and enhancement of existing therapies. Because the development of an entirely new antibiotic class is a lengthy and costly process, molecular re-

engineering of existing antimicrobial agents represents another important strategy. This approach involves modifying selected structural components of an antibiotic molecule to enhance its activity against resistant bacteria or enable it to circumvent resistance mechanisms. A review published in Nature Reviews Bioengineering in 2025 examined several approaches to antibiotic re-engineering, including structural modification, multivalent molecules, and combination-based strategies [8]. Such approaches may allow existing pharmacophores to be optimized without initiating the drug-discovery process from an entirely new molecular scaffold. Nevertheless, re-engineered agents must also undergo evaluation of their pharmacokinetic properties, toxicity, manufacturing feasibility, and clinical efficacy. Therefore, molecular modification may accelerate certain stages of drug development, but it does not eliminate the need for clinical development.

Antimicrobial peptides. Antimicrobial peptides represent a promising biological platform for the development of next-generation antibacterial agents. They can occur naturally in various organisms or be designed synthetically. Many antimicrobial peptides act on bacterial membranes and disrupt their integrity, whereas others target intracellular cellular processes [9]. The multimodal mechanisms of action of antimicrobial peptides distinguish them from conventional antibiotics that often act on a single primary target. However, their therapeutic development is associated with several challenges, including proteolytic degradation, reduced activity in biological environments, toxicity, pharmacokinetic limitations, and manufacturing costs [9]. Bacteria can also adapt to antimicrobial peptides. Such adaptation may involve changes in membrane composition, peptide-degrading mechanisms, or other cellular defense systems. Therefore, peptide engineering aimed at improving molecular stability, selectivity, and antibacterial activity represents an important area of research [9].

Bacteriophage therapy and phage-based approaches. Bacteriophages are viruses that infect bacteria, and lytic phages can destroy bacterial cells during the infection process. Phage therapy is being investigated as a potential complementary or alternative approach to antibiotics for the treatment of infections caused by resistant bacteria [10,11]. An important characteristic of bacteriophages is their high target specificity. This property may reduce their effects on beneficial microbiota; however, it can also complicate clinical application because a particular phage may not exhibit the same activity against all bacterial strains. Consequently, approaches such as phage cocktails, selection of phages with broader host ranges, and the development of genetically engineered phages are being investigated. A 2026 review in Nature Reviews Microbiology highlighted the challenges associated with predicting clinical efficacy, phage selection, manufacturing, standardization, and regulatory requirements [10]. Engineered phages incorporating CRISPR–Cas systems also represent a promising research direction. Studies involving CRISPR–Cas-equipped engineered phages against *Escherichia coli* have investigated their potential to target broader groups of bacterial strains [11]. Nevertheless, the wider clinical implementation of phage therapy requires solutions to several challenges, including manufacturing quality, genetic stability, development of phage resistance, host immune responses, and optimal dosing.

Anti-Virulence Therapy. Whereas conventional antibiotics are designed to kill bacteria or inhibit their growth, anti-virulence therapy aims to reduce the ability of pathogens to cause disease in the host. Potential targets include toxins, adhesion, invasion, and other virulence factors [7]. From a pharmaceutical perspective, this strategy is of interest because it targets the

mechanisms responsible for pathogenicity rather than directly eliminating bacterial viability. In theory, this approach may reduce selective pressure on bacteria in certain circumstances. However, it cannot be generally concluded that anti-virulence agents prevent resistance; this effect must be experimentally evaluated for each drug and molecular target. Modern reviews of non-traditional antibacterial strategies consider anti-virulence agents alongside antimicrobial peptides, bacteriophages, antibodies, and antisense oligonucleotides as promising approaches [7].

Pharmaceutical strategies against biofilms. Biofilms are characterized by bacterial communities attached to surfaces and surrounded by an extracellular matrix. Microorganisms within biofilms may exhibit increased tolerance to antimicrobial agents. Consequently, in biofilm-associated infections, activity against planktonic bacteria alone may not be sufficient. Anti-biofilm strategies may target matrix disruption, reduction of bacterial adhesion, inhibition of biofilm formation, or sensitization of biofilm-associated bacteria to other therapeutic agents. Various bacterial defense systems, including biofilm formation and other stress-response mechanisms, play an important role in bacterial adaptation to antimicrobial therapy [12]. From this perspective, combining anti-biofilm agents with conventional antibiotics may represent a promising direction for future combination pharmacotherapy.

Combination therapy and antibiotic potentiators. One strategy for combating AMR is to exploit the combined effects of two or more therapeutic agents. In combination therapy, one compound may weaken a bacterial defense mechanism and thereby enhance the activity of another drug. A representative example is the combination of β-lactam antibiotics with β-lactamase inhibitors. This approach is designed to limit enzymatic inactivation of the antibiotic by bacterial β-lactamases. Contemporary reviews of ESKAPE pathogens indicate that despite the introduction of new antibiotics and β-lactamase inhibitors, these pathogens remain clinically challenging [13]. Future research may also investigate antibiotic potentiators capable of modulating efflux systems, membrane permeability, or other resistance mechanisms. However, the clinical value of combination therapies must be assessed with consideration of pharmacokinetic compatibility, drug–drug interactions, toxicity, and the potential for subsequent development of resistance.

The current antibacterial pipeline: status and challenges. The WHO 2025 analysis of the antibacterial pipeline evaluates antibacterial products in clinical and preclinical development as of February 15, 2025. The report covers conventional small-molecule agents with direct antibacterial activity as well as non-traditional antibacterial approaches [5]. According to WHO data, 232 antibacterial products were in preclinical development during this period. Their characteristics, including development stage, target pathogens, mechanism of action, whether they represent new or repurposed products, and whether they belong to novel chemical classes, were analyzed [5]. However, the presence of a large number of preclinical candidates does not mean that these agents will necessarily reach clinical practice. Progression of drug candidates into clinical development depends on multiple factors, including biological efficacy, toxicological safety, pharmacokinetic properties, manufacturing standardization, and clinical effectiveness. The economic dimension of antibiotic research and development represents another major challenge. Antibiotics are often administered for relatively short treatment courses, and their prudent use is essential, resulting in a commercial model that differs from that of many other medicines. A Nature Medicine review identified these economic

challenges, declining private investment, and equitable access to new antibiotics as important barriers [3]. Therefore, the development of new antibiotics requires long-term collaboration among governments, academic institutions, the pharmaceutical industry, and international organizations.

The future role of pharmaceutical biotechnology. Pharmaceutical biotechnology represents an important platform for the development of next-generation drugs against AMR. Recombinant technologies, protein engineering, peptide design, phage engineering, and high-throughput screening methods are expanding the possibilities for developing novel biological therapeutics. In addition, the search for new antibiotic-producing microorganisms from natural environments remains relevant. Recent studies have investigated microorganisms inhabiting extreme environments as potential sources of novel bioactive compounds. Such approaches may provide opportunities to discover antibiotics with previously unexplored chemical structures from under-investigated ecological niches [14]. The integration of antibiotic structural re-engineering, identification of novel biological targets, and non-traditional therapeutic platforms may further strengthen the role of pharmaceutical biotechnology in addressing AMR.

Discussion. The analyzed evidence indicates that there is no single universal pharmaceutical strategy for combating AMR. Because bacterial resistance mechanisms are diverse, next-generation therapeutic agents should be developed using complementary mechanisms. Although new antibiotic classes are essential for long-term therapeutic options, the complexity of their development makes the re-engineering of existing drugs and enhancement of their activity through potentiators equally important. At the same time, non-traditional approaches such as antimicrobial peptides, bacteriophages, and anti-virulence agents provide alternative mechanisms for managing bacterial infections [7,9]. WHO pipeline data for 2025 demonstrate that antibacterial research is continuing; however, the ability of new agents to fully address unmet clinical needs remains limited [5]. In particular, the development of agents with novel mechanisms against resistant Gram-negative bacteria classified as critical or high priority by WHO remains an important objective [4]. Future research should focus not only on developing therapeutic agents themselves but also on integrating them with appropriate diagnostics, optimized dosing, and targeted drug delivery. Such a comprehensive approach may improve clinical efficacy and help limit the further development of resistance.

Conclusion. Antimicrobial resistance is one of the most important challenges facing modern pharmacy and medicine, and the increasing prevalence of resistant bacterial infections is intensifying the need for new therapeutic agents. Global studies demonstrate the substantial epidemiological burden of AMR and provide projections indicating that this problem is likely to remain significant in the future [1,2]. The literature analysis demonstrated that important strategies for the development of next-generation drugs against AMR include the identification of novel molecular targets and chemical classes, re-engineering of existing antibiotics, antimicrobial peptides, bacteriophage therapy, anti-virulence agents, antibiofilm agents, and combination therapies. The WHO 2024 priority pathogen list and the 2025 antibacterial pipeline analysis emphasize the need to direct research toward critical and high-priority resistant pathogens [4,5]. In this context, in addition to antibacterial activity, the safety, pharmacokinetic properties, manufacturing feasibility, and clinical advantages of novel agents must be evaluated. Thus, an effective pharmaceutical approach to AMR cannot be limited to the

discovery of new antibiotics. The integration of pharmaceutical biotechnology, molecular biology, structural biology, and advanced drug-design approaches provides an important scientific foundation for the development of novel therapeutic platforms. At the same time, the development of new medicines must be accompanied by rational antibiotic use and international research and development collaboration in order to make a meaningful contribution to reducing the global impact of AMR [3].

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