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Review Article

Exploring the Strategies to Combat Antimicrobial Resistance in ESKAPE Pathogens; A Comprehensive Review

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Abstract

Antimicrobial resistance is a huge challenge for the global health system, bringing about massive mortalities throughout the world. On the landscape of infectious diseases, the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species) organisms have emerged as grave threats, leading to millions of life-threatening infections. These pathogens have developed numerous mechanisms of resistance against conventional antibiotic agents such as penicillins, cephalosporins, glycopeptides, etc. The prospective research is pursuing novel methodologies for combating antimicrobial resistance in ESKAPE bacteria. This review depicts strategies other than conventional antibiotic agents to tackle the rising tendencies of antimicrobial resistance in ESKAPE pathogens. Many *in vitro* and *in vivo* studies have established the effectiveness of phage therapy and endolysins in countering the dominance of ESKAPE pathogens. Antimicrobial peptides, photodynamic therapy with mesoporous nanoparticles, and some other strategies have also demonstrated their potency to kill ESKAPE bacteria. Despite their fruitfulness, many challenges and limitations are also associated with these approaches. This review aims to summarize the progress and advancement in countering the antimicrobial resistance in ESKAPE pathogens. This review also recommends conducting further research to better understand the technicalities of these strategies and to further refine them to compose these methods as promising options for antimicrobial therapy against ESKAPE pathogens.

Keywords: Antimicrobial resistance; ESKAPE pathogens; Phage therapy; Endolysins; Antimicrobial peptides; Photodynamic therapy.

1. Introduction

Over the past few years, a group of anti-microbial resistant bacteria acronymized as ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) is reported to be posing intimidation transcontinentally. These bacteria are competent enough to fade the free antibacterial effect of several antibiotics (Ayobami et al. 2022a). Hence, stipulating a newer paragon of the mechanism of focalization, propagation, and resistance (Pendleton, Gorman, and Gilmore 2013). Antimicrobial resistance has been a fierce challenge for the global healthcare for many decades. Approximately 3 million bacterial infections resistant to antibiotics have been recorded along with more than 35 thousand deaths per year in the United States. It is estimated that about 10 million deaths per year will occur globally, by 2050 (Kadri 2020). The incidence of antimicrobial resistance is increasing day by day.

According to a meta-analysis, the carbapenem resistance proportions for *K. pneumoniae, E. coli, Enterobacter* spp., *P. aeruginosa,* and *A. baumannii* were found to be 35%, 16.6%, 51.2%, 37.1%, and 72.4% respectively. Huge resistance percentages were also recorded against third-generation cephalosporins i.e. 78.7% for *K. pneumoniae* and 78.5% for *E. coli.* The incidence of methicillin resistance in *S. aureus* specimens was recorded to be 48.4% (Ayobami et al. 2022b). This dilemma has resulted in increased bioburden of disease, increased mortality, and decreased choice of antibiotics. This emerging problem requires global action and strict monitoring of stewardship practices. This conundrum has revitalized the demand for newer antimicrobial therapies and repurposed compounds to encounter multidrug-resistant ESKAPE pathogens (Oliveira et al. 2020). ESKAPE pathogens have acquired resistance through mobile genetic elements (MGEs) and genetic mutations (Beatson and Walker 2014). These pathogens embody the top 5 families of bacteria and they are reported to be well-known for causing hospital-acquired infections (HAIs) (Tacconelli et al. 2018). Antibiotics have been the most successful drugs in alleviating the mortality due to infections, in all ages. After the advent of antibiotic medications, the average life expectancy at birth rose to 78.8 years due to the effectiveness of antibiotics in combating infectious diseases (Adedeji 2016). ESKAPE pathogens have developed resistance against fluoroquinolones, macrolides, tetracyclines, lipopeptides, oxazolidinones, and β-lactams. Moreover, their resistance extends to the drugs used as a last resort such as polymyxins, glycopeptides, and carbapenems (Zaman et al. 2017). The two-fold action of lipoglycopeptides which includes disruption of bacterial cell membrane and hindering of peptidoglycan synthesis has rendered it to be still effective against ESKAPE pathogens (Beatson and Walker 2014).

Worldwide initiative for new drugs, adjuvants, and combinatorial therapies is required to combat the resistance. ESKAPE pathogens comprise gram-positive and gram-negative species of bacteria. These nosocomial infections are reported to be fatal for immunocompromised and critically ill patients (Santajit and Indrawattana 2016). Continuous use of antibiotics has elicited multi-drug-resistant (MDR) and extended drug-resistant (XDR) bacteria, which negates the effectiveness of previously therapeutic antibiotics. Production of carbapenemase and extended-spectrum β-lactamases (ESBL) by gram-negative bacteria has forged a therapeutic provocation against the current antibiotic regimen (Mulani et al. 2019). A review comprising of economic and clinical impacts of antimicrobial resistance (AMR) has declared ESKAPE pathogens to be the reason for escalating healthcare care fare by having a massive share in the rate of mortality (Founou, Founou, and Essack 2017). The clinical characteristics of ESKAPE bacteria are depicted in Table 1.

The review summarizes the progress and advancement in countering the antimicrobial resistance in ESKAPE pathogens. Employing strategies such as repurposed compounds, phage therapy, endolysins, photodynamic therapy, and related approaches against multidrug-resistant ESKAPE pathogens are evaluated as possible options to confront antimicrobial resistance in ESKAPE organisms.

2. Challenges in Conventional Antimicrobial Therapy for ESKAPE Pathogens

As we are living in the era of antimicrobial resistance, the major challenge associated with the current antimicrobial therapy against ESKAPE organisms is the impaired action of these agents to wipe out these pathogens (Kalpana et al. 2023). With the passage of time, the ESKAPE bacteria have evolved multiple mechanisms to confront the antimicrobial effects.

Table 1: The table describes the clinical features of ESKAPE bacteria

ESKAPE Species	Association of Resistance	Clinical Features	Treatment	References
Vancomycin-resistant *Enterococcus*	Vancomycin, Cephalosporins, piperacillin, Linezolid, Ampicillin, Teicoplanin	Intra-abdominal infections, pelvic infections, endocarditis, catheter associated-UTI, catheter associated bacteremia	Nitrofurantoin, Daptomycin, Linezolid, Fosfomycin, Chloramphenicol, Doxycycline, Ampicillin and Sulbactam, Omadacycline	(Remschmidt et al. 2018, Mioljević et al. 2013, Safety and Care 2019)
Methicillin resistant *Stapylococcus aureus* (MRSA)	Tetracycline, Fluoroquinolones, Chloramphenicol, Trimethoprim, Aminoglycosides, Macrolides, β-lactams	Osteoarticular infection, endocarditis, Acute bacterial skin and skin structure infection, Pneumonia, bacteremia	Omadacycline, Lefamulin, Tigecycline, Trimethoprim and Sulfamethoxazole, Linezolid, Clindamycin, Daptomycin, Vancomycin	(Malachowa and DeLeo 2010)
K. pneumoniae	Tetracyclines, Third-generation Cephalosporins, Aminoglycosides, Polymyxins, Carbapenems, Fluoroquinolones	Pulmonary infections, bacteremia, soft tissue infections	Aminoglycosides, Tigecycline, Meropenem, Imipenem, Ertapenem	(Zowawi et al. 2015, Prevention and Control 2015)
A. baumannii	β-lactams, Tigecycline , Ceftazidime, Fourth-generation Cephalosporins, Carbapenems, Polymyxins	VAP and bacteremia	Eravacycline, Colistin. Tigecycline, Cefiderocol	(Xie et al. 2018)
P. aeruginosa	Carbapenems, Piperacillin-Tazobactam, Aminoglycosides, Quinolone, Polymyxins, First- and second-generation Cephalosporins	UTI	Piperacillin-Tazobactam , Ceftolozane-Tazobactam, Ceftazidime, Meropenem, Ciprofloxacin	(Safety and Care 2019)
Enterobacter spp.	Carbapenems, Fourth-generation Cephalosporins, Fluoroquinolones, β-lactams , Polymyxins	Blood stream infections	Nitrofurantoin, Cefepime, Ceftriaxone, Ciprofloxacin, Gentamicin, Meropenem, Piperacillin-Tazobactam , Trimethoprim Sulfamethoxazole, Imipenem-Cilastatin	(Giammanco et al. 2017)

2.1 Production of Lactamases

One of the most frequently acquired antimicrobial resistance mechanisms by ESKAPE pathogens is the production of enzymes that neutralize or inactivate antimicrobials. β- Lactamases are the most pervasive cause of cleaving the β-lactam rings in β–lactam antibiotics, among gram-negative bacteria (Bush and Bradford 2016). ESKAPE pathogens destroy β–lactam ring before approaching penicillin-binding protein (PBP). Ambler classification of β–lactam enzymes categorize it on the basis of primary molecular structure (Akhtar, Fatima, and Khan 2022, Ambler 1980, Kaye and Pogue 2015). Whereas, Bush-Jacoby-Medeiros system categorizes them on the basis of functional properties (Bush 2018). A summary of both systems of classification is conferred below in table 2.

Table 2: The table provides an account of the classification of β–lactamases (found in several bacterial species including ESKAPE organisms), as per the Ambler and Bush-Jacoby-Medeiros classification system.

Ambler Classification of Enzymes	Found in	Enzymes	Resistant against	References
Class A	*E. coli,* *K. pneumoniae,* *Enterobacter spp.,* *P.aeruginosa*	Penicillinase, Cephalosporinase, Broad-spectrum β-lactamases, extended-spectrum β-lactamases (ESBLs), and Carbapenemases.	Penicillins (except temocillin), Aztreonam, Cefamandole, Cefoperazone and Methoxy-cephalosporins	(Zhao and Hu 2013, Nomura et al. 2020)
Class B	*P. aeruginosa* (VIM-type enzymes), *K. pneumoniae* (NDM-1-type enzymes), *A. baumannii* (VIM-type enzymes), *Enterobacter cloacae* (NDM-1-type enzymes)	Metallo-β-lactamases (MBLs), Imipenemase metallo-β-lactamases (IMP), Verona integron encoded metallo-β-lactamases (VIM), newly described New Delhi metallo-beta-lactamase-1 (NDM-1) enzymes	All β-lactams, including penicillins, cephalosporins, carbapenems, and β-lactamase inhibitors, except aztreonam.	(Zhao and Hu 2013, Tooke et al. 2019)
Class C	*P. aeruginosa, Enterobacter species* (very low level, no clinically relevant resistance), *Acinetobacter* species, *K. pneumoniae* (if transmitted via plasmid by other bacteria)	Penicillinase, Cephalosporinase (AmpC β-lactamase)	Aztreonam, Penicillin, Most cephalosporins	(Philippon et al. 2022, Tooke et al. 2019)
Class D	*P. aeruginosa*, *Acinetobacter* species. specifically *A. baumannii* (carbapenem-hydrolyzing OXA enzyme)	Oxacillin hydrolyzing enzymes (OXA). OXA-11, OXA-14, and OXA-16	β-lactamase inhibitors (except OXA-18), Carbapenems	(Yoon and Jeong 2021, Sawa, Kooguchi, and Moriyama 2020)

2.2 Production of Aminoglycoside Modifying Enzymes (AMEs)

The incidence of aminoglycoside resistance in ESKAPE bacteria has been encountered frequently with current therapy with antimicrobials (Das et al. 2022). In ESKAPE pathogens, aminoglycoside resistance takes place through aminoglycoside modifying enzymes (AMEs). AMEs are reported to be found on the plasmid and their transmission occurs through horizontal gene transfer (Krause et al. 2016). A decrease in antibiotic potency arises due to the binding of AMEs to the aminoglycosides and rendering changes to its amino and hydroxyl groups (Ramirez and Tolmasky 2010). Lately, AAC(6′)-Ib-cr enzyme has been revealed in *A. baumannii, K. pneumoniae, P. aeruginosa, and Enterobacter* species, which has turned up to be responsible for aminoglycoside and ciprofloxacin resistance (Oliveira et al. 2020). Three classes of AMEs are discussed below in table 3.

Table 3: The table represents the salient features of aminoglycoside modifying enzymes found in ESKAPE pathogens involved in resistance against aminoglycosides

Types	Found in	Mechanism of Resistance	Resistant Against	References
Aminoglycoside acetyltransferases (AACs)	*E. faecalis*, *E.faecium*, *Mycobacterium* species and *Providencia stuartii*	Performs acetylation of selective amino groups present on antibiotic acceptor molecule in an acetyl coenzyme A-dependent reaction	Amikacin, Gentamicin, Tobramycin	(Plattner et al. 2020, Jang et al. 2020)
Aminoglycoside phosphotransferases (APHs)	*S. aureus*, *Enterococcus* species	Catalyze ATP-dependent phosphorylation and reduce hydrogen bonding of -OH groups on the aminoglycosides hence, decreasing the binding capacity of the antibiotic	Amikacin, Gentamicin B, Neomycin, Kanamycin	(Tan et al. 2020)
Aminoglycoside nucleotidyltransferases (ANTs)	*K. pneumoniae*, *S. aureus*	Act by lending AMP to –OH at various positions of aminoglycosides by receiving it from ATP donor	Kanamycin A, B, C, Gentamicin A, Amikacin, Tobramycin, Neomycin B and C, Streptomycin, Spectinomycin	(Mustafa and Abdullah 2020)

2.3 Target Site Modifications

Target site modifications in ESKAPE bacteria oppose the process of antibiotic binding at the target sites rendering resistance to the corresponding agents (Mancuso et al. 2021). Numerous genes are the major players in the expression of antibiotic resistance proteins. Accumulation of mutations in these genes may also accelerate the alteration of antibiotic targets i.e. *mecA* gene which is located within staphylococcal cassette chromosome *mec* (SCCmec), encodes MGEs, regulators, two-component regulatory system (TCRS; MecI and MecR1), site-specific *ccr* recombinase genes, and three joining (J) regions that may encompass resistance factors (Lakhundi and Zhang 2018). *mecA* gene which encodes PBP2a has a reduced affinity for β-lactams, which declares β-lactams and methicillin to be ineffective treatment against MRSA (Lakhundi and Zhang 2018). Topoisomerases are responsible for DNA repair and replication, they have two subunits; A and B, which are encoded by gyrA and gyrB genes (Hooper 2001). Mutations in gyrA and parC escort shift in amino acids present at the binding site of the enzyme, resulting in fluoroquinolone resistance in ESKAPE pathogens (Cabral et al. 1997, Kivata et al. 2019). Qnr-family proteins facilitate the process of resistance through the plasmid-mediated quinolone resistance (PMQR) mechanism in *K. pneumoniae* and *Enterobacter spp*. Qnr-encoded proteins i.e. QnrA, QnrB, and QnrS bind to the DNA gyrase and aid in fluoroquinolone resistance (Robicsek, Jacoby, and Hooper 2006).

2.4 Ribosomal Target Site Alterations

Ribosomal target site alterations are of immense importance. Resistance to a wide range of antibiotics is prompted at the level of ribosomes in ESKAPE bacteria (Weisblum 1995, Lu et al. 2023). The *erm* expression can be constitutive or inducible. Cross-resistance to macrolide-lincosamide-streptogramin B (MLSB) agents is the consequence of constitutive expression whereas, the resistance of 14 to 15-member inducer macrolides such as azithromycin, clarithromycin, and erythromycin is the result of inducible *erm* expression giving rise to constitutively and inducibly resistant strains respectively (Efthymia and Constantinos 2018). Almost 42 classes of the *erm* genes family are present in MGEs. *erm*A is reported to be found on hospital-acquired MRSA strains, *erm*B is found in enterococci, and *erm*C in methicillin-susceptible *S. aureus* depicting plasmid-mediated resistance (Munita and Arias 2016). Mutations in the 23S rRNA and 50S ribosomal subunit gene have led to resistance against linezolid in *Enterococcus* species and *S. aureus* (Shaw and Barbachyn 2011). Methylation of 16S rRNA through enzymes has sequelised aminoglycosides resistance (Doi, Wachino, and Arakawa 2016).

2.5 Alteration of Bacterial Cell Wall Precursors

Bacterial cell wall precursors may also get altered giving rise to resistant strains. Glycopeptide resistance in gram-positive ESKAPE pathogens has emerged over time (Pandey, Mishra, and Shrestha 2021, Denissen et al. 2022). The mechanism of action of glycopeptides is inhibition of incorporation of D-Alanine–D-Alanine peptidoglycan precursor residues hence, inhibiting biosynthesis of the bacterial cell wall. The *van* gene clusters are responsible for the glycopeptide resistance in *enterococci* i.e. *van* gene clusters play their part by changing of peptidoglycan cross-linking target and by producing D, D-carboxypeptidases (Stogios and Savchenko 2020).

2.6 Loss of Porins

Antibiotic agents passively diffuse into the bacterial cells through porin channels present in the outermost membrane of bacterial cells including ESKAPE pathogens (Choi and Lee 2019). Few fluoroquinolones and β-lactam antibiotics which are hydrophilic in nature are affected by loss or downregulation of porin channels as they penetrate the outer membrane of

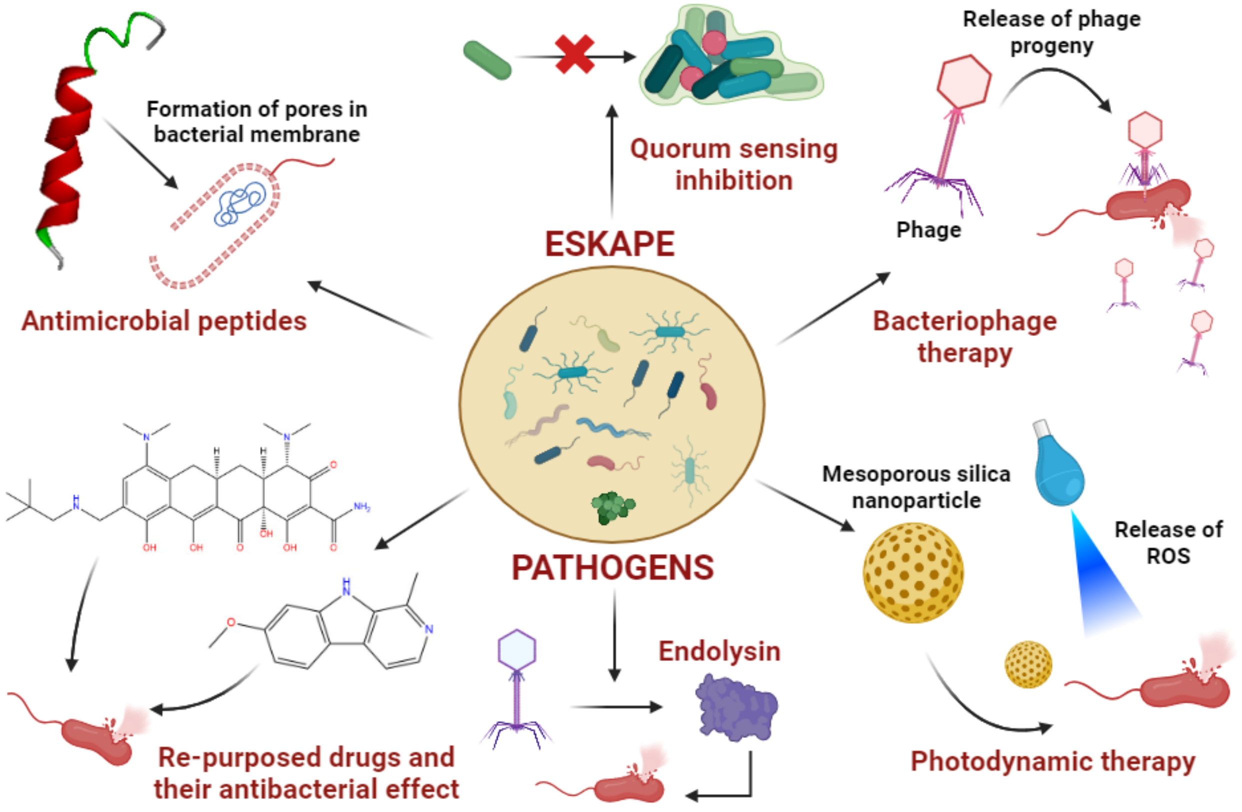

Figure 1: The figure depicts the alternative strategies to attenuate antibiotic-resistant ESKAPE bacteria

bacteria through porins. Reduced carbapenem susceptibility in *P. aeruginosa* is encountered due to modification or loss of OprD porin and resistance against imipenem in *A. baumannii* is due to loss or inactivation of CarO (Gaibani et al. 2022). Similarly, *Enterobacter* species and *K. pneumoniae* subsequently change the porin balance in the membrane. LamB porin overexpression in association with deficiency of Omp35 porin and Omp36 porin is reported to be responsible for decreased β-lactam susceptibility in them (Prajapati, Kleinekathöfer, and Winterhalter 2021).

2.7 Expression of Efflux Pumps

Efflux pumps are responsible for the extrusion of drugs out of the cell (Mohanty, Pachpute, and Yadav 2021). The genes that encode them are found on chromosomes or within MGEs. Six families of efflux pumps are exhibited in ESKAPE pathogens. The most commonly encountered AMR in gram-negative bacteria is demonstrated by a resistance-nodulation-division (RND) type efflux pump. In *P. aeruginosa*, the MexAB-OprAM efflux system when overexpressed endows resistance to β- Lactams, fluoroquinolones, and aminoglycosides (Schweizer 2003). In *K. pneumoniae*, decreased susceptibility to chloramphenicol and quinolone was reported to be due to the expression of the OqxAB efflux pump. Similarly in MDR *K. pneumoniae* and *Enterobacter* species, resistance was reported to be caused by the abundance of AcrAB-TolC (Sun et al. 2020). AdeABC, AdeFGH, and AdeIJK RND-type efflux pumps were responsible for the resistance in *A. baumannii* (Nikaido and Pagès 2012).

2.8 Formation of Biofilms

Another massive challenge in the inhibition of ESKAPE bacterial growth is their rapid tendency to form biofilms. The process of biofilm formation has been observed to be very pronounced *in A. baumannii, P. aeruginosa, S. aureus,* and *Enterococcus* species (Khalil et al. 2023, Chakraborty et al. 2020, Colquhoun and Rather 2020). Microbial cells in association with a surface flock together to form a biofilm. They are surrounded by a polysaccharide matrix. It helps in the swapping of genetic material via plasmid between bacterial cells. As plasmid is one of the sources of antimicrobial resistance so, the formation of biofilm is also related to accentuating antimicrobial resistance (Sharma et al. 2014). Biofilms provide mechanical and biochemical guard that reduces the efficacy of antimicrobial drugs. The deeper the biofilm layer the more resistance against antimicrobials is reported (Høiby et al. 2010).

3. Strategies to Attenuate Antibiotic Resistance in ESKAPE Pathogens

Keeping in view the rapidly strengthening antimicrobial resistance in ESKAPE bacteria, it is necessary to devise new alternative ways to target ESKAPE pathogens. These alternative strategies may assist in attenuating the deadly infections caused by ESKAPE bacteria. After a thorough literature review, some important strategies have been discussed that may facilitate in combating the multidrug-resistant ESKAPE pathogens and provide a substantial bactericidal effect. Figure 1 demonstrates various strategies to combat antibiotic-resistant ESKAPE pathogens.

3.1 Repurposed Compounds as a Strategy to Attenuate ESKAPE Infections

United States Food and Drug Administration (U.S. FDA) has approved certain drugs used in treating the infections caused by ESKAPE pathogens. Cefiderocol, a siderophore cephalosporin, has been reported to be efficacious in treating acute pyelonephritis, nosocomial pneumonia, UTI, and sepsis induced by carbapenem-resistant gram-negative infections (Bonomo 2019). Ellagic acid, which is a source of polyphenols is obtained from a plant, it is also reported to be effective as an antimicrobial against *S. aureus* and *P. aeruginosa* (Kamurai, Mombeshora, and Mukanganyama 2020). Harmine-derived compound (HDC-1), is a bactericidal agent. It acts by inhibiting protein synthesis. It acts on carbapenem-resistant *A. baumannii*. HDC-1 reveals its antimicrobial action by acting on DNA gyrase, topoisomerase II, and trypanothione reductase (Breine et al. 2022). Gallium [Ga(III)] compounds have been repurposed as an antimicrobial by disrupting iron-dependent metabolic pathways, hence inhibiting microbial growth. They impair iron uptake in bacterial cells and suppress respiration and provide oxidative stress, their inhibitory activity was reported in *A. baumannii*, *P. aeruginosa*, Enterobacteriaceae, and *K. pneumoniae* (Hijazi et al. 2018). A fluoroquinolone, Lascufloxacin, is approved in Japan to be used for treating community-acquired pneumonia (CAP) caused by quinolone-resistant *S. aureus* and *Klebsiella* species. It shows broad-spectrum activity against gram-positive bacterial species (Kishii, Yamaguchi, and Takei 2017). A recent tetracycline antibiotic, Omadacycline, is reported to be effective against streptococci and staphylococci comprising methicillin-resistant strains, atypical bacterial, and tetracycline-resistant bacteria. It was used in the treatment of acute bacterial skin and skin structure infections (ABSSSI) and CAP (Dougherty et al. 2019). A tetracycline analog, eravacycline, is reported to be effective against intra-abdominal infections caused by ESBL-producing *Enterobacter* species, aerobic and anaerobic bacteria, and ESKAPE pathogens (Snydman et al. 2018). Ebselen, a non-antibiotic drug, is found to be efficacious against MRSA and VRSA demonstrating bactericidal activity (Younis, Thangamani, and N Seleem 2015).

Many phytochemicals have also been explored for their potential antimicrobial activity against the ESKAPE organisms. Berberine present in *Berberis*

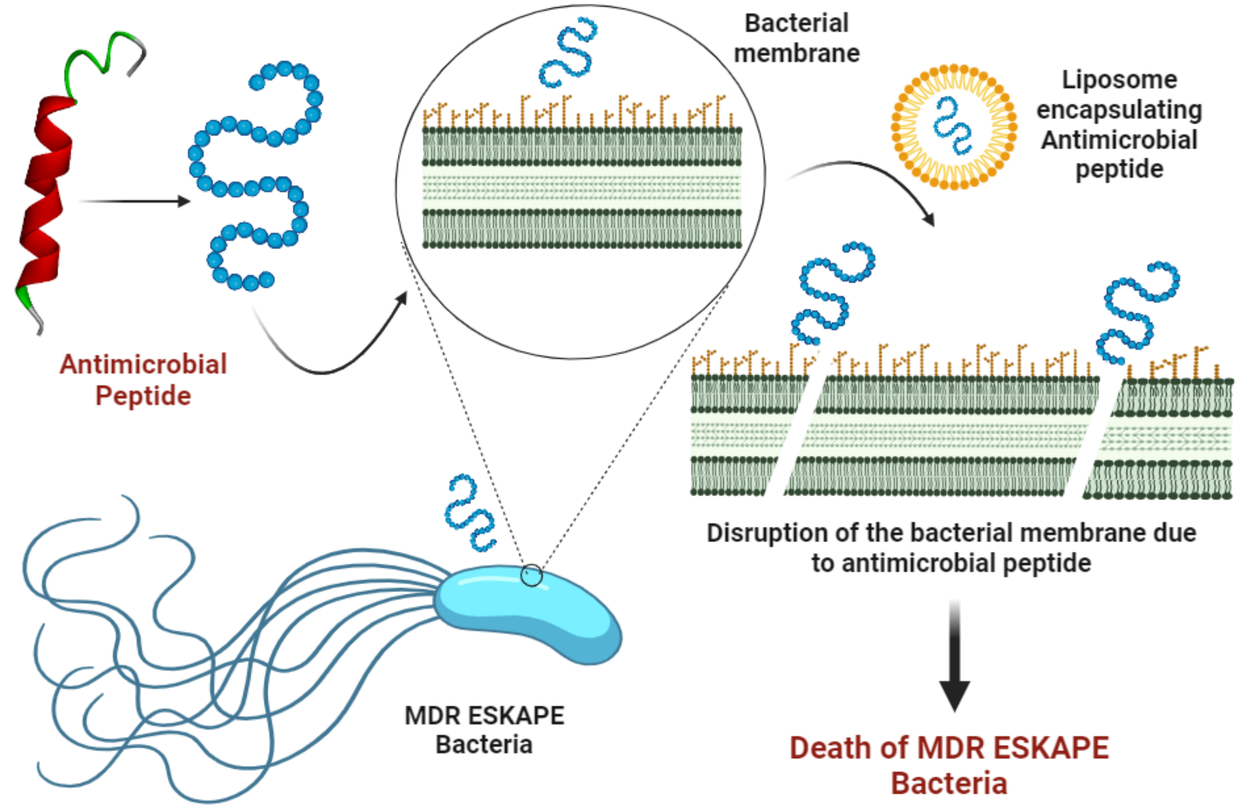

Figure 2: The figure demonstrates the mechanism of the antibacterial effect produced by antimicrobial peptides leading to attenuation of multidrug-resistant (MDR) ESKAPE pathogens

vulgaris, has been evaluated against a wide range of ESKAPE bacteria. Berberine has been reported to have antibacterial effects through intercalation of bacterial DNA, inhibition of bacterial DNA gyrase, topoisomerases, and biofilm formation (Jadimurthy et al. 2022). A phenolic compound, caffeic acid extracted from *Antirhea borbonica*, has been tested against ESKAPE organisms including MRSA, *K. pneumoniae,* and *E. coli*. It has been reported that a potent bactericidal effect has been witnessed against these bacteria. Caffeic acid encapsulated in nanoparticles has also rendered effective antibacterial activity against the ESKAPE group. Besides the natural products, synthetic compounds have also been assessed for their potential antibacterial activities against ESKAPE bacteria. In a study, a library of 643 synthetic compounds was screened to evaluate their activity against the ESKAPE bacteria. About 47 compounds were found to be active against a wide variety of bacteria including ESKAPE pathogens. The scaffolds were reported to possess phenolic, pyrazole, and quinolone nuclei (Mugnaini et al. 2020). In another study, 1,2,3-trizaole-containing compounds and hybrids were tested against ESKAPE organisms. *In vitro* analysis showed a strong antibacterial activity against these bacteria (Deng et al. 2022).

3.2 Photodynamic Inactivation and Nanoparticles as a Strategy to Attenuate ESKAPE Infections

Conjugated polymer nanoparticles (CPNs) which were photoactive, metallated, and porphyrin doped and blue light were used in the photodynamic inactivation of ESKAPE pathogens. CPNs-PDI were experimented with at multiple irradiation doses and various particle sizes. The bactericidal activity was exhibited in *MRSA* at low light doses whereas, in *gram-negative* bacteria it was demonstrated at higher light doses. The simultaneous action of CPNs-PDI acts on striking the mature biofilm generating reactive oxygen species (ROS) hence, disrupting the biofilm. Through cytometry, it was studied that CPNs attach to bacterial envelopes and kill them by inhibiting electron transport and signal transduction pathways. The resulting ROS are also responsible for the damage of essential biomolecules (Martínez et al. 2020).

A study was undertaken to examine the effect of 405 nm blue light on two important ESKAPE bacteria i.e. *P. aeruginosa* and *S. aureus*. This study rendered promising outcomes by showing a significant bactericidal effect of 405 nm blue light on the colonies of *P. aeruginosa* and *S. aureus* by killing more than 95% and 60% bacteria respectively (Tomb et al. 2018). Another study testified the viability of ESKAPE bacteria by irradiating them with violet light of wavelengths 405 nm and 450 nm. The experiment also included the infection of human cell lines (THP-1 and A549 cell lines) with ESKAPE bacteria and subsequent exposure of these infected cell lines to a series of radiation doses of violet light. A complete disinfection was achieved without any cytotoxic on human cells at the provided doses (Bauer et al. 2021).

In another study, the combined effects of gentamicin and photodynamic therapy using methylene blue was compared. The biofilms of *P. aeruginosa* and *S. aureus* were exposed to a series of concentrations of methylene blue with and without gentamicin. The samples were irradiated using a light emitting diode (LED) lamp while the controls were not irradiated. In this experiment, a marked decrease in colony forming units (CFU) was observed for *P. aeruginosa* only. Another study used the photodynamic therapy against all the ESKAPE organisms using the blue and violet spectral light with wavelengths of 450 and 405 nm. The findings revealed a marked reduction in the CFU was recorded. The entire experiment was carried at 37 °C for evaluating the usefulness of this photodynamic therapy in human infections. A study appraised the effects of silver nanoparticles (AgNPs) on the viability of ESKAPE pathogens. The bacterial inoculums were challenged with various concentrations of these AgNPs and significant antibacterial effects were noticed as per the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) assays (Hoenes et al. 2020).

Another study explored the effects of silica-protoporphyrin IX using nanocarriers. Various mesoporous silica nanoparticles were synthesized and loaded with silica-protoporphyrin IX. Afterward, these nanoparticles were dye-doped and added in the cultures of *S. aureus*. These mixtures were incubated at 37 °C for approximately 15 minutes and were poured in 96-well micro-titer plate irradiated with blue light of wavelength 420 nm. These cultures were diluted serially and the dilutions were poured upon growth media to screen the viability of bacterial cells. The results manifested that the release of singlet oxygen from these nanoparticles coupled with photo inactivation affected bacterial cell survival (Zampini et al. 2017). Few nano-liposomal formulations are also in clinical trials. These include amikacin-based liposomes (Arikace™) being studied against the infections caused by *P. aeruginosa*. Another nanoformulation containing ciprofloxacin-loaded liposomes are also in phase-III clinical trial being tested against gram-negative members of ESKAPE group (Mukherjee et al. 2023).

3.3 Antimicrobial Peptides (AMPs) as a Strategy to Attenuate ESKAPE Infections

AMPs are positively charged, host defensive oligopeptides produced by almost all living forms. AMPs attach to bacterial cell membranes via electrostatic interactions and eventually cause cell lysis. AMPs are a component of the innate immune system, playing a role in skin and wound

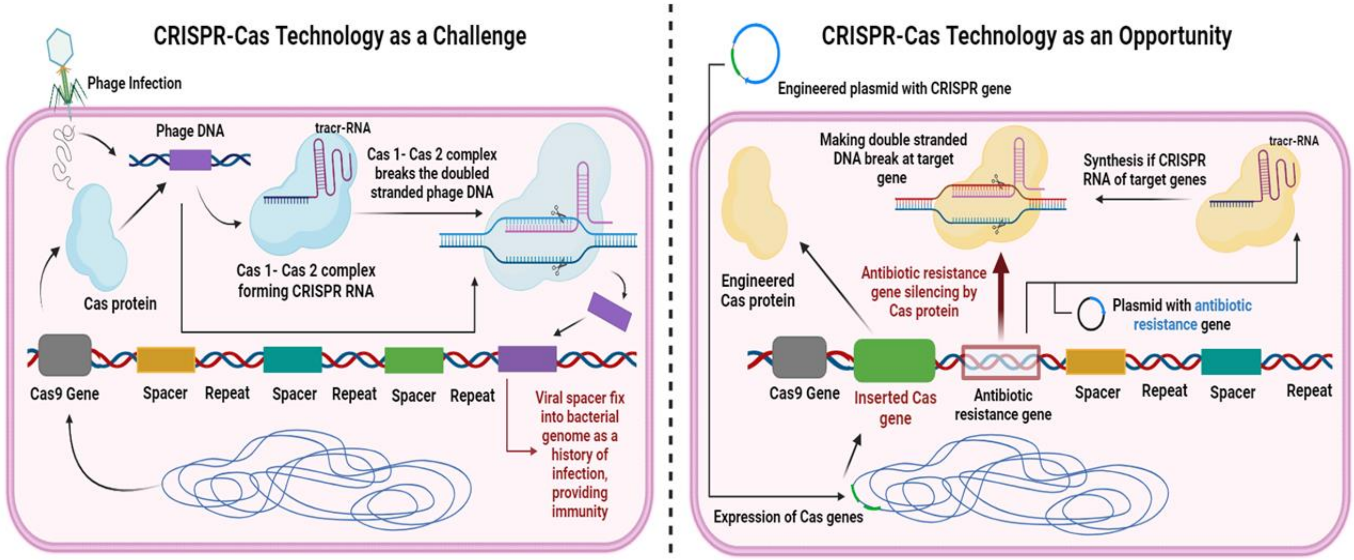

Figure 3: The figure illustrates the CRISPR-Cas system both as an opportunity and a challenge in confronting ESKAPE organisms i.e. CRISPR-Cas aids bacteria to develop immunity against bacteriophage infections and demolishes the phage DNA, while it also helps in targeting the antibiotic resistance genes in ESKAPE pathogens and other bacteria

infections (Pfalzgraff, Brandenburg, and Weindl 2018). Some AMPs are in clinical trials majorly including defensins and cathelicidins (LL-37). They have exhibited potent activity against a huge variety of pathogenic bacteria including the ESKAPE group (Ma et al. 2020). IDR-1018, an AMP, exhibits broad-spectrum anti-biofilm activity by promoting the degradation of guanosine penta- and tetra-phosphate, which is responsible for withstanding stress responses and formation of biofilm (De la Fuente-Núñez et al. 2014). LL37 in conjugation with gold nanoparticles was reported to be effective in accelerating wound healing and skin regeneration in ESKAPE organism-associated infections. It recruits mast cells, T-lymphocytes, neutrophils, and keratinocytes (Comune et al. 2017). IK8L can be used in treating burn wounds infected by *P. aeruginosa.* It demonstrated bactericidal activity by performing membrane lysis (Comune et al. 2017). SAAP-148 was reported to disrupt biofilms and persister cells formed by MRSA and MDR *A. baumannii* associated with skin infections. It permeates the bacterial cytoplasmic membrane and causes bacterial death (de Breij et al. 2018). A potent lytic peptide PTP-7 also shows anti-biofilm activity. PTP-7 is reported to enter the deep layers of *S. aureus* and kill bacteria within biofilms. It acts against gram-positive bacteria and antibiotic-sensitive and resistant *S. aureus* (Kharidia and Liang 2011).

Encapsulated strains of *K. pneumoniae* resist the bactericidal action of antibiotic agents (Vuotto et al. 2014). A study screened the activity of an AMP, pepW, against the encapsulated strains of *K. pneumoniae*. The *in vivo* experiment comprised of inoculation of a group of mice with the culture of *K. pneumoniae* MKP103 strain through intraperitoneal injection followed by administration of pepW peptide, while the control group was inoculated only with *K. pneumoniae* strain. Later on, the mice were sacrificed and the organs were examined for determination of bacterial load. It was found that the group of mice treated with pepW showed significantly lower bacterial loads as compared to the control group, even at very low minimum inhibitory concentrations (MIC) that were approximately 3 µg/mL. Transmission Electron Microscopy (TEM) also displayed the disruption of bacterial capsules by pepW peptide (Fleeman et al. 2020).

Another AMP, ZY4 was studied for its bactericidal effects against multidrug resistant ESKAPE bacteria i.e. *P. aeruginosa* and *A. baumannii.* Strains of *P. aeruginosa* including CMCC10104, CICC21625, and some other strains were tested against the ZY4 peptide *in vitro*. 18C116, CN40, 18C136, and some other strains of *A. baumannii* were also tested against ZY4 peptide. The antibacterial effect was witnessed at MIC 2.0 and 4.5µg/mL and 4.6 and 9.4µg/mL, respectively. Scanning electron microscopy (SEM) analysis divulged that the ZY4 peptide disrupted the cell membrane of the bacteria and led to bacterial cell death. Cell membrane disruption was found only in the ZY4-treated bacterial samples (Mwangi et al. 2019).

The antibacterial activity of another peptide, bacteriocin-like substance (BLS) P43, was assessed against *E. faecalis* and *S. aureus.* Both of these bacteria were cultured and formulated in the form of bacterial suspension. About 100 µl of the bacterial sample was poured into the wells of a 96-well microtiter plate. Afterward, the samples were exposed to BLS P34 peptide and subjected to 3-bromide [4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium (MTT) assay to evaluate bacterial cell viability after 24 hours of incubation at 37ºC. The results demonstrated that the BLS P34 inhibited the formation of biofilms in both *S. aureus* and *E. faecalis* but the findings of MTT assay indicated intact metabolic activity in *E. faecalis.* The grounds behind this activity may be the protease-associated inactivation or cleavage of antimicrobial peptide BLS P34 in *E. faecalis.* More research studies are required to explore this phenomenon and counter the mechanisms of AMP inhibition by *E. faecalis* (Costa et al. 2018). Figure 2 shows the mechanism of bactericidal effect furnished by AMPs.

3.4 Quorum Sensing Interference (QSI) as a Strategy to Attenuate ESKAPE Infections

Quorum sensing (QS) dovetails multiple virulence factors and cell density-dependent gene expression. Various QS networks are found in ESKAPE pathogens which are involved in preventing the formation of biofilm and diminishing their pathogenicity. Potential targets for therapeutic interventions and drug targets are bacterial virulence genes (Bhargava, Sharma, and Capalash 2010). *P. aeruginosa* has a QS system expressing multiple bacterial virulence genes by the LasRI module (E et al. 2018). QSI therapy is reported to regulate the expression of virulence genes it doesn't affect bacterial growth (García-Contreras 2016). Streptomycin, gentamicin, and myomycin are reported to downregulate *abaI gene* in *A. baumannii* hence, inhibiting QS (Saurav et al. 2016). Quorum sensing inhibitors such as *petunidin,* which causes structural modification in the LasR receptor protein which acts as a competitive inhibitor in the LasR receptor pathway eventually inhibiting QS signaling in *K. pneumoniae* (Gopu et al. 2016). A recombinant enzyme*, MomL,* breaks down QS molecules revealing antibiofilm activity and accentuating susceptibility to certain antibiotics acting on *Acinetobacter* strains and *P. aeruginosa* (Zhang, Brackman, and Coenye 2017).

A study has shown that the quorum sensing phenomenon in MRSA is derailed using 5-Flourouracil (5-FU). In the *in vitro* experiment, the concentration of 5-FU used was lower than the concentration required for the cytotoxic effect. At this concentration (0.1 µM), a marked antibacterial activity was observed. To evaluate the effects of 5-FU on autoinducer-2 activity of MRSA, a precursor of autoinducer-2, (S)-4,5-dihydroxy-2,3-pentanedione (DPD) was used to check the quorum sensing activity in the biofilm. No significant autoinducer-2 activity was noticed. *In vivo* experiments also assessed the quorum quenching activity in mice with MRSA infection. These mice were being treated with 5-FU prophylactically. Later on, administration of DPD was done to figure out the activity of autoinducer-2. The results revealed a decline in autoinducer-2 activity along with bacterial death (Sedlmayer et al. 2021).

Another study suggested that the treatment of *S. aureus* biofilms with salicylic acid leads to decreased spread and colonization of the bacterial cells. It was postulated that the inhibition of bacterial cell dissemination was associated with the interference of salicylic acid with *agr* quorum sensing system. The extracellular DNA release was impeded due to potential inhibition of *agr* expression. Later on, this was confirmed virtually through molecular docking and molecular dynamic simulation analysis (Dotto et al. 2021).

3.5 Bacteriophage Therapy as a Strategy to Attenuate ESKAPE Infections

Bacteriophages, being ubiquitous entities, infect pathogenic bacteria with a decent specificity that makes them kill the particular bacteria very precisely without affecting the normal flora of the body. Many resistant bacterial strains are also countered using a cocktail of these phages (Kassa 2021). These lytic phages are isolated from the environmental samples, purified, and characterized to examine their antibacterial activity. Some phage formulations have been approved by U.S. FDA i.e. *E. coli-specific* phages, BAFACOL™ and Finalyse® acquired approval from FDA. Moreover, another phage product, Staphage Lysate(SPL)® containing *Staphylococcus-specific* phages has also been approved by the FDA (Huang et al. 2022). Phase 1/2 of a clinical trial has reported the potent antibacterial activity of a phage cocktail, PP1131, against the bacterial load of *P. aeruginosa* in patients with burns (Jault et al. 2019). A study revealed the lytic activity of a novel phage VTCCBPA43 against a strain of *K. pneumoniae*. *K. pneumoniae* strain MTCC109 was administered intra-nasally with approximately 10^9 colony forming units (CFU) in BALB/c mice to induce pneumonia. The phage suspension (10^9 PFU), instilled intra-nasally, provided promising outcomes in the test group. Histopathological analysis established that pneumonia-associated damage in lung parenchyma was less intense in the test group as compared to the control group (Anand et al. 2020).

E. faecium belongs to the enterococci family of bacteria, responsible for causing hospital-acquired infections in a large population around the globe. Over the past few years, *E. faecium* strains have developed resistance against various antibiotics such as ampicillin, polymyxins, vancomycin, and many other agents (Zhou et al. 2020). A research study employed lytic phage against *E. faecium* infection in *Galleria mellonella* (wax moth larvae). The larvae were infected with a resistant strain of *E. faecium* and later on, the test group was injected with a phage suspension. The test group exhibited a better survival as compared to the control group that showed 100% mortality (Pradal et al. 2023).

S. aureus causes skin infections, meningitis, sepsis, and many other infections. Due to the development of resistance mechanisms, many antibiotics have lost effective coverage of *S. aureus* (Kwiecinski and Horswill 2020). An *in-vivo* study reported the potential antibacterial effects of *S. aureus-specific* phages. The phage was isolated from sewage water samples and the phage suspension was formulated in broth media. Pneumonia was induced in mice using multidrug-resistant *S. aureus* suspension having 10^8 CFU/ml, through an intravenous route via the tail vein. The mice were segregated into three groups. The first group was treated with clindamycin, the second group was treated with phage alone, and a combination of clindamycin and phage was employed in the third group. The group of mice treated with phage alone provided the least viable bacterial load in the lung tissue. The lung samples of the same group had minor lesions and tissue damage as compared to the other two groups (Oduor et al. 2016).

In another study, BALB/c mice were subcutaneously administered with bacterial suspension of *S. aureus* containing 10^8 CFU. Later on, the test group was administered with equal PFU of phage titer subcutaneously. After 24 hours, the size of the skin abscess was determined. The phage-treated group of mice had smaller size lesions with less inflammation, as compared to the control group. The histopathological analysis also rendered promising results as the samples from phage treated group manifested little hallmarks of infection (Ji et al. 2020).

A. baumannii, belonging to the ESKAPE group of pathogenic bacteria, mostly infects individuals with weak immune systems leading to skin and soft tissue infections (SSTIs), sepsis, and other nosocominal infections. The development of multidrug-resistant strains of *A. baumannii* has posed a huge risk for the immunocompromised population (Howard et al. 2012). A case was reported in which a geriatric patient was having pancreatitis complicated by *A.baumannii* infection. The clinical isolates were found to be multidrug resistant. A cocktail of phages was tested in vitro with the bacterial isolates, which inhibited the bacterial growth in less than 6 hours. Later on, this phage cocktail was administered intravenously to the patient. The clinical improvement occurred with phage therapy after two days (El Haddad et al. 2019).

P. aeruginosa is a hospital-acquired ESKAPE pathogen that is naturally resistant to many antibiotics. Endocarditis, meningitis, otitis externa, pneumonia, sepsis and many other infections (Wood and Kuzel 2023). A randomized placebo-controlled clinical trial (phase I/II) was conducted in the United Kingdom. The trial included the groups of patients having otitis, confirmed by microbiological analysis of ear swabs which indicated *P. aeruginosa* infection. The control group was administered with glycerin-phosphate buffer saline mixture into the ear while the experimental group received a bacteriophage cocktail containing six phages. The outcomes were measured at several time points including reduced *P. aeruginosa* counts in phage treated group, fewer patients reported discomfort and inflammation of the ear as compared to the control group (Wright et al. 2009).

In another study, a pulmonary infection model was established in BALB/c mice by injecting *P. aeruginosa* (2×10^4 CFU) by intratracheal route. The test groups of mice were treated with PEV31, a *P. aeruginosa-specific* phage at various PFUs, using the same intratracheal route. Many organs including the lungs were harvested after sacrificing the mice. The lung samples exhibited lower bacterial loads while the expression of pro-inflammatory cytokines was also decreased in the test groups (Chang et al. 2022).

3.6 Endolysins as a Strategy to Attenuate ESKAPE Infections

Endolysins are the proteins isolated from phages that interact with bacterial membranes, cause hydrolysis of the peptidoglycan component, and render a bactericidal effect (Murray and Draper 2021). Endolysins have been proven as a valuable mode of killing bacteria including species such as *Streptococci, E. coli, Listeria monocytogenes,* and ESKAPE organisms (Liu et al. 2023). Endolysin gene were obtained from the genomes of *Myoviridae* bacteriophage family and the coding sequences were amplified using polymerase chain reaction (PCR). The cloning was done in *Escherichia coli* strain for expression and the proteins were collected and afterwards purified. Lysins, LysSi3, and LysAm24 provided *in-vitro* bactericidal activity against a virulent pathogen of the ESKAPE group, *A. baumannii* (Antonova et al. 2019).

In another study, a lysin, LysSAP26 was screened for its activity against ESKAPE bacteria. The gene was obtained from the genome of phage SAP26 and cloned in *E. coli* host after amplification and purified after expression. The *in-vitro* screening of the lysin was done using a minimum inhibitory concentration (MIC) assay. The multidrug-resistant clinical isolates of the ESKAPE pathogens were grown in broth in separate test tubes and the activity of LysSAP26 lysin was observed. Most potent activity was exhibited for *A. baumannii* and *S. aureus* respectively (10 and 20 μg/mL), while decent activity was recorded against *E. faecium* and *P. aeruginosa* (Kim et al. 2020).

Another study was undertaken to test endolysin Ts2631, an enzyme in phage vB_Tsc2631. Propitious antibacterial activity against resistant strains of ESKAPE organisms was recorded. Luria Bertani broth medium was used to grow the clinically isolated ESKAPE bacteria and the *in-vitro* testing of the endolysin was performed to assess its bactericidal activity. The results were very optimistic and it was revealed that the endolysin Ts2631 provided a potent antibacterial effect for all of the ESKAPE organisms in a dose-dependent fashion. A synergistic effect along with the widening of the antibacterial spectrum was also observed if a combination of endolysin with EDTA was used (Plotka et al. 2019).

A bacteriophage, phiSA012, is specific for *S. aureus* strains. phiSA012 was isolated from sewage water and was purified. The DNA was extracted and the gene for the specific endolysin, Lys-phiSA012 was identified and amplified using primers and expressed in *E. coli* DH5*α* to obtain the recombinant endolysin. The MIC and MBC assays were performed on the *S. aureus* suspensions and various concentrations of Lys-phiSA012 endolysin (μg/ml). The findings indicated that Lys-phiSA012 had a potent lytic effect on *S. aureus*, promulgating it as a favorable candidate for antimicrobial therapy in *S. aureus* infections (Fujiki et al. 2018).

4. Opportunities and Challenges in Fighting Antimicrobial Resistance in ESKAPE Pathogens

Countering the spread of ESKAPE infections, the global community is making a lot of efforts. Robust mechanisms for developing antibiotic resistance has made it quite challenging to combat these pathogens (Tacconelli 2017). Like many other bacteria, ESKAPE organisms have also developed immunity against viruses and bacteriophages through expression of clustered regularly interspaced short palindromic repeats–CRISPR-associated proteins (CRISPR- Cas) system (Wang et al. 2022, Barrangou et al. 2007, Touchon et al. 2011). Throughout the genome of ESKAPE bacteria, palindromic sequences are present with spacer regions between them. These spacer regions resemble the genome segments of viruses and phages. Genetic sequences are also present for the expression of Cas protein that binds CRISPR RNA and cleaves the genetic material of phage-infecting bacteria (Wang et al. 2022). This leads to the acquisition of resistance against phage therapy and may pose a huge challenge for treating ESKAPE infections using phage therapy.

On the other hand, engineered CRISPR-Cas technology can be used to target the bacterial genes as well that are responsible for antimicrobial resistance, hence interfering with the pathogenesis of multidrug-resistant bacteria including ESKAPE (Vercoe et al. 2013, Gholizadeh et al. 2020). Using this technology, the resistance genes could be silenced completely either by cleavage or loss of function mutations (Wang et al. 2018). A study reported that *E. faecium* E745 strain was engineered with pVLP3004 plasmid that encoded Cas proteins and pVDM1001 plasmid that encoded CRISPR RNA. This engineering successfully targeted the macrolide resistance gene *msrC* (de Maat et al. 2019). Another study reported that *S. aureus* strain AH1 was engineered with plasmids pLI-252 and pLI-158, having a tendency to encode CRISPR- Cas apparatus with spacer regions. The *mec*A gene, responsible for the expression of penicillin-binding protein 2a (PBP2a) has a low affinity for most of the β-lactam antibiotics. This targeting of *mec*A gene proved to be very effective hence killing more than 90% of the *S. aureus* population (Guan, Wang, and Sun 2017). In another study, resensitization of carbapenem-resistant *Enterobacter* was done by targeting and silencing their specialized *bla*$_{KPC\text{-}3}$-harboring plasmids. This led to the restoration of carbapenem-associated antibacterial effects on these *Enterobacter* strains (Hao et al. 2020). Figure

3 compares the CRISPR-Cas system both as an opportunity and a challenge in the battle against ESKAPE bacteria.

Metallic nanoparticles had been successfully tested and employed as a strategy to provide antibacterial effects in ESKAPE infections (Mukherjee et al. 2023, Lee, Ko, and Hsueh 2019). Many studies have highlighted some mechanisms used by ESKAPE pathogens to evade lysis. A study used silver nanoparticles (AgNPs) and demonstrated that the exposure of ESKAPE organisms with the nanoparticle concentrations leads to upregulation of some genes that may produce resistance against these nanoparticles (Graves et al. 2015). In another study, *P. aeruginosa* PAO1 strain was exposed to copper oxide nanoparticles (CuO NPs) which upheld the expression of P-type ATPase efflux pumps leading to resistance against CuO NPs (Guo et al. 2017). Another study revealed that the growing colonies of *E. coli* when exposed to AgNPs, produce specific extracellular substances that may cause aggregation of the nanoparticles affecting their antimicrobial activity (Faghihzadeh et al. 2018). This could cause problems in anti-ESKAPE therapy using metallic nanoparticles. The research being done on nanotechnology should also address these problems to retain these technologies as a valuable resort for therapy against ESKAPE organisms.

Quorum sensing may have beneficial effects in affecting the populations of pathogenic bacteria including ESKAPE organisms but it may also affect the population of gut microflora. Autoinducer (AI), previously known as acyl-homoserine lactones (AHLs) are released by bacteria and are involved in quorum sensing. A study reported that AI-2 inhibition has also deleterious effects on the gut microflora as AI-2 expressed by *E. coli* also promoted the expansion of the gut microflora population. Hence, interfering quorum sensing in pathogenic bacteria may, non-selectively, affect the population of normal flora as well (Thompson et al. 2015). In 2012, an *in vitro* experiment demonstrated *that P. aeruginosa* has the ability to mutate its genes and develop resistance against quorum sensing inhibitors such as brominated furanones by exaggerated efflux pump function due to mutations (Maeda et al. 2012). Similar observations were made in further studies showing the development of resistance mechanisms in ESPAKE pathogens (García-Contreras et al. 2013, Ding et al. 2018). Further research is required to counter these mechanisms.

AMPs are also an important pillar of antimicrobial therapy against ESKAPE bacteria (Mukhopadhyay et al. 2020, Hicks et al. 2013). Many challenges are associated with the application of AMPs in the current antimicrobial therapy. The AMPs coated inside urinary catheters may lose their effectiveness after being covered with biofilm or after the excessive adsorption of protein molecules. Hydrophilic polymers could be used as a remedy to avoid these problems (Rai et al. 2022). Another major hurdle for antimicrobial peptide therapy is the degradation of these peptides by proteases. Serine proteases present in the gastrointestinal tract are among the major contributors that cause the proteolysis of AMPs (Svendsen et al. 2019). The AMPs also exhibit short half-life which could be improved by techniques such as pegylation (Gong et al. 2017). Nanoformulations of AMPs are a solution to many problems. Nanoparticles encapsulating AMPs have ameliorated their bioavailability and made them target-specific, ruling out any non-selectivity or toxicity (Rai et al. 2016). The AMPs formulated as gold nanoparticles have been shown to be specific and effective against ESKAPE pathogens (Fadaka and Sibuyi 2021, Rajchakit and Sarojini 2017). However, many formulation challenges and high costs pose hurdles in implementing nanoformulations-based AMPs in routine clinical practice (Hussain et al. 2022). Solutions to all these problems should be addressed through subsequent studies in order to refine these strategies as an alternative to traditional antibiotic drugs. The safety profiling for all these novel strategies should be done to make them an effective part of the clinical settings. In order to cope with challenges such as scarcity of efficacy data, this review suggests the conduction of more randomized controlled trials.

5. Conclusion and Future Prospects

The contemporary prevalence of antimicrobial resistance is a huge jeopardy for the global community. The current antibiotic therapy is losing its impact on the control of many infections, including those inflicted by ESKAPE organisms. Many other antimicrobial strategies have indicated optimistic outcomes in terms of attenuating the multidrug-resistant ESKAPE pathogens. Many drugs are being repurposed, and their antimicrobial potential against ESKAPE pathogens is being postulated in light of *in silico, in vitro,* and *in vivo* studies. Phage therapy had been promising in diminishing the ESKAPE pathogens that were resistant to several potent antibiotics. Phage therapy has been effective in many *in vivo models,* including SSTI, pulmonary infection, and sepsis caused by ESKAPE organisms. The phage formulations and endolysins are under consideration in various clinical trials as well (Górski et al. 2020, Duplessis and Biswas 2020). Robust regulatory affairs of biotechnological products are filtering the most efficacious products onto the market. Several studies have established the effectiveness of marketed phage preparations such as SalmoFREE® and Stafal® (Dvořáčková et al. 2019, Clavijo et al. 2019). Therapies such as quorum sensing interference, AMPs, and photodynamic therapy have also produced potent antibacterial effects against ESKAPE pathogens, making them a suitable alternative option to treat infections caused by these bacteria. Further studies should be done in order to detect the novel mechanisms for resistance that may be prospectively developed by ESKAPE bacteria. This review suggests the conduct of more studies to find ways to implement these strategies by overcoming all the challenges associated with them. At the level of the community, the implementation of these strategies can alleviate the burden of ESKAPE infections and subsequent mortality.

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All the data related to this manuscript including research articles that were analyzed for this review are available with the authors.

Author Contribution

Main idea and conceptualization, initial draft by AI, literature collection, and review by AI & LB, graphics, language, and grammar by AI & LB, analysis and proofreading by LB, review editing and final draft by AI All authors read and approved the final manuscript.

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