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Overview of antimicrobial resistance and mechanisms: The relative status of the past and current

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ABSTRACT

Antibiotic development is not new to the medical community, but the emergence of antibiotic resistance has become the most serious threat to global health and food security. It results in longer hospital stays, more expensive medical treatments, and greater mortality rates around the world. The basic categories used to describe antibiotic resistance originating from both natural and genetically driven processes are natural, acquired, cross-resistance, multidrug, and pan-drug resistance. Bacterial intrinsic resistance is characterized by continued improvement of resistance mechanisms via cell wall structure and other cellular features. Resistant drug uptake, target site change, efflux pump mechanism, and target site mutation are examples of resistance mechanisms. The presence of resistant bacteria and antibiotic residues in the environment requires urgent global action to combat antimicrobial resistance (AMR). Discovering new antibiotics is not the only prerequisite for dealing with this scenario; continuous national surveillance of antibiotic resistance gene level dissemination is also necessary. This review provides the most up-to-date status of the mechanisms of AMR against several antibiotics on the market and how the resistant bacteria have evolved with diverse mechanisms for their survival. It also discusses the significant clinical consequences and the impact of resistant bacteria exposure on public health. Further, it puts together a global understanding of the prevalence of resistant genes and offers recommendations to stop the further spread with some guidelines.

1. Introduction

Current methods for treating antibiotic-resistant bacteria pose a new global dilemma as resistant bacteria and antibiotic-resistant genes spread among humans, animals, and the environment, as reported by Levy (1992). As a result, investigations on antibiotic-resistant bacteria have also focused on antibiotic overuse in a wide range of animal and human disorders. (Levy, 1992). Increased antimicrobial resistance (AMR) is linked to the increasing number of antibiotic-resistant organisms, their regional variations, and individual potency (Levy, 2002). Many years ago, studies revealed that Gram-negative bacteria were more typically engaged in life-threatening infections than Gram-positive bacteria (Ramasubramanian, 2011). The multiple evolutionary forms of resistant mechanisms have created a worrisome situation with a higher level of risk worldwide. The widespread abuse of antibiotics in humans and animals is a direct result of the significant handling factors, which have opened the door for the abrupt expansion of the pharmaceutical industry ((Martinez et al., 2008; Hawkey and Jones, 2009).

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Along with the emergence of antibiotic-resistant bacteria in hospitals and other clinical settings, severe medical effects of antibiotic uses are significantly increasing. Earlier research linked widespread antibiotic use to resistance, resulting in prolong hospital stays (Laxminarayan and Brown, 2001). In 2001, a study by Levy reported that an individual's severity of antibiotic resistance is related to the number of individuals infected and their total count in the environment (Levy, 2001). Gram-negative bacterial infections pose a severe problem that needs further study and effective treatment. A review study published in 2011 outlined the goals of antimicrobial stewardship programs, the legal framework required to set them up, the necessary antimicrobial stewardship tactics, an evaluation of the actions completed, and other monitoring systems (Tamma and Cosgrove, 2011). Gram-negative bacteria proliferation presents a challenge in clinical treatment (Lautenbach et al., 2001). The study also discovered that the period needed to start natural therapy for Gram-negative bacterial infections caused by strains that produce extended-spectrum β-lactamases (ESBLs) was almost six times longer than that for Gram-negative infections by strains that do not produce ESBL. Other studies confirmed the production of ESBLs and delayed antimicrobial therapy in patients with Gram-negative bacteremia (Schwaber and Carmeli, 2007). According to earlier findings, using aminoglycosides in the treatment resulted in the development of β-lactam resistance in patients with sepsis caused by Gram-negative bacteria. In 2005 and 2008 reports, all available proofs demonstrated that the ratio of Gram-negative bacteria resistant to commonly available antibiotics in clinical settings was increasing concurrently (Paterson and Bonomo, 2005; Giske et al., 2008). A study conducted by Nadgir and Biswas (2023) on antibiotic diseases and their impact on disease management that reflects globally with similar reasons includes misuse of antibiotics, reduced output on pharmaceutical firms in generating new medicines, and putting our advanced medical treatment system at risk. Gram-negative bacterial infections are in particular the most utterly growing concern to the pharmaceutical sector and bringing the pre-antibiotic era back (Nadgir and Biswas, 2023). Antibiotics such as tigecycline and colistin, regarded as "salvage" medicines in medical treatment, have shown a substantial increase in resistance power ((Falagas and Kasiakou 2006; Paterson and Doi, 2007). An epidemiological analysis of the antibiotic resistance treatment report published in 2012 showed a correlation between death rate and delayed poor antimicrobial therapy. To lower the risk of mortality during the early stages of infection, critically ill patients must be treated with broad-spectrum empiric antimicrobial therapy. Patients who are immunocompromised, hospitalized in the intensive care unit, recently took broad-spectrum antibiotics, and underwent empiric antimicrobial treatment are at increased risk of developing multidrug-resistant Gram-negative bacterial infections that are resistant to previously prescribed medications (Tamma et al., 2012).

The World Health Organization (WHO) has identified AMR as one of the three most severe threats to human health. In previous studies, authors used the term ESKAPE pathogens to account the higher frequency of infections among humans, referring to organisms such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* sp. Table 1 shows the profile of antibiotic resistance for ESKAPE pathogens, showing their resistance properties to different antibiotics. A vast number of epidemiological reports show that the pharmaceutical library currently lacks important antibiotic classes that are effective against multidrug-resistant Gram-negative bacteria (Bassetti et al., 2011). The very recent findings are saying that humans are prone to resistant pathogen infections as they are highly influenced through hospitals and other communal settings. The environmental hotspots are thus disseminating the resistant genes among the bacterial community (Kunhikannan et al., 2021). Environmental bacteria may acquire antibiotic resistance by co-existence, evolution, or horizontal gene transfer (HGT), which can significantly impact antimicrobial resistance compared to vertical gene transfer (Saha and Sarkar, 2021).

2. Status of resistance mechanism in various forms

2.1. Nature and acquired resistance

The broadest spectrum β-lactams are antibiotic molecules classified according to their chemical structures. The carbapenem family includes imipenem, ertapenem, meropenem, and doripenem, the recently developed drug molecules with the broadest spectrum of activity (Pitout and Laupland, 2008). *Escherichia coli* isolates and associated ESBLs can hydrolyze the most considerable amount of carbapenem, which has been observed internationally since 2020. Increased consumption of carbapenems has become a growing concern that has significantly impacted the hospitalized patient community. As a result, the available antibacterial agents are critical for treating nosocomial infections with carbapenem resistance, including those are related to organ transplants and major surgeries. Owing to the accumulation of carbapenemase genes everywhere, carbapenem-resistant *Enterobacteriaceae* has been observed at a higher level worldwide. According to the Alliance for the Prudent Use of Antibiotics (APUA) newsletter, serine β-lactamases (serinebased) and metallo-β-lactamases (zinc based) are the two types of carbapenemase enzymes. Ambler class A or D serine–based enzymes have less hydrolytic activity than metalloenzymes that are not highly hydrolyzed by aztreonam and can be inhibited by β-lactamase inhibitors. Because they can hydrolyze all β-lactam antibiotics except aztreonam and are resistant to β-lactamase inhibitors, Ambler class B acquired carbapenemases are the most clinically significant ones. Previous research has focused on metallo-β-lactam and serine-based enzymes found primarily in the Enterobacteriaceae family of bacteria and the non-lactose-fermenting bacteria such as *P. aeruginosa* and *A. baumannii*. Antibiotics, including piperacillin cephalosporins, fluoroquinolones, and aminoglycosides have a poor response rate for treating multidrug-resistant microorganisms (Nordmann et al., 2012). Queenan and Bush (2007) simplified the classification of carbapenemases into three molecular classes of β-lactamases from the Enterobacteriaceae group, namely Ambler classes A, B, and D β-lactamases, with effective activity. Carbapenem resistance mechanisms includes,

1. the acquisition of carbapenemase genes that degrade carbapenems
2. less antibiotic uptake toward porin expression and
3. overexpression of β-lactamases that inhibit carbapenem activity.

Carbapenemase enzymes include (i) the KPC-type enzymes; (ii) the VIM, IMP, and NDM metallo-β-lactamases (MBL); and (iii) the OXA-48-type enzymes, which are mainly evolving in clinical settings around the world (Nordmann et al., 2012).

In 2007, the AMR in Gram-negative bacteria was explained based on the expression of antibiotic-inactivating enzymes and non-enzymatic mechanisms present in the resistant strains (Alekshun and Levy, 2007). Resistance in Gram-negative strains was reported through various mechanisms such as antibiotic-inactivating enzymes or efflux pump or horizontal plasmid transfer of mobile genetic elements carrying resistance genes. Plasmid-encoding β-lactamases, aminoglycoside-modifying enzymes, or non-enzymatic mechanisms like Qnr with fluoroquinolone resistance in *Enterobacteriaceae* have been reported as the main mechanisms (Luyt et al., 2014; Bassetti and Righi, 2015; Ruppe et al., 2015). The diverse forms of resistance mechanisms acquired by the resistant bacteria under multiple biochemical pathways broadly categorized into antibiotic molecules alterations upon target site, antibiotic activating enzymes activations and active sites under alterations, reduced condition of membrane permeability and efflux pump activity expressions (Ahmed et al., 2023).

In the study by Kumarasamy et al. (2010), the resistant mutants were found to be involved in the increased accumulation of ESBL enzymes. The "carbapenem" antibiotic family, developed by the pharmaceutical industry in the 1990 s, has high activity against β-lactamases enzymes. Similarly, various β-lactamases, such as imipenemase, Verona

Table 1
Antimicrobial resistance profile of ESKAPE pathogens.

Multidrug-resistant bacteria	Characteristics	Description	Reference
Escherichia coli	• Gram-negative facultative anaerobic rod-shaped bacterium • Responsible for nosocomial infections	• Overall 101 (91.8%) isolates were MDR conferring resistance to at least three drug classes.High frequency of resistance was observed for tetracycline ($n = 102$; 92.7%), trimethoprim/sulfamethoxazole ($n = 93$; 84.5%), streptomycin ($n = 87$; 79.1%), and ampicillin ($n = 88$; 80%)	Aworh et al. (2021)
		• Samples collected from poultry and domestic pigs • Highly resistant to tetracycline (63.5%), nalidixic acid (53.7%), ampicillin (52.3%), and trimethoprim/sulfamethoxazole (50.9%)	Kimera et al. (2021)
		• 51.6%, 65.3%, and 53.7% of *E. coli* were MDR, extended-spectrum β-lactamase-producing *Enterobacteriaceae*(ESBL-PE), and quinolone-resistant, respectively	
		• Samples were obtained from Msimbazi River basin in Tanzania (river water, sediment, and crop soil) • Quinolone-resistant *E.coli* obtained	Kimera et al. (2021)
Staphylococcus aureus	• Gram-positive cocci-shaped bacterium • Responsible for hospital-acquired infections	• *E. coli* isolates were highly resistant to ciprofloxacin (39.7%) and trimethoprim/ sulfamethoxazole (38%)	
		• Methicillin- and vancomycin-resistant coagulase-negative *Staphylococcus* was obtained from nasal swab of hospitalized patients. • Twenty-two (10.9%) isolates were MR-CoNS harboring *mecA* gene.	Al-Tamimi et al. (2020)
		• CoNS and MR-CoNS isolates were highly resistant to benzylpenicillin, erythromycin, fosfomycin, and imipenem. • 1091 *Staphylococcus aureus* isolates collected from one New York hospital	
		• AMR profile in *S. aureus* associations between β-lactams and other antimicrobial classes (macrolides, lincosamides, and fluoroquinolones) were common.	Cazer et al. (2021)
		• Samples were obtained from healthy horses. • Of these isolates, 37.1% were identified as methicillin-resistant staphylococci (MRS).	Othman et al. (2021)
Klebsiella pneumoniae	• Gram-negative bacteria • Nosocomial pathogen	• New Delhi metallo-β-lactamase (NDM) in a Peruvian hospital • Isolated from patients were admitted for a diagnosis of COVID-19	Arteaga-Livias et al. (2021)
		• Totally 42 multidrug resistant *K. pneumoniae* were isolated • All isolates contained the $bla_{\text{CTX-M}}$gene, while 41/42(97%) contained bla_{TEM}, 36/42(86%) contained bla_{OXA},and 35/42(83%) harbored bla_{SHV}genes.	Mbelle et al. (2020)
		• Samples obtained from hospitalized patients. • The highest prevalence of resistance was observed against ciprofloxacin (75%), trimethoprim–sulfamethoxazole (73%), and nitrofurantoin (68%). Virulence-associated genes including *entB*, *traT*, *ybts*, *magA*, *iucC*, *htrA*, and *rmpA* were found in 80%, 62%, 75%, 5%, 30%, 72%, and 48% isolates, respectively.	Mirzaie and Ranjbar (2021)
Acinetobacter baumannii	• Gram-negative aerobic nonmotile bacteria • Cause various healthcare-associated infections and nosocomial infections. • One of the red alert pathogens	• The overall rate of carbapenem non-susceptible and multidrug resistance rates in *Acinetobacter* species was 56.7% and 71.6%, respectively. • Significant ascending trends of antimicrobial resistance was shown for meropenem (12.5%–60.7%), ceftazidime (82.1%–100%), ciprofloxacin (59.4%–74.4%), ceftriaxone (87.1%–98.6%), cefepime (80.0%–93.3%), and pipracillin-tazobactam (67.8%–96.3%).	Ayenew et al. (2021)
		• Isolated from hospitalized patients • Of 177 *A. baumannii*, 91.0% were identified as MDR. • Mostly collected from respiratory tract specimen.	Yadav et al. (2020)
		• All 122 multidrug-resistant *A. baumannii*isolates were resistant to majority of the antibiotics used except polymyxin and tigecycline. • 96 MDR *A. baumannii* isolates had MICs of >512 mg/L to amikacin and arbekacin, high resistance to aminoglycosides.	Shrestha et al. (2016)
		• Of 96 pan-aminoglycoside-resistant isolates, 75 isolates had 16SrRNAmethylasewith all isolates harboring *armA* gene.	
Pseudomonas aeruginosa	• Gram-negative, aerobic, nonspore-forming rod shaped • Opportunistic human pathogen • Forms antibiotic-resistant biofilms • Responsible for nosocomial infections and wound infections	• The results exhibited that from 200 isolates 52 (26%) were *P. Aeruginosa* and in that 20 (38.46%) were recorded as MDR. • Totally 90% MDR were formed biofilm. • *Psl*A gene were detected in all biofilm forming isolates.	Abdulhaq et al. (2020)
		• Multidrug-resistant *P. aeruginosa* used for 20% ($n = 16$). • The 83.75% ($n = 67$) of bacterial isolates demonstrated biofilm phenotype.	Kamali et al. (2020)
		• Collected from various wound samples. • Of samples, 119 (58.6%) were confirmed MDR. • Resistant to β-lactams drugs and most effective drugs were tigecycline and colistin.	Ijaz et al. (2019)
Enterobacter cloacae	• Belongs to Enterobacteriaceaefamily • Gram-negative, facultative anaerobic bacteria • Mostly cause nosocomial infections • Rarely cause community-acquired infections including UTI	• Recently, carbapenem-resistant *E. cloaceae* complex has emerged. • Heat-shock protein sequence, pulsed-field gel electrophoresis, comparative genomic hybridization, and, multilocus sequence typing are used to molecular identification and characterization.	Annavahala et al. (2019)

integron-encoded MBL, *K. pneumonia* carbapenemase, and oxacillinase are available and can be easily hydrolyzed by antibiotics. The Ambler classification which categorizes β-lactamase enzymes into four types based on the amino acid sequences found in the enzymes, is the most well-known classification method for β-lactamases. Class A enzymes derived from plasmid-mediated penicillinases can inhibit lactamase and block their expression. In addition, extended-spectrum cephalosporins contain class A β-lactamase enzymes. The second most crucial class is class B enzymes, MBL, which have higher substrate specificity that binds with penicillins, cephalosporins, and the most effective carbapenems. Another well-known Class C enzyme is chromosomally encoded cephalosporinases, also known as AmpC β-lactamases, which are resistant to inhibition by β-lactamase inhibitors. Finally, class D β-lactamases strongly prefer oxacillin antibiotics as a substrate. They are known as oxacillinase enzymes in the carbapenemase enzyme family. NDM-producing bacteria show high resistance activity against most antibiotics including fluoroquinolones, aminoglycosides, β-lactams, and carbapenems. However, they are susceptible to only two antibiotics, colistin and tigecycline (Kumarasamy et al., 2010).

2.2. Resistance mechanisms based on susceptibility

The term "multidrug resistance," or MDR, is defined as "resistance to more than one class of antimicrobial agents." As the drug resistance problem grows, standardized standards to characterize and categorize microorganisms resistant to several antimicrobial agents are required (Magiorakos et al., 2012). The most commonly used term to describe multidrug resistance among the bacterial community is MDR. MDR is diagnosed based on the pattern of antibiotic susceptibility test results showing resistance to various antimicrobial agents from classes or subclasses that available in the market. The scientific literature refers to this as "resistance to three or more antimicrobial classes" in Gram-negative bacteria (Cohen et al., 2008; Hidron et al., 2008; Gould, 2008).

Extensive drug resistance (XDR) is a term used to describe a bacterial group that has resistance to antimicrobial drugs. These bacteria are epidemiologically most significant for their resistance to all, or the most approved, antimicrobial agents on the market. Hence, the medical community has used various generic terms to describe the level of resistance such as “extreme drug resistance”, “extensive drug resistance,” "extremely drug resistant,” and "extensively drug resistant” (Tseng et al., 2007; Karageorgopoulos and Falagas, 2008; Park et al., 2009).

The term “pan-drug resistance” PDR is originated from the Greek word “pan,” meaning “all.” PDR refers to bacterial isolates that are “resistant to all antimicrobial agents ”to all antimicrobial agents of all classes available in the medical community, including all subclasses. Various studies have defined PDR as “resistant to all commercially available antimicrobial agents,” “resistant to all antimicrobials routinely tested,” and “resistant to all antibiotic classes available for empirical treatment” (Kuo et al., 2004). Thus, the definition of the PDR was approved to help interpret and avoid misinterpretation of antimicrobial susceptibility test reports based on resistance activity. The term PDR is used to categorize bacterial species that are not susceptible to any antimicrobial agents available on the market and to indicate that the bacteria are pan-drug resistant (Magiorakos et al., 2012).Cross--resistance occurs when a resistant isolate shows resistance to all the antibiotics belonging to the same class due to a single mechanism. However, the degree of resistance to such antibiotic classes that are more active with the drug may be lower. Different antibiotics resistant status conditions, such as MDR, XDR, PDR, and cross-resistance, can be categorized based on their degree of resistance in a single bacterium (Fig. 1).

3. Mechanisms of antibiotic resistance in bacteria

3.1. Restricted drug uptake

The restricted drug uptake mechanism occurs through changes in the porin channels in the cell membrane using the β-lactam rings. Alternatively, the resistant bacteria can use the efflux pump mechanism via β-lactam pumps to escape the periplasmic space. Among the β-lactam resistance mechanisms, the restricted drug uptake mechanism is common in *P. aeruginosa*, *A. baumannii*, and Enterobacteriaceae. Another example is *P. aeruginosa*, which can exhibit this mechanism due to the

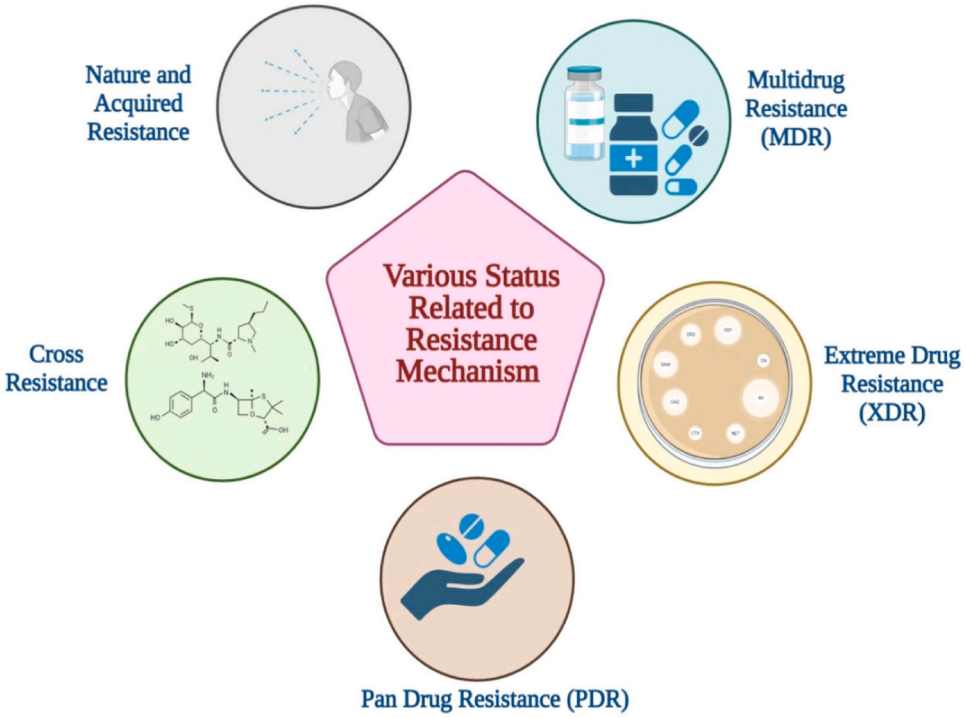

Fig. 1. Overview of various status related to antibiotic resistance conditions.

loss of mutation or the OprD2 porin alterations in the entry channel (Byrne et al., 2019).

3.2. Target mutations and modification

In this mechanism, the drug-resistant bacteria cells naturally develop mutations in genes, drastically impacting the drug's ability to function. In many cases, the mutational changes lead to cell homeostasis, which is maintained only in the presence of the antibiotic molecule at the site. Overall, the resistance mechanisms caused by mutation are developed due to modifications of the antimicrobials through (i) less drug uptake, (ii) activation of efflux mechanisms, or (iii) changes in the metabolic pathways (Samreen *et al.*, 2021).

3.3. Transporter family and efflux pump mechanism

The efflux pump mechanism is the most important resistance mechanism used by resistant bacteria for pumping antibiotics from the cells to the external environment by using transporter proteins. As the demand for antibiotics grows, studying these efflux pump inhibitions has become more appealing worldwide. The molecules that can inhibit such efflux pump resistance mechanisms are known as efflux pump inhibitors and are considered effective tools in the fight against the resistant bacteria. They generally follow some inhibition mechanisms and are sourced from both natural and synthetic compounds (Munita and Arias, 2016).

4. Resistance mechanisms and driving force of antibiotics use

Antibiotics are called "antimicrobial agents" or molecules. A molecule is "a chemical substance made by a microorganism that kills or slows the growth of another microorganism". Since the introduction of antimicrobial agents in 1937, the growth of resistant bacteria and their resistance mechanisms has led to the concept known as AMR. The ability of infection-causing microbes to withstand the effect of antimicrobial agents, which inhibits their growth or kills them, is another feature that helps explain AMR. Also, this condition has other facets, such as high medical expenses, follow-up visits, and routine health checkups. Because of the evolutionary nature of resistant bacteria, AMR is unavoidable due to their inherent ability for survival, mutation, and adaptation to resistance under stress and a higher level of exposure to antimicrobial agents (Fig. 2). The study also concluded that AMR cannot be reversed or eradicated but can be subjected to treatments that slow down the actions of antibiotic resistance mechanism. In 2001, the WHO established the Global Strategy for Containment of Antimicrobial Resistance and defined the appropriate use of antimicrobials as "cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing drug-related toxicity and the development of antimicrobial resistance" (Byrne et al., 2019). Samreen *et al.* (2021) concluded in a study that, the environment can serve as a reservoir of antibiotic-resistant bacteria and ARGs, as well as a breeding ground for resistance. As a result, it is the most common mode of transmission for resistant bacteria linked with fecal matter in water, sewage infrastructure, and organic fertilizers.

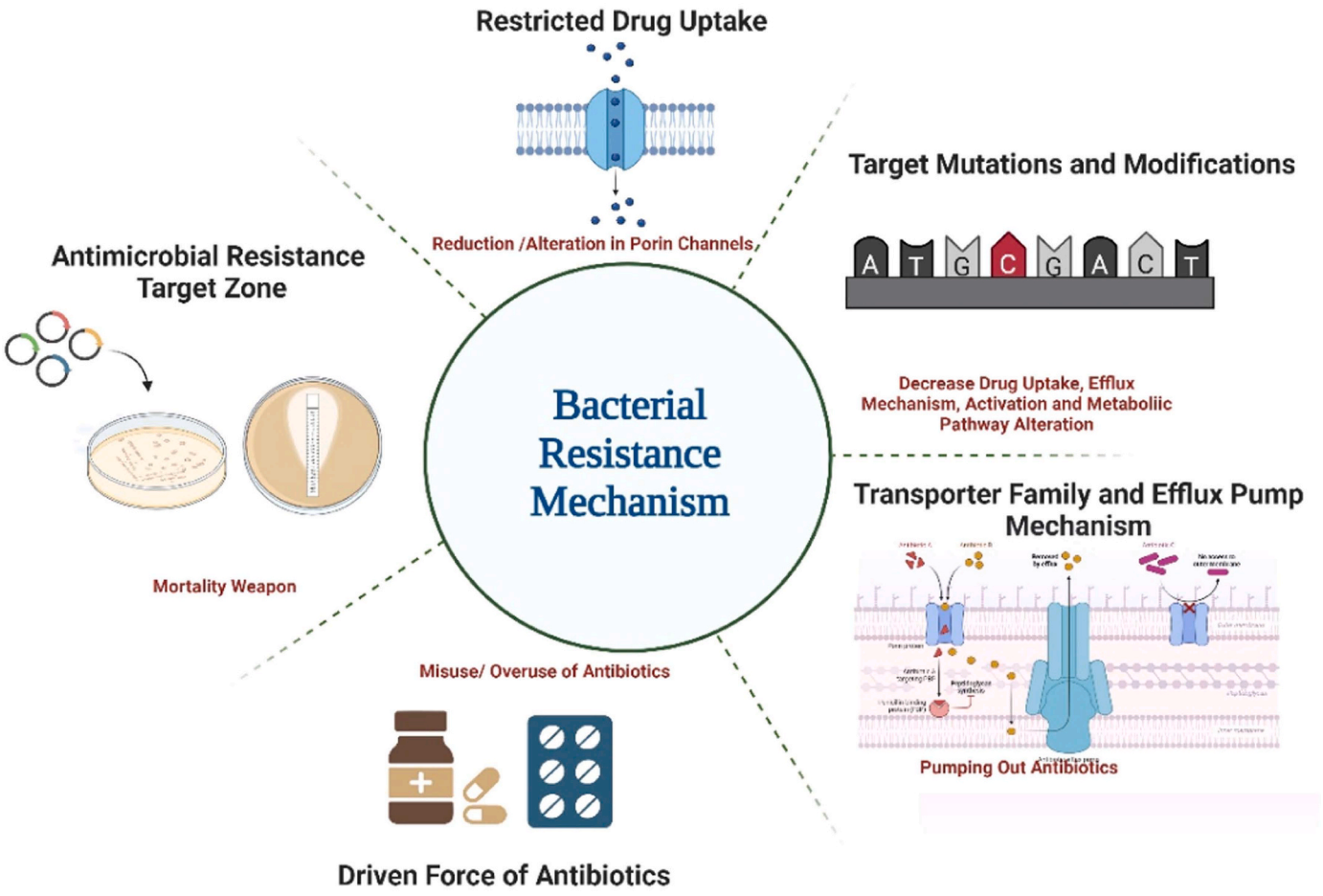

Fig. 2. Schematic overview of bacterial resistance mechanisms.

4.1. Antibiotic resistance development through livestock

The widespread use of antimicrobials in the treatment and development of livestock and animal feeding has significantly impacted antibiotic resistance spread through resistant bacteria. In all developed and developing countries, food-producing animals such as poultry, pigs, and cattle are highly exposed to high doses of antibiotics to prevent bacterial infections and create safer and better economic conditions for commercial development. The epidemiological data about antibiotic usage in livestock showed that India occupied the fourth highest place in the world in 2018, followed by China, the United States, and Brazil. However, during the past 10 years, the non-therapeutic use of antibiotics in animal husbandry has also increased, which has led to the development of resistant bacteria and a critical situation in the field of public health (GAO, 2004). According to theories about how resistant bacteria evolve, AMR is unavoidable because of the bacteria's innate capacity for survival, mutations, frequency of resistance development, and adaptation to stress and a higher level of exposure to commercially available antimicrobial agents through various forms and mechanisms (Fig. 3).

Other sources of antibiotic usage and, in turn, the spread of its resistance are biological wastes, dairy products, meat products, and through animal farms. In addition, potential pathogens in animals that cause zoonotic infection are also another source for the spread of antibiotic resistance genes (ARGs). Owing to the import and export of animal food from various countries, the level of spread has increased worldwide. A study in early 1999 showed the spread of avoparcin, which is a glycopeptide antibiotic mainly used as an animal growth promoter in developed nations against vancomycin-resistant enterococci (VRE) in animal food (Wegener et al., 1999). The presence of a large quantity of resistance-developing antibiotics in the environment in various forms can cause direct contact resistance transfer among the public (Allen, 2014). Developed countries have strictly prohibited using antibiotics as animal growth promoters under various health parameters (Heuer et al., 2011). Among the types of gene transfer mechanisms present in bacteria, horizontal gene transfer plays a vital role in developing the transfer of MBL without using those antibiotics in agriculture. Over the past years, the development of resistance to antibiotics has been mainly due to natural and sudden mutations in genes, showing that the number of microorganisms originating from nonclinical environments is significant (Martinez et al., 2008). A recent review on multiple facets of drug resistance has emphasized the shortage of new antimicrobial agents and insisted on conducting an epidemiological and surveillance research analysis to prevent antibiotic resistance. In-depth knowledge and awareness of antibiotic resistance is the key to success in controlling MDR pathogens. Therefore, strict government prophylaxis policies should be prepared and implemented to monitor the proper use of antibiotics (Saha and Sarkar, 2021).

5. Impacts of the AMR danger zone

The increasing use of broad-spectrum antibiotics is contributing to the development of MDR organisms. A higher number of ICU patients are experiencing extended hospital stays due to prolonged use of antibiotics during recovery. However, treating MDR organisms with antibiotics against is highly complicated, with patients experiencing harmful side effects and the pharma industry benefitting economically. Previous studies have reported the risk of developing antibiotic resistance over 10 years with notable antibiotics such as third-generation cephalosporins, vancomycin, imipenem, and intravenous fluoroquinolones.

Another necessary antibiotic, colistin, was used frequently in the last decade, but its effect on creating resistance among the bacteria was

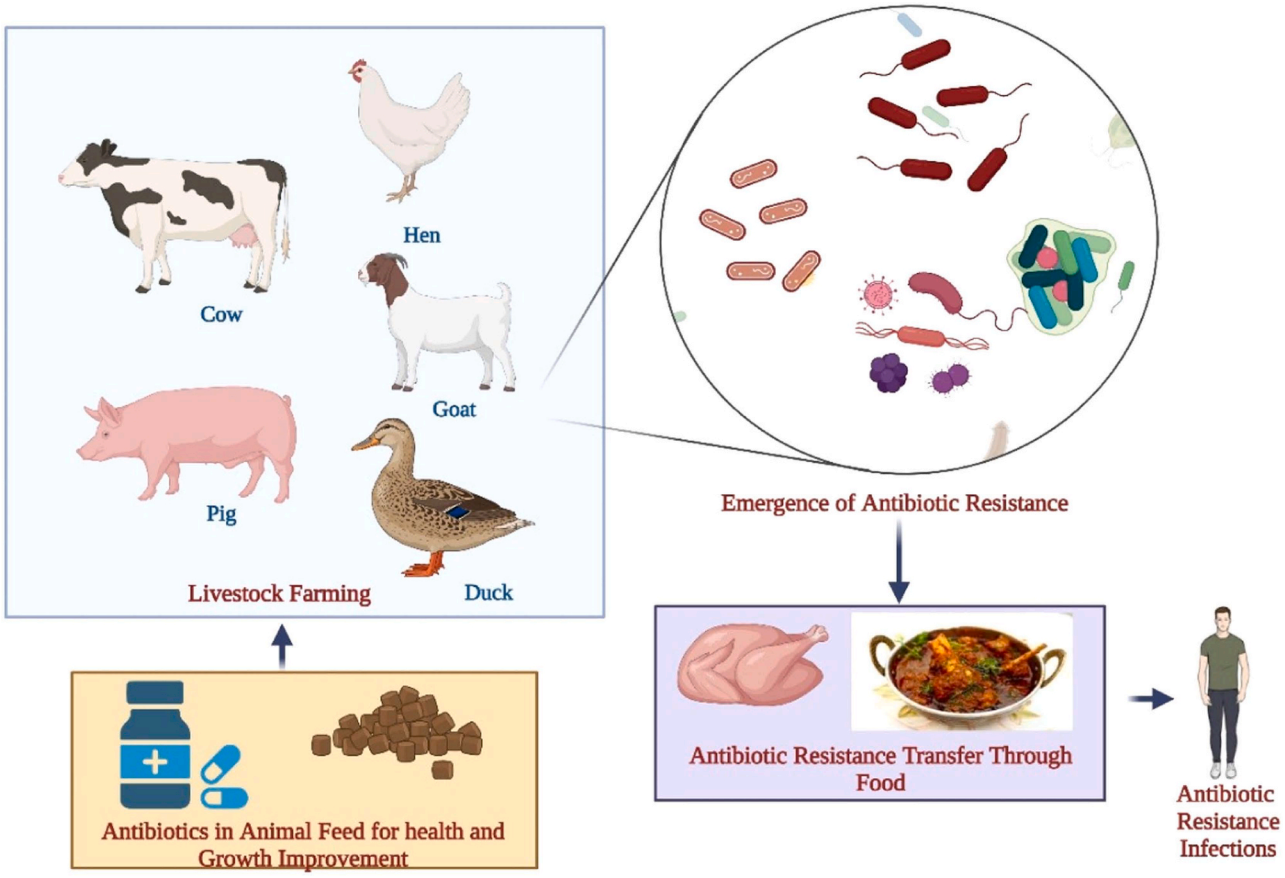

Fig. 3. Pictorial representation of development of antibiotic resistance through livestock.

lesser compared to the previously listed antibiotics. Bonten and Mascini (2003) documented four core drivers of rapidly growing bacterial resistance: induction, selection, introduction, and dissemination of resistant strains. In general, serious infections caused by Gram-negative resistant bacteria increase mortality rates worldwide and there are very few effective antibiotics against these infections. In this antibiotic development period, reduction therapy with minimal use of wide-spectrum antimicrobials has been tested. The effectiveness of antibiotics against resistant bacteria is evaluated after a few hours of treatment as part of resistance analysis (Bonten and Mascini, 2003; Brusselaers et al., 2011.

The WHO has highlighted the problem of resistant bacterial infections caused by microbes, which can cause prolong illness, a higher chance of dying, longer stays in the ICU, and other long-term health conditions. These conditions increase the chances of transmitting resistant bacteria both among hospital staff and the patient community. If any resistant bacteria–infected patients do not respond to the first-line antibiotic, physicians are advised to proceed to the next level of second- or third-line drugs, which are more expensive. Several factors drive the use of more advanced and effective antibiotics even for common bacterial infections, such as incorrect antibiotic use, patient factors, overprescription by physicians, monotherapy, misuse of antibiotics as a business model by hospitals, prescriptions from the veterinary sector, commercial and marketing promotion, over-the-counter sale of antibiotics, prevailing microbiological testing methods, and the role of globalization in economic growth. Basic infection control practices such as hand washing and disinfection, are critical but the shortage of healthcare staff is also a significant contributor to the spread of resistant bacteria (Larson and Kretzer, 1995).

6. Future directions to tackle antibiotic resistance

To protect humans and cattle from the spread of antibiotic resistance, it is necessary to adopt a substitute non-antibiotic approach that is both significantly safer and free of antibiotics. Ongoing research on replacing resistant microorganisms has been focused on effective techniques from both traditional and modern technologies (Fig. 4).

6.1. *Alternative mechanisms to treat resistant bacteria*

6.1.1. *Fecal microbiota transplantation and two-component systems (TCS)*

Alternative measures to address antibiotic resistance are of great interest to drug discovery researchers worldwide. Dietary supplements to boost an individual's immune system area healthy method to stop the development of the resistant bacterium, even in critically ill and hospitalized patients. Another promising method is fecal microbiome transformation, which involves transferring healthy flora containing fecal matter from a healthy person to a recipient who is ill with enteric infections using methods such as enema, nasogastric, nasoduodenal, and colonoscopy.

Also, the antibiotics related factors disrupt the normal balance of colonic flora and reduce "colonization resistance, by reintroducing normal flora via donor feces, the imbalance can be corrected, the cycle broken, and normal bowel function reestablished (Bakken et al., 2011). This technology is also known as fecal transfusion, fecal transplant, fecal enema, human probiotic infusion, and stool transplant, and it is called "transformation" when used to treat cattle (Depeters and George, 2014).

The two-component systems (TCS) are regulatory elements found in bacteria. They are crucial to bacterial growth and virulence properties. Identifying bacterial TCS in the cell cycle and cell envelope of the

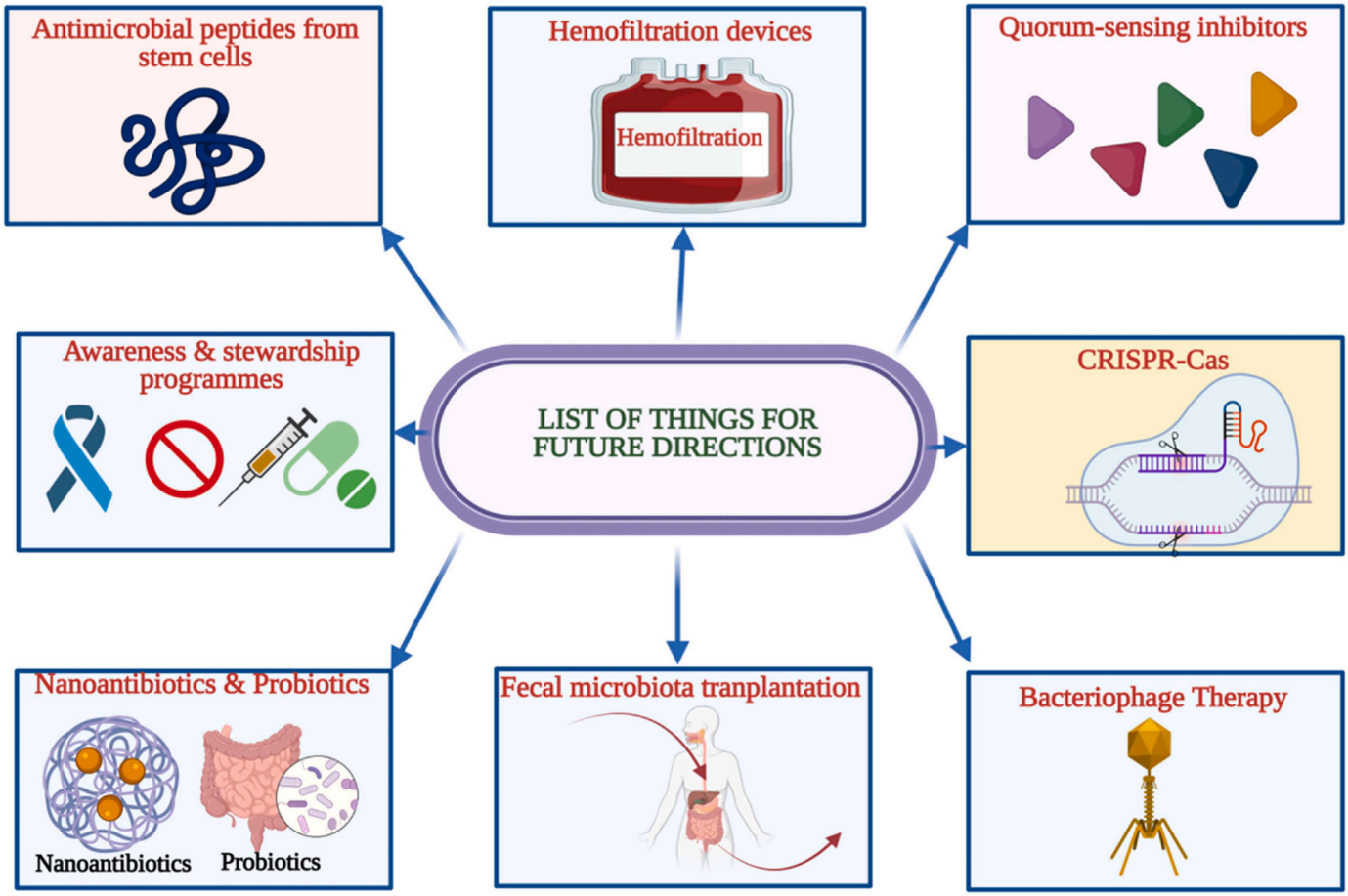

Fig. 4. List of options to combat antimicrobial resistance in the near future.

bacteria and ensuring their integrity have been considered vital to developing antimicrobials for drug-resistant bacteria (Cardona et al., 2018).

6.1.2. Antimicrobial Peptides against Resistance

In the fight against several diseases, mesenchymal stem cells (MSCs) have emerged as a promising remedy for better therapeutic options against a wide range of acute and chronic diseases. According to recent reports, these stem cells are capable of enhancing immunogenic modulation, tissue healing, and inflammation control systems (Harman et al., 2017). Recent research has shown that human stem cells produce valuable products that act as effective antimicrobial peptides to eradicate AMR-developing bacterial cells by directly inhibiting their cell wall synthesis mechanism (Alcayaga-Miranda et al., 2017). Thus, the research and development on these unique peptides from human stem cells to combat bacterial infections are in progress, along with resistance development which focuses on the future directions for alternate therapies. The AMPs, lipocal, hepcidin, and LL-37 are found to have antibacterial properties against common pathogens such as *E. coli*, *S. aureus* and *K. pneumoniae*. They are derived from human bone marrow and umbilical cord MSCs (Mccarthy et al., 2020). A study conducted in 2020 found that stem cells from human infants are highly effective against imipenem-resistant *P. aeruginosa*, with notable compounds identified (Ren et al., 2020). Recent peptide-based treatments for the specific resistant species have been noted, and research in recent years has demonstrated the efficacy of antimicrobial peptides in animals, plants, insects, and bacteria showing a wide range of features (Table 2).

6.1.3. Incorporation of hemofiltration machines to combat resistant bacteria

A severe bacterial infection in a patient leads to organ damage due to the overproduction of cytokines at the site of the infection and subsequent accumulation of immune cells. In such clinical conditions, hemofiltration machines can be attached to the injury site to remove bacterial accumulation and cytokines (Liu et al., 2018). A study conducted by Cui et al. (2018) confirmed that the application of a hemofilter reduces the level of serum with bile acid microbial metabolites containing total bilirubin, direct bilirubin, total bile acids, lactate, and IL-6 in patients with septicemia (Cui et al., 2018).

6.1.4. Quorum-sensing mechanism of bacteria

Quorum sensing and biofilm formation are natural survival mechanism of bacteria that involve a sequence of intracellular communications under various conditions. According to a study, bacterial species have a wide range of biological compounds with potential quorum-sensing properties. In this era of pandemic, the issue of antibiotic resistance in the medical community and the research sector has paved the way for the development of quorum-sensing inhibition technologies, creating an antibiotic-resistant-free, safe situation for patients with complications and serious illness (Kang et al., 2014).

6.1.5. Application of CRISPR-Cas in antimicrobial resistance

Clustered regularly interspaced short palindromic repeats (CRISPR)-cas is a typical natural property inherited by bacteria for their defense, particularly against bacteriophages. It is the most specific approach to genome-editing technology (Barrangou et al., 2007). This system can kill bacteria in vivo while creating a safe zone of antibiotic-free treatment in patients to prevent further spread. Removal of *AMR* genes results in the sensitization of the bacteria to antibiotics (Bikard et al., 2014). The development of the CRISPR-editing system in the phage has phage-based handling consequences. A new system, called the nano-based CRISP-R-editing system has been introduced. This system offers better options known as nanosized CRISPR complexes, which are active against the mec-A gene in methicillin-resistant *S. aureus* (Kang et al., 2017).

Table 2
Peptide-based therapeutics against drug-resistant bacteria.

Peptide	Description	Reference
Melittin	• Natural peptide obtained from bee venom • Remove vancomycin resistant *Staphylococcus aureus* (VRSA) from third-degree burn infection on mouse model • The minimum inhibitory concentration and minimum bacterial concentration ranges from 0.125 to 2 μg/ml and 0.125–4 μg/ml • The single dose melittin used to treat VRSA at a range of 16 μg • The dermal toxicity and in vivo hemolysis werenot conducted	Bevalian et al. (2021)
Cm-P5	• Snail-based antimicrobial peptide • Their cyclic-monomeric and dimeric derivatives showed potent spectrum against multidrug resistant bacteria • It also exhibited antifungal and antiviral activity	Gonzalez-Garcia et al. (2021)
Melittin	• Component of apitoxin • Produced from *Apis mellifera* • Minimum inhibitory concentration ranges from 0.12 to 4 μg • Act as model of nonsurgical methicillin-resistant *Staphylococcus aureus* (MRSA)-infected skin wounds	Lima et al. (2021)
eCAPs	• Engineered cationic antimicrobial peptide • Showed promising potentials against MDR	Deslouches et al. (2020)
Arenicin-3	• Amphipathic peptide • Obtained from marine lugworm *Arenicola marina* • Enhance membrane permeability in bacteria and cause ATP release • Cause mutation in phospholipid transporter gene*mlaC*	Elliott et al. (2020)
Lactoferricin (17−30) [Lfcin (17−30)]	• Demonstrated antimicrobial and antibiofilm activity against multidrug resistant enteroaggregative *E. coli* • The minimum inhibitory concentration, minimum bactericidal concentration, and minimum biofilm eradication concentration is 32, 32, and 32 μM, respectively	Vergis et al. (2020)
Bip-P-113	• Displayed minimal inhibitory concentration, antibiotics synergism, and supernatant LPS-neutralizing activities • Potent therapeutics against vancomycin-resistant *Enterococcus faecium* and *S. aureus*	Wu et al.(2020)
Uy234, Uy17, and Uy192	• Obtained from *Urodacusyaschenkoi* • All the three are showed potent antibacterial activity against MDR	Cesa-Luna et al. (2019)

(*continued on next page*)

Table 2 (*continued*)

Peptide	Description	Reference
SET-M33	• The α-helical structure of these peptides was validated by circular dichroism (CD) • Very active when synergistically combined with QnCs-BUAP+Uy-234 • It showed *in vitro* and *in vivo* antibacterial activities against MDR and XDR • Synergistic effect was explored with rifampin, meropenem, aztreonam, and tobramycin	Pollini et al. (2017)
Hominicin	• Obtained from *Staphylococcus homonis* MBBL 2–9 • It was purified by chloroform extraction, ion-exchange column chromatography, and reverse-phase HPLC • Showed potent spectrum against methicillin-resistant *S. aureus* (MRSA) ATCC 1143	Kim et al. (2010)

6.1.6. Development of immunogenic compounds

The traditional concept of vaccine development to safeguard patients from resistant bacteria is indeed commendable. However, by disrupting host–microbial interactions through immunotherapeutic methods based on natural biomolecules can help patients fight against the deadly pathogens that cause serious infections. Using immunotherapeutic agents for patients with drug-resistant bacteria will result in highly boosted immune systems based on immune cell response. In contrast, the disadvantages of using such immune booster agents include a lack of timely delivery to patients to overcome such critical situations. A study in 2004 reported on the pegfilgrastim–G-CSF (granulocyte colony-stimulating factor), which improves the production of blood cells (Molineux, 2004). Treatments of many fatal bacterial infections caused by bacteria such as *Clostridium difficile*, *Mycobacterium tuberculosis*, *Streptococcus* sp., and *S. aureus* are also in the pipeline of various drug discovery processes. These are based on new recombinant vaccine technology at both the initial and secondary levels. A study by Kumar et al. (2021) suggested continuing the research on the development of recombinant DNA vaccines to suppress resistant bacteria with virulence factors and overcome the natural defense mechanisms present in the host body.

6.1.7. Phage-based resistance therapies

Bacteriophage therapy is a practical approach for combating resistant bacterial infections. Since the introduction of bacteriophage therapy in Georgia in the 1920 s, it has been under the development for widespread use (Wittebole et al., 2014). Failure in dealing with drug-resistant bacterial infections in patients' makes treatment more complex and, in some cases, results in treatment will be failure. However, the study of bacteriophages in these drug-resistant bacteria has gained interest in the research community due to their presence and specificity for species with harmless characteristics. The most crucial step in the phage therapy technology is the perfect selection of phage before application (Wittebole et al., 2014). Knowledge for phage application within resistant bacteria is specific to the technical systems and knowledge available for phage selection, as well as the specific target site approach for every attempt, followed by continuous monitoring of the results to limit the side effects during the phage application for antimicrobial-resistant bacteria. Phage-mediated therapies are delivered through whole-phage particles, phage cocktails, phage antibiotic synergy, and phage-derived enzymes (Fig. 5).

Modified lysin with greater therapeutic benefits and a significant selection of bacteriophages against this resistant bacterium are more potent, active, and promising in comparison to multidrug-resistant bacteria which also have more possibilities of qualities (Kumar et al., 2021). The opposite side of phage therapy involves the release of various bacterial components from gram-negative bacteria as a result of bacterial lysis by lytic phages at the conclusion of their antibacterial action, such as endotoxin. This could explain a variety of negative effects on the host, including the establishment of an inflammatory cascade that results in multiple organ failure. However, this potential issue only applies to the currently available rapid bactericidal medications (Wittebole et al., 2014).

6.1.8. Nanotechnology in the treatment of Resistant Bacteria

An alternative method of studying the bacterial secretion system is using nanomechanical systems, such as nano-syringes, to directly deliver medicines into the cells without interrupting other mechanisms. Such targeted antimicrobial delivery into the cytoplasm of a targeted cell can significantly reduce the growth of AMR, particularly the bacterial type III secretion system (T3SS), which is involved in Gram-negative bacteria pathogenesis mechanisms (Mcshan and De Guzman, 2015). Nanoparticulate materials are becoming a new tool for treating resistant bacteria using targeted nano-based drug delivery. The nano-antibiotics system can both deliver antibiotic substances to the targeted site and act as an antimicrobial property-based compound for safe delivery. It is a promising approach to tackle these antibiotic-resistant bacteria in a critical situation when the host mechanism shows no defense mechanism to stop the resistant bacteria. Nano-antibiotics are a successful approach because of their ability to reach the site in a lesser volume. They have some antimicrobial defense mechanisms, such as bacterial wall disruption, biofilm inhibition, and host immune response (Baptista et al., 2018). A study in 2020 showed that the diverse mechanisms of nano-antibiotics are likely to be effective against antibiotic-resistant bacteria. The researchers demonstrated that bismuth nanoparticle properties exhibit broad anti-candidal activity, which slows the development of antibiotic resistance (Vazquez-Munoz et al., 2020). Therefore, the nano-antibiotic system of alternative antimicrobial therapy is becoming the most promising one in the medical community. In addition, probiotics are animal-derived foods used to combat normal and resistant bacteria. Probiotics have a high microbial load and show a high biological activity in the host immune system. This probiotic food system can protect people of all ages from infections while reducing the economic crisis caused by the uncontrolled use of antibiotics. Many pharma industries aim to create a wide range of probiotic-based products, such as probiotic-based drugs and dietary supplements, to take a prophylactic measure. Even probiotic products are fortified with immunogenic properties, which can effectively combat resistant bacteria rather than taking inappropriate antibiotics for a variety of minor infections (Mohamadzadeh et al., 2009).

7. One health concept in AMR

The One Health concept is a successful initiative to tackle the antibiotic resistance scenarios in the environment as inhabited by human beings, higher and smaller animals, plants, and natural bioresources. This approach has been approved and is being implemented by several countries through stewardship initiatives and is considered as "the mutual attempt of various disciplines—working locally, countrywide and worldwide—to accomplish optimal health for humans, livestock and our environment" (Fletcher, 2015). In veterinary care, antibiotic resistance develops primarily through horizontal gene transfer mechanisms in animal growth activities, such as animal rearing, where a small amount of antibiotic supplement is given for extended periods and also the antibiotics are used for growth promotion, disease prevention, and as treatments for resistance genes. Because the antibiotics used in

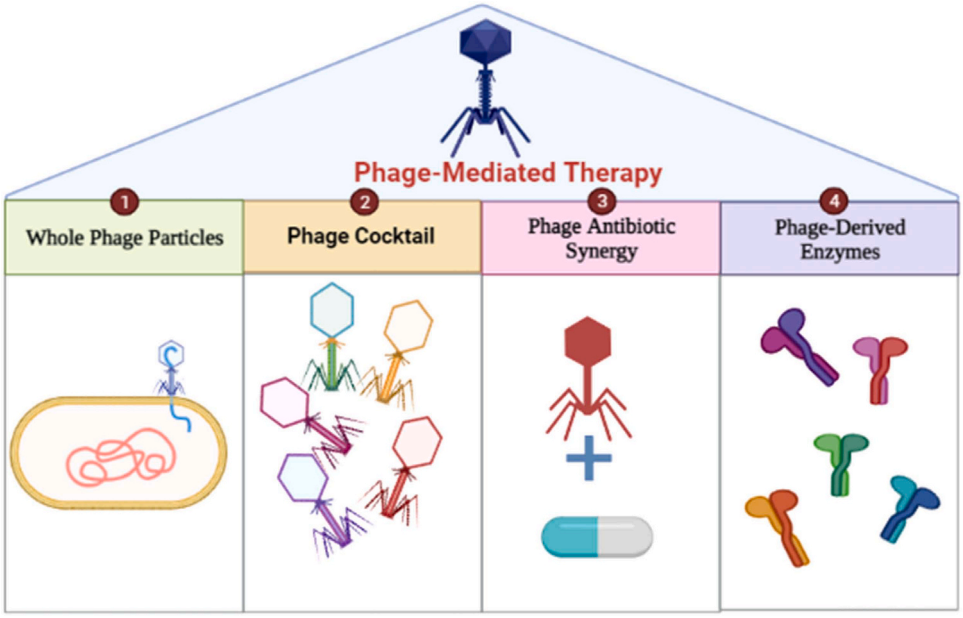

Fig. 5. Various therapeutic approaches based on phages.

animals and humans have nearly identical properties, the likelihood of resistant bacteria transferring from animals to humans and from humans to animals is very high, as is the rapid multiplication of resistant bacteria. Thus, the One Health approach aims to mitigate the rapid development of AMR through animals, humans, and the environment in a cyclical manner (Kumar et al., 2021). A recent review suggests that the molecular mechanisms that have been evolved by the resistant bacteria are becoming critical to identifying the worldwide resistance patterns of antimicrobial attributes and also the development of novel drugs against resistant bacteria (Darby et al., 2023).

8. Global challenges towards resistance eradication

Global research is focusing on health-oriented growth for dietary supplements for humans and livestock without limitations on health and hygienic strategies. Around the globe, surveillance programs are regularly organized as the frequency and spread of antibiotic resistance has increased sharply, disproportionately impacting young children, the elderly, patients with impaired immune systems, and patients with life-threatening illnesses. Antibiotic treatment has undeniably been revised for all bacterial and fungal infections, particularly in hospitalized patients. A strict monitoring system and stewardship should be implemented to ensure close monitoring and prophylaxis of uncontrolled use of antibiotics in the clinical sector, veterinary sector, and agricultural field, particularly in many commercial farming practices such as aquaculture, sericulture, and shrimp culture. Considering the current situation with XDR, the health and research departments should collaborate to investigate alternative methods of preventing drug resistance other than antibiotic treatment alone. According to a 2020 study, the most effective method to limit the evolution of antibiotic resistance is to employ alternate manufacturing and marketing techniques for animal-derived foods (Wright et al., 2019; Singh, 2020). To combat or reduce antibiotic resistance, numerous cutting-edge molecular and nano-based drug delivery technologies are currently being developed. Genetically modified organisms or probiotic products have shown the most significant impact in restricting antibiotic-resistant germs (Kumar et al., 2016). A higher level of transmission of resistant bacteria among the human or domestic animal microbiota results from the mobilization of ARGs in the external environment. Recent research conducted by Larsson and Flach (2022) on the existence of resistant bacteria in the water bodies, particularly in the sewage water microbiota, raises concerns about the severity of the resistance. If the water outflow is not considered for the environmental resistance data analysis, the buildup of resistance genes, whether through isolates or any metagenomes, would be riskier ((Kimera et al., 2021; Larsson and Flach, 2022).

9. Conclusion

AMR has become a global issue with wide-ranging implications. However, there are no national-level studies tracking the development of this resistance in different sectors such as hospitals, veterinary care, agriculture, and other biological fields interacting with microbes. In both veterinary medicine and public health, there is a desire for increased antimicrobial surveillance of antibiotic use. Additionally, knowledge of resistance development and its effects should be adequately disseminated towards the public at large, along with the essential instructions for dealing with this in all relevant ways. To reduce the inappropriate use of antibiotics in various disciplines, educational and research communities must create new monitoring systems and proactive methods. In all these critical conditions, antibiotic resistance poses a significant threat to the environment, human life, and animal life. To limit the synthetic manufacturing of antibiotics, it is strongly encouraged to consider traditional forms of natural medicines or alternative technologies such as phage therapy. The epidemiological data must be reviewed regularly for the situational preparation of therapies and technological development. Before reaching the point of a pandemic, the fight against AMR must involve the health, educational, and other sectors.

CRediT authorship contribution statement

R. Jayakumar: Writing – review & editing. **M. Prathaban:** Writing – review & editing. **M. Duraimurugan:** Writing – review & editing. **V. Chandrasekar:** Writing – review & editing. **Willie J.G.M. Peijnenburg:** Writing – review & editing. **N. Sharmila Devi:** Writing – original draft, Methodology, Investigation, Conceptualization. **R. Mythili:** Software, Data curation. **Tijo Cherian:** Writing – review & editing. **R. Dineshkumar:** Writing – review & editing. **G. K. Sivaraman:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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