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REVIEW ARTICLE

Current Strategy for Implementing Advanced Tech to Address Multidrug-Resistant Bacteria

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Abstract: ***Introduction*:** This review explores emerging technological strategies aimed at combating Multidrug-Resistant Bacteria (MDRB), including MRSA, CRE, and VRE. These pathogens pose a critical public health threat due to rising resistance to conventional antibiotics. The study synthesizes findings on advanced approaches like nanotechnology, host-directed therapies, novel antimicrobials, combination regimens, and phytochemicals.

***Methods*:** A comprehensive literature review was performed using databases such as PubMed, Scopus, Web of Science, and Google Scholar, with keywords including "nanoparticles," "host-directed therapy," and "phytochemicals." Inclusion criteria prioritized peer-reviewed studies on antimicrobial interventions for MDRB. Data were grouped thematically and analyzed narratively to identify effective technologies and existing research gaps.

***Results*:** Nanoparticles (*e.g.*, AgNPs, ZnO NPs) showed antibacterial effects *via* membrane disruption and reactive oxygen species generation. Host-directed therapies, like cytokine modulators and immune checkpoint inhibitors, improved bacterial clearance. New antibiotics such as Cefiderocol and Eravacycline effectively targeted resistant Gram-negative strains. Combination therapies improved antibiotic efficacy, especially against biofilm-forming bacteria. Phytochemicals such as gingerol enhanced antibiotic activity and disrupted resistance mechanisms.

***Discussion*:** These technologies offer promising alternatives to failing antibiotics, especially against pathogens with complex resistance mechanisms. However, limitations include toxicity concerns (nanoparticles), immunological variability (host therapies), lack of clinical validation, and cost barriers. Integration into clinical practice remains limited by regulatory and logistical challenges.

***Conclusion*:** Advanced therapeutic strategies hold strong potential for addressing MDRB. However, successful clinical translation requires further research, global cooperation, and investment in regulatory infrastructure.

Keywords: Multidrug-resistant bacteria, nanotechnology, antibiotic resistance, host-directed therapy, phytochemicals, combination therapies.

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1. INTRODUCTION

The emergence of Multidrug-Resistant Bacteria (MDRB) is recognized as one of the most significant challenges to global public health today. These so-called "superbugs" exhibit resistance to multiple antibiotic classes, rendering many conventional treatment options ineffective. Notably, organisms such as Methicillin-Resistant *Staphylococcus Aureus* (MRSA), Carbapenem-Resistant *Enterobacteriaceae* (CRE), and Vancomycin-Resistant *Enterococcus* (VRE) have become formidable adversaries in healthcare settings. These pathogens not only cause severe infections but also significantly increase mortality rates, length of hospital stays, and healthcare costs.

1.1. Background on Multidrug-Resistant Bacteria (MDRB)

1.1.1. Global Threat of Superbugs

Antibiotics, once considered miracle drugs, revolutionized medicine and dramatically reduced mortality rates for bacterial infections. However, the overuse and misuse of these drugs, particularly in healthcare and agriculture, have accelerated the development of antibiotic resistance. MDRB, resistant to multiple classes of antibiotics, are now widely prevalent, with millions of cases reported annually. According to the World Health Organization (WHO), drug-resistant infections account for approximately 700,000 deaths each year globally, a number projected to rise to 10 million by 2050 if no effective interventions are implemented.

1.1.2. Methicillin-Resistant Staphylococcus Aureus (MRSA)

Staphylococcus aureus, a common pathogen that resides on the skin and mucous membranes, can cause a wide range of infections, from mild skin infections to life-threatening conditions such as pneumonia, bloodstream infections, and sepsis. The development of methicillin resistance in *S. aureus* transformed this organism into a formidable pathogen. MRSA is characterized by its ability to withstand β-lactam antibiotics, including methicillin, oxacillin, and penicillin, which were once effective treatments. The genetic basis of this resistance lies in the acquisition of the *mecA* gene, which encodes an altered Penicillin-Binding Protein (PBP2a). This protein significantly reduces the binding affinity of β-lactam antibiotics, rendering them ineffective against MRSA. MRSA is particularly prevalent in healthcare settings, where immunocompromised patients and invasive procedures provide ample opportunities for infection. Community-acquired MRSA strains are also on the rise, further complicating infection control efforts.

MRSA poses a significant public health threat due to its widespread prevalence and limited treatment options. Vancomycin, once the primary treatment for MRSA, is now compromised as strains with reduced susceptibility, such as Vancomycin-Intermediate *Staphylococcus Aureus* (VISA) [1] and Vancomycin-Resistant *Staphylococcus Aureus* (VRSA), have emerged. The resistance of MRSA to even the most potent antibiotics underscores the urgent need for alternative treatment strategies, including new drugs and non-antibiotic therapies.

1.1.3. Carbapenem-Resistant Enterobacteriaceae (CRE)

Among the most dangerous MDRBs are Carbapenem-Resistant *Enterobacteriaceae* (CRE) [2], a family of bacteria that includes species such as *Escherichia coli* and *Klebsiella pneumoniae*. These organisms are responsible for severe healthcare-associated infections, including pneumonia, urinary tract infections, and sepsis. Carbapenems, a class of antibiotics often considered the last line of defense against resistant Gram-negative bacteria, have become ineffective against CRE due to the production of carbapenemase enzymes. These enzymes, such as Klebsiella Pneumoniae Carbapenemase (KPC) [3] and New Delhi Metallo-β-lactamase (NDM) [4], degrade carbapenems and other β-lactam antibiotics, rendering them ineffective.

CRE infections are notoriously difficult to treat, with mortality rates exceeding 50% in some cases. Treatment options are limited to a handful of antibiotics, such as polymyxins and tigecycline, both of which have significant limitations, including toxicity and variable efficacy. CRE infections have become a global threat, with outbreaks reported in hospitals worldwide. The rapid spread of CRE, driven by the horizontal transfer of resistance genes *via* plasmids, highlights the urgent need for new therapeutic approaches and stringent infection control measures.

1.1.4. Vancomycin-Resistant Enterococcus (VRE)

Enterococcus species, particularly *Enterococcus faecium* and *Enterococcus faecalis*, are normal inhabitants of the human gastrointestinal tract but can cause serious infections, particularly in immunocompromised individuals. Vancomycin-Resistant *Enterococcus* (VRE) [5] strains emerged in the 1980s and have since become major pathogens in healthcare settings. VRE is primarily resistant to vancomycin due to the acquisition of the *vanA* or *vanB* genes, which modify the antibiotic's target site, preventing its binding and thereby inhibiting its bactericidal effect.

VRE infections, particularly in the bloodstream and urinary tract, are associated with high morbidity and mortality. The resistance mechanisms in VRE limit the effectiveness of vancomycin, which was previously the mainstay of treatment for serious *Enterococcus* infections. Daptomycin and linezolid are now the preferred treatments for VRE, but the emergence of resistance to these agents further complicates management. The ability of *Enterococcus* to survive on environmental surfaces for extended periods and its transmission through healthcare workers exacerbate the challenge of controlling VRE infections in hospitals.

1.1.5. Overview of Antibiotic Resistance Mechanisms

Antibiotic resistance in bacteria arises through several mechanisms, enabling them to evade the effects of antimicrobial agents. These mechanisms include drug inactivation, alteration of target sites, reduced permeability, and active drug efflux. Together, these resistance strategies enable MDRB to survive and proliferate in the presence of once-effective antibiotics.

Many bacteria produce enzymes that degrade or inactivate antibiotics, rendering them ineffective. One common example is the production of β-lactamase enzymes, which hydrolyze the β-lactam ring found in penicillins and cepha-

losporins. This enzymatic degradation neutralizes the bactericidal activity of these antibiotics. An even more concerning mechanism is the production of carbapenemase enzymes by Carbapenem-Resistant Enterobacteriaceae (CRE), which can degrade carbapenem antibiotics, often considered the last line of defense against resistant Gram-negative infections.

Another resistance strategy involves modifying the antibiotic's target site within the bacterial cell. For instance, Methicillin-Resistant Staphylococcus Aureus (MRSA) alters Penicillin-Binding Proteins (PBPs), reducing the binding affinity of β-lactam antibiotics and rendering them ineffective. Similarly, Vancomycin-Resistant Enterococcus (VRE) modifies its cell wall target, which impairs vancomycin's ability to inhibit cell wall synthesis, thereby compromising treatment efficacy.

Gram-negative bacteria like CRE also exhibit resistance through reduced permeability. Their outer membrane serves as a natural barrier to many antibiotics, and mutations in porin protein channels, which typically allow molecules to pass into the cell, further reduce membrane permeability. This limits antibiotic access to intracellular targets, contributing significantly to drug resistance.

Efflux pumps represent an additional resistance mechanism used by various bacteria, including multidrug-resistant Pseudomonas aeruginosa. These membrane proteins actively expel antibiotics from the bacterial cell before the drugs can reach their intended targets. This expulsion process allows bacteria to resist multiple classes of antibiotics, such as fluoroquinolones and β-lactams [6].

The global threat posed by MDRB, including MRSA, CRE, and VRE, underscores the need for innovative strategies to combat antibiotic resistance. These pathogens exploit multiple mechanisms to evade the effects of antibiotics, making them highly resilient to conventional therapies. As the prevalence of MDRB continues to rise, the development of alternative therapeutic approaches, including nanotechnology, host-directed therapies, and novel antibiotics, is critical. Addressing this growing threat requires a multidisciplinary approach that combines advancements in medical technology with responsible antibiotic stewardship and stringent infection control practices in healthcare settings.

2. METHODOLOGY

2.1. Search Strategy

We conducted a comprehensive literature search using databases including PubMed, Scopus, Web of Science, and Google Scholar to identify relevant studies published in English up to March 2025. Keywords used in various combinations included: "multidrug-resistant bacteria," "antibiotic resistance," "nanoparticles," "host-directed therapy," "novel antibiotics," "combination therapies," and "phytochemicals." Boolean operators such as AND, OR, and NOT were applied to refine search results.

2.1. Study Selection

Articles were included if they met the following criteria: (1) addressed mechanisms or interventions related to multidrug-resistant bacterial infections, (2) focused on clinical or preclinical evaluations of advanced technologies or therapies, and (3) were peer-reviewed. Exclusion criteria included articles not available in full text, non-English language papers, editorials, and studies that did not provide specific information on MDR interventions.

2.2. Data Extraction and Synthesis

Key data extracted from selected studies included the type of intervention, bacterial targets, study model (*in vitro*, *in vivo*, clinical), outcomes, and limitations. Information was compiled into the following thematic categories: nanotechnology, host immune modulation, novel antibiotics, combination strategies, and natural product-based therapies. A narrative synthesis approach was employed to analyze trends, highlight promising interventions, and identify knowledge gaps across these categories.

3. MECHANISMS OF RESISTANCE IN BACTERIA

Antibiotic resistance is one of the most pressing challenges in modern medicine. Multidrug-Resistant Bacteria (MDRB) [7] exploit a variety of mechanisms to evade the effects of antimicrobial agents, making infections caused by these pathogens difficult to treat. These resistance mechanisms include the inactivation of drugs by bacterial enzymes, reduced permeability and active drug efflux, and genetic mutations that alter drug targets. The cumulative impact of these resistance strategies compromises the efficacy of current treatment options, posing a significant threat to global health.

3.1. Common Resistance Mechanisms.

3.1.1. Drug Inactivation Through Bacterial Enzymes.

One of the most common mechanisms of bacterial resistance is the inactivation of antibiotics through bacterial enzymes. These enzymes either degrade or chemically modify antibiotics, rendering them ineffective. β-lactamase enzymes, for instance, are produced by many Gram-negative and Gram-positive bacteria, and hydrolyze the β-lactam ring present in antibiotics such as penicillins, cephalosporins, and carbapenems. This destruction of the β-lactam ring neutralizes the antibiotic's bactericidal activity, preventing it from inhibiting bacterial cell wall synthesis.

A specific example is the production of carbapenemase enzymes, such as Klebsiella Pneumoniae Carbapenemase (KPC) and New Delhi Metallo-β-lactamase (NDM), by Carbapenem-Resistant *Enterobacteriaceae* (CRE) [8]. These enzymes not only break down carbapenem antibiotics, which are often considered the last line of defense against Gram-negative infections, but they also exhibit activity against a broad range of β-lactam antibiotics. As a result, CRE infections are often resistant to multiple classes of antibiotics, significantly limiting treatment options and leading to high mortality rates.

Another key example of drug inactivation is the modification of aminoglycoside antibiotics through enzymatic processes such as acetylation, phosphorylation, or adenylation. These modifications reduce the antibiotic's ability to bind to its target site on bacterial ribosomes, thereby preventing it from inhibiting protein synthesis. Bacteria such as *Pseudo-*

monas aeruginosa and *Enterococcus faecalis* are notorious for employing such mechanisms to resist aminoglycoside antibiotics, further complicating treatment strategies.

3.1.2. Reduced Drug Permeability and Efflux Pumps

The bacterial cell envelope, particularly in Gram-negative bacteria, plays a crucial role in resistance by limiting the permeability of antibiotics. Gram-negative bacteria possess an outer membrane that acts as a physical barrier, preventing many antibiotics from reaching their target sites. Porins, which are protein channels located in the outer membrane, allow the passage of small molecules, including antibiotics. However, bacteria can mutate these porins to decrease their permeability, thus preventing antibiotics from entering the cell.

For instance, mutations in the porin channels of *Pseudomonas aeruginosa* and *Escherichia coli* [9] have been observed to reduce the uptake of β-lactams and carbapenems, significantly impairing the efficacy of these drugs. Additionally, changes in membrane composition, such as increased hydrophobicity, further restrict antibiotic penetration. This mechanism is particularly problematic in Gram-negative bacteria, as their outer membrane already presents a formidable barrier to antibiotic entry, making them inherently more resistant than Gram-positive bacteria.

Efflux pumps represent another critical mechanism through which bacteria resist antibiotics. These pumps, located in the bacterial cell membrane, actively expel antibiotics from the cell before they can reach their target sites. Efflux systems can be specific to certain antibiotics or may be capable of pumping out a wide range of drugs, leading to multidrug resistance. One of the best-characterized efflux pumps is the AcrAB-TolC system found in *E. coli* and *Klebsiella pneumoniae*, which confers resistance to multiple antibiotic classes, including fluoroquinolones, β-lactams, and tetracyclines [10].

The overexpression of efflux pumps is particularly problematic in Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and CRE. For example, *P. aeruginosa* overproduces the MexAB-OprM efflux pump, which actively removes fluoroquinolones, aminoglycosides, and β-lactams from the cell. The increased expression of efflux pumps not only leads to resistance to individual drugs but also contributes to the accumulation of multiple resistance traits, making these pathogens extraordinarily difficult to treat.

3.1.3. Genetic Mutations That Alter Drug Targets

Genetic mutations in bacteria are another major mechanism of resistance, especially when these mutations alter the antibiotic's target site. Antibiotics exert their effects by binding to specific bacterial targets, such as enzymes or structural components involved in cell wall synthesis, protein synthesis, or DNA replication. Mutations that modify the structure of these targets can reduce the binding affinity of the antibiotic, rendering it ineffective.

A prominent example is Methicillin-Resistant *Staphylococcus Aureus* (MRSA), which harbors the *mecA* gene. This gene encodes an altered form of Penicillin-Binding Protein (PBP2a) [11], which has a low affinity for β-lactam antibiotics. As a result, MRSA is resistant to all β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems. This genetic alteration is a major factor behind the global prevalence of MRSA infections, particularly in hospital settings where antibiotic use is high.

In addition, fluoroquinolone resistance is often mediated by mutations in bacterial DNA gyrase and topoisomerase IV, enzymes involved in DNA replication. These mutations reduce the ability of fluoroquinolones to bind to their targets, diminishing their ability to inhibit bacterial replication. Mutations in these enzymes are common in Gram-negative pathogens such as *E. coli*, *Klebsiella pneumoniae*, and *Salmonella*, contributing to the rapid spread of resistance to fluoroquinolones, which are critical drugs for treating severe bacterial infections.

Moreover, Vancomycin Resistance in *Enterococcus faecium* and *Enterococcus faecalis* (VRE) [12] is mediated by the acquisition of the *vanA* or *vanB* genes, which encode enzymes that alter the structure of the bacterial cell wall. These alterations prevent vancomycin from binding to its target, thereby inhibiting its ability to block cell wall synthesis. VRE infections are particularly concerning in hospital settings, as treatment options are limited to only a few antibiotics, such as daptomycin and linezolid, and resistance to these agents is also emerging.

3.1.4. Impact on Current Treatment Strategies

The widespread emergence of these resistance mechanisms has severely impacted the efficacy of current treatment strategies for bacterial infects. In particular, infections caused by Gram-negative bacteria have become increasingly difficult to treat due to their intrinsic and acquired resistance mechanisms, including the presence of an impermeable outer membrane, the production of β-lactamases, and the overexpression of efflux pumps. These factors contribute to the high level of resistance seen in pathogens such as CRE, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [13], all of which are classified as critical threats by the World Health Organization (WHO).

In Gram-positive bacteria, resistance mechanisms such as altered drug targets and drug inactivation have also led to a decrease in treatment efficacy. MRSA infections, for example, were once treatable with β-lactam antibiotics, but the emergence of resistance has necessitated the use of alternative agents, such as vancomycin. However, the rising prevalence of Vancomycin-Resistant Strains (VISA and VRSA) highlights the limitations of relying on single antibiotics for treating resistant infections.

In response to these challenges, clinicians have increasingly turned to combination therapies, which involve the use of multiple antibiotics to overcome resistance mechanisms. For example, combining β-lactam antibiotics with β-lactamase inhibitors, such as clavulanic acid or tazobactam, can restore the activity of β-lactams against β-lactamase-producing bacteria. Similarly, combination therapies involving polymyxins and carbapenems have shown some success in treating CRE infections.

However, the development of new antibiotics remains a critical priority, as resistance to existing drugs continues to spread. The use of last-resort antibiotics, such as colistin and

tigecycline, is becoming more common, but these drugs often have significant limitations, including toxicity and variable efficacy. Furthermore, the increasing prevalence of pan-drug-resistant strains, which are resistant to all available antibiotics, underscores the urgent need for novel therapeutic strategies.

The mechanisms of antibiotic resistance shown in Fig. (**1**) including drug inactivation, reduced permeability, efflux pumps, and genetic mutations—pose significant challenges to the treatment of bacterial infections. These mechanisms are particularly problematic in MDRB, such as MRSA, CRE, and VRE, which are responsible for some of the most difficult-to-treat infections in healthcare settings. The development of alternative treatment strategies, including combination therapies and novel antibiotics, is essential to combat the growing threat of antimicrobial resistance. Additionally, a deeper understanding of bacterial resistance mechanisms will be critical for the design of future therapeutic interventions.

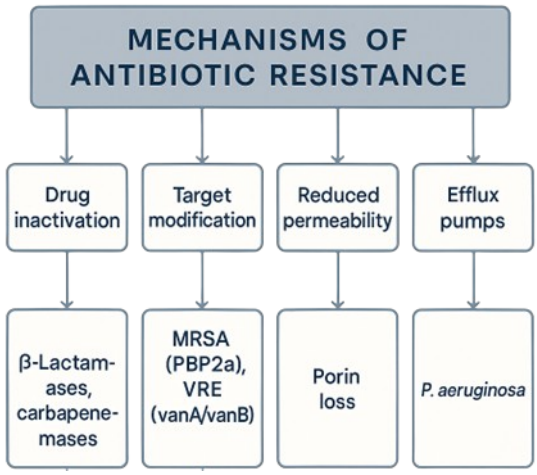

Fig. (1). Mechanisms of antibiotic resistance. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4. NANOTECHNOLOGY IN COMBATING MDRB.

The emergence of Multidrug-Resistant Bacteria (MDRB) [14] has necessitated innovative approaches to combat bacterial infections, as conventional antibiotics continue to lose efficacy. Nanotechnology has attracted significant attention as a promising tool in addressing MDRB due to its unique properties, such as enhanced surface area-to-volume ratio, tunable surface chemistry, and the ability to bypass conventional resistance mechanisms. Nanoparticles (NPs), particularly metal and metal oxide nanoparticles, have demonstrated potent antibacterial activity, offering novel solutions for both drug delivery and direct antimicrobial action. This section explores nanoparticle-based approaches, their applications, efficacy, and future potential in the fight against MDRB (Table **1**).

4.1. Nanoparticle-Based Approaches

Nanoparticles, due to their nanoscale dimensions, exhibit physical and chemical properties that are distinct from their bulk counterparts. In the context of antibacterial applications, nanoparticles, especially metal (*e.g.*, silver, gold) and metal oxide (*e.g.*, zinc oxide, titanium dioxide), have garnered attention for their ability to interact directly with bacterial membranes, disrupt cellular processes, and improve drug delivery to infection sites.

Silver Nanoparticles (AgNPs) exhibit strong antibacterial properties through multiple mechanisms. One primary mechanism involves their interaction with bacterial cell membranes. Due to electrostatic attraction between the positively charged AgNPs and the negatively charged bacterial membrane, these nanoparticles adhere to the surface and increase membrane permeability. This disruption leads to leakage of essential cellular components, including ions, proteins, and nucleic acids, ultimately resulting in bacterial cell death.

Another key mechanism is the generation of Reactive Oxygen Species (ROS) [15]. AgNPs stimulate the production of ROS such as hydrogen peroxide and hydroxyl radicals, which induce oxidative stress within bacterial cells. This oxidative stress damages proteins, lipids, and DNA, triggering apoptosis. Notably, this mode of action is effective against both antibiotic-sensitive and antibiotic-resistant strains, making it a powerful tool for overcoming conventional resistance mechanisms.

In addition to membrane disruption and oxidative damage, AgNPs also interfere with intracellular processes by interacting directly with bacterial DNA. This interaction hampers DNA replication and transcription. Furthermore, AgNPs can bind to ribosomal subunits, thereby inhibiting

Table 1. Nanoparticle-based therapies for MDRB.

Nanoparticle	Type	Target Bacteria	Mechanism of Action	Clinical/Preclinical Stage
Silver nanoparticles (AgNPs) [17]	Metal	*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*	Cell membrane disruption, ROS generation	Preclinical
Zinc oxide nanoparticles (ZnO NPs) [13]	Metal oxide	*Staphylococcus aureus*, *Acinetobacter baumannii*	ROS generation, enhanced antibiotic penetration	Preclinical
Gold nanoparticles (AuNPs) [44]	Metal	*Methicillin-Resistant Staphylococcus Aureus* (MRSA)	Disruption of bacterial cell walls, DNA binding	Clinical
Chitosan nanoparticles [45]	Polysaccharide	MDR *Pseudomonas aeruginosa*	Increased antibiotic delivery to bacterial cells	Preclinical

protein synthesis. These effects combine to suppress bacterial growth and reproduction, leading to the effective eradication of pathogens that are otherwise resistant to standard antibiotic treatments.

4.1.2. Metal Oxide Nanoparticles: Zinc Oxide (ZnO)

Zinc Oxide Nanoparticles (ZnO NPs) have similarly been recognized for their antimicrobial efficacy against MDRB. For example, AgNPs, ZnO NPs exhibit size-dependent antibacterial properties and can effectively kill bacteria through various mechanisms:

Zinc Oxide Nanoparticles (ZnO NPs) exhibit antimicrobial activity through several interconnected mechanisms. They can physically interact with bacterial membranes, increasing membrane permeability and leading to leakage of intracellular contents. Due to their small size, ZnO NPs are capable of penetrating bacterial membranes more efficiently than larger particles, allowing them to reach and interact with internal cellular structures more effectively.

A major mechanism underlying their antibacterial action is the generation of Reactive Oxygen Species (ROS), similar to that observed with silver nanoparticles. These ROS induce oxidative stress, damaging essential cellular components—such as lipids, proteins, and nucleic acids—ultimately compromising bacterial viability. The consistent production of ROS is considered one of the most critical factors contributing to the antimicrobial potency of ZnO NPs.

Additionally, ZnO NPs exhibit photocatalytic properties, which enable them to generate ROS upon exposure to Ultraviolet (UV) light. This unique feature enhances their bactericidal activity, making them particularly effective in applications like antimicrobial surface coatings and disinfectants. These photocatalytic effects are especially valuable in healthcare settings, where light-activated ZnO-based materials can help prevent bacterial colonization on medical devices and high-contact surfaces.

4.1.3. Enhanced Drug Delivery Systems Using Nanoparticles

Beyond their direct antimicrobial action, nanoparticles offer significant advantages in drug delivery systems. By serving as carriers for conventional antibiotics, nanoparticles can improve the pharmacokinetics and bioavailability of antibiotics, particularly in cases of MDRB infections where higher drug concentrations are required to overcome resistance mechanisms. Nanoparticles provide several benefits in drug delivery:

Nanoparticles offer significant advantages in drug delivery, particularly for targeting Multidrug-Resistant Bacteria (MDRB). They can be engineered to selectively target bacterial cells while minimizing harm to human cells. This specificity is achieved by functionalizing the surface of nanoparticles with ligands that bind to receptors on bacterial cells, enabling targeted delivery of antibiotics. Such an approach not only enhances the effectiveness of treatment but also reduces unintended side effects associated with off-target drug activity.

In addition to targeting, nanoparticles improve the stability and bioavailability of antibiotics. Encapsulating drugs within these carriers protects them from premature degradation in the body, thereby extending their half-life and allowing a greater concentration to reach the site of infection. This is especially important in treating infections caused by MDRB, which often require sustained high levels of antibiotic exposure for effective clearance.

Nanoparticles can help circumvent one of the most common resistance mechanisms in bacteria by targeting efflux pumps that expel antibiotics. By acting as drug reservoirs, nanoparticles enable a controlled release of antibiotics, ensuring that therapeutic concentrations are maintained within the bacterial cell for longer durations. This sustained delivery increases the likelihood of successful bacterial eradication even in strains that have developed robust resistance mechanisms.

For example, nanoparticles have been utilized to deliver antibiotics such as vancomycin and colistin to combat resistant Gram-negative bacteria, including *Pseudomonas aeruginosa* and CRE [16]. Studies have shown that nanoparticle-based drug delivery systems significantly enhance the antibacterial effects of these antibiotics, making them more effective against MDRB.

The applications of nanoparticle-based approaches in combating MDRB are wide-ranging, spanning from clinical treatments to preventive measures in healthcare settings.

4.2. Disruption of Biofilm Production

Biofilm formation is a significant factor in the persistence of MDRB infections, as biofilms provide a protective environment for bacteria, making them more resistant to antibiotics. Nanoparticles have shown great promise in disrupting biofilm production and eliminating established biofilms.

Silver Nanoparticles (AgNPs) [17] have been shown to inhibit the initial stages of biofilm formation by interfering with bacterial adhesion to surfaces. In addition, studies have demonstrated that AgNPs can penetrate established biofilms, destabilizing the Extracellular Polymeric Substances (EPS) that hold the biofilm together. This allows for more effective penetration of antibiotics into the biofilm, increasing their efficacy against resistant bacterial cells embedded within the biofilm matrix.

Similarly, ZnO NPs have been found to prevent biofilm formation by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, two common MDRB responsible for nosocomial infections. By generating ROS and disrupting the biofilm structure, ZnO NPs enhance the susceptibility of biofilm-associated bacteria to antibiotic treatment. This dual action, disrupting biofilms and killing bacteria, makes nanoparticles an attractive option for treating chronic infections caused by biofilm-forming MDRB.

4.3. Applications in Medical Devices and Wound Care

The application of nanoparticles in coating medical devices, such as catheters, stents, and wound dressings, offers a preventive strategy against MDRB infections. Devices coated with AgNPs or ZnO NPs can prevent bacterial colonization and biofilm formation, significantly reducing the risk of healthcare-associated infections.

Nanoparticle-infused wound dressings have also shown promising results in accelerating wound healing while preventing infection by MDRB. For instance, AgNP-coated dressings are used in the treatment of burn wounds, where infections caused by MDRB, such as *Pseudomonas aeruginosa*, can lead to severe complications. The antimicrobial properties of AgNPs, combined with their ability to promote wound healing by reducing inflammation and enhancing tissue regeneration, make them ideal for wound care applications.

4.4. Future Potential and Clinical Considerations

While nanoparticle-based approaches have demonstrated significant potential in combating MDRB, several challenges must be addressed before widespread clinical implementation. One of the primary concerns is the potential toxicity of nanoparticles to human cells. Although metal and metal oxide nanoparticles are effective against bacteria, their nonspecific mechanisms, such as ROS generation and membrane disruption, may also harm human tissues if not properly controlled. Therefore, further research is needed to fine-tune nanoparticle formulations and ensure targeted antibacterial activity while minimizing cytotoxic effects.

Additionally, the long-term environmental impact of nanoparticles, particularly when used in medical devices and wound dressings, requires careful consideration. The potential for nanoparticles to accumulate in the environment and cause ecological harm is an emerging area of research that must be addressed before large-scale application.

Clinical trials involving nanoparticle-based therapies are currently limited, and more extensive studies are required to determine the optimal dosages, delivery methods, and safety profiles of these treatments. Nevertheless, the future potential of nanoparticles in the fight against MDRB remains bright, with the possibility of integrating these technologies into a comprehensive strategy to address the global threat of antibiotic resistance.

Nanotechnology offers a promising new frontier in the battle against multidrug-resistant bacteria. Metal and metal oxide nanoparticles, particularly AgNPs and ZnO NPs, exhibit potent antimicrobial properties through mechanisms such as cell membrane disruption, ROS generation, and interference with bacterial DNA replication. Their ability to disrupt biofilm production and enhance drug delivery to infection sites further underscores their potential as a solution to MDRB infections. However, before nanoparticle-based therapies can be widely adopted, further research into their safety, efficacy, and environmental impact is essential. Nanotechnology, when used alongside traditional antibiotics and other therapeutic approaches, could play a pivotal role in addressing the growing threat of antimicrobial resistance.

Despite the promising antimicrobial activity of metal-based nanoparticles such as silver (AgNPs) and zinc oxide (ZnO NPs), their clinical translation remains limited. Several formulations are currently in preclinical or early-phase clinical development, including topical AgNP-based products by NanoBio Corporation and nanoparticle-conjugated cationic steroid antibiotics (CERAGENINs) under development by Ceragenix Pharmaceuticals [17]. However, no metal nanoparticle-based antimicrobial agent has yet received FDA approval for systemic use. One key barrier is the absence of standardized regulatory pathways for evaluating the safety and efficacy of nanoparticle-based drugs. Toxicological studies have raised significant concerns about AgNP-induced cytotoxicity, including mitochondrial dysfunction, oxidative stress, and genotoxicity in human cells. Additionally, bioaccumulation and unpredictable in vivo distribution complicate dose optimization and risk-benefit assessments. A Phase I clinical trial investigating the safety of silver-based wound treatments (NCT01239684) [18] reflects the cautious approach to translating nanotechnology into human use. Most preclinical evaluations of nanoparticle therapies employed sample sizes of 6–12 animals per group, based on standard toxicology protocols to detect $\geq 30\%$ differences in bacterial load with 80% power at $\alpha = 0.05$. Statistical significance in these studies was commonly assessed using a one-way ANOVA followed by Tukey's post hoc test to compare treatment groups, which is suitable for evaluating multiple treatment arms against controls. These challenges highlight the urgent need for robust and long-term toxicological data, regulatory clarity, and environmental risk assessments to ensure that nanoparticle-based antimicrobials can be safely and effectively integrated into clinical practice.

While silver and zinc oxide nanoparticles demonstrate potent antibacterial and antibiofilm activity *in vitro*, clinical translation remains limited. The potential cytotoxicity to human tissues, inconsistent regulatory standards, and the lack of phase III trials pose significant hurdles. Moreover, long-term environmental impacts of metal nanoparticles remain largely unstudied, limiting their broad acceptance in clinical settings.

5. HOST-DIRECTED THERAPIES

In the ongoing battle against Multidrug-Resistant Bacteria (MDRB), traditional strategies have predominantly focused on targeting the pathogens themselves. However, as bacteria continuously evolve to evade antimicrobial treatments, there is an increasing interest in Host-Directed Therapies (HDTs). These approaches aim to boost the host's own immune responses to better control and eliminate infections. Unlike conventional antibiotics, which directly attack bacterial cells, HDTs work by enhancing the body's innate and adaptive immune mechanisms, modulating the immune response to fight off resistant pathogens more effectively. This section explores key strategies to boost host immunity and provides examples of therapeutic interventions, including the use of immunomodulatory drugs and biologics, to combat MDR infections.

Host-directed therapies are designed to enhance the natural immune responses of the host to combat infections. By boosting immune cell function, promoting cytokine production, and modulating immune pathways, HDTs can enhance the body's ability to clear resistant bacterial infections. These strategies focus on leveraging the body's inherent capacity to fight infection and can be particularly effective when combined with traditional antimicrobial therapies.

Host-directed therapies provide a promising alternative to antibiotics by enhancing immune responses. However, variability in individual immune responses, the risk of hyperin-

flammation, and the high costs of biologics, such as monoclonal antibodies, limit their scalability and standardization in treatment protocols.

5.1. Pharmacological Interventions to Enhance Immune Cell Function and Cytokine Production

One of the key goals of host-directed therapy is to enhance the function of immune cells, particularly phagocytes, which are responsible for engulfing and destroying pathogens. Pharmacological agents can be used to stimulate the activity of these cells, thereby boosting the immune response to bacterial infections. For instance, macrophages and neutrophils play a critical role in the initial stages of the immune response by recognizing, engulfing, and killing bacteria. Certain pharmacological interventions can enhance the bactericidal activity of these immune cells, improving their ability to clear infections, even in the presence of resistant pathogens.

Leukotriene B4 (LTB4) [19], a lipid mediator, has been shown to enhance macrophage bactericidal function. It does this by promoting the production of Reactive Oxygen Species (ROS), which are toxic to bacterial cells. By increasing the production of ROS, LTB4-treated macrophages exhibit enhanced capacity to kill MDRB, offering a potential avenue for host-directed interventions. Moreover, ROS production in phagocytes can be pharmacologically enhanced by drugs that activate the NADPH oxidase system, a key component in ROS generation during the immune response.

Additionally, cytokine production can be targeted to enhance immune responses. Cytokines are signaling molecules that regulate immune cell communication and coordination during infections. Cytokines such as Interleukins (*e.g.*, IL-2, IL-6) and Interferons (*e.g.*, IFN-γ) play a vital role in orchestrating the immune response against bacterial infections. Pharmacological interventions that stimulate cytokine production can help to amplify the immune response, particularly in patients whose immune systems may be compromised or overwhelmed by infection. For example, the administration of Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) has been shown to boost neutrophil and macrophage function, improving the host's ability to clear bacterial infections.

5.2. Strategies to Manipulate Host Immune Pathways to Clear Resistant Pathogens

Manipulating host immune pathways to enhance the clearance of resistant pathogens represents another promising strategy for host-directed therapy. One such approach involves the activation of Toll-Like Receptors (TLRs), which are pattern recognition receptors that recognize microbial components and initiate immune responses. TLR signaling pathways play a crucial role in recognizing pathogens and triggering the production of pro-inflammatory cytokines that promote the recruitment of immune cells to the site of infection.

For example, activation of TLR2 and TLR4 has been shown to enhance the immune response against Gram-positive and Gram-negative bacteria, respectively. Agonists that specifically target these receptors can be used to boost the host's immune response against MDRB. Furthermore, pharmacological agents that enhance TLR signaling can increase the production of antimicrobial peptides, which are small proteins that directly kill bacteria. This strategy is particularly valuable in infections where conventional antibiotics have failed due to bacterial resistance mechanisms.

Another host-directed strategy involves targeting immune checkpoint pathways, which regulate the balance between immune activation and suppression. For instance, the PD-1/PD-L1 pathway [20], which normally functions to prevent overactivation of the immune system, can be manipulated to boost immune responses against bacterial infections. Blocking PD-1 or PD-L1 with monoclonal antibodies (similar to cancer immunotherapy) may enhance the host's ability to clear bacterial infections by preventing the suppression of immune cell activity.

Additionally, autophagy, a cellular process that involves the degradation and recycling of cellular components, plays an essential role in eliminating intracellular pathogens. Drugs that enhance autophagy, such as rapamycin, can potentially boost the host's ability to clear bacteria that reside within host cells. This approach is particularly valuable in combating intracellular pathogens such as *Mycobacterium tuberculosis* [21], which can evade the immune system by hiding inside host cells.

5.3. Therapeutic Examples

5.3.1. Use of Immunomodulatory Drugs Like Statins to Reduce Infection-Related Complications

Immunomodulatory drugs that modulate the immune system to reduce the severity of infections have shown promise in treating MDR infections. Statins, widely known for their cholesterol-lowering effects, have been found to possess immunomodulatory properties that may reduce infection-related complications. Statins inhibit the enzyme HMG-CoA reductase but also exert pleiotropic effects, including anti-inflammatory and immunomodulatory actions.

Several studies have demonstrated that statins can reduce the risk of infection-related complications in patients with sepsis, pneumonia, and other bacterial infections. Statins have been shown to downregulate the production of pro-inflammatory cytokines, such as IL-6 and TNF-α [22], which are often elevated in severe infections. By reducing the excessive inflammation associated with infections, statins may help to mitigate tissue damage and improve outcomes in patients with MDR infections.

In addition to their anti-inflammatory effects, statins may also enhance the clearance of bacteria by boosting the activity of immune cells. For instance, studies have shown that statins can enhance macrophage phagocytic activity, increasing their ability to engulf and destroy bacteria. These findings suggest that statins could be repurposed as adjunctive therapies for MDR infections, particularly in cases where excessive inflammation contributes to disease severity shown in Table **2**.

5.4. Potential of Monoclonal Antibodies and Other Biologics in Combating MDR Infections

Monoclonal Antibodies (mAbs) and other biologics have emerged as promising therapeutic tools for combating MDR infections. Unlike conventional antibiotics, which target bacterial cells, monoclonal antibodies target specific compo-

Table 2. Host-directed therapies targeting MDRB.

HDT Type	Mechanism	Pathogen Target(s)	Clinical Stage
IFN-γ (Interferon-gamma) [25]	Macrophage activation, enhanced phagocytosis	*M. tuberculosis*, MDR pathogens	Phase II (NCT02735707)
GM-CSF [18]	Stimulates granulocyte/macrophage production	Broad, especially immunocompromised	Investigational
Anti-PD-1 (Checkpoint inhibitor) [20]	Reverses immune exhaustion	Chronic infections, MDR TB	Experimental/Off-label
Vitamin D Supplementation [21]	Enhances innate immunity *via* cathelicidin expression	*M. tuberculosis*, Gram-positive	Clinical (adjuvant)
IL-7 [23]	T-cell homeostasis and expansion	Sepsis, MDR infections	Early-phase trials

nents of the immune system or bacterial virulence factors, enhancing the host's ability to fight infections. Several monoclonal antibodies have been developed to target bacterial toxins, immune checkpoints [23], and pathogen-associated molecular patterns.

One example is the use of monoclonal antibodies to neutralize bacterial toxins. Toxins produced by bacteria such as *Staphylococcus aureus* and *Clostridium difficile* can cause significant damage to host tissues and contribute to disease severity. Monoclonal antibodies that specifically bind to and neutralize these toxins can prevent tissue damage and improve patient outcomes. For instance, bezlotoxumab, a monoclonal antibody that targets *C. difficile* toxin B [24], has been approved for the prevention of recurrent *C. difficile* infection, a common complication in hospitalized patients.

In addition to targeting toxins, monoclonal antibodies can also be used to enhance immune cell function. For example, monoclonal antibodies that block immune checkpoints, such as PD-1 or CTLA-4, can enhance the activity of T cells and other immune cells, improving the host's ability to clear infections. These immune checkpoint inhibitors, which have been successfully used in cancer immunotherapy, are now being explored for their potential to treat MDR infections.

Other biologics, such as cytokine-based therapies, are also being developed to boost the host immune response. For example, Interferon-gamma (IFN-γ) therapy has been shown to enhance the immune response against intracellular bacteria such as *Mycobacterium tuberculosis*. By promoting the activation of macrophages and enhancing their ability to kill bacteria, IFN-γ therapy has the potential to improve outcomes in patients with difficult-to-treat infections.

Host-directed therapies represent a novel approach to combating multidrug-resistant bacteria by boosting the host's immune response rather than directly targeting the pathogens. By enhancing immune cell function, modulating cytokine production, and manipulating immune pathways, these therapies can provide an effective complement to traditional antimicrobial treatments. Pharmacological interventions such as statins and monoclonal antibodies have shown promise in reducing infection-related complications and enhancing the host's ability to clear resistant pathogens. As research in this field continues to advance, host-directed therapies may play an increasingly important role in addressing the global challenge of antibiotic resistance.

5.4.1. Clinical Translation and Challenges of Host-Directed Therapies

While Host-Directed Therapies (HDTs) offer an innovative approach to combating multidrug-resistant bacteria by enhancing the host's immune response, their clinical application remains largely investigational. Cytokine-based treatments such as Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and Interferon-gamma (IFN-γ) have demonstrated immunostimulatory effects that enhance macrophage function and bacterial clearance in preclinical models and select clinical settings. Clinical trial NCT02735707 [25] enrolled 32 immunocompromised patients, with a sample size calculated to detect a $\geq 20\%$ change in macrophage activity markers with 90% confidence. Outcomes were analyzed using paired t-tests for within-subject changes and repeated-measures ANOVA to assess longitudinal immune response trends, which is appropriate for time-course cytokine data. In preclinical HDT studies using murine models, survival curves were compared using Kaplan–Meier analysis with log-rank testing, allowing evaluation of treatment timing and host response. In parallel, immune checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4 inhibitors, which are already FDA-approved for cancer, are now under investigation for their potential to reverse immune exhaustion during severe infections. Despite this promise, several hurdles impede their clinical adoption for bacterial diseases. First, inter-individual variability in immune response complicates dose optimization and patient selection. Second, immune hyperactivation risks cytokine storms, especially in critically ill patients, necessitating cautious use and intensive monitoring. Third, biologics like monoclonal antibodies are expensive to produce and distribute, making them less feasible in low-resource settings. To date, no HDTs have been approved for MDR bacterial infections, despite their success in oncology and certain infectious diseases, such as tuberculosis, underscoring a critical gap between research promise and clinical application.

6. NOVEL ANTIMICROBIALS AND COMBINATION THERAPIES

As Multidrug-Resistant Bacteria (MDRB) continue to undermine the efficacy of conventional antibiotics, there is an urgent need to develop novel antimicrobial agents and combination therapies. These approaches aim to overcome

Table 3. Novel antibiotics for MDRB approved or in development.

Antibiotic	Class/Mechanism	Target Pathogens	Clinical Stage / Approval
Cefiderocol [16]	Siderophore cephalosporin	CRE, *P. aeruginosa*, *A. baumannii*	FDA approved (2019)
Eravacycline [26]	Fluorocycline (protein synthesis inhibitor)	ESBL-producing Enterobacteriaceae, *A. baumannii*	FDA approved (2018)
Delafloxacin [16]	Anionic fluoroquinolone	MRSA, *S. pneumoniae*, *E. coli*	FDA approved (2017)
Plazomicin [16]	Next-gen aminoglycoside	CRE, aminoglycoside-resistant strains	FDA approved (2018)
Zoliflodacin [18]	Spiropyrimidinetrione (GyrB inhibitor)	*N. gonorrhoeae* (resistant strains)	Phase III trials

resistance mechanisms, extend the lifespan of existing antibiotics, and provide effective treatment options for infections caused by highly resistant pathogens. In this section, we will explore the development of new antibiotics and drug classes, focusing on those recently approved by regulatory agencies, such as Cefiderocol and Eravacycline [26]. Additionally, we will examine the potential of combination therapies in addressing resistant infections and the challenges associated with developing these therapeutic approaches.

6.1. New Antibiotics and Drug Classes

The discovery and approval of new antibiotics are crucial in the fight against MDRB. However, the development pipeline for antibiotics has historically lagged behind other areas of drug discovery due to scientific, economic, and regulatory hurdles. Nevertheless, some promising agents have recently emerged that target critical drug-resistant bacteria, providing new hope for effective treatment shown in Table **3**.

6.1.1. Cefiderocol: A Trojan Horse Against Gram-Negative Pathogens

Cefiderocol is a novel siderophore cephalosporin antibiotic that was approved by the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of complicated Urinary Tract Infections (cUTI) caused by Gram-negative bacteria, including Carbapenem-Resistant *Enterobacteriaceae* (CRE) and *Pseudomonas aeruginosa*. Cefiderocol's unique mechanism of action allows it to overcome several resistance mechanisms common in Gram-negative pathogens.

Cefiderocol acts as a "Trojan horse [27]," exploiting the iron uptake mechanisms of bacteria. It binds to iron and is actively transported into bacterial cells *via* iron transport channels. Once inside, it inhibits cell wall synthesis by binding to Penicillin-Binding Proteins (PBPs) [28], similar to other cephalosporins. However, its ability to enter bacterial cells through these iron channels gives it an advantage over other antibiotics that are blocked by efflux pumps or porin mutations. This novel mechanism allows Cefiderocol to remain effective against Gram-negative bacteria that have developed resistance to many β-lactams, including carbapenems. As such, Cefiderocol represents a significant advancement in the treatment of difficult-to-treat Gram-negative infections.

6.1.2 Eravacycline: A Tetracycline for Resistant Infections

Eravacycline, another FDA-approved antibiotic, is a synthetic fluorocycline that belongs to the tetracycline class. Approved in 2018 for the treatment of complicated Intra-Abdominal Infections (cIAIs), Eravacycline is effective against a broad spectrum of Gram-positive and Gram-negative pathogens, including MDR strains such as Extended-Spectrum β-Lactamase (ESBL)-producing *Enterobacteriaceae* and *Acinetobacter baumannii* [29].

Eravacycline works by inhibiting bacterial protein synthesis by binding to the 30S ribosomal subunit. One of its key advantages is that it remains active against many pathogens that have developed resistance to other tetracyclines, such as doxycycline and minocycline. It is particularly effective against drug-resistant *Acinetobacter baumannii*, which is a critical priority pathogen due to its role in hospital-acquired infections, especially in intensive care units.

The introduction of Cefiderocol and Eravacycline highlights the continued innovation in antibiotic development, particularly in addressing the growing threat of Gram-negative pathogens. However, while these new agents provide much-needed treatment options, their widespread use must be carefully managed to prevent the rapid emergence of resistance, as has been observed with previous antibiotics.

6.1.2.1. Combination Therapies

In addition to the development of novel antibiotics, combination therapies offer a powerful approach to overcoming bacterial resistance. By combining two or more antimicrobial agents, it is possible to target multiple resistance mechanisms simultaneously, thereby enhancing the overall efficacy of treatment. Combination therapies are particularly useful against MDRB, where monotherapy often fails due to the bacteria's ability to neutralize individual drugs.

6.1.2.2. Clinical Implementation and Limitations of Novel Antimicrobials

The recent approval of novel antibiotics such as Cefiderocol and Eravacycline represents significant progress in combating Multidrug-Resistant (MDR) bacterial infections. Cefiderocol, a siderophore cephalosporin, was approved by the FDA in 2019 for complicated Urinary Tract Infections (cUTIs) and hospital-acquired infections caused by Gram-negative pathogens, including Carbapenem-Resistant Enterobacteriaceae (CRE). Clinical trials such as APEKS-NP (NCT03032380) [30] enrolled 292 patients, with a power calculation aimed to demonstrate non-inferiority with a margin of 12.5% and 80% statistical power. Primary outcomes were analyzed using logistic regression models, adjusting for baseline infection severity. Non-inferiority was evaluated by two-sided 95% confidence in-

tervals for the difference in clinical cure rates. Survival analyses and adverse event frequencies were compared using Chi-square tests and Cox proportional hazards models, appropriate for categorical and time-to-event data, while the CREDIBLE-CR trial (NCT02714595) [31] confirmed its efficacy against highly resistant strains, though with slightly higher all-cause mortality in some patient subgroups. Similarly, Eravacycline, a fluorocycline antibiotic approved in 2018, demonstrated favorable outcomes in the IGNITE1 and IGNITE4 trials for complicated intra-abdominal infections, especially against MDR *Acinetobacter baumannii* and ESBL-producing *Enterobacteriaceae*. However, post-marketing surveillance has reported emerging resistance to Cefiderocol, particularly due to mutations in β-lactamase genes such as NDM and PER. Moreover, both antibiotics are linked to high acquisition costs, making them less accessible in low- and middle-income countries. While these agents broaden the therapeutic arsenal, their long-term success will depend on antibiotic stewardship programs, ongoing resistance surveillance, and global pricing and access initiatives.

6.2. Benefits of Combinatorial Approaches.

One of the most promising applications of combination therapy is in the treatment of Carbapenem-Resistant *Enterobacteriaceae* (CRE). CRE infections are notoriously difficult to treat because these bacteria produce carbapenemase enzymes that degrade carbapenem antibiotics, rendering them ineffective. However, studies have shown that pairing polymyxins (such as colistin) with carbapenems, such as meropenem, can significantly enhance treatment efficacy.

Polymyxins, including colistin, disrupt the bacterial outer membrane, increasing its permeability. This makes it easier for other antibiotics, such as meropenem, to penetrate the bacterial cell and exert their effects. Additionally, carbapenems can inhibit the synthesis of bacterial cell walls, creating a synergistic effect when combined with polymyxins. This combination has been shown to improve clinical outcomes in patients with CRE infections, especially in cases where carbapenems alone have failed.

Another example of an effective combination is the pairing of β-lactam antibiotics with β-lactamase inhibitors, such as tazobactam or clavulanic acid. β-lactamase inhibitors work by inhibiting the enzymes that bacteria produce to degrade β-lactam antibiotics, thereby restoring the efficacy of the antibiotic. Combination therapies using piperacillin-tazobactam or amoxicillin-clavulanate have proven effective against a range of resistant pathogens, including ESBL-producing *Enterobacteriaceae* [32].

Combination therapies also hold promise for treating biofilm-associated infections, which are particularly difficult to eradicate due to the protective nature of the biofilm matrix. By using antibiotics that target different aspects of bacterial metabolism or biofilm formation, combination therapies can penetrate biofilms more effectively and prevent the bacteria from developing further resistance.

6.3. Challenges in Developing Combination Treatments

Despite the potential benefits of combination therapies, developing effective combinations poses several challenges. One of the primary challenges is the risk of antagonism, where the combined effect of two drugs is less than the effect of either drug alone. This can occur if the drugs interfere with each other's mechanisms of action, or if one drug induces bacterial stress responses that reduce the efficacy of the other drug.

Another challenge is the development of resistance to both drugs in the combination. Bacteria can rapidly adapt to selective pressures, and the use of combination therapies could lead to the emergence of strains that are resistant to multiple drugs simultaneously. This has been observed in some cases of combination therapy involving colistin, where bacteria have developed resistance to both colistin and the co-administered carbapenem, leaving few treatment options available.

Furthermore, the pharmacokinetics and pharmacodynamics of combination therapies can be difficult to optimize. The drugs used in combination must have compatible dosing regimens and should achieve therapeutic concentrations at the infection site without causing excessive toxicity. Determining the appropriate dosages and schedules for combination therapies often requires extensive clinical trials, which can be costly and time-consuming.

Finally, regulatory challenges may also hinder the development of combination therapies. Approving a combination of two or more existing drugs requires demonstrating that the combination is both safe and more effective than the individual drugs alone, which adds complexity to the approval process.

The emergence of novel antibiotics, such as Cefiderocol and Eravacycline, and the increasing use of combination therapies provide hope in the fight against multidrug-resistant bacteria. These new strategies offer much-needed treatment options for infections caused by critical pathogens like CRE and *Acinetobacter baumannii*. However, the development and deployment of these therapies must be approached cautiously, as the risk of resistance development remains high. Combination therapies, in particular, offer significant promise for enhancing the efficacy of existing antibiotics but also present unique challenges, including the potential for antagonism, resistance, and pharmacokinetic complications. Continued innovation and careful management of these therapies will be essential to combat the growing threat of MDRB.

New antibiotics like Cefiderocol offer hope against MDRB, especially Gram-negatives. Yet resistance to these drugs is already emerging, and high development costs paired with limited commercial incentives reduce pharmaceutical investment. Combination therapies show promise, but pharmacokinetic mismatches and lack of comprehensive clinical data limit their optimization.

7. PHYTOCHEMICALS AND NATURAL PRODUCTS

In the quest to combat Multidrug-Resistant Bacteria (MDRB), the discovery of new antimicrobial agents is a pressing need. Phytochemicals, bioactive compounds derived from plants, have garnered increasing attention as potential sources of new antimicrobial agents. These compounds, often secondary metabolites, have been shown to exhibit significant antibacterial properties, making them

Table 4. Synergistic phytochemical-antibiotic combinations against MDRB.

Phytochemical	Antibiotic Partner	Target Pathogens	Synergistic Mechanism
Curcumin [43]	Ciprofloxacin	*S. aureus*, *E. coli*	Inhibits efflux pumps, enhances DNA damage
Gingerol [44]	Tetracycline	*P. aeruginosa*, *S. aureus*	Membrane disruption, anti-efflux activity
Eugenol [45]	Ampicillin	*E. coli*, *K. pneumoniae*	Cell wall destabilization, increased permeability
Berberine [43]	Azithromycin	*MRSA*, *E. coli*	Inhibits multidrug efflux transporters
Carvacrol [44]	Chloramphenicol	*S. typhi*, *P. aeruginosa*	Disrupts membrane integrity, enhances uptake

promising candidates in the fight against resistant pathogens. Additionally, the synergistic effects of phytochemicals with conventional antibiotics offer an exciting avenue to enhance the efficacy of existing drugs. This section will explore the role of plant-derived compounds, such as *Zingiber officinale* (ginger) [33] and *Vernonia auriculifera* [34], in combating MDRB, as well as the potential for phytochemical-antibiotic combinations to overcome bacterial resistance.

7.1. Plant-Derived Compounds

Plants have long been used in traditional medicine for their antimicrobial properties, and modern science has begun to validate the efficacy of many plant-derived compounds against a broad spectrum of pathogens. Phytochemicals such as alkaloids, flavonoids, terpenoids, tannins, and phenolic compounds often serve as the plant's defense mechanisms against microbial invasion. Many of these secondary metabolites are now being studied for their potential to address the growing threat of antimicrobial resistance shown in Table **4**.

7.1.1. Zingiber Officinale (Ginger)

Zingiber officinale [35], commonly known as ginger, is a well-known medicinal plant with a long history of use in both culinary and therapeutic contexts. The rhizome of the ginger plant contains several bioactive compounds, including gingerol, shogaol, and paradol, which are known for their anti-inflammatory, antioxidant, and antimicrobial properties.

Studies have shown that ginger extracts exhibit broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria, including MDR strains. For example, 6-gingerol, the major phenolic component of ginger, has demonstrated potent antibacterial effects against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The antimicrobial activity of ginger is thought to stem from its ability to disrupt bacterial cell membranes, leading to increased permeability and causing leakage of intracellular components, ultimately resulting in cell death. Gingerol and its derivatives also appear to inhibit bacterial quorum sensing, a communication mechanism that bacteria use to regulate biofilm formation and virulence. This property makes ginger particularly effective at preventing the formation of biofilms, which are a major contributor to antibiotic resistance.

7.2. Vernonia Auriculifera

Another promising plant with significant antimicrobial potential is *Vernonia auriculifera*, an herbaceous plant commonly found in tropical and subtropical regions. In traditional medicine, *Vernonia* species have been used to treat various infections, including bacterial and fungal diseases. The antimicrobial properties of *Vernonia auriculifera* are attributed to its diverse array of secondary metabolites, including sesquiterpene lactones, flavonoids, and polyphenols.

Research has demonstrated that extracts from *Vernonia auriculifera* are effective against a wide range of MDR pathogens, including *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. Sesquiterpene lactones [36], such as vernolide and vernodalol, are believed to be the primary active components responsible for the plant's antimicrobial activity. These compounds interfere with bacterial protein synthesis and disrupt cellular metabolic processes, leading to bacterial death. *Vernonia* extracts also exhibit strong antioxidant properties, which may contribute to their ability to reduce oxidative stress in infected tissues, thereby enhancing the host's immune response to bacterial infections.

7.2.1. Synergy with Conventional Antibiotics

One of the most promising aspects of phytochemicals in antimicrobial therapy is their ability to act synergistically with conventional antibiotics. Combining plant-derived compounds with existing antibiotics can enhance their efficacy, reduce the dosage required, and potentially reverse resistance in MDR pathogens. This synergistic approach holds great promise in addressing the challenges posed by antibiotic resistance, as shown in Fig. (**2**) [37].

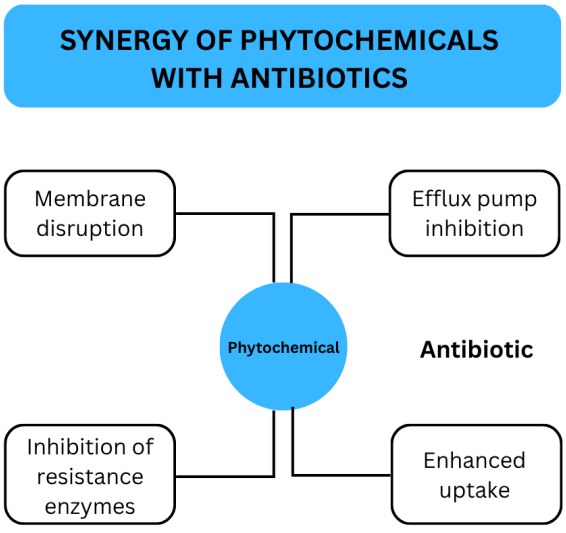

Fig. (2). Synergy of Phytochemicals with Antibiotics.

7.3. Examples of Successful Phytochemical-Antibiotic Combinations

Numerous studies have explored the potential of phytochemical-antibiotic combinations, revealing promising results in combating resistant strains of bacteria. One notable example is the combination of ginger extracts with commonly used antibiotics, such as ciprofloxacin and ampicillin. Studies have shown that gingerol enhances the antibacterial activity of these antibiotics against resistant strains of *Escherichia coli* and *Staphylococcus aureus*. This synergistic effect is thought to result from gingerol's ability to increase bacterial membrane permeability, allowing antibiotics to penetrate bacterial cells more effectively. Additionally, the inhibition of biofilm formation by gingerol further contributes to the enhanced efficacy of the antibiotic.

Another example is the combination of *Vernonia auriculifera* extracts with tetracycline, an antibiotic commonly used to treat bacterial infections. Research has demonstrated that this combination exhibits enhanced bactericidal activity against resistant strains of *Klebsiella pneumoniae* and *Acinetobacter baumannii*. The sesquiterpene lactones present in *Vernonia* extracts appear to inhibit bacterial efflux pumps, which are one of the key mechanisms by which bacteria expel antibiotics and develop resistance. By inhibiting these pumps, the plant extract enhances the intracellular concentration of tetracycline, making it more effective against resistant bacteria.

7.4. Potential in Overcoming Resistance

The potential for phytochemical-antibiotic combinations to overcome resistance lies in the ability of plant-derived compounds to target multiple bacterial processes simultaneously. Unlike conventional antibiotics, which typically target a single bacterial pathway (*e.g.*, cell wall synthesis [38], protein synthesis [39]), phytochemicals often have multiple mechanisms of action. This makes it more difficult for bacteria to develop resistance to phytochemical-antibiotic combinations, as they would need to acquire multiple resistance mechanisms simultaneously.

For instance, phenolic compounds such as flavonoids and tannins have been shown to enhance the activity of β-lactam antibiotics against resistant *Enterobacteriaceae* by disrupting the bacterial cell membrane and inhibiting β-lactamase enzymes [40]. Similarly, terpenoids such as those found in *Vernonia auriculifera* can inhibit bacterial quorum sensing, making it harder for bacteria to form biofilms and communicate, which are key factors in antibiotic resistance.

Moreover, the use of phytochemical-antibiotic combinations may reduce the risk of toxicity associated with high doses of antibiotics. By enhancing the efficacy of antibiotics, phytochemicals allow for lower doses to be used, potentially reducing side effects and minimizing impact on beneficial gut microbiota.

Phytochemicals and natural products offer a valuable and underexplored resource in the fight against multidrug-resistant bacteria. Plant-derived compounds such as those from *Zingiber officinale* and *Vernonia auriculifera* have demonstrated significant antimicrobial activity, both as standalone agents and in combination with conventional antibiotics. The synergistic effects of these phytochemicals with antibiotics offer a promising strategy to overcome resistance, reduce the required antibiotic dosage, and enhance overall treatment efficacy. As the threat of antibiotic resistance continues to grow, further research into the therapeutic potential of phytochemicals, particularly in combination with antibiotics, is essential to developing more effective and sustainable antimicrobial therapies [41].

7.5.Clinical Translation and Challenges of Phytochemicals

Although plant-derived compounds such as gingerol from *Zingiber officinale* and sesquiterpene lactones from *Vernonia auriculifera* have demonstrated potent *in vitro* activity against MDR bacteria, no phytochemical has yet received FDA or EMA approval for use as an antimicrobial agent. Most phytochemicals remain in preclinical development, with only a few entering early-phase human trials. For example, curcumin—widely studied for its antimicrobial and anti-inflammatory properties—is being evaluated for its therapeutic role in infected wounds and inflammation in trials like NCT04769772 [42], although not specifically for MDR infections. The major obstacle to clinical translation is the lack of extract standardization, as the bioactive composition of herbal formulations can vary by geography, harvest time, and processing method. Moreover, many phytochemicals suffer from low oral bioavailability, rapid metabolism, and poor aqueous solubility, limiting their therapeutic concentrations *in vivo*. While compounds like gingerol and curcumin are generally regarded as safe and show low systemic toxicity, their instability under physiological conditions and short plasma half-life pose significant formulation and dosing challenges. Additionally, clinical trials directly assessing phytochemicals in MDR infections are lacking, making efficacy claims difficult to substantiate. Moving forward, nanoparticle delivery systems, synthetic analogues, and purified compound formulations may help overcome these barriers and enable phytochemicals to reach regulatory and clinical benchmarks for antimicrobial use [43].

Phytochemicals offer a rich source of antimicrobial agents and synergize well with antibiotics. However, challenges such as batch-to-batch variability, poor bioavailability, and lack of regulatory frameworks hinder their clinical translation. Few have reached human trials, and standardization remains a major bottleneck.

8. FUTURE DIRECTIONS AND CHALLENGES.

Despite recent progress, the fight against Multidrug-Resistant Bacteria (MDRB) requires continuous innovation and diversified strategies. Several promising research areas are emerging that could redefine antimicrobial therapy. Notably, bacteriophage therapy offers a precision approach that selectively targets MDR strains without disrupting the host microbiome. Similarly, CRISPR-Cas-based antimicrobials are being engineered to directly disable resistance genes. Artificial Intelligence (AI) is increasingly being used to screen novel antimicrobial compounds and optimize drug repurposing, accelerating discovery timelines. Other innovations include biofilm-targeted nanoparticles and stimuli-responsive delivery systems designed to release drugs at infection sites [43].

However, critical challenges remain unresolved. The adaptive evolution of bacterial resistance continues to outpace drug development, even affecting newly approved antibiotics like cefiderocol. The lack of rapid, point-of-care diagnostics contributes to empiric overuse of broad-spectrum agents. Regulatory ambiguity persists for novel treatment modalities, such as nanomedicines and host-directed therapies, slowing their clinical translation, as shown in Fig. (**3**). Additionally, insufficient pharmaceutical investment in antimicrobial R&D, especially in Low- and Middle-Income Countries (LMICs), limits global preparedness.

Future research must bridge these gaps through interdisciplinary collaboration, translational pipelines, and supportive policy environments to ensure promising therapies reach clinical use efficiently and equitably [44, 45].

8.1. Importance of Developing Technologies in Response to Evolving Resistance

The dynamic nature of bacterial evolution necessitates continuous research and development of novel antimicrobial technologies. MRB has demonstrated an extraordinary capacity to develop resistance to nearly every class of antibiotics, often within a few years of their introduction to clinical practice. As a result, the development of new therapeutic strategies must be a continuous process, as no single approach will be sufficient to overcome the ongoing threat of resistance.

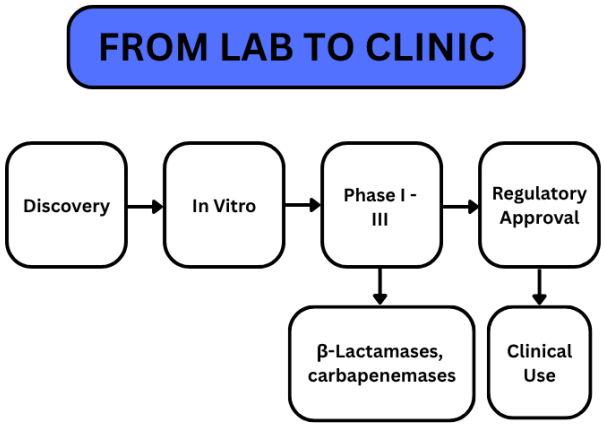

Fig. (3). Clinical translation roadmap: Lab to Clinic.

Recent advances in fields such as nanotechnology, host-directed therapies [46], and combination treatments have provided promising alternatives to traditional antibiotics. For example, nanoparticles offer novel mechanisms of action that bypass traditional resistance pathways, while host-directed therapies aim to enhance the immune system's ability to combat infections rather than targeting the bacteria directly. However, bacterial pathogens will likely continue to evolve in response to these new strategies, making it imperative to stay ahead of this evolutionary arms race.

Ongoing research is essential for identifying novel drug targets, understanding molecular mechanisms of resistance [47], and developing therapies that either restore the efficacy of existing antibiotics or provide new ways to eradicate resistant bacteria. This research must not only focus on discovering new compounds but also on enhancing drug delivery systems, exploring combinatorial approaches, and investigating how non-antibiotic treatments can be integrated into existing treatment paradigms.

8.2. Current Gaps in Translating Strategies from Research to Clinical Practice

Despite the promise of many emerging technologies, there are notable gaps in translating these innovations from the research stage to clinical practice. One significant challenge lies in the lengthy and complex process of advancing a therapeutic approach from preclinical studies to human trials and, eventually, to clinical use. Many promising strategies remain in the experimental phase, and few have been approved for widespread use in clinical settings.

For example, while nanoparticle-based therapies have demonstrated efficacy in laboratory studies, concerns remain about their safety, stability, and long-term effects in humans. The potential toxicity of certain nanoparticles and their accumulation in tissues or the environment pose serious concerns that must be addressed before these therapies can be widely implemented. Similarly, host-directed therapies, though promising, face challenges related to individual variability in immune responses, which complicates the development of standardized treatments.

Another significant gap lies in the infrastructure for clinical trials. Testing new antimicrobial agents [46], particularly for MDRB, requires specialized facilities and patient populations that can support rigorous clinical testing. Moreover, the heterogeneity of bacterial infections and the emergence of resistance across different geographical regions make it difficult to design trials that can generate universally applicable data.

8.3. Challenges in Regulatory Approval, Manufacturing Costs, and Accessibility

The path to regulatory approval for new antimicrobial therapies is fraught with challenges. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) [48] and the European Medicines Agency (EMA) [49], require extensive evidence of a drug's safety and efficacy before approval. This process is often time-consuming and expensive, particularly for antimicrobial drugs, which must undergo rigorous testing to ensure they do not contribute to further resistance. This is especially true for combination therapies, where each component must be individually tested and proven to contribute to the overall effectiveness without causing adverse interactions.

Manufacturing costs also pose a significant barrier to the widespread adoption of new technologies. Nanoparticle-based treatments, for example, require complex production processes that can be prohibitively expensive at scale. Additionally, the cost of raw materials for biologics, such as monoclonal antibodies used in host-directed therapies, can drive up the price of treatments, making them inaccessible to lower-income populations or healthcare systems with limited resources.

Accessibility is another pressing issue. Many of the countries most affected by MDRB, particularly in low- and middle-income regions [50], lack the healthcare infrastruc-

Table 5. Challenges and future directions in combating MDRB.

Challenge	Description	Proposed Solutions
Antibiotic resistance evolution [16]	Rapid genetic adaptation of pathogens to evade drugs	Stewardship programs, surveillance networks
Lack of new antibiotics [18]	Decline in antibiotic discovery and R&D investment	Incentivize pharma, public–private partnerships
Regulatory barriers for new agents [13]	Lack of clear frameworks for novel therapies (*e.g.*, nanomedicines)	Streamlined regulatory pathways, adaptive trial designs
Poor clinical translation of alternatives [25]	Limited human trial data for HDTs, phytochemicals, and nanoparticles	Robust toxicological studies, clinical validation
Cost and accessibility [23]	High cost of novel drugs and biologics limits global access	Tiered pricing, global access programs

ture and financial resources to implement advanced therapies. Even if new treatments are approved, ensuring they are available and affordable in these regions remains a significant challenge. This disparity in access exacerbates the global burden of antimicrobial resistance, as infections continue to spread unchecked in parts of the world where new treatments are most needed.

8.4. The Role of Global Collaboration and Funding in Advancing Technologies

Overcoming implementation barriers requires a concerted global effort involving governments, pharmaceutical companies, academic institutions, and international organizations. Collaboration on a global scale is essential for pooling resources, sharing knowledge, and ensuring that advances in antimicrobial therapies are widely accessible.

One of the key drivers of progress is funding. Governments and international organizations, such as the World Health Organization (WHO) [51] and the Global Antibiotic Research and Development Partnership (GARDP) [52], play a critical role in financing research into new antimicrobial treatments. These organizations can help bridge the funding gap for early-stage research and clinical trials, enabling the development of new therapies that might not otherwise receive sufficient investment from the private sector. Public-private partnerships also offer a promising model for leveraging the strengths of both sectors to accelerate the development of novel antibiotics and alternative treatments.

Additionally, international collaboration is crucial for addressing regulatory challenges. Harmonizing regulatory frameworks across countries can streamline the approval process for new antibiotics and ensure that these therapies are available to patients more quickly. Collaborative efforts to establish global clinical trial networks can also help generate the data needed to support regulatory approval and identify the most effective therapies for different populations [53].

Finally, global initiatives aimed at improving access to essential medicines must be a priority. Equitable distribution of new treatments, particularly to regions where MDRB are most prevalent, will be critical to mitigating the global threat posed by antibiotic resistance. This requires not only financial investment but also the development of innovative delivery models that can overcome logistical challenges in resource-limited settings.

The future of combating multidrug-resistant bacteria lies in continuous research and innovation, coupled with effective translation of new technologies from the laboratory to the clinic. While promising advances such as nanotechnology, host-directed therapies, and phytochemical-antibiotic combinations show great potential, significant challenges remain in terms of regulatory approval, manufacturing costs, and ensuring global accessibility. Addressing these challenges will require sustained global collaboration and funding, as well as innovative approaches to regulatory processes and clinical trial infrastructure. Only through concerted efforts across the scientific, regulatory, and healthcare communities can we hope to meet the evolving threat of antibiotic resistance shown in Table **5**.

9. LIMITATIONS

This review is a synthesis of published findings and does not include primary experimental data. While it aims to provide a comprehensive overview of emerging therapeutic strategies against Multidrug-Resistant Bacteria (MDRB), its conclusions are inherently limited by the scope and quality of the referenced literature.

The clinical translation of nanotechnology-based therapies, particularly metal nanoparticles, remains largely unvalidated in large-scale, randomized clinical trials. Preclinical success does not always translate into human efficacy due to factors such as cytotoxicity, bioaccumulation, and regulatory uncertainties [54].

In the case of phytochemicals, the high variability in extract composition, limited pharmacokinetic data, and absence of standardized formulations significantly impact reproducibility and clinical reliability. Furthermore, most data are limited to in vitro or small-animal models.

Host-Directed Therapies (HDTs), although promising in concept, face challenges related to inter-individual immune variability, which complicates both the design and generalizability of clinical trials. Safety risks such as immune overactivation and the high cost of biologics further limit their immediate applicability in resource-limited settings.

Finally, the rapid and evolving nature of antimicrobial resistance presents a moving target for researchers. Conclusions drawn from current data may become outdated as new resistance mechanisms and clinical outcomes emerge [55].

CONCLUSION

The rising threat of Multidrug-Resistant Bacteria (MDRB) demands an integrated and forward-looking therapeutic approach. This review has examined a wide range of emerging strategies from nanotechnology and host-directed therapies to phytochemicals and novel antimicrobials, each offering unique strengths and encountering specific limitations. While clinical advances like cefiderocol and eravacycline mark important milestones, most alternatives remain in early development due to toxicity concerns, regulatory inertia, or translational gaps.

Actionable insights point to the benefits of combination therapies, such as phytochemicals enhancing antibiotic efficacy or nanoparticles improving drug delivery. To transition these innovations from the lab to the clinic, establishing antimicrobial stewardship programs, global resistance monitoring, and affordable access models is essential.

Pathways to implementation include fostering Public–Private Partnerships (PPPs) that de-risk early-stage development, introducing regulatory reforms to accommodate non-traditional agents, and expanding local production capacities in underserved regions. Encouraging policies that incentivize antibiotic innovation while ensuring equitable access can help balance public health and market sustainability.

Ultimately, tackling MDRB will require a multifaceted strategy that blends scientific innovation with policy coordination and public health investment. Cross-sector collaboration between researchers, industry, regulators, and global health agencies is vital to convert emerging discoveries into durable, accessible treatments for resistant infections worldwide.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

GARDP	=	Global Antibiotic Research and Development Partnership
HDTs	=	Host-Directed Therapies
MDRB	=	Multidrug-Resistant Bacteria
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Ketebo, A.A.; Din, S.U.; Lee, G.; Park, S. Mechanobiological analysis of nanoparticle toxicity. *Nanomaterials,* **2023**, *13*(10), 1682. http://dx.doi.org/10.3390/nano13101682 PMID: 37242097

[2] Ali, M. What function of nanoparticles is the primary factor for their hyper-toxicity? *Adv. Colloid Interface Sci.,* **2023**, *314*, 102881. http://dx.doi.org/10.1016/j.cis.2023.102881 PMID: 36934512

[3] Kakakhel, M.A.; Jamil, A.; Narwal, N. Effects of silver nanoparticles on Ctenopharyngodon idella: Synthesis, characterization, antibacterial activity, and toxicological assessment. *Microsc. Res. Tech.,* **2024**. PMID: 39535459

[4] Ahmadi, M.; Ayyoubzadeh, S.M.; Ghorbani-Bidkorpeh, F. Toxicity prediction of nanoparticles using machine learning approaches. *Toxicology,* **2024**, *501*, 153697. http://dx.doi.org/10.1016/j.tox.2023.153697 PMID: 38056590

[5] Vanivska, K.; Dianová, L.; Halo, M.; Štefunková, N.; Lenický, M.; Slanina, T.; Tirpák, F.; Ivanič, P.; Stawarz, R.; Massányi, P. Toxicity of nanoparticles on animal and human organism: Cell response. *J. Microbiol. Biotechnol. Food. Sci.,* **2024**, 10844. http://dx.doi.org/10.55251/jmbfs.10844

[6] Zahari, N.I.N.; Engku Abd Rahman, E.N.S.; Irekeola, A.A.; Ahmed, N.; Rabaan, A.A.; Alotaibi, J.; Alqahtani, S.A.; Halawi, M.Y.; Alamri, I.A.; Almogbel, M.S.; Alfaraj, A.H.; Ibrahim, F.A.; Almaghaslah, M.; Alissa, M.; Yean, C.Y. A review of the resistance mechanisms for *β*-lactams, macrolides and fluoroquinolones among *Streptococcus pneumoniae. Medicina,* **2023**, *59*(11), 1927. http://dx.doi.org/10.3390/medicina59111927 PMID: 38003976

[7] S, N.V.; S, R.I.R. Exploring the complexities of nanoparticle toxicity: A review of methodological approaches. *Proceedings of the 2024 International Conference on Sustainable Communication Networks and Application (ICSCNA),* Theni, India, 2024, pp. 189-196.. http://dx.doi.org/10.1109/ICSCNA63714.2024.10864012

[8] Sivan, G.; Pamanji, R.; Koigoora, S.; Joseph, N.; Selvin, J. In vivo toxicological assessment of silver nanoparticles in edible fish, Oreochromis mossambicus. *Toxicol. Res.,* **2024**, *13*(1)

[9] Khatun, Z.; Rahman, F.; Chowdhury, M.N.; Sultana, A. Antifungal resistance in *Candida* species: A bit from the totality. *J. Anti-Infect. Agents,* **2024**, *22*(3), 218.

[10] Rafiq, M.; Khan, M.; Hashim, S.; Ali, Z. Management of gingivitis: Contemporary approaches and recent therapeutic advancements. *J. Anti-Infect. Agents,* **2024**, *22*(2), 203.

[11] Sharma, N.; Kurmi, B.D.; Singh, D.; Mehan, S.; Khanna, K.; Karwasra, R.; Kumar, S.; Chaudhary, A.; Jakhmola, V.; Sharma, A.; Singh, S.K.; Dua, K.; Kakkar, D. Nanoparticles toxicity: An overview of its mechanism and plausible mitigation strategies. *J. Drug Target,* **2024**, *32*(5), 457-469. http://dx.doi.org/10.1080/1061186X.2024.2316785 PMID: 38328920

[12] Rodriguez-Monguio, R.; Seoane-Vazquez, E.; Powers, J.H. A comparative assessment of approvals and discontinuations of systemic antibiotics and other therapeutic areas. *Healthcare,* **2023**, *11*(12), 1759. http://dx.doi.org/10.3390/healthcare11121759 PMID: 37372877

[13] Parums, D.V. Editorial: First regulatory approvals for CRISPR-Cas9 therapeutic gene editing for sickle cell disease and transfusion-dependent β-thalassemia. *Med. Sci. Monit,* **2024**, *30*, 944204. http://dx.doi.org/10.12659/MSM.944204 PMID: 38425279

[14] Kayki-Mutlu, G.; Aksoyalp, Z.S.; Wojnowski, L.; Michel, M.C. A year in pharmacology: New drugs approved by the US Food and Drug Administration in 2023. *Naunyn Schmiedebergs Arch. Pharmacol.,* **2024**, *397*(5), 2949-2970. http://dx.doi.org/10.1007/s00210-024-03063-1 PMID: 38530400

[15] Sharma, R.; Ghosh, S.; Choudhury, A. Monkey pox: Virology, epidemiology, vaccines, and therapeutic approaches. *J. Anti-Infect. Agents,* **2023**, *21*(4), 180.
[16] Rahman, M.M.; Hossain, S.; Mahmud, S.; Ahmed, T. A review on emerging impact of antitubercular activity of 1,2,4-triazole derivatives. *J. Anti-Infect. Agents,* **2023**, *21*(4), 184.
[17] Singh, A.; Irfan, H.; Fatima, E.; Nazir, Z.; Verma, A.; Akilimali, A. Revolutionary breakthrough: FDA approves CASGEVY, the first CRISPR/Cas9 gene therapy for sickle cell disease. *Ann Med. Surg.,* **2024**, *86*(8), 4555-4559. http://dx.doi.org/10.1097/MS9.0000000000002146 PMID: 39118728
[18] Safety and pharmacokinetics of nb-001 for the treatment of wounds; NCT01239684. **2010**. Available from: https://clinicaltrials.gov/study/NCT01239684.
[19] Gholap, A.D.; Khuspe, P.R.; Pardeshi, S.R.; Uddin, M.J.; Das, U.; Hatvate, N.T.; Rojekar, S.; Giram, P.; Khalid, M.; Choonara, Y.E.; Faiyazuddin, M. Achieving optimal health with host-directed therapies (HDTs) in infectious diseases—a new horizon. *Adv. Ther.,* **2024**, *8*(4), 2400169. http://dx.doi.org/10.1002/adtp.202400169
[20] Ahmed, S. Challenges with newly approved CRISPR gene technologies. *Mol. Med. Commun,* **2023**, *3*(2), 85. http://dx.doi.org/10.55627/mmc.003.02.0455
[21] Papapetropoulos, A.; Topouzis, S.; Alexander, S.P.H.; Cortese-Krott, M.; Kendall, D.A.; Martemyanov, K.A.; Mauro, C.; Nagercoil, N.; Panettieri, R.A.; Patel, H.H.; Schulz, R.; Stefanska, B.; Stephens, G.J.; Teixeira, M.M.; Vergnolle, N.; Wang, X.; Ferdinandy, P. Novel drugs approved by the EMA, the FDA, and the MHRA in 2023: A year in review. *Br J. Pharmacol.,* **2024**, *181*(11), 1553-1575. http://dx.doi.org/10.1111/bph.16337 PMID: 38519837
[22] Atillasoy, C.; Elmansy, L.; Gourlias, P. 2512. A decade in review: An analysis of the Qualified Infectious Disease Product (QIDP) designation. *Open Forum Infect. Dis.,* **2023**, *10*(Suppl 2), ofad500.2130. http://dx.doi.org/10.1093/ofid/ofad500.2130
[23] Al Musaimi, O. FDA-approved antibacterials and echinocandins. *Antibiotics,* **2025**, *14*(2), 166. http://dx.doi.org/10.3390/antibiotics14020166 PMID: 40001410
[24] Davies, K.; Philippidis, A.; Barrangou, R. Five years of progress in CRISPR clinical trials (2019–2024). *CRISPR J.,* **2024**, *7*(5), 227-230. http://dx.doi.org/10.1089/crispr.2024.0081 PMID: 39436279
[25] *A Study of S-649266 (Cefiderocol) in Adult Subjects With Complicated Urinary Tract Infections, Including Pyelonephritis Clinicaltrialsgov Identifier: NCT02735707*; U.S. National Library of Medicine: Bethesda, MD, **2016**.
[26] Kim, M.B.; Lee, Y.J. Characterisation of the CRISPR-Cas systems in Enterococcus faecalis from commercial broiler farm environments and its association with antimicrobial resistance. *Br Poult Sci.,* **2025**, *66*(4), 523-530. http://dx.doi.org/10.1080/00071668.2025.2451268
[27] Kadkhoda, H.; Gholizadeh, P.; Samadi Kafil, H.; Ghotaslou, R.; Pirzadeh, T.; Ahangarzadeh Rezaee, M.; Nabizadeh, E.; Feizi, H.; Aghazadeh, M. Role of CRISPR-Cas systems and anti-CRISPR proteins in bacterial antibiotic resistance. *Heliyon,* **2024**, *10*(14), 34692. http://dx.doi.org/10.1016/j.heliyon.2024.e34692 PMID: 39149034
[28] Mayorga-Ramos, A.; Zúñiga-Miranda, J.; Carrera-Pacheco, S.E. CRISPR-Cas-based antimicrobials: Design, challenges, and resistance. *ACS Infect. Dis.,* **2023**, *9*, 1283-1302. http://dx.doi.org/10.1021/acsinfecdis.2c00649 PMID: 37347230
[29] Rafiq, M.S.; Shabbir, M.A.; Raza, A.; Irshad, S.; Asghar, A.; Maan, M.K.; Gondal, M.A.; Hao, H. CRISPR-Cas system: A new dawn to combat antibiotic resistance. *BioDrugs,* **2024**, *38*(3), 387-404. http://dx.doi.org/10.1007/s40259-024-00656-3 PMID: 38605260
[30] *Study to Evaluate the Efficacy and Safety of Plazomicin in Patients With Serious Infections Due to Carbapenem-Resistant Enterobacteriaceae (CRE)*; U.S. National Library of Medicine: Bethesda, MD, **2017**.
[31] *TANGO II: A Study of the Efficacy and Safety of Meropenem-Vaborbactam vs Best Available Therapy in Subjects With Serious Infections Due to Carbapenem-Resistant Enterobacteriaceae*; U.S. National Library of Medicine: Bethesda, MD, **2016**.
[32] Zhang, X.; Huang, Z.; Zhang, Y. Mitigating antibiotic resistance: CRISPR in detection. *Biosensors,* **2024**, •••, 14. PMID: 39727898
[33] Qiao, W.; Wang, L.; Luo, Y.; Yang, T. FDA-approved antibacterial agents (2003–2023): Synthesis and applications. *Eur J. Med. Chem.,* **2025**, *285*, 117267. http://dx.doi.org/10.1016/j.ejmech.2025.117267 PMID: 39808973
[34] Preethi, C.; Gopal, S. Unleashing CRISPR-Cas9 to combat antimicrobial resistance. *Indian J. Appl. Res.,* **2024**. http://dx.doi.org/10.36106/ijar/2301776
[35] Yang, J.; Zhang, J.; Feng, Z.; Ma, Y. The role and mechanisms of antimicrobial peptides in overcoming multidrug-resistant bacteria. *Molecules,* **2024**, *30*(1), 128. http://dx.doi.org/10.3390/molecules30010128 PMID: 39795190
[36] Taheri-Araghi, S. Synergistic action of antimicrobial peptides and antibiotics: Current understanding and future directions. *Front Microbiol.,* **2024**, *15*, 1390765. http://dx.doi.org/10.3389/fmicb.2024.1390765 PMID: 39144233
[37] Zhang, T.; Jin, Q.; Ji, J. Antimicrobial peptides and their mimetics: Promising candidates of next-generation therapeutic agents combating multidrug-resistant bacteria. *Adv. Biol.,* **2025**, *9*(4), 2400461. http://dx.doi.org/10.1002/adbi.202400461 PMID: 39913150
[38] Shaikh, R.; Singh, P.; Ansari, A.; Firdous, N. Fabrication of eucalyptus oil-loaded ciprofloxacin hydrochloride topical films for enhanced treatment of post-operative wound infection. *J. Anti-Infect. Agents,* **2023**, *21*(4), 176.
[39] Shang, L.; Chen, C.; Sun, R.; Guo, J.; Liu, J.; Wang, M.; Zhang, L.; Fei, C.; Xue, F.; Liu, Y.; Gu, F. Engineered peptides harboring cation motifs against multidrug-resistant bacteria. *ACS Appl. Mater. Interfaces,* **2024**, *16*(5), 5522-5535. http://dx.doi.org/10.1021/acsami.3c15913 PMID: 38266749
[40] Guo, X.; Miao, X.; An, Y.; Yan, T.; Jia, Y.; Deng, B.; Cai, J.; Yang, W.; Sun, W.; Wang, R.; Xie, J. Novel antimicrobial peptides modified with fluorinated sulfono-γ-AA having high stability and targeting multidrug-resistant bacteria infections. *Eur J. Med. Chem.,* **2024**, *264*, 116001. http://dx.doi.org/10.1016/j.ejmech.2023.116001 PMID: 38056301
[41] Hetta, H.F.; Sirag, N.; Alsharif, S.M.; Alharbi, A.A.; Alkindy, T.T.; Alkhamali, A.; Albalawi, A.S.; Ramadan, Y.N.; Rashed, Z.I.; Alanazi, F.E. Antimicrobial peptides: The game-changer in the epic battle against multidrug-resistant bacteria. *Pharmaceuticals,* **2024**, *17*(11), 1555. http://dx.doi.org/10.3390/ph17111555 PMID: 39598464
[42] *A Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Intravenous SPR206 in Hospitalized Adults With Complicated Urinary Tract Infections*; U.S. National Library of Medicine: Bethesda, MD, **2021**.
[43] Alam, M.; Farooqi, A.; Siddiqui, M.A.; Azmi, A.S. Phytochemicals as adjuvant therapies in RND efflux-mediated multidrug resistant *Pseudomonas aeruginosa* infections. *J. Anti-Infect. Agents,* **2024**, *22*(2), 198.
[44] Belaidi, M.; Bensalem, O.; Rachedi, K.; Harzallah, D. Methicillin, β-lactams, and clindamycin resistance profiles of *Staphylococcus aureus* strains isolated from patients with UTI in Bechar Province (Algeria). *J. Anti-Infect. Agents,* **2023**, *21*(3), 173.
[45] Kumar, D.; Sharma, P.; Jain, V.; Yadav, R. Cefradine Schiff bases and their metal salts as potential anti-infective agents. *J. Anti-Infect. Agents,* **2024**, *22*(3), 213.
[46] Salman, S.; Shaikh, M.; Yadav, K.; Nasir, M.; Abbas, Z. Antibiotic resistance in *Morganella morganii* species: Mechanisms, prevalence and clinical implication. *J. Anti-Infect. Agents,* **2024**, *22*(2), 207.
[47] Zhang, J.; Liu, M.; Guo, H.; Gao, S.; Hu, Y.; Zeng, G.; Yang, D. Nanotechnology-driven strategies to enhance the treatment of drug-resistant bacterial infections. *Wiley Interdiscip Rev. Nanomed Nanobiotechnol,* **2024**, *16*(3), 1968. http://dx.doi.org/10.1002/wnan.1968 PMID: 38772565
[48] Palucci, I.; Salustri, A.; De Maio, F.; Pereyra Boza, M.C.; Paglione, F.; Sali, M.; Occhigrossi, L.; D'Eletto, M.; Rossin, F.; Goletti, D.; Sanguinetti, M.; Piacentini, M.; Delogu, G. Cysteam-

ine/cystamine exert anti-Mycobacterium abscessus activity alone or in combination with amikacin. *Int. J. Mol. Sci.,* **2023**, *24*(2), 1203. http://dx.doi.org/10.3390/ijms24021203 PMID: 36674717

[49] Moghaddam, M.M.; Fazel, P.; Fallah, A. Host and pathogen-directed therapies using exosomes and antimicrobial peptide-derived stem cells: Focus on pulmonary infections and sepsis. *Stem Cell. Rev. Rep,* **2023**, *19*, 2166-2191. http://dx.doi.org/10.1007/s12015-023-10594-2 PMID: 37495772

[50] Taya, T.; Teruyama, F.; Gojo, S. Host-directed therapy for bacterial infections -Modulation of the phagolysosome pathway-. *Front Immunol.,* **2023**, *14*, 1227467. http://dx.doi.org/10.3389/fimmu.2023.1227467 PMID: 37841276

[51] Casas, C.G.; Shukla, A. Engineering immunomodulatory biomaterials to combat bacterial infections. *Front Biomater Sci.,* **2024**.

[52] Shapira, T.; Christofferson, M.; Av-Gay, Y. The antimicrobial activity of innate host-directed therapies: A systematic review. *Int. J. Antimicrob Agents,* **2024**, *63*(5), 107138. http://dx.doi.org/10.1016/j.ijantimicag.2024.107138 PMID: 38490573

[53] Han, J.F.; Lou, Q.; Ding, Z.Z.; Zheng, G.S.; Ni, Q.C.; Song, R.W.; Liu, K.K.; Zang, J.H.; Dong, L.; Shen, C.L.; Shan, C.X. Chemiluminescent carbon nanodots for dynamic and guided antibacteria. *Light Sci. Appl.,* **2023**, *12*(1), 104. http://dx.doi.org/10.1038/s41377-023-01149-8 PMID: 37142602

[54] van den Biggelaar, R.H.G.; Walburg, K.V.; van den Eeden, S.V.D. Identification of kinase inhibitors as host-directed therapies for intracellular bacteria. *bioRxiv,* **2023**.

[55] Wang, H.; Guo, J.; Yang, Y.; Wang, N.; Yang, X.; Deng, L.; Cao, X.; Ran, Z.; Fang, D.; Xu, K.; Zhu, Y.; Zhao, J.; Fu, J.; Hao, Y. $CuFeS_2$ nanozyme regulating ROS/GSH redox induces ferroptosis-like death in bacteria for robust anti-infection therapy. *Mater. Des,* **2024**, *239*, 112809. http://dx.doi.org/10.1016/j.matdes.2024.112809