



Innovative Approaches to Combat Antimicrobial Resistance: A Review of Emerging Therapies and Technologies

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Abstract

The threat of antimicrobial resistance (AMR) presents a challenge in infectious diseases, leading to higher illness and deaths worldwide. No new antibiotic has been introduced, leaving healthcare systems vulnerable to resistant pathogens. Researchers are exploring innovative approaches to overcome this growing resistance crisis. One promising strategy is synergistic therapy using combined drugs to enhance efficacy and reduce resistance. Other approaches focus on targeting the specific enzymes or proteins responsible for resistance mechanisms, thereby neutralizing the defense strategies of microorganisms. Advances in drug delivery systems have also shown promise in improving the effectiveness of existing antimicrobial agents. Biotechnological breakthroughs, such as bacteriophages and antibodies, have seen partial clinical implementation, while newer approaches like antimicrobial peptides (AMPs), lysins, and probiotics are still under development. Emerging technologies such as CRISPR-Cas and engineered phages demonstrate significant potential in preclinical studies, offering precision targeting of resistance genes and pathogen-specific lysis, respectively. However, their translational success hinges on overcoming delivery challenges, scalability, and regulatory hurdles. Additionally, physicochemical methods that disrupt microbial activity are being explored as alternative treatments. While innovative therapies like phage-derived lysins and CRISPR-Cas systems show promise in preclinical models, their clinical impact remains to be validated through large-scale trials. Their integration into mainstream medicine will depend on addressing practical challenges such as manufacturing consistency, cost considerations, and real-world efficacy assessments. These efforts are crucial for addressing the growing threat of AMR and advancing more effective, sustainable infection control strategies in clinical settings.

Keywords Antimicrobial resistance · Combination therapy · Antimicrobial peptides · Genetically modified phages · CRISPR-Cas technology

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Introduction

Antibiotic resistance (AR), a subcategory of antimicrobial resistance (AMR), occurs when bacteria evolve mechanisms to evade the effects of antibiotics. Multidrug-resistant (MDR) microorganisms can withstand numerous antimicrobial drugs, complicating therapy [1]. The World Health Organization (WHO) characterizes antimicrobial resistance as a bacterium exhibiting resistance to an antimicrobial agent, enabling it to counteract the effects of a previously encountered antibiotic [2]. Bacterial antimicrobial resistance significantly affects health; social identifiers have been established for worldwide group movements to address the issue, including proposals for international AR agreements [3]. Antimicrobial resistance (AMR) is projected to result in over 700,000 fatalities worldwide a year, with a minimum of 35,000 occurring in the USA, hence becoming a substantial public health issue [4, 5].

Without intervention to mitigate the proliferation of AR, fatalities are anticipated to reach 10 million by 2050, accompanied by economic losses exceeding \$100 trillion [6]. In the USA, antibiotic-resistant diseases impact about two million individuals annually, resulting in almost \$20 billion in economic losses [7]. Moreover, one in six persons can have a foodborne infection each year from *Salmonella*, *Escherichia coli* O157, *Listeria monocytogenes*, *Clostridium perfringens*, *Staphylococcus aureus*, or *Campylobacter*. These infections result in around 128,000 hospitalizations and 3,000 fatalities, incurring costs of about \$90 billion in the USA [8].

The World Health Organization (WHO) has ranked AR among the top three public health threats of the twenty-first century [9] (Fig. 1).

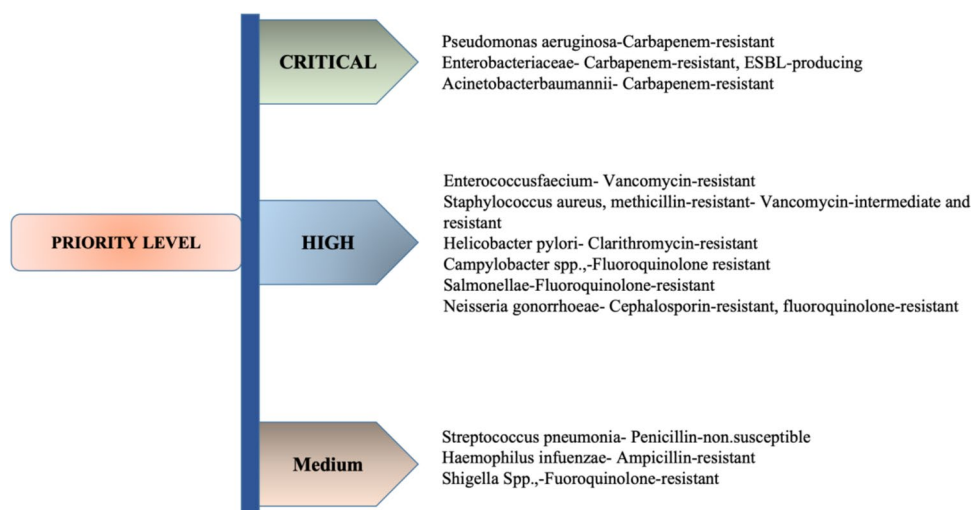
Previous studies have used the term ESKAPE pathogens to denote the increased incidence of infections in people, referencing species such as *Enterococcus faecium*,

Staphylococcus aureus, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. Epidemiological studies indicate that the current pharmacological library lacks crucial antibiotic classes effective against multidrug-resistant Gram-negative bacteria [11].

Gram-negative bacteria, which are distinguished from Gram-positive bacteria by the presence of an outer membrane, have proved to be particularly difficult to target. The development of new therapeutics has significantly relied on modifying pre-existing drug scaffolds in conventional antibiotic discovery efforts. Following decades of optimization focused on identical chemical structures, these efforts can no longer keep up with the rapid expansion of resistance. Even “novel” antibiotics developed through conventional approaches remain fundamentally limited in their structural and target diversity, rendering them susceptible to cross-resistance from intrinsic and pre-existing mechanisms. Researchers have increasingly turned to alternative strategies to expand the antibiotic arsenal in response to these limitations and the growing threat of widespread resistance [12]. The challenges outlined above underscore the intricate nature of antimicrobial resistance (AMR). They emphasized the necessity for continuous research and better methods to obtain insights to gain a deeper understanding of AMR and to effectively counter this escalating global public health concern [5].

In this context, this review discusses the most promising emerging therapies and technologies to address AMR, including combination therapy, enzyme-targeting approaches, and bio-based alternatives, such as phage-derived proteins, plant-based compounds, bacteriocins, and advanced approaches, such as phage therapy, CRISPR-Cas systems, and nanotechnology. This analysis offers perspectives on future directions, emphasizing the need for creative, multidisciplinary approaches to combat this worldwide threat.

Fig. 1 Updated list of priority pathogens underscores the urgent need for new antibiotics to address emerging resistance. Modified from Zyman et al. (2022) [10]



Mechanisms of Antimicrobial Resistance Acquisition

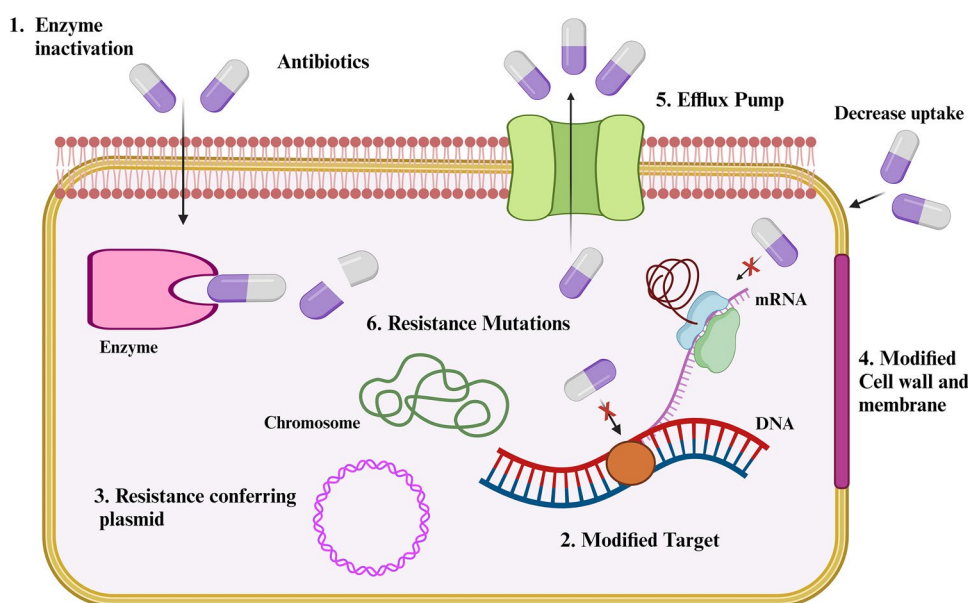
Antibiotic resistance (AR) in bacteria is fundamentally categorized into acquired and intrinsic resistance. Bacteria inherently insensitive to a particular antimicrobial agent or class of agents exhibit intrinsic resistance, often called innate resistance. This insensitivity typically arises from the absence or inaccessibility of target structures for specific antimicrobials. For example, cell wall-free bacteria, such as *Mycoplasma* spp., are resistant to β -lactam antibiotics and glycopeptides, whereas Gram-negative bacteria exhibit resistance to vancomycin because the drug cannot penetrate their outer membrane. This may also result from the presence of export systems or species-specific inactivating enzymes produced by some bacteria, such as the AcrAB-TolC system or AmpC β -lactamase in some members of *Enterobacteriaceae*. Thus, intrinsic resistance is a characteristic of certain bacterial genera or species [13, 14]. In contrast, acquired resistance is a characteristic unique to a strain and may result from mutations in chromosomal target genes or the acquisition of foreign resistance genes. This category may also include mutations that increase the expression of multidrug transporter systems. There are three primary categories of resistance: (i) enzymatic inactivation, which involves the breakdown or chemical alteration of antimicrobial agents; (ii) reduced intracellular accumulation, achieved through decreased influx and/or increased efflux of antimicrobials; and (iii) modification of cellular target sites, which can occur through mutations, chemical changes, or protective mechanisms for the target sites. This category also includes the overexpression of sensitive targets or the substitution of sensitive target structures with alternative resistant ones [14–17] (Fig. 2). Notably,

Acinetobacter baumannii and *P. aeruginosa* exemplify the challenges posed by acquired resistance, as these adaptable Gram-negative pathogens cause severe infections, especially among immunocompromised patients [18]. Their genomic plasticity and ability to acquire mobile genetic elements drive antibiotic resistance (AR) and pathogenicity, making them significant contributors to the global burden of antimicrobial resistance [19, 20].

Adaptive resistance further contributes to variations in antibiotic efficacy both in vitro and in vivo and can explain the ineffectiveness of some clinical antibiotic treatments [21]. The genetic adaptability of bacteria enables the development of antimicrobial resistance through either mutation in their genes or the acquisition of resistance genes from foreign DNA via HGT [16]. HGT enables antibiotic-sensitive bacteria to acquire resistance-modulating genes through three main mechanisms: transformation, conjugation, and transduction. Through HGT, antibiotic-sensitive bacteria can acquire resistance-modulating genes, allowing bacteria to transmit their genetic material using transformation, conjugation, or transduction [21].

In the process of transduction, a bacteriophage that infects bacteria transfers genetic material from a resistant donor bacterium to another bacterium while introducing its genetic material into the donor cell, where it integrates into the bacterial genome. As the bacteriophage replicates, it creates new bacteriophages that carry genomes with resistance genes. When these bacteriophages infect another bacterium, they introduce resistance genes into the genome of the newly infected bacterium [22]. In conjugation, a plasmid carrying an antibiotic resistance (AR) gene is transferred from a donor bacterium to a recipient, requiring a type IV secretion system (T4SS) and pilus to mediate cell-to-cell contact and

Fig. 2 Mechanism of antimicrobial resistance in bacteria. Adapted from Mutuku et al. (2022) [25]



plasmid transfer [23]. In contrast, transformation involves the uptake of free DNA released from lysed bacteria, which can be incorporated into the genome of another bacterium [24]. One or more of the following expression patterns occur when bacteria acquire resistance genes through the aforementioned processes.

Antimicrobial Resistance from a One Health Approach

The concept of One Health is not new, as evidenced by the fact that names such as One World, One Medicine, and One Health have been in use for at least 200 years [26]. It recognizes that infections can spread from people to animals and that environmental factors are important in developing and spreading diseases [27]. This highlights the necessity of interdisciplinary cooperation in fields including ecology, environmental sciences, and medicine to advance a thorough understanding of health concerns and provide efficient solutions [28].

In veterinary medicine, antibiotic resistance (AR) often arises from HGT during animal husbandry, where antibiotics are used for growth promotion, disease prevention, and treatment over extended periods. The similarity in the features of antibiotics used in both animals and humans significantly increases the probability of resistant bacteria moving between these two groups and the swift proliferation of such resistant strains.

Consequently, the One Health strategy aims to mitigate the rapid spread of antimicrobial resistance (AMR) among animals, humans, and the environment in a cyclical manner [29, 30]. Recent research suggests that the molecular pathways established by resistant bacteria are crucial for understanding the global patterns of antibiotic resistance (AR) and developing new treatments [31]. In this context, the One Health approach represents a vital framework emphasising the need for a unified effort to integrate human, animal, and environmental health. By encouraging interdisciplinary collaboration and advocating responsible antibiotic use across all sectors, this approach seeks to address AMR more effectively. This holistic approach deepens our understanding of resistance mechanisms and ensures a more sustainable and comprehensive response to the challenges posed by AMR in the future. Ultimately, it safeguards the health of the population, animals, and the environment. Bio-based alternatives to antibiotics, such as bacteriophages, antimicrobial peptides, and probiotics, adhere to One Health principles by specifically targeting pathogens without disrupting the ecological balance [32]. These alternatives often have a narrow host range, thereby reducing the risk of collateral damage to beneficial microorganisms [33]. Additionally, they can be designed to degrade naturally in the environment,

minimizing the potential for environmental contamination and the spread of resistance genes [34–36]. By integrating these bio-based solutions into a comprehensive One Health approach, we can effectively address pathogens while minimizing ecological impact, thus achieving a more sustainable and holistic approach to combatting antimicrobial resistance.

Bio-Based Antimicrobial Agents

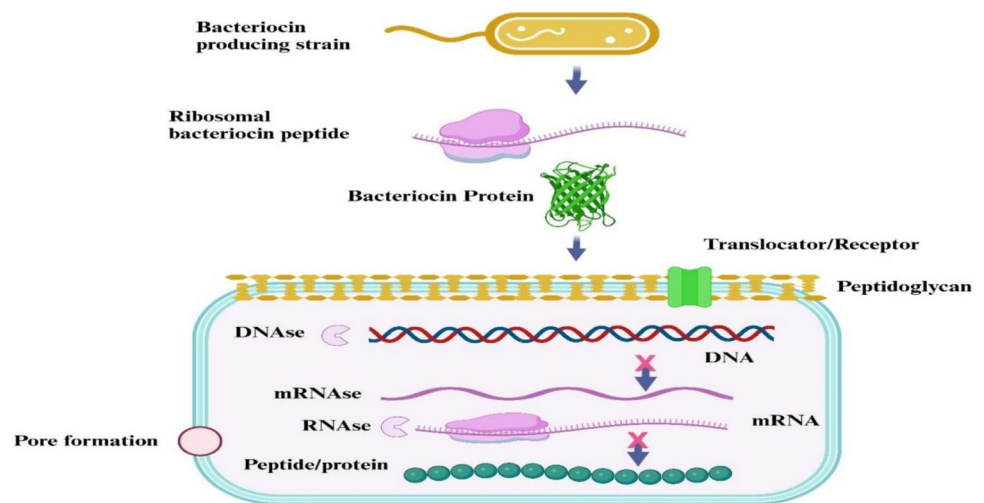
Bio-based antimicrobial agents are promising alternatives to conventional antibiotics because of their high specificity, environmental biodegradability, and low propensity to induce resistance. These agents, sourced from natural organisms such as bacteria and bacteriophages, exert antimicrobial effects through diverse and often synergistic mechanisms. This section provides an overview of the key bio-based initiatives currently under investigation for their potential to combat drug-resistant pathogens.

Bacteriocins

Bacteriocins are ribosomally synthesized antimicrobial peptides (AMPs) produced by both Gram-negative and Gram-positive bacteria, with considerable diversity in structure, size, mode of action, activity range, metabolic traits, and cell receptors [37]. Bacteriocins are broadly classified into two groups: class I, characterized by extensive post-translational modifications, and class II bacteriocins do not undergo such modifications [38]. Although both Gram-negative [39] and Gram-positive bacteria [40] can produce bacteriocins, most known cases come from Gram-positive bacteria, especially Lactic Acid Bacteria (LAB) [41]. They vary in terms of cellular receptors, length, molecular weight, metabolic properties, genetic origin, and immune system interactions [42, 43]. Bacteriocins act via several mechanisms such as increasing cytoplasmic membrane permeability by pore formation, inhibiting cell wall synthesis, and interfering with metabolic pathways [44]. Their potency at nanomolar concentrations makes them attractive therapeutic candidates, albeit with narrow spectra [45] (see Fig. 3). Recent advances in artificial intelligence (AI) have overcome traditional discovery bottlenecks, enabling the prediction and optimization of bacteriocins with enhanced stability and activity [46].

Bacteriocins have garnered significant interest as potential antimicrobial agents against various viral, bacterial, and fungal species [41, 47, 48], including biofilm-embedded pathogens. Additionally, bacteriocins are effective against bacterial biofilms, a common form of bacterial resistance [49]. In agriculture and animal husbandry, bacteriocins are used to prevent key animal and plant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA),

Fig. 3 Antimicrobial activity of bacteriocins against pathogenic bacteria. Modified from Yang et al. (2014) [38]



vancomycin-resistant *Enterococcus* (VRE), Shiga toxin-producing *Escherichia coli*, *Agrobacterium*, and enterotoxigenic *Escherichia coli*. They have been thoroughly investigated, particularly in broilers, piglets, and cattle, owing to their ability to prevent significant animal and plant pathogens [50]. The bacteriocin nisin, generated by *Lactococcus lactis*, is marketed as Nisaplin in the food sector and has been granted EU approval as a food preservative [51]. Another bacteriocin that is available commercially is pediocin PA-1, also known as Alta 2341, which prevents *Listeria monocytogenes* from growing in meat products [52]. Certain bacteriocins in the medical industry, including *E. coli* colicin A and E1, have demonstrated efficacy against tumor cells by inhibiting the proliferation of 11 human tumor cell lines and a human standard fibroblast cell line (MRC5) [53].

Despite their therapeutic promise, clinical translation faces hurdles such as proteolytic degradation and rapid clearance. Innovative delivery systems (e.g., nanoparticle encapsulation) have been developed to address these challenges [54]. Synergistic combinations with antibiotics further enhance their efficacy and reduce resistance risks, positioning bacteriocins as key players in the post-antibiotic era.

Phage-Derived Proteins

Endolysins, or lysins, are peptidoglycan hydrolases encoded by bacteriophages, that together with holins, degrade bacterial cell walls and induce lysis [55, 56]. These enzymes are highly selective for bacteria and have no adverse effects on human or animal cells [57]. Endolysins exhibit strong efficacy against antibiotic-resistant pathogens, rapid bacteriolytic activity, high affinity for targets, low resistance potential, and effectiveness against both planktonic and biofilm cells (Fig. 4) [58, 59]. The clinical development of endolysins is more advanced for Gram-positive bacteria,

while progress for Gram-negative pathogens is slower due to the outer membrane barrier, which limits access to the peptidoglycan layer [58].

Recent advances have integrated artificial intelligence to design optimized lysin variants [60, 61], while nanoparticle delivery systems have enhanced stability and tissue penetration [62]. Synergistic pairings, particularly those involving β -lactam antibiotics, have demonstrated synergistic activity against resistant strains [63]. Expanding upon these advancements, engineering techniques like merging with peptides that permeate the outer membrane or receptor-binding domains have been employed [64]. Studies have demonstrated the synergistic activity of engineered endolysins, including artilyns and chimeolysins, which combine lytic domains or enhance membrane penetration, resulting in broad-spectrum and potent activity against drug-resistant bacteria [65–67].

Commercial interest in endolysin therapy has led to the development of products such as Staphfect SA.100 (Microes), used for chronic *S. aureus* skin conditions [68], Artilysin® product series, which has demonstrated efficacy against resistant strains of *P. aeruginosa* and *A. baumannii* [69], and Rephasin® SAL200 (Intron Biotechnology), in phase II clinical trials [70]. Exebacase CF301 (ContraFect) is the first lysin-based agent in US human clinical trials, targeting *S. aureus*, including MRSA, a lysin-based agent capable of directly lysing *S. aureus*, including MRSA strains. Notably, Exebacase CF301 stands out among phage-derived lytic enzymes as the first to advance to human clinical trials in the USA [71]. Unlike small-molecule antibiotics, the modular design of lysins facilitates optimization for safety and pharmacokinetics, accelerating their development [72].

Despite these advances, challenges remain in terms of immunogenicity, delivery, and large-scale production. Current research focuses on protein engineering to minimize immune recognition and extend plasma half-life, with

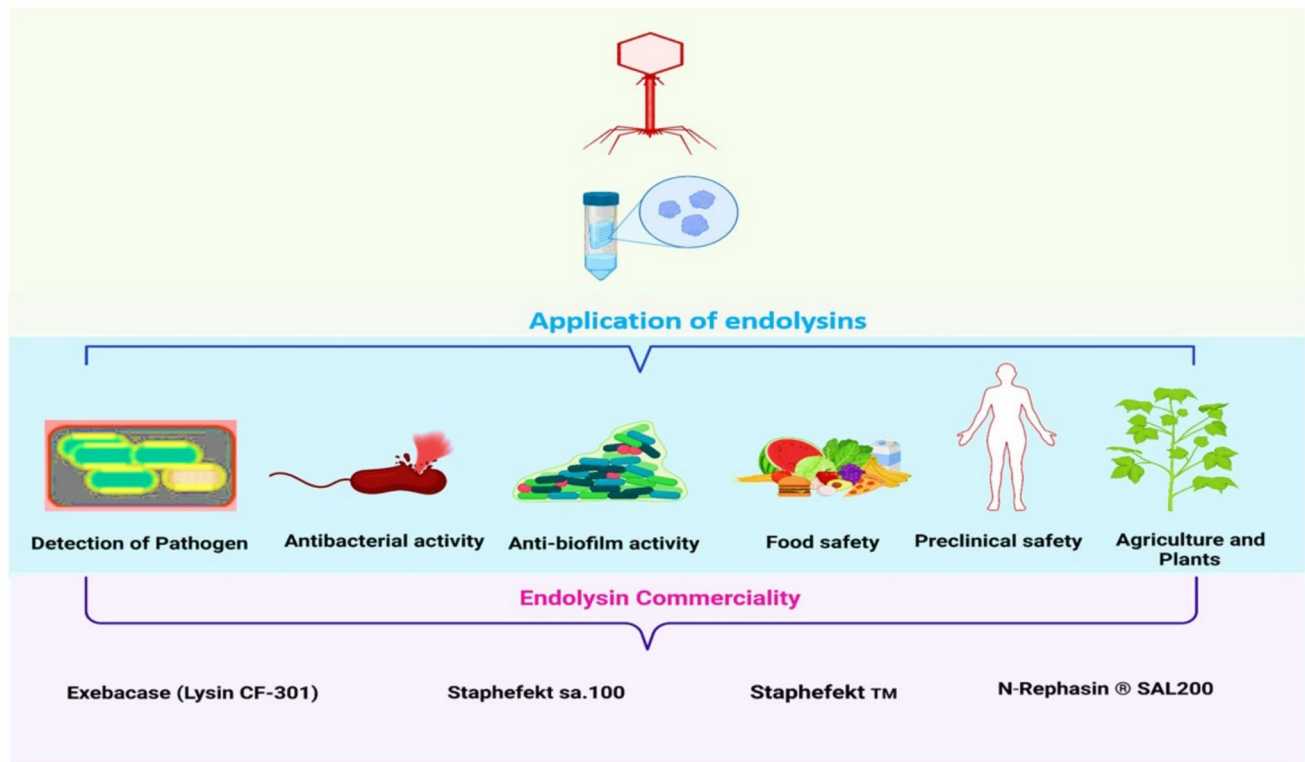


Fig. 4 Applications of phages-derived endolysin as promising antimicrobial agents. Cited from Rahman et al. (2021) [59]

chimeric constructs showing particular therapeutic promise [73]. Future efforts must focus on the clinical validation of engineered lysins and combinatorial therapies to effectively address resistance challenges.

Phage Therapy: Targeting Resistant Bacteria

Bacteriophages engage in parasitic relationships with their hosts, utilizing the bacterial biosynthetic machinery for replication [74]. Although bacteriophages exhibit pathogenic behavior toward their host cells, they are generally considered safe for therapeutic use because of their high specificity for bacterial hosts; however, their safety profile can vary depending on factors such as phage preparation, dosage, and individual immune responses. While adverse effects are rare, immune reactions or inflammatory responses may sometimes occur, necessitating careful clinical evaluation. Phages follow two primary life cycles: the lytic cycle, which is particularly valuable for AMR treatment as it directly lyses pathogens (Fig. 5), and the lysogenic cycle, in which phage DNA integrates into host genomes [75].

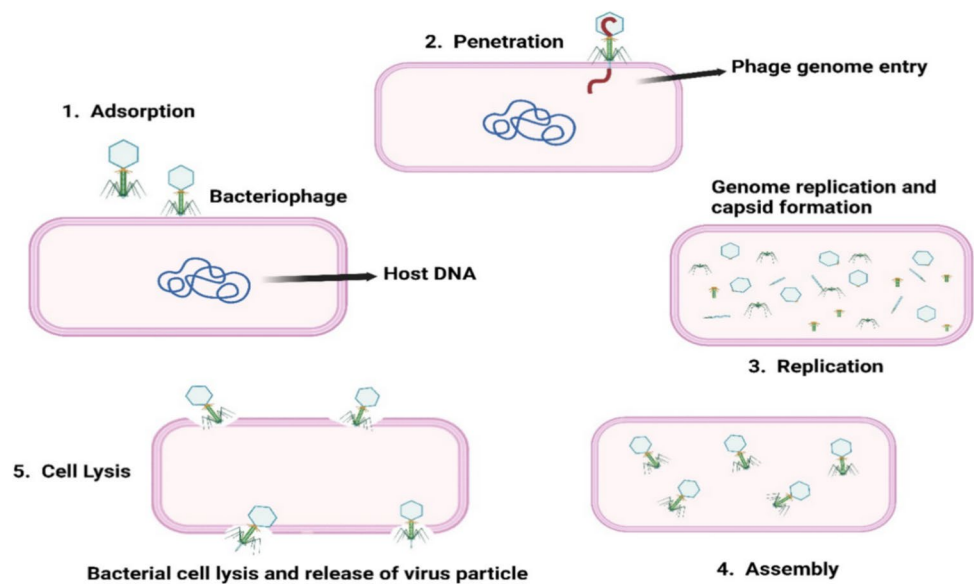
Bacteriophages offer several advantages that make them a promising alternative to antibiotics. Their elevated host specificity targets selected bacterial strains without disrupting the host gut microbiota, unlike antibiotics, which affect

both harmful and beneficial bacteria. Additionally, phages are cost-efficient [76] and can target multidrug-resistant bacteria without exerting selective pressure that promotes resistance [77]. Further benefits include compatibility with cocktail formulations, biofilm inhibition capability [78], and potential use in patients with antibiotic allergies [79]. Recent advances in AI have optimized phage selection through machine learning algorithms that predict ideal phage-host pairings and resistance patterns, accelerating therapeutic development [80].

Preclinical studies have demonstrated phage efficacy in animal models of pneumonia [81], orthopedic infections [82], and bloodstream infections [83]. However, clinical results vary significantly by administration route and formulation; topical phage therapy successfully treated *P. aeruginosa* ear infections [84], whereas oral preparations failed against *E. coli* diarrhea due to inadequate gastrointestinal delivery [85]. Delivery hurdles remain significant, particularly for systemic infections, where phage pharmacokinetics, stability, and tissue penetration require nanoparticle encapsulation or lipid-based carriers [86]. Significant achievements encompass the clearance of *P. aeruginosa* bacteremia through the application of phage monotherapy [87].

Ongoing multicenter trials (PHAGOPIED, PHOSA, and PHAGOBURN) are addressing efficacy gaps in diabetic ulcers, bone/joint infections, and burns [88]. Synergistic

Fig. 5 Representing various five stages of the bacteriophage Lytic cycle. Modified from Huang et al. (2022) [93]



approaches with antibiotics show particular promise, as phages can sensitize resistant bacteria to conventional drugs while minimizing the emergence of resistance [89]. Globally, Russia and Georgia have clinically deployed phages [90, 91], while the USA focuses on FDA-approved trials (Voelker 2019) and IPATH-led research [92]. As traditional antibiotics become increasingly ineffective against resistant strains, the convergence of synthetic phage engineering and predictive AI analytics is fundamentally reshaping the landscape of precision antimicrobial interventions for difficult-to-treat bacterial diseases.

Genetic and Molecular Tools

Advances in genetic engineering have opened new avenues for precise and targeted interventions for antimicrobial resistance. Among these, CRISPR-Cas systems are transformative tools capable of selectively disabling resistance genes. This section delves into the molecular innovations that are reshaping the counteraction of resistance at the genetic level.

CRISPR-Cas: Precision Against Resistance

The CRISPR-Cas system, derived from the prokaryotic adaptive immune mechanism, has emerged as a powerful tool in genetic engineering and antimicrobial research [94]. Its precise DNA-targeting and editing capabilities enable the targeted disruption of AR genes, providing a promising strategy to address resistance driven by HGT and antibiotic misuse [95]. CRISPR-Cas employs a Cas nuclease guided by a single guide RNA (sgRNA) to recognize and cleave AR genes (ARGs), rendering bacteria susceptible to first-line antibiotics [96]. The mechanism involves three main stages:

adaptation, where Cas proteins integrate pathogen DNA fragments (spacers) into the host CRISPR array; expression, in which the array is transcribed into precursor CRISPR RNA (pre-crRNA) and processed into mature crRNA; and interference, where the Cas-sgRNA complex targets complementary DNA sequences, causing double-strand breaks and disabling the target gene [97]. CRISPR-Cas systems are classified into two classes, six types, and 33 subtypes based on their Cas protein composition. Class 1 systems (types I, III, IV) use multi-protein complexes, whereas class 2 systems (types II, V, VI) rely on single effector proteins, such as Cas9 and Cas12, making them more suitable for therapeutic applications [98].

Unlike broad-spectrum antibiotics, CRISPR-Cas systems can be engineered to selectively target resistance genes in pathogenic bacteria, thereby minimizing the disruption of commensal microbiota. However, challenges such as off-target effects and incomplete delivery efficiency may inadvertently impact non-target species, highlighting the need for refined targeting approaches and in vivo validation of these methods. For instance, CRISPR-Cas9 delivered via bacteriophages eradicated methicillin-resistant *Staphylococcus aureus* (MRSA) in murine osteomyelitis models, reducing the bacterial load by 99% without affecting beneficial flora [99]. Similarly, Cas3-mediated degradation of *C. difficile* virulence genes in mice suppressed toxin production and biofilm formation [100]. In another approach, conjugative plasmids engineered to deliver CRISPR-Cas into *E. faecalis* selectively cleaved resistance genes (e.g., *vanA*), reducing *Vancomycin-Resistant Enterococci* (VRE) colonization in the gut [101]. Phage-CRISPR hybrids further enhance delivery and specificity; for example, *E. coli*-specific phages modified to deliver Cas9 disrupted β -lactamase genes, resensitizing bacteria to ampicillin [102].

Despite its potential, CRISPR-Cas faces challenges, including delivery efficiency in complex environments, off-target effects, and immune responses. Mismatched sgRNA binding may disrupt host or microbiota genes, although machine learning algorithms are being developed to predict sgRNA specificity [103, 104]. Furthermore, bacterial anti-CRISPR proteins (Acrs) and host immunity may neutralize CRISPR, but encapsulating Cas in lipid nanoparticles or engineering Acr-resistant variants can overcome these barriers [105]. Ongoing clinical trials are evaluating the safety of CRISPR-Cas in humans, and multimodal therapeutic strategies, such as coupling CRISPR with probiotics or narrow-spectrum antibiotics, may offer interim solutions.

Ecological and Microbiome-Based Strategies

The ecological context of AMR, including host-microbiome interactions and environmental reservoirs, is increasingly recognized as a critical factor in the spread and persistence of resistance mechanisms. Approaches that modulate microbial communities or exploit ecological mechanisms, such as plant-derived antimicrobials, quorum sensing disruption, and microbiome restoration, offer sustainable and targeted solutions. This section examines these microbiome-informed solutions in detail.

Plant-Derived Compounds

Since ancient times, herbal medicine has been a fundamental approach for treating various medical conditions, such as colds, diarrhea, dental issues, and labor pain [106]. They constitute the initial treatment preference for patients owing to their association with reduced side effects, as well as their cost-effectiveness and affordability, particularly in developing nations. These remedies remain especially important in developing nations because of their affordability and reduced side effects [107]. Although nearly 17,000 plant species have been identified, only approximately 3000 have been used for medicinal applications [108]. The World Health Organization reports that 80% of the world's population relies on traditional medicine to address healthcare requirements [106]. Given this widespread reliance, researchers are increasingly exploring plant-derived antimicrobial compounds as alternatives or adjuncts to conventional antibiotics, particularly in the face of increasing resistance rates. Plants have been thoroughly examined as a primary source for the development of novel therapeutic compounds and the potential application of crude extracts in the treatment of various diseases [109].

Plants defend themselves against microbes by producing diverse bioactive compounds, including polyphenols, alkaloids, terpenes, phenolics, organosulfur compounds,

and essential oils [110, 111]. These phytochemicals exhibit multifaceted antimicrobial mechanisms of action, such as disrupting bacterial cell wall synthesis—for example, berberine targeting FtsZ in *E. coli* [112], inhibiting efflux pumps, for example, naringenin and geraniol [113, 114], interfering with biofilm formation [115]. In contrast, organosulfur compounds disrupt membrane integrity [116, 117]. However, their efficacy varies significantly across bacterial species, and challenges such as poor bioavailability and chemical stability must be addressed to fully harness their potential. [118].

Despite their promise, the clinical application of plant-derived antimicrobials faces significant challenges, including low solubility, rapid degradation, and insufficient tissue penetration. Advances in nanotechnology, such as nanoparticle encapsulation and lipid-based carriers, are being explored to enhance stability and enable targeted delivery [119, 120]. Combining phytochemicals with conventional antibiotics has emerged as a viable approach to overcome resistance. For example, synergies between ceftiofur and phosphorylcholine have demonstrated improved efficacy against mastitis-causing pathogens [111]. In contrast, alkaloid-antibiotic combinations, such as clavine with tetracycline, exhibit enhanced activity against multidrug-resistant *E. coli* [121]. Artificial intelligence (AI) is revolutionizing the discovery and optimization of plant-derived antimicrobials. Machine learning models can predict synergistic drug pairs [122], and identify novel bioactive compounds from underutilized plant species [123]. These AI-driven approaches accelerate screening and optimize pharmacokinetic properties, bridging the gap between traditional knowledge and modern therapeutic development [124].

Quorum Sensing: Disrupting Bacterial Communities

Quorum sensing (QS) is a bacterial communication system that regulates gene expression in response to population density through small signaling molecules, known as autoinducers (AIs). As the cell numbers increase, AIs accumulate in the environment. When they reach a threshold concentration, they activate receptors that coordinate population-wide behaviors, such as biofilm formation, virulence, antibiotic tolerance, and motility [125].

Although QS indirectly contributes to antimicrobial tolerance, direct molecular links remain under investigation. QS systems follow a conserved process involving three main steps: synthesis of AIs, detection by specific receptors, and activation of gene expression via a positive feedback loop [125–128]. This regulatory cascade ensures synchronized behavior once a critical cell density is reached [129].

In Gram-positive bacteria, QS typically involves producing and detecting short signaling peptides, which interact with two-component phosphorylation systems to regulate gene expression. These peptides are actively exported from the cells and modulate critical behaviors such as sporulation, competence, and the expression of virulence factors [130, 131]. For example, in *B. subtilis*, peptide-based QS controls the initiation of sporulation and biofilm formation through phosphorylation cascades [132]. Although phosphorylation cascades play a crucial role in regulating sporulation and biofilm formation, the exact mechanisms and interactions among various kinases and phosphatases are still intricate and not completely elucidated. In contrast, Gram-negative bacteria utilize N-acyl homoserine lactones (AHLs) in LuxI/LuxR-type systems, which were first identified in *Vibrio fischeri* [133, 134]. These N-acyl homoserine lactones molecules freely diffuse across membranes and accumulate in the environment, allowing population-density-dependent regulation of diverse phenotypes including biofilm development, motility, and the production of extracellular enzymes and toxins [135]. Notably, Quorum sensing (QS) in Gram-negative pathogens such as *P. aeruginosa* controls virulence gene expression and biofilm maturation, which are linked to increased antibiotic tolerance [136]. In *P. aeruginosa*, QS-controlled biofilm maturation creates a protective extracellular matrix that reduces antibiotic penetration and fosters persister cell formation, thereby indirectly enhancing antibiotic tolerance [137]. Some species, such as *E. coli*, lack AI production machinery but retain receptors to detect AIs from neighboring microbes [138].

Targeting QS through quorum quenching (QQ) has emerged as an approach to mitigate pathogenicity without exerting a selective pressure on bacterial viability. QQ methods include the inhibition of AI biosynthesis, neutralization using antibodies or binding agents, and enzymatic degradation of signaling molecules [139–141]. Several natural and synthetic quorums sensing inhibitors (QSIs), such as ajoene, polyphenols, and azithromycin, have shown efficacy, although their mechanisms are often not fully defined [142–145]. Quorum quenching enzymes, including lactonases, acylases, and oxidoreductases, target AHLs and AI-2 signals and have shown promise in disrupting microbial communication in healthcare and environmental settings [146, 147].

Recent developments in artificial intelligence (AI) have accelerated the discovery and structural optimization of QSIs by predicting molecular interactions. However, their clinical translation is hindered by poor bioavailability and delivery inefficiencies. Combinatorial strategies involving nanocarriers and antibiotic co-delivery are being explored to enhance the therapeutic impact and limit resistance development.

Probiotics, Prebiotics, and Postbiotics

Prebiotics, probiotics, and postbiotics are increasingly recognized as complementary interventions for addressing global antimicrobial resistance (AMR), though their efficacy and safety vary significantly depending on microbial ecology and clinical context. These microbiome-based interventions offer distinct mechanisms and risk profiles in the context of antimicrobial resistance, requiring careful consideration of host and environmental factors in their development. Probiotics, defined as live microorganisms that provide health benefits, play a dual role in resistance dynamics. In antibiotic-naïve individuals possessing colonization-permissive microbiomes, probiotic strains such as *Lactobacillus* and *Bifidobacterium* may indirectly reduce the prevalence of AR genes by competitively excluding pathogenic bacteria and restoring gut microbial balance. However, the extent of this effect depends on the probiotic strains used, host microbiota composition, and clinical context, with outcomes varying between studies [148]. Despite these potential benefits, probiotic administration during antibiotic therapy poses risks. Research indicates that probiotics may unintentionally enhance the mucosal resistome by facilitating the proliferation of vancomycin-resistant commensals such as *Clostridium citroniae* and *Blautia* species [149]. Furthermore, concerns remain regarding the HGT of resistance determinants (e.g., tet and erm genes) from probiotic strains to pathogens, particularly in susceptible populations, such as newborns or immunocompromised individuals [150].

Prebiotics (indigestible fibers that support beneficial microorganisms) and synbiotics (probiotics + prebiotics) provide a more reliable therapeutic profile [151]. By selectively activating indigenous beneficial bacteria, these chemicals improve gut barrier integrity, generate antibacterial short-chain fatty acids (SCFAs) [152], and diminish colonization by multidrug-resistant pathogens [151]. Clinical investigations have indicated their effectiveness in reducing *Clostridioides difficile* infection rates and vancomycin-resistant *Enterococcus* colonization among hospitalized patients [151].

Postbiotics, which are non-viable microbial cells and their metabolic byproducts, have emerged as safe alternatives. This group includes heat-inactivated bacteria, cell lysates, and bioactive metabolites, such as bacteriocins and exopolysaccharides. Postbiotics mitigate HGT hazards while preserving anti-inflammatory and barrier-enhancing characteristics [153]. For example, postbiotics generated from *Lactobacillus plantarum* have been assessed for their ability to reduce AR genes in hospital-acquired infections. Postbiotics generated from *Lactobacillus plantarum* are being assessed for their ability to

reduce AR genes in hospital-acquired infections [154]. Their stability and uniform inter-individual responses render them especially appropriate for post-antibiotic recovery or immunocompromised individuals. Postbiotics, characterized by minimal resistance and consistent formulations, represent an encouraging advancement. Future studies should emphasize strain-specific effects, appropriate dosage, and delivery routes to enhance clinical efficacy. These initiatives highlight the potential of microbiome manipulation to mitigate AR; however, their application requires thorough ecological and clinical validation [149, 155].

Fecal Microbiota Transplantation: Restoring Gut Health

Fecal microbiota transplantation (FMT) has emerged as a powerful tool for restoring gut microbial balance, with its most established application being the treatment of recurrent *Clostridioides difficile* infection (rCDI). This procedure, which involves transferring processed donor stool via colonoscopy, capsules, or other delivery methods [156], capitalizes on the dual roles of the gut microbiome in pathogen exclusion and metabolic regulation, including systemic inflammation-mediated host-microbiota cross-talk [157–159]. For rCDI, FMT demonstrates remarkable 85–90% resolution rates by reintroducing competitive microbial communities, earning its FDA-approved status for this indication [160, 161].

Beyond rCDI, FMT has potential in combating antimicrobial resistance via three important mechanisms: (1) reducing the carriage of ESBL-producing Enterobacteriales [162], (2) decreasing antimicrobial resistance gene abundance [163], and (3) restoring colonization resistance against multidrug-resistant pathogens [158, 164]. Artificial intelligence is now being deployed to optimize donor-recipient matching, with machine learning algorithms analyzing microbial engraftment patterns and predicting clinical outcomes [165, 166].

Delivery challenges remain a significant hurdle, particularly for oral formulations that face gastric acid degradation and enemas with variable colonic retention [167]. Novel approaches include enteric-coated capsules, lyophilized preparations, and microbiome stabilization techniques that are currently under development [168]. The most promising dual-modality approach pairs FMT with non-absorbable antibiotics for MDR pathogen decolonization, demonstrating superior efficacy to monotherapies [162, 164, 169], or with probiotics to sustain microbial restoration [170].

Critical knowledge gaps persist regarding donor-recipient compatibility [171], long-term immunomodulatory effects [172], and development of standardized protocols for non-CDI applications [173]. Emerging solutions include engineered microbial consortia and phage-assisted FMT, which may overcome the variability in donor samples [174, 175]. While broader applications remain under investigation, FMT's unique capacity to remodel microbial ecosystems positions it as a versatile tool against antimicrobial resistance.

Cross-Cutting Technologies

As the complexity of AMR increases, integrated technological platforms are becoming essential for enhancing therapeutic precision and overcoming delivery challenges. Innovations such as nanotechnology and artificial intelligence transcend conventional disciplinary boundaries, offering scalable and customizable tools to support AMR approaches. This section highlights these multifaceted enablers and their transformative potential for AMR management.

Nanotechnology: Innovative Resistance Solutions

Nanotechnology has emerged as a powerful weapon against antimicrobial resistance, overcoming the key limitations of conventional antibiotics. The unique properties of nanomaterials, including their small size (10–100 nm) and high surface area-to-volume ratio, enable enhanced biofilm penetration and targeted drug delivery to infection sites [176, 177]. While metallic nanoparticles, such as silver (AgNPs) and copper oxide (CuO NPs), exert antimicrobial effects through ion release and reactive oxygen species generation [178, 179], their clinical translation faces significant delivery challenges, including rapid clearance, off-target effects, and variable performance in different biological environments [180]. To address these limitations, advanced delivery systems, such as lipid-based carriers and polymeric nanoparticles, have been developed to protect payloads and improve pharmacokinetics [181–183].

Recent progress in artificial intelligence and machine learning has enhanced nanomedicine by enabling the prediction and optimization of nanoparticle formulations for targeted antimicrobial applications and improving the understanding of complex biological interactions involving nanoparticles and microbial communities [184, 185].

These computational approaches complement experimental methods for designing multifunctional nanocarriers with enhanced targeting capabilities. Equally promising are integrated therapeutic platforms that merge nanotechnology with conventional treatments, including nanoparticle-antibiotic conjugates to circumvent resistance mechanisms and CRISPR-based systems for precision editing of resistance genes in microbial communities [186, 187]. Hybrid systems, such as bismuth-silver nanoparticles, demonstrate the potential of this approach by simultaneously targeting bacterial and fungal pathogens [188].

Looking forward, the field must address the remaining challenges in scalable manufacturing and safety profiling [177]. However, the ability of nanotechnology to combat antimicrobial resistance through multiple mechanisms makes it a transformative tool for managing infectious diseases. Notably, membrane-disruptive nanoparticles, such as cationic polymer-coated silver nanoparticles, can physically destabilize and penetrate the outer membranes of Gram-negative bacteria [189]. These approaches demonstrate how innovative materials science can overcome the evolutionary barriers to antimicrobial efficacy.

AI-Powered Therapies for Combating MDR Bacteria

Artificial intelligence (AI) and machine learning (ML) are transforming the battle against multidrug-resistant (MDR) bacteria by addressing the critical challenges of antimicrobial resistance. One of the most significant contributions of AI is its ability to accelerate drug discovery. Unlike traditional methods, which are slow and costly, AI-driven approaches rapidly analyze vast chemical and biological datasets, enabling the identification of novel antimicrobial compounds and the repurposing of existing drugs [124]. Furthermore, predictive algorithms can identify synergistic drug combinations by targeting bacterial genomic vulnerabilities, thereby reducing the likelihood of resistance development [190].

Beyond drug discovery, AI plays a pivotal role in advancing precision medicine for the treatment of infectious diseases. By integrating patient-specific data, such as genetic background, immune status, and microbiome composition, ML models can recommend tailored antimicrobial therapies, which is particularly crucial in cases where standard treatments fail [191]. Moreover, AI systems can predict pathogen responses and even forecast resistance emergence during treatment, allowing clinicians to proactively adjust therapies [192].

In addition to optimizing treatments, AI facilitates the rational design of next-generation therapeutic agents. For instance, machine learning has guided the development of antimicrobial peptides (AMPs) with enhanced efficacy against MDR pathogens [123]. Similarly, AI-driven approaches are being used to engineer bacteriophages for targeted bacterial elimination [193, 194], and to design probiotics that restore healthy microbiota [195]. Additionally, AI assists in optimizing drug delivery systems to ensure maximum therapeutic impact while minimizing adverse effects.

A critical advantage of AI-powered strategies is their ability to predict resistance mechanisms. By analyzing evolutionary trends and genetic mutations, ML models can predict resistance risks and guide the development of proactive measures [196]. AI-powered clinical decision support systems further enhance this predictive capability, which synthesize real-time patient data to improve diagnostics and treatment precision, ultimately reducing antibiotic misuse [197].

In conclusion, AI represents a paradigm shift in the management of MDR infections through accelerated drug discovery, personalized medicine, innovative therapeutics, and resistance prediction. As these technologies evolve, their integration into clinical and research settings will be essential for developing sustainable solutions to the global antimicrobial resistance crisis.

Limitations and Strengths of the Current Study

This manuscript provides a comprehensive overview of emerging therapies and technologies aimed at combating antimicrobial resistance (AMR); however, several limitations should be considered. Many of the discussed approaches, including phage therapy and CRISPR-Cas systems, require further validation in human clinical trials to establish their safety, efficacy, and long-term effects. Challenges related to the delivery of CRISPR-Cas and certain nanotechnology-based interventions remain substantial. Additionally, there is potential resistance to these novel agents, and limitations in bioavailability and stability may hinder the clinical translation of plant-based and biotechnological compounds.

Nonetheless, the review offers meaningful insights for both researchers and clinicians. It underscores innovative strategies and presents a multidisciplinary perspective by integrating microbiology, biotechnology, nanotechnology, and artificial intelligence. This comprehensive approach provides a strong foundation for guiding future research priorities in AMR.

Table 1 Different alternative antimicrobial approaches, mechanisms of actions, clinical stages, critical advantages, major challenge, and challenges

Strategy	Key mechanism	Clinical stage	Critical advantage	Major challenge	Key references
Bacteriophage therapy	Host-specific bacterial lysis	Phase II trials (PHOSA)	Targets MDR pathogens precisely	Narrow host range, immune response	[198, 199]
CRISPR-Cas systems	Gene editing of resistance factors	Preclinical (animal models)	Can reverse resistance mechanisms	Delivery challenges, off-target effects	[200, 201]
Bacteriocins	Membrane disruption via antimicrobial peptides	Approved (Nisaplin®)	Reduced resistance development compared to conventional antibiotics	Limited spectrum, stability issues	[202, 203]
Endolysins	Peptidoglycan degradation	Phase II trials (Rephasin®)	Effective against biofilms	Limited Gram-negative activity	[59, 204]
Quorum sensing inhibitors	Disrupt bacterial communication	Preclinical	Reduces virulence without killing bacteria	Limited clinical data	[205, 206]
Probiotics	Competitive exclusion of pathogens	Clinical use (Lactobacillus spp.)	Restores gut microbiome balance	Strain-specific effects, HGT risk	[207, 208]
Plant-derived compounds	Multi-target antimicrobial activity	Preclinical/adjuvant use	Broad-spectrum, low toxicity	Poor bioavailability	[209, 210]
Fecal microbiota transplant	Microbiome restoration	FDA-approved for rCDI	Reduces AMR gene burden	Donor variability	[211, 212]
Nanotechnology	Enhanced drug delivery and penetration	Preclinical	Overcomes biofilm barriers	Potential toxicity	[213, 214]

Conclusions and Future Perspectives

Antimicrobial resistance (AMR) remains a major global health threat, rendering many conventional treatments ineffective against multidrug-resistant (MDR) bacteria. This review explored a diverse array of innovative solutions, including bacteriophage therapy, antimicrobial peptides, CRISPR-Cas systems, quorum sensing inhibitors, plant-derived compounds, microbiome-based interventions, nanotechnology, and AI-powered tools that collectively represent a new frontier in the fight against AMR. The Summary of different strategies are given in Table 1.

These approaches offer targeted mechanisms that preserve the host microbiota and enhance drug delivery while reducing the potential for resistance. Synergistic therapeutics and AI-guided drug design further augment therapeutic precision, enabling personalized interventions tailored to microbial profiles and patient-specific data.

Future research should focus on integrating synergistic approaches such as phage–antibiotic combinations and CRISPR-nanoparticle systems to maximise impact. Artificial intelligence has the potential to enhance discovery pipelines and optimize clinical decision-making

processes. The adoption of the One Health framework, sustained investment, and robust international collaboration are essential for translating scientific advances into scalable, real-world solutions.

In summary, coordinated efforts across disciplines and sectors are required to combat AMR. By prioritizing innovation, precision, and sustainability, the global health community can develop effective and long-term responses to multidrug-resistant infections.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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