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EDITED BY
Tânia Martins Silva,
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REVIEWED BY
Ramona Iseppi,
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University of Delhi, India
Mohamed Halawa,
Cooper Medical School of Rowan University, United States

*CORRESPONDENCE
Vijay Soni,
vis2032@med.cornell.edu
Vinayak Singh,
vinayak.singh@uct.ac.za

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Alternative therapeutics to control antimicrobial resistance: a general perspective

Biplab Singha[1], Vinayak Singh[2,3,4]* and Vijay Soni[5]*

[1]Department of Microbiology and Physiological Systems, University of Massachusetts Chan Medical School, Worcester, MA, United States, [2]Holistic Drug Discovery and Development (H3D) Centre, University of Cape Town, Cape Town, South Africa, [3]South African Medical Research Council Drug Discovery and Development Research Unit, University of Cape Town, Cape Town, South Africa, [4]Institute of Infectious Disease and Molecular Medicine (IDM), University of Cape Town, Cape Town, South Africa, [5]Division of Infectious Diseases, Weill Department of Medicine, Weill Cornell Medicine, New York, NY, United States

Antimicrobial Resistance (AMR) is a critical global health challenge, and in this review article, we examine the limitations of traditional therapeutic methods and the emerging role of alternative therapies. By examining the reasons behind the failure of conventional treatments, including the inadequacy of one-drug-one-enzyme approaches, the complex evolution of AMR, and the impact of drug biotransformation, we better understand why conventional treatments failed. Moreover, the review discusses several alternative therapies, including RNA-based treatments, aptamers, peptide-based therapies, phage therapy, and probiotics, discussing their applications, advantages, and limitations. Additionally, we discuss the obstacles to develop these therapies, including funding shortages, regulatory barriers, and public perception. This comprehensive analysis aims to provide insight into the future of AMR, emphasizing the need for innovative strategies and practical approaches.

KEYWORDS

antimicrobial resistance (AMR), alternative therapies, biofilm disruption, RNA-based treatments aptamers, peptide-based therapies, phage therapy, probiotics, drug biotransformation

1 Introduction

One of the 20th century's most influential medical inventions is antibiotics, the most important class of pharmaceuticals. There is no doubt that antibiotics have proved to be a boon to human society in the fight against bacteria, saving millions of lives as a result (Ribeiro da Cunha et al., 2019). Microorganisms such as bacteria, fungi, parasites, and viruses develop antimicrobial resistance (AMR) when they become resistant to the antimicrobial drugs, such as antibiotics, that are used to treat them. With the rapid growth of AMR infection rates and the lack of new antimicrobial medications introduced to combat this problem, AMR has become one of the greatest concerns of the 21st century (Gajdacs and Albericio, 2019). The development of AMR presents significant challenges to traditional therapies. As pathogens evolve resistance mechanisms, once effective treatments become obsolete. This resistance arises from several factors. Such as over-prescription and misuse, incomplete treatment courses, global accessibility, agricultural use, lack of new antibiotics, hospital-acquired infections, environmental spread, genetic mutations, biofilm formation, etc. (Figure 1). Common instances of resistant pathogens include "Methicillin-resistant *Staphylococcus aureus* (MRSA) (Singh et al., 2023), "Vancomycin-resistant

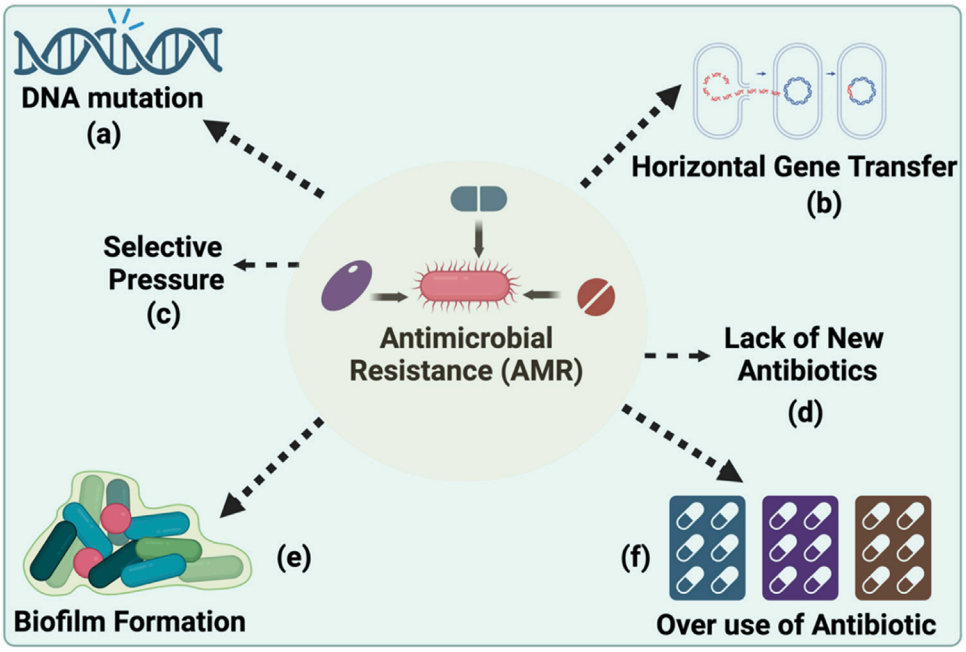

FIGURE 1
Key Drivers of Antimicrobial Resistance Development. **(A)** DNA mutations and **(B)** horizontal gene transfer as genetic mechanisms by which bacteria acquire and disseminate resistance. **(C)** Selective pressure, resulting from the **(D)** lack of novel antibiotics, is shown to favour the survival of resistant strains and **(E)** the role of biofilm formation in sheltering bacterial communities from antibiotic penetration and the impact of a lack of new antibiotics entering the market, which exacerbates the challenge of addressing resistant infections and **(F)** overuse and misuse of antibiotics, is shown to favour the survival of resistant strain. (Created using Biorender.com).

Enterococcus (VRE) (Singh et al., 2023), and "multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB)" (Singha et al., 2024). The resistance mechanisms are varied, involving genetic changes that confer the ability to deactivate antimicrobials, modify drug targets, or prevent drug penetration.

As the "Silent Pandemic," AMR requires urgent attention and should be managed more effectively rather than being considered an issue for the future. By 2050, it is estimated that AMR may become the world's leading cause of death without preventative measures. In 2019, more than 1.2 million people died directly as a result of AMR, and this figure is expected to rise to approximately 20 million deaths per year by 2050 if insufficient efforts are made to control AMR (Watkins and Bonomo, 2016). In the 21st century, we must focus on alternative therapies that do not rely on traditional antibiotics to bypass AMR. A number of studies have demonstrated the connection between COVID-19 and antimicrobial resistance (AMR), including the finding that severe cases often involved *vanB* clones of *Enterococcus faecium* in German intensive care units, and were accompanied by deaths due to infection with *Enterobacter cloacae*, which produces the New Delhi metallo-beta-lactamase. There was also an increase in the incidence of invasive fungal infections, exemplified by a deadly co-infection with resistant *Candida glabrata* and bacteria in Italy, as well as evidence that antimicrobial treatments for Aspergillus infections were ineffective (Singh and Sodhi, 2023). In order to monitor the spread of antibiotic resistance genes, whole-genome sequencing is one of the most popular tools (Sodhi et al., 2023).

Several alternative methods are available for avoiding the use of high doses of antibiotics to kill antibiotic-resistant bacteria: Phage Therapy, Probiotics, Antimicrobial Peptides (AMPs), Fecal Microbiota Transplantation (FMT), Host Defence Peptides, Metal Ions and Compounds, Antibody Therapies, Plant-Based Compounds, CRISPR-Cas Systems. An integrated approach to managing infections without contributing to the rise of AMR involves combining these alternative therapies with strategies to preserve the efficacy of existing anti-microbials. The purpose of this article is to summarize the fundamental mechanism behind AMR, limitations of routine therapeutic approaches, alternative therapies capable of combating AMR and its advantages and disadvantages, and future challenges.

The alarming issue of AMR is largely attributed to the failure of traditional one-drug one-enzyme therapeutics. This conventional approach to treating infections, where a single drug targets a specific bacterial enzyme or pathway, becomes ineffective as bacteria evolve resistance mechanisms (Prestinaci et al., 2015). This resistance can render standard antibiotics powerless, leading to treatment failures. Methicillin-resistant *S. aureus* (MRSA) illustrates how AMR undermines traditional, one-drug, one-enzyme treatments. *Staphylococcus aureus* infections were initially treated with penicillin, but as the bacteria developed resistance, methicillin was introduced as a penicillinase-resistant alternative. MRSA, characterized by the *mecA* gene that encodes a penicillin-binding protein with a low affinity for β-lactam antibiotics, including methicillin, rendered these treatments ineffective (Ali Alghamdi et al., 2023). As a result of the genetic evolution of MRSA, a broader issue in bacterial adaptation is highlighted, emphasizing the challenge of antibiotic resistance in previously treatable bacterial infections. The emergence of MRSA has had significant clinical

TABLE 1 List of bacteria that possess intrinsic resistance.

Resistance toward "class" of antibiotics	Microorganism	Target	Reference
Glycopeptides, Lipopeptides	All Gram negatives	Cell-Wall and cell-membrane	Reygaert (2018)
Aztreonam	All Gram positives	Cell-Wall	Morroni et al. (2021)
Ampicillin	*Klebsiella* spp.	Cell-Wall	Fu et al. (2007)
Sulfonamides, Cephalosporins, Chlorampheicol, Ampicillin and tetracycline	*P. aeruginosa*	Folic acid synthesis, Bacterial-ribosomes	Reygaert (2018)
Ampicillin, Glycopeptides	*Acinetobacter* spp.	Bacterial cell wall	Kyriakidis et al. (2021)
Aminoglycosides, Cephalosporins, Lincosamides	*Enterococcus* spp. or *Enterococci*	Bacterial cell wall, Bacterial ribosome	Hollenbeck and Rice (2012)
Cephalosporins	*Listeria monocytogenes*	Bacterial cell wall	Krawczyk-Balska and Markiewicz (2016)

TABLE 2 List of bacteria that possess acquired resistance.

Bacteria species	Resistance toward antibiotics	Acquired resistance mechanism	Target	Reference
Streptococcus	Penicillin	Production of beta-lactamase enzymes	Cell wall synthesis of bacteria	Bush and Bradford (2020)
E. coli	Tetracycline	Efflux pumps and ribosomal protection	Protein-synthesis machinery of bacteria	Perewari et al. (2022)
Staphylococcus	Methicillin	Altered penicillin-binding proteins	Bacterial cell wall synthesis	(Hartman and Tomasz, 1981; Fishovitz et al., 2014)
Pseudomonas	Ciprofloxacin	Mutations in DNA gyrase and topoisomerase	Bacterial DNA replication	Mouneimne et al. (1999)
Enterococcus	Vancomycin	Thickening of cell wall	Bacterial cell wall synthesis	Wagner et al. (2024)
Mycobacterium	Rifampicin	Mutations in RNA polymerase	Bacterial RNA synthesis	Li et al. (2021)
Streptococcus	Erythromycin	Methylation of ribosomal RNA	Bacterial protein synthesis	Weisblum (1995)
Enterobacter	Aminoglycosides	Modification of antibiotic target site	Bacterial protein synthesis	Kapoor et al. (2017)
Salmonella	Chloramphenicol	Production of acetyltransferase enzyme	Bacterial protein synthesis by binding to the 50S ribosomal subunit	Kapoor et al. (2017)
Enterococcus	Linezolid	Mutations in ribosomal RNA	Same as Chloramphenicol	(Ruiz-Ripa et al., 2020; Zarzecka et al., 2022)
E. coli	Trimethoprim	Mutations in dihydrofolate reductase	Bacterial folate synthesis	Midgley and Smith (1973)
Pseudomonas	Colistin	Lipopolysaccharide modification	Bacterial cell membrane	Sabnis et al. (2021)

implications. It requires alternative, often more expensive antibiotics, such as vancomycin or linezolid, which can have more side effects. Moreover, MRSA infections are associated with higher morbidity and mortality rates, especially in healthcare settings where patients are more vulnerable. This situation illustrates the broader challenge of AMR: as bacteria continue to develop resistance to existing drugs, the efficacy of standard antibiotic therapies is diminished, necessitating the development of new drugs and treatment strategies. Bacteria are complex organisms that receive and transfer DNA at an alarming frequency with seemingly little or no cost to themselves; contrary to previous dogma, the presence of an antibiotic has little impact on the transfer of mobile bacterial DNA but can select for newly acquired resistant mechanisms.

2 Mechanisms of AMR development

There are two main forms of antibiotic resistance: natural and acquired. When it comes to intrinsic resistance, it can either be innate (it can be expressed in the organisms) or mediated (the resistance genes are normally present in the bacteria, but they are activated to resistance levels after antibiotic treatment) (Reygaert, 2018) (Table 1). On the other hand, acquired resistance may result from bacteria

TABLE 3 Mechanism for AMR development.

Mechanism	Description
Limiting Drug Uptake	• Lipopolysaccharide Barrier: Gram-negative bacteria have an outer membrane composed of lipopolysaccharide, a glycolipid that acts as a permeability barrier, reducing the effectiveness of various antibiotics • Porin Protein Modifications: Alterations in outer-membrane porin proteins, which are channels for hydrophilic antibiotics (like β-lactams and fluoroquinolones), can lead to acquired drug resistance. Changes in the quantity and type of these proteins affect antibiotic entry and bacterial susceptibility • Mutations in Porin Expression: Mutations that impair the expression or function of porin proteins can result in high levels of resistance, especially when coupled with other mechanisms such as efflux pumps or enzymatic antibiotic degradation • Biofilm Formation: Some bacteria, like *E. coli* and *Pseudomonas aeruginosa*, form biofilms–communities of microbes encased in self-produced exopolysaccharide. Biofilms obstruct antibiotic penetration, prevent the establishment of bactericidal concentrations throughout the biofilm, and confer tolerance and resistance to antibiotics (Pallee Shree et al., 2022)
Drug target modification	• *S. pneumoniae* can modify its penicillin-binding protein, leading to decreased efficacy of penicillin antibiotics (Zhou et al., 2022) • *Mycobacterium tuberculosis* can change the structure of the ribosomal RNA target, resulting in resistance to rifampicin • *E. coli* can acquire mutations in DNA gyrase, the target of fluoroquinolones, making these drugs less effective • In the case of Vancomycin-resistant Enterococci (VRE), alterations in cell wall precursor targets prevent vancomycin from binding effectively
Inactivation of Drug	• Enzymatic Inactivation: Bacteria can inactivate antibiotics either by degrading the antibiotic molecule or by transferring a chemical group to it. β-lactamases produced by Enterobacterales are key examples, inactivating β-lactam antibiotics by breaking the β-lactam ring structure • β-Lactamase Activity: These enzymes, initially known as penicillinases and cephalosporinases, target the β-lactam ring, preventing the antibiotic (penicillin and cephalosporins) from binding to penicillin-binding proteins. This mechanism is found in several Enterobacterales and Gram-positive bacteria like *Staphylococcus aureus* and *Enterococcus* spp. • Tetracycline Hydrolysis: Some bacteria express an enzyme coded by the *tetX* gene, which hydrolyzes tetracycline, rendering it ineffective • Chemical Modification of Antibiotics: The transfer of acetyl, phosphoryl, and adenyl groups to antibiotics is a common method of inactivation. Phosphorylation and adenylation mainly target aminoglycosides, while acetylation is used against a variety of drugs, including aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones
Efflux of Drug	• Efflux Pump Mechanism: Bacteria utilize energy-dependent efflux pumps on the cytoplasmic membrane to expel antibacterial agents, including antibiotics, from the cell. This process helps control internal concentrations of harmful compounds and contributes to drug resistance • First Discovery and Evolution: The initial plasmid-encoded efflux pump was identified in *E. coli* in 1980, pushing tetracycline out of the cell. Since then, many resistant bacteria, both Gram-positive and Gram-negative, have been found to possess diverse efflux mechanisms • Multidrug Efflux Systems: Most efflux systems are chromosomally encoded and capable of multidrug efflux, contributing to intrinsic drug resistance in bacteria. In contrast, substrate-specific efflux pumps (e.g., for chloramphenicol, tetracyclines, and macrolides) are often found on mobile genetic elements • Types of Efflux Pumps: Six main types based on structure and energy source: ATP-binding cassette (ABC) superfamily, major facilitator superfamily (MFS), multidrug and toxic compound extrusion (MATE) family, small multidrug resistance (SMR) family, resistance–nodulation–division (RND) superfamily, and drug metabolite transporter (DMT) superfamily. Gram-positive bacteria primarily use ABC and MFS pumps, while clinically significant efflux systems in Gram-negative bacteria belong to the RND superfamily, involving an outer-membrane channel, periplasmic protein, and cytoplasmic membrane pump

(Continued in next column)

TABLE 3 (*Continued*) Mechanism for AMR development.

acquiring genetic material through translation, conjugation, transposition (Lerminiaux and Cameron, 2019), or mutations in its own chromosomal DNA (Culyba et al., 2015) (Table 2).

AMR mechanisms based on the structure as mentioned in Table 3: 1) limitation of drug uptake; 2) drug target modification; 3) drug inactivation; and 4) drug efflux. Due to structural differences, Gram-negative bacteria can utilize above mentioned, all four mechanisms. In contrast, Gram-positive bacteria are less likely to utilize drug efflux mechanisms due to the absence of lipopolysaccharide in the outer membrane (Munita and Arias, 2016).

2.1 Limitation of drug uptake

There is an inherent permeability shield created by the lipopolysaccharide (LPS) layer in most Gram-negative bacteria, making them more resistant to certain antibiotics than Gram-positive bacteria. For example, glycopeptide antibiotics, e.g., vancomycin, inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminus of cell wall precursor units, is ineffective against Gram-negative bacteria because of the lack of penetration through the outer membrane, which is a prime illustration of the efficiency of this natural barrier (Munita and Arias, 2016) Modifying the outer membrane permeability strongly affects hydrophilic molecules, such as lactams, tetracyclines, and fluoroquinolones (Darby et al., 2023). In addition, alterations to envelope structure, such as porin loss or changes to phospholipid and fatty acid content of the cytoplasmic membrane, can affect the ability of a drug to penetrate the cell and contribute to the emergence of AMR (Delcour, 2009). Mycobacteria, produce a polysaccharide capsule coat that prevents hydrophilic molecules from entering the cell (Draper, 1998; Kumar et al., 2022). It has been shown that polar molecules have difficulties entering

enterococci cell walls due to porin channel downregulation. A recent study suggests that reductions in porin expression significantly increase resistance to carbapenems among members of the Enterobacterales order, *Acinetobacter spp*., and *Pseudomonas spp*. (Iredell et al., 2016). Biofilms are another mechanism that aids bacteria in colonizing, resulting in the development of AMR. Due to the use of biofilm as a protection against antibiotics, *P. aeruginosa* has become a leading cause of morbidity and mortality in individuals with cystic fibrosis and immunocompromised individuals (Pang et al., 2019).

2.2 Drug efflux

Many pathogenic bacteria exhibit antibiotic efflux as one of their most common resistance mechanisms (Webber and Piddock, 2003; Li et al., 2015). All bacterial efflux pumps are located on the inner membrane. Gram-negative bacteria have three components in their cell envelope, i.e., outer membrane, peptidoglycan layer, and inner membrane. Gram-positive bacteria have only two components in their cell envelope, i.e., peptidoglycan layer and inner membrane. Many antibiotics are actively transported out of the cell by bacterial efflux pumps, which contribute to Gram-negative bacteria's intrinsic resistance. Six types of efflux pump families have been identified in bacteria, i.e., ATP-binding cassette (ABC) superfamily, major facilitator superfamily (MFS), small multidrug resistance (SMR) family, proteobacterial antimicrobial compound efflux (PACE) family, multidrug and toxin extrusion (MATE) family, and resistance-nodulation-cell division (RND) superfamily. AMR is associated with ATP-binding cassette efflux pumps (ABCs). Many substances, including antibiotics, are transported across cellular membranes using the energy from ATP hydrolysis. MacAB-TolC is an ABC family efflux pump contributing to AMR in *Salmonella enterica* serovar Typhimurium (Kudirkiene et al., 2018). Efflux pumps are known to confer resistance to macrolide antibiotics. By actively expelling these antibiotics from the bacterial cell, the MacAB-TolC system reduces their intracellular concentration, diminishing their effectiveness. These ABC efflux pumps can render certain antibiotics ineffective in pathogenic bacteria. Consequently, targeting these efflux pumps could be a potential strategy for overcoming AMR and improving antibiotic efficacy (Bogomolnaya et al., 2013). In host-pathogen communication, MFS transporters play an important role in adhesion, invasion, intracellular survival, and biofilm formation. Inhibiting MFS transporters is a promising strategy for combating drug resistance and reducing pathogenic virulence. Inactivating the MFS efflux pump, AbaF of *A. baumannii* reduces bacterial virulence in a *Caenorhabditis elegans* model (Sharma et al., 2017; Pasqua et al., 2021). The pathogen *Neisseria gonorrhoeae* (*N. gonorrhoeae*) causes gonorrhoea, a sexually transmitted disease. In *N. gonorrhoeae*, FarAB is a MFS pump, promotes resistance to long-chain fatty acids such as oleic, linoleic, and palmitic acids (Lee and Shafer, 1999). A foodborne pathogen, *Listeria monocytogenes* (*L. monocytogenes*), can penetrate the intestinal barrier and quickly spread to the liver and spleen. MdrM and MdrT are two MFS pumps that play a significant role in the pathophysiology of *L. monocytogenes*. MdrM and MdrT play a significant role in bile resistance and modulate the cytosolic surveillance pathway of innate immunity, contributing to the spread of bacteria and the invasion of tissues (Crimmins et al., 2008). The Small Multidrug Resistance (SMR) family is a group of efflux pumps found in bacteria that contribute to AMR by expelling various antimicrobial agents from the bacterial cell, thereby decreasing drug susceptibility. An example of an SMR family efflux pump involved in AMR is the EbrAB efflux system in *Bacillus subtilis* (Masaoka et al., 2000). This efflux pump has been shown to confer resistance to certain dyes, detergents, and disinfectants structurally similar to antimicrobial compounds. Another well-documented case is the QacA and QacB transporters in *S. aureus*, which confer resistance to quaternary ammonium compounds - a class of disinfectants commonly used in hospital settings. These examples illustrate the role of SMR family pumps in protecting bacteria from a range of chemically diverse antimicrobial substances, thus contributing to the broader problem of AMR (Oliveira-Tintino et al., 2023). The Proteobacterial Antimicrobial Compound Efflux (PACE) family of efflux pumps is a recent addition to the known efflux systems contributing to AMR. These pumps can expel a broad range of antimicrobial compounds, which contributes to the survival of bacteria in the presence of toxic substances, including antibiotics and disinfectants. An example of a PACE family efflux pump contributing to AMR is AceI, found in *Acinetobacter baumannii*. AceI provides resistance to various biocides, including chlorhexidine, a common disinfectant used in healthcare settings (Short et al., 2021). The Multidrug And Toxin Extrusion (MATE) family of efflux pumps is another group of transporters implicated in AMR. These pumps typically utilize the proton or sodium gradients across the bacterial cell membrane to extrude a wide variety of compounds, including antibiotics and toxins, from the cell. The MATE family efflux pump involved in AMR is NorM, which was first characterized in *Vibrio parahaemolyticus* (Stephen et al., 2022). NorM is capable of conferring resistance to a variety of compounds, including fluoroquinolones, a class of broad-spectrum antibiotics (Poole, 2000). This resistance occurs as NorM actively expels these antibiotics from the cell, lowering their intracellular concentration and thereby diminishing their efficacy. The ability of MATE pumps like NorM to reduce the effectiveness of antibiotics underlines the critical need to develop new therapeutic strategies to combat AMR. The Resistance-Nodulation-Cell Division (RND) superfamily of efflux pumps is a key player in bacterial AMR. These pumps are primarily found in Gram-negative bacteria and are known for their ability to expel a wide variety of substances, including antibiotics, detergents, dyes, and bile salts, which contribute significantly to the multidrug resistance phenotype. The RND efflux pump involved in AMR is the AcrAB-TolC system in *Escherichia coli* (Anes et al., 2015). This tripartite pump spans the entire cell envelope and can actively expel multiple classes of antibiotics, such as β-lactams, fluoroquinolones, and tetracyclines, from the bacterial cell. This efflux system significantly reduces the concentration of antibiotics within the bacterial cell, thereby protecting the bacteria from their bactericidal effects and contributing to the problem of AMR. The AcrAB-TolC system is a prime target for the development of new drugs designed to inhibit efflux pumps and restore antibiotic efficacy (Jang, 2023).

2.3 Drug inactivation

Bacteria can neutralize antibiotics through either degradation of the antibiotic molecule or chemical modification, rendering the drug

ineffective. Chemical modification of the drug: Bacteria produce enzymes that attach different chemical groups to drugs. As a result, the antibiotic will not be able to bind to its target in the bacterial cell. The most effective method of drug inactivation through chemical group transfer is the transfer of phosphoryl, acetyl, and adenyl groups to the compound. Aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones are all examples of drugs that use acetylation as a mechanism of action. Adenylation and phosphorylation are thought to be the mechanisms by which aminoglycosides are targeted. An aminoglycoside modifying enzyme (AME) alters the hydroxyl or amino groups of the aminoglycoside molecule covalently, resulting in the inactivity of the aminoglycoside molecule, leading to the development of AMR (Munita and Arias, 2016).

2.4 Drug target modification

Target modification is a prevalent strategy bacteria use to confer resistance to antibiotics (Reygaert, 2018). Alterations in penicillin-binding proteins (PBPs), both in their structure and quantity, contribute to β-lactam antibiotic resistance, affecting the drug's ability to bind effectively (Bush and Bradford, 2016). For instance, the *mecA* gene in *S. aureus* leads to a PBP alteration that significantly diminishes or entirely inhibits the binding of β-lactam drugs (Foster, 2017). Similarly, resistance to macrolides, streptogramins, and lincosamides involves the erythromycin ribosome methylase (*erm*) gene family, which methylates 16S rRNA, thereby modifying the antibiotic binding site (Peterson and Kaur, 2018). Furthermore, mutations in DNA gyrase or topoisomerase IV, which are the targets of fluoroquinolones, can change the enzymes' structures enough to prevent the drugs from attaching, resulting in resistance (Nainu et al., 2021).

3 Alternative therapies: pioneering strategies to combat AMR

AMR has no natural boundaries and has silently evolved into a global public health issue threatening populations from high, medium, and low-risk countries. The increased frequencies of AMR, especially among clinically significant pathogens such as *Enterococcus* species, *S. aureus, Klebsiella pneumoniae, A. baumannii*, *Pseudomonas aeruginosa, Enterobacter species*, and *E. coli*, has put tremendous pressure on the healthcare, veterinary, and agriculture industries, making it one of the world's most urgent public health concerns. Further, in a 'One Health' context, the consequences of the spread of AMR bacteria from food animals may profoundly impact both animal health and public health. Considering the global health impact of AMR bacteria and the need for new antibiotics, new strategies are being implemented to protect and treat (multidrug-resistant) MDR, (extensively drug-resistant) XDR, and (pandrug-resistant) PDR infections, as even so-called 'antibiotics of last resort' are becoming ineffective in clinical settings. To combat this problem, a few alternative approaches have been widely utilized in recent years (Table 4).

3.1 RNA based

A strategy that also has the potential to generate novel antimicrobials is RNA silencing, naturally processed in bacteria, it was first described in 1985 and is now recognized as a regulator of a wide range of genes. A single m-RNA (antisense sequence) contains cis and trans sequences that are complementary and, upon binding, can reversibly block translation. Synthetic antisense sequences can potentially be developed to repress the translation of enzymes that enable bacteria to resist antibiotics (Good and Stach, 2011). RNA silencing is applied in the discovery of new antimicrobial compounds, determination of the stringency requirement for those targets, development of highly sensitized antimicrobial screens, and mode of action. Defeating AMR is a critical global issue that requires immediate attention. The development of alternative strategies to combat bacterial pathogens is of utmost importance. To address this issue, RNA-based therapies, such as synthetic sRNAs or (Clustered regularly interspaced short palindromic repeats) CRISPR guide RNAs, are attractive strategies (Parmeciano Di Noto et al., 2019). In particular, extended-spectrum beta-lactams, carbapenems, or colistin resistance genes can be targeted by both approaches. However, it is important to develop systems that are not only capable of delivering highly effective RNA elements but may also be rapidly modified upon the acquisition of new resistances by bacteria and thus limit their selection for MDR strains. Additionally, a combined system targeting several mRNAs in a coordinated manner would be more effective. RNA-based therapies represent a novel approach in combating AMR, utilizing the unique mechanisms of RNA molecules to target and inhibit bacterial growth. For instance, RNA interference (RNAi) can be employed to silence essential bacterial genes, with small interfering RNAs (siRNAs) designed to be complementary to bacterial mRNA, leading to its degradation and hindering bacterial survival. Similarly, antisense RNA (asRNA) therapies use synthetic RNA strands to block mRNA translation in bacteria, effectively preventing the production of key proteins. An example of this is the use of asRNA targeting essential genes in antibiotic-resistant strains of *S. aureus*, effectively reducing its virulence (Saberi et al., 2016). Furthermore, RNA silencing can also be applied to the development of antibacterial screening methods. As a result, genes of interest can be knocked down. Merck Research Laboratories (New Jersey, American) used a strain of *S.* aureus that expressed antisense RNA to screen 250,000 natural products for inhibitors of the FabF/FabH pathway, preventing the biosynthesis of fatty acids (Young et al., 2006). It is also possible to use RNA silencing to determine the mode of action of novel antibiotics; for instance, novel inhibitors of enoyl-acyl carrier protein reductase (Fabl) have been discovered using RNA silencing (Good and Stach, 2011). Additionally, the CRISPR-Cas system, adapted from bacterial immune defences, offers a way to specifically target and dismantle antibiotic resistance genes (Tao et al., 2022). The precision of these RNA-based methods allows for targeted attacks on resistant bacteria while minimizing the impact on beneficial microbiota, offering a promising alternative to traditional antibiotics. Despite their potential, challenges such as effective delivery and stability in the human body remain to be fully addressed for these therapies to become a mainstay in the fight against AMR. Virulence, resistance genes, and mobile genetic

TABLE 4 Alternative Therapies and their role to combat AMR.

Category of therapeutics	Name of therapy	Mechanism of action and applications	Reference
Probiotics and Prebiotics	*Lactobacillus spp*., *Bifidobacterium spp*	Competitive inhibition of pathogenic bacteria, restoration of gut microbial homeostasis	Dempsey and Corr (2022)
Bacteriophage Therapy	Lytic bacteriophages	Specific targeting and lysis of bacterial cells, reduction in antibiotic use	Hibstu et al. (2022)
Phytotherapy (Herbal Medicine)	Allicin (from Garlic), Cichoric acid (from Echinacea)	Natural antimicrobial compounds, immunomodulatory effects	Arreola et al. (2015)
RNA based Therapies	RNA Interference (RNAi), Antisense Oligonucleotides (ASOs)	Effective in silencing resistance genes and restoring antibiotic efficacy	Hosnedlova et al. (2022)
Immunomodulatory Therapies	Monoclonal antibodies	Target-specific pathogens, modulation of host immune response	Chung et al. (2023a)
Antimicrobial Peptides (AMPs)	Cathelicidins, Defensins	Disruption of bacterial cell membranes, direct antimicrobial activity	Kosciuczuk et al. (2012)
Traditional Medicine Systems	Ayurvedic compounds, TCM formulations	Utilization of holistic herbal compounds with antimicrobial and immune-boosting properties	Wang et al. (2023)
Fecal Microbiota Transplantation (FMT)	Donor microbiota transplantation	Reconstitution of healthy gut microbiota, combating dysbiosis and resistant pathogens	Biazzo and Deidda (2022)
Biofilm Disruption Agents	Dispersin B, DNase I	Degradation of biofilm matrix, enhancement of antibiotic penetration	Pinto et al. (2020)

elements are appealing target candidates to combat antibiotic-resistant bacteria. It has been reported that some sRNAs are involved in antibiotic uptake (GcvB, RyhB, MicF, ErsA), drug efflux (DsrA RydC, SdsR, NrrF), biofilm formation (RprA OmrA/B, McaS, RybB, RydC), and modification of lipopolysaccharide and cell wall synthesis (MgrR, MicA, Sr006) (Felden and Cattoir, 2018; Tao et al., 2022). While most of these sRNAs have been extensively studied in *E. coli* and *Salmonella*, we need to understand the role of sRNA more extensively to use it as a new strategy in combating XDR and MDR bacteria (Dersch et al., 2017).

3.2 Aptamer

Over the past half-century, significant advances have been made in treating infectious diseases. However, many problems exist associated with developing effective therapies and dealing with antibiotic side effects and pathogen drug resistance. The development of aptamers could be an essential tool for expanding new therapeutic factors based on their ability to block pathogen microorganisms through binding of specifically to targets such as proteins and pathogens. In addition, they are simple, cheap, and have fewer side effects than conventional antibiotics. Aptamers, small single-stranded oligonucleotides (DNAs or RNAs), have emerged as powerful and flexible tools for therapeutic goals (Thiel and Giangrande, 2009). They offer several advantages over antibodies, including lower complexity and immunogenicity, higher affinity and specificity against various targets, flexibility, and stability (Zhou and Rossi, 2017). The antimicrobial activities of aptamers have been demonstrated in various studies, showing potential in addressing multidrug-resistant bacterial strains such as *Salmonella*. Aptamer G9 targets the polyphosphate kinase (PPK) gene, which is responsible for managing polyP metabolism and evading immune detection and is the key to the persistence of *M. tuberculosis* (Shum et al., 2011). Aptamers have been evaluated for their role in inhibiting biofilm formation, a major challenge in treating chronic infections, as they are resistant to current antibiotics and immune responses. A study has shown binding of specific aptamer to the flagella of *S. choleraesuis*, preventing biofilm formation (Ning et al., 2015). Furthermore, this study demonstrated that aptamer pre-treatment of *S. choleraesuis* biofilms could significantly reduce the amount of ampicillin needed for similar inhibition as well as prevent the development of antibiotic-resistant strains. As a result, the use of aptamers pre-treatment could eliminate the need for highly potent antibiotics in high doses. They have also been used to inhibit microbial toxins, which are important factors in bacterial pathogenesis. A key virulence factor produced by antibiotic resistance *S. aureus* is the alpha-toxin, which damages host epithelial tissue and targets cell membranes. To prevent alpha-toxin-mediated tissue damage, aptamers (AT-27, AT-33, AT-36, and AT-49) target the toxin (Okano, 1974). To explore aptamers as intracellular delivery vehicles, addressing the limitations of conventional antibiotic therapy, such as low intracellular drug concentrations and the development of multidrug resistance (Gopinath et al., 2016; Afrasiabi et al., 2020). Aptamer-nanoparticle conjugates are highlighted for their potential in antimicrobial activities and drug delivery. Additionally, aptamer-siRNA/miRNA conjugates are discussed for their promising modulatory effect on virulence, drug resistance, and pathogenesis (Afrasiabi et al., 2020). Aptamer-drug conjugates, like aptamer-ampicillin conjugate, have shown synergistic effects against biofilms, aiding drug penetration and reducing tolerance to drugs (Afrasiabi et al., 2020; Guan and Zhang, 2020).

3.3 Peptide based

Bacterial resistance to antibiotics and the rapid increase in infectious diseases due to AMR bacteria. Currently, antibiotic resistance and the associated infections are widespread and pose

severe health and economic burdens globally, necessitating a massive demand for alternative treatment approaches. Additionally, many emerging alternative treatment options are at different stages of preclinical and clinical trials (Paul et al., 2023; Rossino et al., 2023). Antimicrobial peptides (AMPs), have an amino acid length ranging from 15 to 150, and hold promises as valuable therapeutic options against drug-resistant pathogens (Lazzaro et al., 2020). AMPs are low molecular weight oligopeptides that are found in plants, animals, and humans. They play a crucial role in the host's innate immune response and have broad-spectrum antimicrobial activity. The AMPs hold promise as a viable therapeutic approach against drug-resistant pathogens. AMPs are oligopeptides with low molecular weight (Mba and Nweze, 2022). They have broad-spectrum antimicrobial activities against pathogenic microorganisms. AMPs are nonspecific and target components of microbes that facilitate immune response by acting as the first-line defence mechanisms against invading pathogenic microbes. The diversity and potency of AMPs make them good candidates for alternative use. They could be used alone or in combination with several other biomaterials for improved therapeutic activity. They can also be employed in vaccine production targeting drug-resistant pathogens (Mba and Nweze, 2022). This review covers the opportunities and advances in AMP discovery and development targeting AMR bacteria. Briefly, it presents an overview of the global burden of the AMR crisis, portraying the global magnitude, challenges, and consequences. After that, it critically and comprehensively evaluates the potential roles of AMPs in addressing the AMR crisis, highlighting the major potentials and prospects. Studies have shown that AMPs disrupt bacterial cell membranes, which can enhance the effectiveness of antibiotics on AMR strains. For example, peptides like P4-9 have been shown to increase cell membrane permeability in drug-resistant *P. aeruginosa*, enhancing the impact of antibiotics like novobiocin (Razquin-Olazaran et al., 2020). This effect, known as "Post-Antibiotic Effect-associated Permeabilization," persists even after the peptide is removed. Another aspect is the use of D-enantiomeric peptides, such as DJK-6, which have been effective in preventing and eradicating biofilms in resistant strains of *K. pneumoniae* (Ribeiro et al., 2015) and *P. aeruginosa* (de la Fuente-Nunez et al., 2015). These also potentiate the activity of β-lactam antibiotics. Similarly, other AMPs like brevinin-1, derived from frog skin secretions, have broad-spectrum activity against pathogens including MRSA and *Enterococcus faecalis* (Mba and Nweze, 2022). Furthermore, the potential impact of modifying AMPs has been found useful with enhance therapeutic impacts. Such as the modified N6NH2 peptide exhibited improved stability and antimicrobial activity (Han et al., 2020). These peptides can act through various mechanisms, including cell permeabilization, interaction with DNA, and forming outer membrane vesicles. In conclusion, AMPs not only offer a promising avenue for combating antibiotic-resistant bacteria but also have potential applications in vaccine design due to their immunomodulatory properties. This makes them a valuable tool in addressing the global crisis of AMR. Moreover, various studies have shown the effect of AMP and their combination with other medication or antibiotics against clinical infections (Table 5).

3.4 Phage therapy

Phage therapy, an innovative approach to combating AMR, involves bacteriophages (viruses that specifically infect bacteria) to treat bacterial infections, particularly those resistant to conventional antibiotics (Singha et al., 2023a). Phage therapy will become more popular in the twenty-first century since antibiotics kill bacteria in a broad spectrum, whereas bacteriophages are highly specific to their target bacteria. For example, in cases of drug-resistant *S. aureus* infections, phage therapy can be employed where specific phages are identified that selectively target and lyse these resistant bacterial cells, without harming beneficial microbiota (Yang et al., 2014; Pincus et al., 2015). In a recent study, a patient with multidrug-resistant *Mycobacterium abscessus* infection had been unable to respond to antibiotics, although cocktail of drugs can effectively eradicate drug-susceptible *M. absecssus* infections (Dedrick et al., 2023; Hatfull, 2023). Cystic fibrosis (CF) patients are particularly susceptible to chronic lung infections caused by AMR-Achromobacter. A recent study has shown that lytic phages could be an alternative method to combat AMR-Achromobacter infections (Winzig et al., 2022). This targeted action is particularly beneficial in combating biofilms, common in chronic wounds and notoriously resistant to standard antibiotic treatments. Phage therapy's adaptability also allows it to evolve in response to bacterial resistance mechanisms, offering a dynamic solution to the growing challenge of AMR. In phage therapy, specific bacteriophages are selected for their ability to penetrate and disrupt these biofilms. For instance, phages like the Pseudomonas-specific phage ΦKZ have been studied for their efficacy against *P. aeruginosa* biofilms (Aghaee et al., 2021). These phages can invade the biofilm matrix, replicate within bacterial cells, and cause cell lysis, which not only kills the bacteria but can also disrupt the structure of the biofilm, making it more susceptible to antibiotics and the immune system. Clinical case reports and studies have shown that phage therapy can be effective in reducing *P. aeruginosa* density in biofilms and improving clinical outcomes, especially in cases where antibiotics alone were insufficient. This approach highlights the potential of phage therapy as a complementary treatment or alternative in cases where antibiotic resistance is a significant challenge. The available literature on the use of phages and phage-derived proteins for combating bacterial infections, specifically those of multidrug-resistant bacteria, increasingly shows promise for the prospect of phage therapy as either an alternative or a supplement to antibiotics. However, discrepancies in recent findings on the immunomodulatory effects, the host range, and the potential for horizontal gene transfer make it abundantly clear that we need a better understanding of the interaction between phage, microbiome, and human host before implementing phage therapy on a large scale.

Phage genome engineering involves extending their utility beyond their natural capabilities, such as by removing genes that promote lysogeny or introducing genes that enhance antibacterial activity (Sarkis et al., 1995; Pires et al., 2016; Hatoum-Aslan, 2018). To accomplish precise genome editing, advanced methods, such as recombination and CRISPR-Cas systems have been developed. As an example, the Bacteriophage Recombineering of Electroporated DNA (BRED) technique allows the production of recombinants without selection, which can be used to construct specific deletions,

TABLE 5 Synergistic Combination of AMPs with Other molecules such as Antibiotics.

AMP	Synergistic molecules	Target bacteria	Reference
Dermaseptin	Dermaseptin	*P. aeruginosa, S. aureus, E. coli*	Yin et al. (2018)
Nisin	Colistin	*Pseudomonas* bioflims	Jahangiri et al. (2021)
Tridecaptin B	Rifamcipin	*A. baumannii*	Jangra et al. (2020)
Gad-1	Kanamycin, ciprofloxacin	*P. aeruginosa*	Portelinha and Angeles-Boza (2021)
Tridecaptin M	Rifamcipin	Extremely drug-resistant *A. baumannii* (MRSA)	Zairi et al. (2014)
Ranalexin	Endopeptidase lysostaphin	*S. aureus* (MRSA)	Jangra et al. (2020)
P10	Ceftazidim	*P. aeruginosa, A. baumannii*	Jahangiri et al. (2021)
Lactoferricin	Ciprofloxacin	*P. aeruginosa*	Jahangiri et al. (2021)

as demonstrated in phages that target *Mycobacterium* and *E. coli* (Marinelli et al., 2008; Feher et al., 2012; Shin et al., 2014; Pan et al., 2017; Singha et al., 2023b).

3.5 Natural products

AMR is a critical issue, and natural products provide potential alternative therapies, offering a wealth of novel compounds with diverse antimicrobial properties. Various natural compounds, including those derived from plants, microbes, and marine organisms, have unique mechanisms that can combat resistant pathogens, often with a reduced likelihood of resistance developing. As an example, tea tree oil, obtained from *Melaleuca alternifolia* leaves, has been demonstrated to be effective against several bacteria and fungi, including some strains that are resistant to the oil (Carson et al., 2006). Curcumin, the active ingredient in turmeric, is another notable example. Besides fighting microbes directly, it has also shown promise in enhancing the efficacy of existing antibiotics and reducing bacterial resistance (Hussain et al., 2022). Furthermore, the antimicrobial potential of allicin, derived from garlic, and berberine, found in plants such as goldenseal, illustrates the wide variety of possibilities offered by natural products (Bhatwalkar et al., 2021; Hussain et al., 2022). Various compounds have been studied for their ability to combat infections, including those resistant to traditional antibiotics. Natural products can be used to address AMR, but there are challenges associated with their use. Variations in compound concentration, difficulties with standardization and mass production, and the need for extensive clinical trials to confirm efficacy and safety are significant challenges. However, these challenges also present opportunities for innovation in pharmaceutical development and healthcare practices. The integration of natural products into the mainstream medical field requires a multidisciplinary approach, involving botanists, chemists, pharmacologists, and clinicians. This collaborative effort is essential for the successful identification, extraction, and development of these natural compounds into safe and effective therapeutic agents. In addition to scientific research, regulatory frameworks must evolve to support the integration of natural products into treatment protocols, ensuring quality control and patient safety. Moreover, public awareness and education about the potential and limitations of natural products as alternative therapies are crucial for their acceptance and appropriate use (Rossino et al., 2023).

3.6 Antibodies

World Health Organization (WHO) released a list of innovative antibacterial approaches in April 2021, including the use of antibodies as a form of antibiotic therapy. Historically, serum antibodies were commonly used to treat infectious diseases before the widespread use of antibiotics (Bhatwalkar et al., 2021). Since antibiotic resistance is on the rise, there has been renewed interest in exploring vaccines for bacterial infections. Antibodies are therapeutic agents that harness the immune system to provide therapeutic benefits. As a result of their reduced clearance rate, lower toxicity, and increased longevity (the half-life of IgG antibodies is approximately 21 days), human monoclonal antibodies are especially advantageous. Furthermore, their high specificity enables them to target pathogens without disrupting the body's normal bacterial flora. Numerous monoclonal antibodies are currently being developed, are undergoing clinical trials, and are showing promise against various pathogens (Motley et al., 2019). These include nosocomial infections such as *S. aureus* and *P. aeruginosa*, as well as challenging pathogens such as *A. baumannii*. A human monoclonal antibody developed by Trellis Biosciences inhibits biofilm formation among multiple bacteria by targeting the DNABII protein, an essential component (Zurawski and McLendon, 2020). Roche is also developing a conjugate of an antibody and an antibiotic that targets *S. aureus* (Peck et al., 2019). The conjugate enhances the effectiveness of the antibiotic by bringing it into proximity to the bacteria. MEDI3902, a bi-specific antibody targeting a surface polysaccharide of *P. aeruginosa*, inhibits its ability to form biofilms. This is another development by AstraZeneca PLC (Chung J. et al., 2023).

Moreover, recent clinical trials have evaluated suvratoxumab, a monoclonal antibody designed to treat ventilator-associated pneumonia caused by *S aureus* in patients using mechanical ventilation in intensive care settings. To reduce the harmful effects of this toxin, this antibody targets the toxin. Although many of these monoclonal antibodies are still in the early stages of clinical trials, a few shows potential for commercial development.

To enhance the role of monoclonal antibodies in combating drug resistance, further research is essential to provide an alternative that is less likely to contribute to the growing problem of antibiotic resistance. Besides antibodies, studies have indicated cytokines, particularly interleukins and IFN-γ, are pivotal in enhancing the immune system response against intracellular pathogens, influencing the control of infections such as listeriosis and tuberculosis. Studies on mice show that IFN-γ boosts macrophage activity to suppress *L. monocytogenes* and *Mycobacterium bovis*, while anti-TNF antibodies can worsen infection outcomes (Li et al., 2020). This underscores the nuanced role of cytokines in AMR and their potential as therapeutic targets (Kaufmann and Flesch, 1990). Study has shown mucosa-associated invariant T (MAIT) cells play important roles against antimicrobial-resistant infections through their capacity to directly clear multidrug-resistant bacteria and overcome mechanisms of AMR (Leeansyah et al., 2021; Meermeier et al., 2022).

3.7 Probiotics

Probiotics are live microorganisms that produce antimicrobial metabolites and compete with microbes for nutrients. In contrast, antibiotics are active substances that directly fight pathogens. Among the most common strains used in human consumption are *Lactobacillus* and Bifidobacterium. Research has indicated that these organisms possess antimicrobial properties and are effective against several human pathogens. Recent research has demonstrated that probiotics have antimicrobial properties and enhanced immunological functions beyond gut health (Mazziotta et al., 2023; Petrariu et al., 2023). Several mechanisms are involved in their action, including the production of inhibitory substances such as bacteriocins and hydrogen peroxide, competition for adhesion sites, and competition for nutrients. Research has demonstrated that probiotics inhibit pathogenic bacteria and modulate the immune system (Neal-McKinney et al., 2012; Sikorska and Smoragiewicz, 2013; Markowiak and Slizewska, 2017). It includes increasing macrophage activity and modifying cytokine profiles to increase phagocytic activity (Jain et al., 2008; Dong et al., 2012; Zhao et al., 2012; Plaza-Diaz et al., 2017). Probiotics have a wide range of benefits, including anti-mutagenic (Yu and Li, 2016; Casas-Solis et al., 2020), anti-carcinogenic (Wollowski et al., 2001; Devaraj et al., 2019; Casas-Solis et al., 2020), and antidiarrheal properties (Liu et al., 2017; Devaraj et al., 2019), in addition to stimulating the immune system (Casas-Solis et al., 2020) and managing skin conditions such as atopic dermatitis and acne (Rather et al., 2016; Huang et al., 2017; Lise et al., 2018). Probiotics may be an adjunct strategy for controlling and preventing infectious diseases. For example, certain strains of Bifidobacterium can inhibit the growth of *S. aureus*, one of the most important pathogens associated with systemic and peri-implant infections (Lahtinen et al., 2007). A notable characteristic of multi-resistant bacteria such as MRSA is the ability of probiotics to disrupt and prevent the formation of bacterial biofilms. Probiotics can kill *S. aureus* through quorum-sensing inhibition, while *Bacillus* sp. produces antifungal lipopeptides, such as fengycin (Chung and Raffatellu, 2019). *Pediococcus acidilactici* has been shown to mitigate the virulence of *P. aeruginosa* by inhibiting motility and biofilm formation (Lee et al., 2020), and in the context of *S. aureus* biofilms on titanium surfaces, strains of *Lactobacillus brevis* and *Bifidobacterium bifidum* demonstrated significant inhibitory effects.

Additionally, probiotic lactobacilli have been implicated in reducing MRSA biofilm formation through various mechanisms, including competition and production of bacteriocin-like substances (Sikorska and Smoragiewicz, 2013). Probiotics against *Helicobacter pylori* infection are gaining much attention to enhance antibiotic regimens for eradication and mitigating conditions such as diarrhoea. Further, some *Lactobacillus* strains have been shown to prevent the formation of biofilms and disrupt those that have already formed. Furthermore, probiotics have been proposed to manage COVID-19-associated intestinal dysbiosis, with the potential to regulate the gut microbiota and minimize the risk of secondary infection (Xu et al., 2020). In infectious diarrhoea, the synergistic effects of probiotics and prebiotics have enhanced anti-rotavirus responses, reducing the intensity and duration of rotavirus-related diarrhoea.

3.8 Metal ions and compounds

Metals play a dual role with bacteria, essential for survival yet toxic at high levels, driving interest in metal-based compounds as potential antimicrobials amid rising antimicrobial resistance (AMR). Metalloantibiotics, including metal ions, nanoparticles, and complexes, though not yet in clinical use, show promise for novel antibiotic developments. Research has highlighted the significance of essential metals for bacterial processes and the immune system's strategies to alter metal homeostasis to combat infections. Strategies leveraging specific bacterial metal uptake pathways, such as metallophores and siderophores, alongside the antimicrobial properties of metals like silver, copper, and zinc, offer innovative approaches to targeting bacterial infections. Metalloantibiotics, particularly those with investigated actions like rhenium and ruthenium complexes, demonstrate diverse structures and mechanisms, presenting a potential breakthrough in antibiotic therapy. Additionally, applications in antimicrobial photodynamic therapy and diagnostic imaging highlight the versatile benefits of metal complexes in addressing AMR. Metal-mediated antibacterial therapy is most commonly used with copper, whose history dates back to ancient Greece where it was used to treat lung disease and to purify water (Frei et al., 2023). It remains widely used in products to prevent bacterial growth, owing to its stability and cost-effectiveness compared to silver, and its ability to readily bind to bacterial surface groups. It also shows potential synergy with other drugs, enhancing the efficacy against resistant bacteria. The action of copper is hypothesized to involve the generation of hydroxyl radicals from its ions in an aqueous environment, leading to bacterial cell damage (Imlay et al., 1988; Sodhi et al., 2023). Copper has shown high inhibitory activity for Gram-positive bacteria. Copper ions also inactivate enzymes and impair membrane function, notably in *E. coli* (Macomber and Imlay, 2009). The study indicating copper complexed with antibiotics such as ciprofloxacin would be more efficient in against *P. aeruginosa* (Tewes et al., 2019). Cu(II) is especially studied for its effectiveness against diseases like tuberculosis and cancer (Macomber and Imlay, 2009).

TABLE 6 List of phytochemicals that have demonstrated antibacterial activity against clinically important microorganisms.

Plant species	Plant derived molecules	Target	Reference
Petroselinum crispum, *Matricaria chamomilla* *Apium graveolens*, *Basella rubra*, *Cynara scolymus*, *Origanum vulgare*, and *Portulaca oleracea*	Apigenin	*P. aeruginosa, K. pneumoniae, Salmonella typhimurium, Enterobacter aerogenes, and Proteus mirabilis*	(Dharambir Kashyap et al., 2018; Jadimurthy et al., 2023)
Azadirachta indica	Nimbolide	*H. pylori*	Wylie et al. (2022)
Sanguinaria canadensis L., Chelidonium majus L., Fumaria officinalis L., and Bocconia frutescens L	Sanguinarine	*P. aeruginosa*	Raneri et al. (2018)
Camellia sinensis, Brassica oleracea, Malus domestica	Kaempferol	*K. pneumoniae*	Sun et al. (2019)
Grapes, peanuts, berries	Resveratrol	*E. coli*, vancomycin-intermediate *Staphylococcus aureus* (VISA), *S. aureus, Campylobacter* species, and *Vibrio* species	Vestergaard and Ingmer (2019)

Quinolone-based copper complexes that target DNA gyrase, an enzyme crucial for DNA replication, have been examined, offering new avenues for antibacterial compounds against resistant strains. Additionally, a complex of Cu(II) with nalidixic acid showcased broader antibacterial activity compared to the antibiotic alone. The reduced polarity of such complexes due to chelation allows for better membrane penetration and thus enhanced bacterial cell growth inhibition.

3.9 Traditional medicine system

Plant-derived pharmaceuticals are an important source of addressing multidrug resistance (MDR). There is potential for these plants to produce novel antibiotics and chemosensitizers to combat multidrug resistance, by focusing on the secondary metabolites they produce, which may offer new, biocompatible therapeutic options. Using traditional knowledge from practices such as Ayurveda and Traditional Chinese Medicine, ethnobotany and ethnopharmacology are vital for discovering beneficial medicinal plants and developing new drugs. Secondary metabolites of plants, which are essential for defence, have shown promise for therapeutic use, possibly offering protection against the development of resistance to some synthetic drugs. As herbal medicines become more widely recognized for their efficacy, lower side effects, and cost-effectiveness, they are becoming increasingly popular. The use of medicinal plants to develop drugs against resistant microbes (Table 6), however, requires continued research and international collaboration.

3.10 Fecal microbiota transplantation (FMT)

In a recent study, Fecal Microbiota Transplantation (FMT) was found to be effective in decolonizing various common resistant pathogens, such as vancomycin-resistant *E. faecium* and *K. pneumoniae carbapenemase* (Caballero et al., 2015; Mrazek et al., 2019). In another study shown, mice treated with fecal microbiota transplantation (FMT) from murine and human donors showed significant reductions in multidrug-resistant *P. aeruginosa* within 7 days of the transplant. This study also suggests that donors from the same species may offer greater colonization resistance. According to Stalenhoef et al., a patient after one FMT session failed to eradicate an ESBL-producing multi-antibiotic-resistant *E. coli* strain, but was able to eradicate MDR *P. aeruginosa* within 3 months (Stalenhoef et al., 2017). Furthermore, Biernat et al. reported that their first patient was able to eliminate all infections after three weekly FMT sessions, while the second patient was still unable to remove MDR *E coli* and *Citrobacter freundii* after four weekly FMT sessions (Biernat et al., 2020).

3.11 Biofilm disruption agents

A biofilm disruption agent is a substance that interferes with the structure and function of a biofilm, the protective layer that bacteria form to protect themselves against external threats, including antibiotics. These agents can effectively treat antibiotic-resistant infections (AMR) as they break down the biofilm matrix, exposing the bacteria to antibiotics and the immune system, thus enhancing treatment effectiveness. Dispersin B is an enzyme that specifically targets and breaks down polysaccharide intercellular adhesin (PIA), an essential component of biofilms formed by *Staphylococcus epidermidis* and *S. aureus* (Lister and Horswill, 2014; Nguyen et al., 2020). Dispersin B disrupts the biofilm by degrading PIA, making bacteria more susceptible to antibiotics and immune response (Abdelkader et al., 2023). Methicillin-resistant *S. aureus* (MRSA), a type of AMR bacteria, is particularly susceptible to this treatment. C-2-decenoic acid (C2DA), a medium-chain fatty acid produced by *P. aeruginosa*, and D-amino acids have emerged as potential disruptors of biofilms in various bacteria, including antibiotic-resistant strains like MRSA (Ali Alghamdi et al., 2023). It has been demonstrated that C2DA inhibits and disperses biofilms in both Gram-positive and Gram-negative bacteria, suggesting its dual effectiveness in inhibiting biofilm initiation and promoting its dispersion (Jennings et al., 2012; Chung and Toh, 2014). C2DA has been demonstrated to enhance antibiotic effectiveness against biofilms, including those by Jennings et al. (2012) and Davies and Marques (2009), although it does not eradicate them completely, indicating the need for combination therapy to

achieve the best results (Jennings et al., 2012). In addition, Kolodkin-Gal et al. have observed that D-amino acids have the ability to dismantle biofilms by integrating into bacterial cell walls and disrupting the structural integrity of the biofilm matrix (Kolodkin-Gal et al., 2010).

4 Advantages and disadvantages of alternative therapeutics

Alternative therapeutics hold promise for offering new solutions in the fight against infections, especially in the face of growing antibiotic resistance. However, they are not a magic bullet and face several challenges before widespread adoption. The future will likely see a combination of optimized antibiotics and well-researched alternatives used strategically to combat different types of infections and minimize resistance development. It is important to remember that research in this field is ongoing, and the landscape of potential alternatives is constantly evolving. Here, we summarize a general overview, and specific advantages and disadvantages may vary depending on the individual therapeutic approach being considered.

4.1 Advantages

1. Potential for targeting diverse resistance mechanisms: Unlike traditional antibiotics that often target one specific bacterial process, alternative therapies can aim at different pathways involved in resistance, potentially overcoming broader spectrum resistance (Park et al., 2011).
2. Reduced selective pressure for further resistance development: Since they often work with different mechanisms, alternative therapies may exert less selective pressure on bacteria, potentially slowing down the emergence of new resistance (Takahashi et al., 2004).
3. Enhanced immune system involvement: Some alternative approaches, like phage therapy or immunomodulatory strategies, can stimulate the body's own defence mechanisms, offering a more holistic approach to fighting infections (Howard et al., 1977).
4. Reduced side effects and potentially fewer drug interactions: Alternative therapies can potentially offer benefits over antibiotics in terms of side effects, especially for patients with pre-existing conditions or concerns about antibiotic-associated adverse events (Lei et al., 2019).
5. Potential for addressing non-bacterial infections: Some alternative approaches, like phage therapy or CRISPR-based interventions, might have applications beyond bacterial infections, offering broader utility in the fight against microbial resistance (Laverty et al., 2011).

4.2 Disadvantages

1. Limited clinical data and evidence: Many alternative therapies are still in early stages of research and development, lacking robust clinical data and established efficacy compared to conventional antibiotics.
2. Difficulties in targeting specific bacteria: Some alternative therapies might struggle to selectively target specific bacterial pathogens, potentially harming beneficial bacteria in the microbiome and leading to other complications.
3. Cost and accessibility challenges: Developing, manufacturing, and delivering some alternative therapies might be more expensive than traditional antibiotics, raising concerns about accessibility, especially in resource-limited settings.
4. Regulatory uncertainties and approval processes: Regulatory frameworks for approving alternative therapies might not be clear or established, leading to delays and uncertainties in bringing them to market.
5. Lack of standardization and quality control: Ensuring consistent quality and effectiveness across different formulations or producers of alternative therapies can be a challenge, requiring robust quality control measures.

Overall, while alternative therapies offer promising avenues for tackling antibiotic drug resistance, significant challenges remain before they can fully replace or complement traditional antibiotics.

5 Challenges in developing alternative therapies and future directions

AMR is a ticking time bomb in the medical world, and despite several advantages and motivations, developing alternative therapies presents a multitude of challenges. Here are some key hurdles to overcome.

5.1 Scientific and technological hurdles

1. Targeting different mechanisms: Unlike conventional antibiotics that directly kill bacteria, alternatives often target different, more complex mechanisms, like interfering with resistance pathways or modulating the microbiome (Alaoui Mdarhri et al., 2022). This can be difficult to achieve effectively and selectively.
2. Limited understanding of resistance: The sheer diversity and rapid evolution of bacterial resistance mechanisms make it hard to predict how effectively new therapies will work and for how long these will survive without generating resistance (McCubbin et al., 2021).
3. Lack of robust preclinical models: Testing alternative therapies often requires sophisticated models that accurately mimic human infections and resistance profiles. Developing and validating such models is time-consuming and expensive.
4. Safety and efficacy concerns: New therapies need to be thoroughly tested for safety and efficacy in humans, which can be a lengthy and costly process (Saarela, 2019). Additionally, ensuring effectiveness against diverse resistant strains adds another layer of complexity.

5.2 Economic and policy hurdles

1. Low commercial viability: Compared to drugs for chronic diseases, antibiotics are used for shorter durations, limiting their profit potential for pharmaceutical companies. This disincentivizes investment in research and development.
2. Regulatory challenges: Regulatory pathways for approving alternative therapies are not well-established, leading to delays and uncertainties. Governments and agencies need to adapt their processes to accommodate these innovative approaches.
3. Lack of awareness and infrastructure: Knowledge and adoption of alternative therapies among healthcare professionals and communities need to be improved. Building infrastructure and addressing logistical challenges for delivery, especially in resource-limited settings, is crucial.

5.3 Other challenges

1. Public perception and overuse: Misuse and unnecessary antibiotic use fuel the emergence and spread of resistance. Addressing public perception and promoting responsible antibiotic use remains a critical aspect.
2. Collaboration and knowledge sharing: Effective development and implementation of alternative therapies require collaboration between researchers, clinicians, policymakers, and industry players. Sharing knowledge and resources openly is essential.

Despite these challenges, the urgent need for effective solutions against AMR drives continuous research and development. Exploring diverse approaches like phage therapy, antimicrobial peptides, CRISPR-based interventions, and immunomodulatory strategies holds promise for the future. Continued research, development, and collaboration between researchers, clinicians, and policymakers are crucial to overcome these hurdles and harness the potential of these innovative approaches in effectively combating AMR (Robinson et al., 2016).

6 Conclusion

The fight against drug-resistant bacteria enters a new chapter with growing research into promising non-antibiotic therapies. These approaches hold immense potential to combat the alarming rise of antibiotic resistance, offering a potent alternative to conventional weapons. However, we must tread cautiously. While these therapies present highly sophisticated modes of action, extensive clinical trials are still needed to solidify their efficacy and safety. Therefore, implementing them as routine treatments demands careful consideration. In addition to treating AMR bacteria with alternative therapies, we should also consider strategies for sustainable remediation of antibiotics utilizing waste products, biochar, and microbial fuel cells (Kushneet Kaur Sodhi, 2022). Ultimately, a deep understanding of resistance patterns and mechanisms of action is crucial. This knowledge will empower clinicians to tailor antimicrobial treatment, paving the way for personalized and precise medicine.

Author contributions

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