From Penicillin to Peptide-Mimicking Polymers: Therapeutic Design of Amphiphilic Antibacterial Agents Against ESKAPE Pathogens

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The discovery of penicillin has transformed medicine, dramatically reducing deaths from formerly lethal bacterial diseases. Nearly a century later, this achievement has been jeopardized as antimicrobial resistance (AMR) spreads, with ESKAPE bacteria emerging as one of the most serious threats to human health. These multidrug-resistant (MDR) organisms have increasingly rendered many existing antibiotics ineffective, heightening the urgency for novel therapeutic strategies. As a result, research efforts are increasingly focused on discovering new agents that can circumvent traditional resistance routes. Amphiphilic synthetic polymers have emerged as promising alternatives that mimic the structure and function of natural antibacterial peptides (ABPs). They exhibit broad-spectrum antibacterial activity, selectively disrupt bacterial membranes, and possess chemical tunability, offering control over hydrophobicity, cationic charge, and molecular architecture. Such properties make them highly adaptable and effective in targeting multidrug-resistant bacteria, particularly those implicated in hospital-acquired infections. This review examines the evolution of antibacterial strategies, from conventional antibiotics to peptide-mimicking amphiphilic polymers, focusing on their mechanisms of action and design principles. With their ability to overcome traditional resistance pathways and improved biocompatibility compared to ABPs, these polymers represent a cutting-edge advancement in antibacterial chemistry. They hold great promise in addressing the growing AMR crisis, particularly against high-priority pathogens like the ESKAPE species. Their unique features indicate enormous potential as next-generation therapeutics against ESKAPE pathogens, opening up novel opportunities for future research and clinical uses.

Keywords: Amphiphilic synthetic polymers, antimicrobial resistance (AMR), multidrug-resistant (MDR), ESKAPE pathogens, antibacterial polymer

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Before the advent of antibiotics, humans were highly susceptible to various infectious diseases. Over the past few centuries, humans have utilized natural ingredients in medicine, such as various plant parts for wound healing, pain relief, or protection from injury. This suggests that medicines are essential to human survival, even if people are unaware of the active components of phytochemicals and their efficacy. Even before the term "antibiotic" was created, some natural substances had antibacterial qualities [1]. According to Kourkouta et al. [2], "antibiotic" describes compounds that are naturally created from a variety of microorganisms including bacteria and fungi, and that can stop the growth of other microorganisms and kill their cells.

With the passing of time and the advancement of technology, the foundations of the efficacy of various medicinal plants in treating specific ailments are beginning to be revealed, resulting in the move from an empirical framework to a more evidence-based approach [3]. Various medications are widely utilized not only to cure diseases, but also in agriculture, livestock, and fisheries as growth enhancers and growth protectants [2]. This supports the United Nations Sustainable Development Goal 3: Good Health and Well-Being, by fostering innovation in effective, safe, and sustainable antibacterial treatments for current and future generations.

Antibiotics may have existed in the microbial world for millions of years [4]. In the pre-antibiotic era, infectious diseases such as smallpox, cholera, diphtheria, pneumonia, typhoid fever, plague, tuberculosis, typhus, and syphilis were widespread, and were the leading causes of morbidity and death [5]. Since the discovery of the first antibiotic, penicillin, by Alexander Fleming in 1928 [6], the high mortality rate due to bacterial infections has been significantly reduced. The interaction between an antibiotic and bacteria is the beginning of the mechanism of bacterial killing. In many cases, cationic functional groups such as amino acids or quaternary ammonium moieties enable electrostatic attraction to the negatively charged bacterial surface, facilitating the initial binding step. The electrostatic interaction between the bacterial anionic cell wall and the respective functional group in an antibiotic causes significant damage to the cell membrane, resulting in bacterial cell rupture [7].

Antibiotic resistance was initially documented in 1924 [8], and is defined as the ability of disease-causing bacteria to counteract the therapeutic effects of antibacterial drugs [9]. This resistance can arise due to spontaneous mutations in the deoxyribonucleic acid (DNA) of chromosomes, or can occur in addition to chromosomes, such as when bacteria switch plasmids or transposons [10]. The ability of bacteria to evolve is also one of the main factors in the problem of resistance to antibiotics [11]. There are other factors that contribute to the increase in resistance to these antibiotics, including the widespread abuse of antibiotics and their overuse in both human and veterinary medicine, as well as ineffective prevention and control measures. These factors have paved the way for the world to enter what is often referred to as the post-antibiotic era, a period in which common infections may no longer be treatable with existing drugs [12]. This problem has been exacerbated by the unnecessary use of antibiotics in COVID-19 patients [13]. Some of the most prevalent resistance mechanisms include the modification or deactivation of the antibacterial itself, changes in the permeability of the outer membrane, the emergence of the efflux pump, and changes in the bacterial target site [14]. The overuse of antibiotics has gradually reduced their efficacy, with repercussions that affect not just individual patients but also public health globally.

The escalating global crisis of antimicrobial resistance (AMR) poses a significant threat to human health and socioeconomic stability. A major obstacle to global healthcare is the rising issue of antibiotic resistance, which makes it more challenging to treat infections that were once treatable. The widespread inappropriate and excessive use of antimicrobials in human and animal medicine, coupled with inadequate prevention and control strategies, have fuelled the proliferation of AMR. This affects patients with various diseases, leading to serious infections in hospital settings [15]. This scenario is pushing the world toward a post-antibiotic era, characterized by prolonged illness, increased mortality, and less effective treatments and preventive measures for infectious diseases worldwide, leading to substantial economic burdens [12, 16]. A report from the World Health Organization (WHO) in 2019 attributed 700,000 deaths to AMR. A report by O'Neill and colleagues estimated that by 2050, antimicrobial resistance may cause up to 20 million deaths, surpassing cancer as a leading cause of mortality, and generate economic costs exceeding 2.9 trillion USD [17, 18].

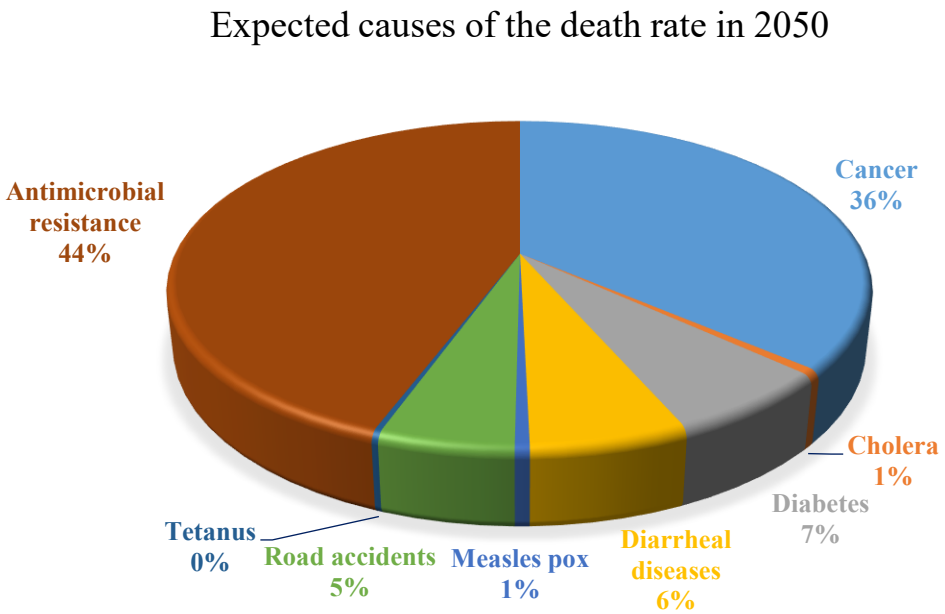

Figure 1. Expected causes of the death rate in 2050 by O'Neill and colleagues
Source: Paneri & Sevta 2023 [17].

The WHO and the US Centers for Disease Control and Prevention (CDC) have designated several antibiotic-resistant diseases as high priority, and these are known to be caused by the ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) [19, 20].

Despite advancements in medical technology, the issue of resistance to certain antibacterial medications persists, leading to the emergence of more aggressive strains that are resistant to conventional treatments [9]. To address this challenge, the medical and scientific community must continuously adapt strategies to keep pace with the evolution of these pathogens, while consumers also need to remain informed and vigilant. Humans have recently faced the threat of multidrug-resistant (MDR) pathogens. Numerous research studies have been conducted and are ongoing worldwide to address this global problem. A range of substitutes have been selected, including both synthetic and natural medications. Therefore, caution should be taken when developing antibacterial medications to address the resistance issue. Understanding how these antibacterial medications inhibit or destroy bacterial cells is crucial. To get the intended outcome, discussions for this development should be conducted in groups of scientists from different scientific disciplines.

The emergence of multidrug-resistant bacteria (MDR), which are resistant to more than three classes of antibiotics [21–23], has coincided with the ongoing contraction of antibiotic development [18]. The lack of new antibiotic development has worsened the problem, with limited inventive solutions available to combat these resistant infections [24, 25]. This global issue has caused an urgent need for new, effective, selective, and biocompatible forms of antimicrobial drugs [15, 26]. The resistance mechanisms include biofilm formation [27], horizontal gene transfer [28, 29], and efflux pump activity, among others [30]. This scenario stresses the crucial necessity of comprehensive approaches to tackle AMR, which include the discovery of new antimicrobial medications, refinement of diagnostic methodologies, and prevention measures such as immunization [31, 32].

Developing functional materials such as amphiphilic polymers is a viable strategy for fighting bacterial infections. Such versatility is illustrated by studies on amphiphilic polymers meant to mimic antimicrobial peptides (AMPs) that are currently highlighted as the replacement for conventional antibiotics [33–35]. The capacity of an amphiphilic polymer to alter its features, such as molecular weight, polymer architecture, and hydrophobicity/cationic charge ratios, enables the optimisation of antibacterial activity and biocompatibility [36, 37]. These properties allow these polymers to disrupt bacterial membranes [38], get beyond resistance mechanisms [39] and be structurally flexible for various biomedical applications.

This review discusses the potential of novel synthetic polymers as antibacterial agents. The goal is to make these synthetic polymers mimic antibacterial peptides (ABP), but with better characteristics. With their unique amphiphilicity, the killing mechanism of these agents appears promising.

Antibiotic Resistance

The perfect antibiotic can destroy or stop the growth of dangerous bacteria in the host without compromising the infection location. It should not harm the host nor interfere with beneficial microbes. It may also be less susceptible to antibiotic resistance [40]. According to this concept, antibiotics ought to be able to stop bacteria from growing while also safeguarding the host, the human body. To combat antibiotic-resistant bacteria, the CDC identifies four broad strategies: (i) preventing infection and resistance transmission; (ii) identifying resistant bacteria; (iii) expanding the use of antibacterials currently in use; and (iv) developing and researching novel antibiotics [41]. Numerous research projects are underway to create novel antibiotics that fit these requirements.

The majority of antibiotics now on the market are antibacterial drugs that only work against Gram-positive bacteria [42], and not Gram-negative bacteria [40]. This is also mentioned in a recent report by Kristen and Hergenrother [43] that expanded Gram-positive antibacterials to broad-spectrum antibacterials, including those capable of killing Gram-negative bacteria. In addition to being potentially fatal, antibiotic resistance has significant financial costs [9]. Patients may experience more severe infections, which result in longer hospital stays and worse clinical outcomes. This causes patients to lose faith in contemporary medications and raises doubts about the diagnosis of the disease [44]. The four main forms of antibacterial resistance are: (i) natural resistance (intrinsic, structural); (ii) developed resistance; (iii) cross-resistance; and (iv) multidrug and other types of resistance [45].

Antimicrobial resistance in humans includes the use of over 80% antibiotics in animal and agriculture [46, 47]. In animal production, antibiotics are frequently used to cure illnesses, defend against sickness, and stimulate growth [48]. Evolution and mutations in bacteria can also result in antimicrobial resistance. In this evolutionary process, bacterial cells make alterations in their genes (plasmids or chromosomes), which are then transferred to progeny cells by vertical gene transfer, resulting in intrinsic or natural resistance [49]. Changes in drug targets in cells or mutations that randomly modify bacterial chromosomes decrease the permeability of antibacterial drugs, causing chromosomal resistance [45].

Table 1. WHO-recommended global priority list of antibiotic-resistant bacteria.

Priority	Types of pathogens	Resisted medications
Priority 1: Critical	*Acinetobacter baumannii*	Carbapenem
	Pseudomonas aeruginosa	Carbapenem
	Enterobacteraceae	Carbapenem, third-generation cephalosporins
Priority 2: High	*Enterococcus faecium*	Vancomycin
	Staphylococcus aureus	Methicillin, Vancomycin
		Clarithromycin
	Helicobacter pylori	Fluoroquinolone
	Campylobacter	Fluoroquinolone
	Salmonella spp.	Third-generation cephalosporin
	Neisseria gonorrhoeae	Fluoroquinolone
Priority 3: Moderate	*Staphylococcus pneumoniae*	Penicillin
	Haemophilus influenzae	Ampicillin
	Shigella spp.	Fluoroquinolone

Source: (Mukhopadhyay et al. 2020) [54]

In response to the growing worldwide threat of AMR, international health authorities have stressed the critical need for integrated measures and drug development priorities. The WHO released a list of infections for which new antimicrobials must be developed promptly in February 2017. It has been determined that this pathogen poses a serious risk to human health and that a novel antibacterial drug is crucially needed. ESKAPE pathogens, which comprise both Gram-positive and Gram-negative bacteria, have been given "priority status" in this list [26]. According to Ma and coworkers [50], this pathogen frequently causes potentially fatal nosocomial infections in critically sick patients and individuals with compromised immune systems [51].

Gram-negative bacterial pathogens make up the majority of the WHO list [52]. *Klebsiella species, Enterobacter species, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are among the Gram-negative bacteria of ESKAPE pathogens that are known to be resistant to many drugs [53]. As shown in Table 1, the WHO has created a global priority list of pathogens that are resistant to antibacterial drugs [54]. This list makes it feasible to do more specific studies on new antibacterial agents.

Resistance mechanisms allow bacteria to withstand the effects of antibacterial medications by either spontaneous gene alterations in microorganisms or the exchange of genetic components across bacteria. Different resistance strategies, including low drug intake, efflux pumps, target alteration, deactivation of drug enzymes, and various other methods, could be developed by these bacterial strains [55].

Conventional Antibacterials

This review highlights current and emerging antibacterial strategies against multidrug-resistant ESKAPE pathogens, focusing on the contrast between conventional agents and peptide-inspired polymeric alternatives. Regardless of the increasing resistance among ESKAPE species, β-lactam antibiotics continue to be one of the most extensively utilized antimicrobial medicines in clinical, agricultural, and aquacultural contexts [56]. Antibacterial *β*-lactams (BLA) were among the first antibiotics used. BLA inhibits the production of bacterial cell walls after covalent binding to penicillin-binding proteins, an enzyme implicated in the final stages of peptidoglycan (PG) layer cross-linking in the cell walls of both Gram-negative and Gram-positive bacteria [57]. Gram-negative bacteria pose a significant threat because they have a double membrane in their cells that acts as a barrier and prevents most antibacterials from penetrating [58]. To address this issue, extensive research is being conducted to identify antibacterial compounds capable of killing Gram-negative bacteria.

Biological approaches are also being used in finding solutions to these problems. Now, there are three main ways to manufacture biological antibacterial drugs: the direct addition of organic antibacterial agents, the packaging of inorganic antibacterial agents, and the use of polymer antibacterial agents with permanent copolymers that form covalent bonds with polymer networks. In parallel, antibacterial peptides (ABPs) have gained attention for their amphiphilic nature and ability to mimic host defence mechanisms [59]. To better contextualize their roles, the relative advantages, limitations, and potential applications of conventional antibacterial agents and peptide-inspired strategies are summarized in Table 2.

Table 2. Comparison of conventional antibacterial agents and antibacterial peptides (ABPs).

Approach	Advantages	Limitations	References
Conventional agents (organic, inorganic, permanent copolymer)	Established efficacy; scalable production; wide availability	Increasing resistance; toxicity concerns; limited specificity	[60], [61]
Antibacterial peptides (ABPs)	Broad-spectrum activity; low resistance potential; mimic natural defences	Stability issues; high cost of production; short half-life	[62], [63]

Some of the challenges in discovering antibacterial drugs include the difficulty of penetrating bacterial cells and the scarcity of suitable compounds as starting points. Synthetic antibacterial drugs developed must be able to penetrate bacterial cells comprehensively, especially in the case of Gram-negative bacteria [64] which are more resistant to antibacterial drug polymers [65]. The second challenge is the difficulty of designing antibacterial drug molecules that can distinguish between bacterial cell membranes and host cell membranes [66]. Finding this opposing trait is obviously tough, but still possible.

A study by Ritsema et al. [67] stated that to obtain the appropriate confinement and release characteristics of antibacterial drugs, the polarity depends on the composition of the polymer used. Hydrophilic antibacterial drugs can completely confine bacteria, while hydrophobic drugs can only confine bacteria moderately. In addition to conventional antibiotics, a wide range of antibacterial agents with diverse functional groups have been reported in recent years, as summarized below [68]:

- Free halogens
- Ozone
- Chlorine dioxide
- Metal oxides
- Quaternary ammonium/phosphonium salts
- Peptides
- Guanidine N-halamin

ESKAPE Pathogens

ESKAPE pathogens are a group of bacteria consisting of Gram-positive (*Enterococcus faecium* and *Staphylococcus aureus*) and Gram-negative bacteria, namely *Klebsiella pneumoniae*, *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter species* [54, 69]. Since the world does not want to experience another pandemic like COVID-19, antibacterial resistance by this category of pathogens is something that must be treated seriously. The cell forms of the ESKAPE pathogens are depicted in Figure 2. Each of the ESKAPE pathogens possesses unique biological and structural characteristics that contribute to their survival and virulence. These differences extend to how they develop and express resistance to antibiotics, making each pathogen a distinct challenge in clinical treatment. These exclusive resistance mechanisms highlight the complexity of treating infections caused by ESKAPE pathogens. Figure 3 shows an overview of the general mechanism of antibacterial resistance.

The healthcare burden has risen as a result of ESKAPE pathogens, which are linked to the highest mortality rates and account for almost one-fifth of nosocomial infections [70]. The WHO recently included the ESKAPE pathogens in a list of 12 microorganisms that require immediate treatment using new antibacterial medications [71]. This prioritization reflects the severe clinical challenges these pathogens pose in hospital settings, where they are frequent causes of ventilator-associated pneumonia [72], bloodstream infections [73], and surgical site infections [74]. Conventional therapies are often ineffective, with carbapenem-resistant *K. pneumoniae* [75] or vancomycin-resistant *E. faecium* [76] leaving clinicians with limited treatment options. In response, current therapeutic strategies under investigation include novel β-lactam/β-lactamase inhibitor combinations [72], antimicrobial peptides [77, 78], and polymer-based alternatives [79], although none have yet closed the gap between clinical need and effective therapy. Components such as adhesins, fibronectin-binding proteins, PNAGs, pili, and fimbria that help bacterial cells colonize the host and cause diseases make this group of pathogens malignant [69].

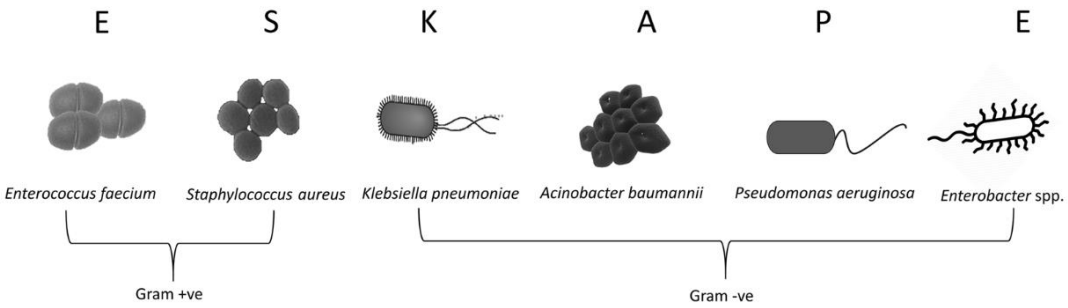

Figure 2. The ESKAPE pathogens.

Source: Idris & Nadzir 2023 [22].

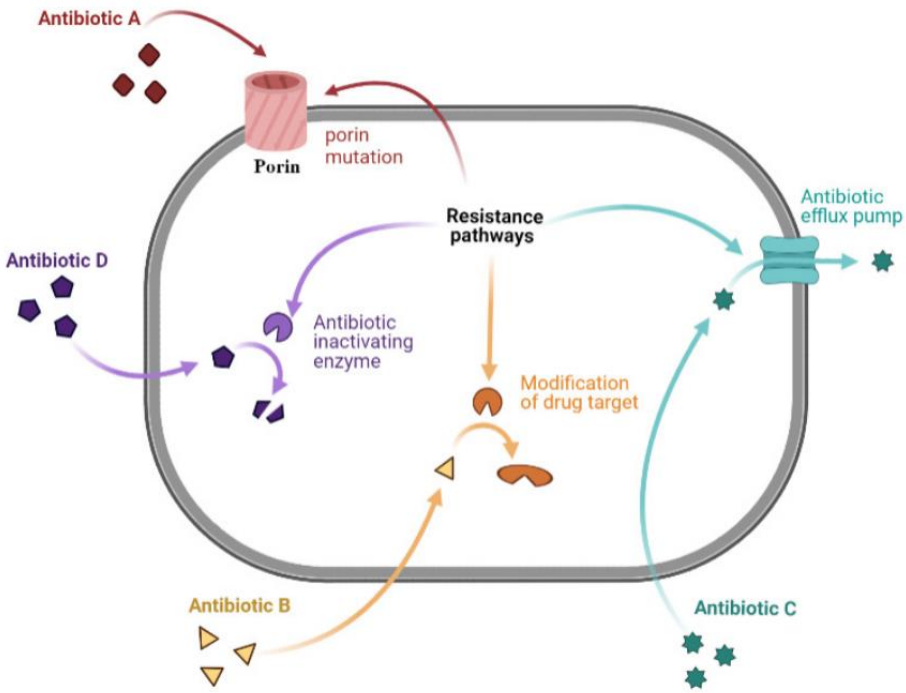

Figure 3. Overview of the general mechanism of antibacterial resistance: Antibiotic A corresponds to the mechanism of porin mutation; B to modification of antibiotic targets; C to antibiotic flux; and D to the inactivation of the drug by bacterial enzymes.

Source: Iskandar et al. 2022 [11]

According to de Macedo et al. [80], the ESKAPE pathogens are especially harmful as they exhibit varying degrees of antimicrobial resistance (AMR), including multidrug resistance (MDR), extensive drug resistance (XDR), and pandrug resistance (PDR). The fact that these bacteria can develop new genetic features just makes the situation worse. They carry a wide variety of resistance genes. According to De Oliveira et al. [21], ESKAPE infections have emerged as an outstanding example of how resistance, pathogenesis, and transmission can come together in both hospital and community settings. They adopt a variety of tactics to avoid antibiotic therapy, e.g., Gram-positive pathogens such as *S. aureus* and *E. faecium* often rely on mechanisms like altered penicillin-binding proteins or production of β-lactamases [81], whereas Gram-negative pathogens such as *P. aeruginosa* and *K. pneumoniae* combine outer membrane impermeability with efflux systems [82], making them particularly difficult to treat. They are also able to create enzymes and protective biofilms that render antibiotics inactive, making their removal substantially harder [50]. It is quite difficult to create novel antibacterial treatments because of the diversity of resistance mechanisms. The lack of new broad-spectrum antibacterial

medications despite significant research efforts in this area highlights the gap between scientific investigation and effective clinical treatments.

Understanding bacterial resistance mechanisms requires first examining the architecture of the cell envelope, since many antibiotics exert their action by targeting or bypassing these structural barriers. The main structural part of the bacterial cell wall is composed of peptidoglycan (PG). This polymer wraps around the cell and helps it endure internal pressure by forming a big, mesh-like structure from glycan chains that have been cross-linked by peptides. The PG layer, which is tens of nanometres thick in Gram-positive bacteria, is typically characterized as a solid, homogeneous structure that provides the cell with its mechanical strength and shape [83]. The situation is more complicated with Gram-negative bacteria. The outer membrane (OM), which covers the much thinner PG layer, is one of the key structural properties of these bacteria [84]. Because the outer leaflet contains lipopolysaccharides (LPS) and the inner leaflet is composed of phospholipids, this outer membrane has a distinct composition. The OM acts as an efficient barrier, shielding bacteria from dangerous substances in their surroundings, thanks to the asymmetry and unique chemical characteristics of LPS [85]. As this structure helps bacteria survive, it also makes it considerably more difficult for antibiotics to enter. Thus, this situation is a significant barrier to drug development today.

The development of new antibacterial drugs against Gram-negative bacteria has been particularly challenging, with no new antibiotic classes approved in the past 50 years [86]. This difficulty is largely due to the unique structure of Gram-negative bacteria, which possess a thick and complex outer membrane that limits the entry of therapeutic agents [87]. Most existing antibacterial drugs rely on targeting intracellular mechanisms, which requires the compounds to penetrate the bacterial membrane. However, even small molecules face difficulty crossing the outer membrane of Gram-negative bacteria, preventing them from accumulating within the cell and effectively reaching their targets [43]. Therefore, the main challenge is not a lack of promising therapeutic targets but rather the fact that many compounds cannot enter the intracellular area where these targets are found. This highlights a persistent gap in drug design strategies, where physicochemical optimization for membrane penetration remains underprioritized in the face of escalating resistance.

Antibacterial Peptide Drugs (ABPs)

In response to the AMR threat, antibacterial peptides (ABPs) have gained attention as natural defence molecules found in host organisms, offering a different approach to fighting infection. Unlike conventional antibiotics that target specific metabolic pathways, ABPs bind directly to bacterial membranes and disrupt their structure, leading to cell death [88]. An ABP is a type of natural amphiphilic cationic polymer that has a small relative size, consisting of 10-50 amino acids [54]. The amino acid sequence of an ABP is diverse, but most are amphiphilic with both basic and hydrophobic clusters. These opposite charges allow an ABP to penetrate anionically charged bacterial membrane cells, while being specific yet non-toxic [89]. Among the factors that influence its effectiveness of ABPs are its composition of amino acids, positive charges (cations), its amphiphilic nature, and size [90]. These properties indicate ABPs are the right substitute for antibacterial drugs to overcome the MDR problem.

These peptides have broad-spectrum properties with strong activity against microbes, viruses, parasites and even tumour cells [91]. The mechanism of action of ABPs against bacteria is by disrupting the integrity of the bacterial membrane. As a result, there occurs the formation of structures such as an α-helix or a β-sheet [92] by chains of such peptides or polymers, through electrostatic interactions with negatively charged membrane cells. Next, the hydrophobic residue penetrates the non-polar membrane core [66, 93]. ABPs are also capable of inhibiting protein and nucleic acid synthesis, cell division and protease activity [94]. This shows the importance of two moieties with different hydrophilic and hydrophobic properties in a single molecule of an ABP polymer.

Meanwhile, a research group led by Nguyen [95] stated that cationic ABPs not only have the potential to overcome the problem of bacterial resistance, but are also able to act against viruses, parasites and tumour cells [91]. In addition, the length of the fatty acid chain bound to these compounds also plays a role in the mechanism of ABPs [96]. These properties give ABPs a lot of potential to be used in the pharmaceutical field to overcome the problem of antibacterial drug resistance. One of the main advantages of ABPs over conventional antibacterials is that they are suitable for use by individuals with low immune systems [97]. More importantly, ABPs with targeted activities have turned out to be a good option for specific killing against pathogens [98]. The mechanism of ABP activity against bacteria works by interacting with various targets within the cell and with other membrane components [99]. The addition of an ABP to a hydrogel matrix as an antibacterial agent was able to completely inhibit the growth of pathogens [100]. Although ABPs have antibacterial medicinal properties, improvements are needed to provide resistance to the hydrolysis and decomposition of these compounds. These additions mostly do not interfere with their antibacterial properties.

However, the application of ABPs are limited due to several shortcomings [101] including low stability and high cytotoxicity [102]. This is because

its toxic properties are not just limited to bacteria [103]. Thus, the development of ABP-based antibacterial drugs needs to be designed with specific characteristics for a bacterium or microorganism. The amino acid-based ABP content facilitates the decomposition of these polymer molecules [104]. Furthermore, metabolic instability and a large number of peptide bonds limit the effectiveness of ABPs [105] because amino acids are susceptible to decomposition by protease enzymes [103]. The cost of manufacturing ABPs is also high and they are difficult to synthesize in large quantities [106]. Recent efforts to address these challenges include nanoparticle-based delivery, peptide–polymer conjugates, and chemical modifications to enhance protease resistance. Despite these advances, ABPs remain constrained, and the development of synthetic amphiphilic polymers has gained momentum as they not only mimic the antibacterial mechanism of ABPs but also offer greater stability, tunability and scalability.

Synthetic Amphiphilic Polymers

Amphiphilic polymers are macromolecules that contain both hydrophilic and hydrophobic segments. Depending on their architecture, such as block [107] or graft copolymers [108], or star-shaped structures [109], they can be designed to have strong antimicrobial characteristics [110]. The cell membrane of negatively charged bacteria are easily attracted to the positive part of this polymer [106]. Polymers of such antibacterial agents have demonstrated the peculiarities of ABP activity, including a broad spectrum of activity, rapid biocidal kinetics, and a low tendency for the development of bacterial resistance [66]. Furthermore, chemically stable amphiphilic polymers have longer activity, limited residual toxicity, are not easily volatile and are not able to penetrate through the skin due to their macromolecular structure and high molecular weight [42]. A study by Rahman and colleagues [93] found several parameters to be considered to obtain antibacterial agent activity and bio-compatibility in synthetic polymers, namely a hydrophobic to hydrophilic moieties balance, amphiphilic face, molecular weight, charge properties and polymer structure. This is because amphiphilic block polymers have specific molecular characteristics, and are also produced by controlled polymerization methods [111]. Amphiphilic polymers can be varied in terms of molecular sidechain structure, polymer architecture, and copolymer composition [112].

Biocide polymer mechanisms of action fall into two primary categories. Contact killer surfaces can (i) be coated with immobile antimicrobials (via covalent bonds) that kill bacteria upon direct contact, and (ii) contain polymer compounds that release antimicrobial agents, such as metal nanoparticles, low-molecular-weight biocides, or antibiotics [113]. Cationic polymers are often used as antibacterial agents, with the advantage of being low cost. The polymer toxicity of antibacterial agents can be reduced by hydrophobic chain modifications to the polymer composition [65]. Therefore, amphiphilic polymers in the presence of both charges are expected to be able to balance the properties of the antibacterial and toxic agents. A study by Duman et al. [114] found that antibacterial activity was enhanced by the presence of imidazolium cations that have a higher positive charge density and long alkyl chains.

Alkyl groups with long chains are seen to have good antibacterial properties, but are highly toxic to humans (haemolytic) [115]. Therefore, to obtain biocidal polymers that are low in haemolytic activity, the ratio of hydrophobic to hydrophilic moieties should be minimal [115]. Other approaches, such as incorporating biodegradable linkers [116] or stimuli-responsive designs [117], have also been explored to reduce haemolysis. The presence of cation groups is also necessary in the chemical structure of these compounds; one that stands out in biocidal polymer applications is the quaternary ammonium group (NH_4^+) [118]. The presence of a positive charge in the structure of the amphiphilic polymer attracts bacterial membrane cells that have a negative charge (LPS layer); in turn, the destruction of bacterial cells occurs on its own due to the inclusion of large hydrophobic portions of the cationic polymer [119]. This happens when the electrical balance of membrane cells is disrupted, leading to the destruction of membrane cell integrity, resulting in cell leakage and subsequently bacterial cell death [59]. Other cationic carriers like phosphonium possess higher cytotoxicity towards mammalian cells [120], while sulfonium is less explored, with limited data on its biomedical use [121].

A study by Zhang et al. [122] found that quaternary ammonium salt monomers were copolymerized in resins to produce antibacterial agents. The presence of hydrophobic and hydrophilic moieties in the structure of such polymers plays an important role in providing optimal results in the development of antibacterial agents. The hydrophobic properties in polymer chains also help in the adsorption of polymers of antibacterial agents onto bacterial membrane cells [123] which influences the action of bacterial eradication by polymers [36]. To form these bonds, the appropriate hydrophobic properties need to be taken into account to produce synthetic polymers capable of acting on the bacteria. Long carbon chains have high antibacterial agent properties, and short carbon chains exhibit low haemolytic properties [66, 124]. This is because long chains contribute to hydrophobic properties that facilitate the penetration of polymers into bacterial membranes [125]. As an alternative, the addition of cyclic chain polymers provides an alternate design method. Their unique architecture has been linked to enhanced blood compatibility and better cell compatibility with mammalian cells, allowing for a more balanced optimization of antibacterial activity and safety [126]. This demonstrates that the structure of the polymer and the correct selection of chain

lengths are crucial factors in producing amphiphilic polymers with effective antibacterial properties. Therefore, the development of new polymers of antibacterial agents should take these properties into account.

The antibacterial efficacy of quaternary ammonium salts is influenced by the length of the polymer side chain, with longer chains enhancing antibacterial activity while concurrently reducing initial bacterial adhesion and biofilm formation [127]. In addition to the length of the chain, the topology of amphiphilic polymers is also important to ensure their effectiveness as an antibacterial agent, as star-shaped systems and branched polymer structures have good biological activity profiles [88].

Since the properties of an antibacterial agent are often studied in an aqueous medium, its solubility in solvents is very important. Nevertheless, solubility under experimental conditions does not always translate directly to physiological environments, where ionic strength and protein-rich conditions may affect polymer stability and activity. Modification of polymer side chains using tertiary amines is one method to increase solubility [128]. This is due to the properties of amine compounds that can form hydrogen bonds with water molecules [129]. In addition, amine compounds are also capable of dissolving in some organic solvents [130]. Designing amphiphilic polymers with balanced hydrophilic and hydrophobic segments offers a promising strategy to sustain solubility and activity under physiological conditions.

The selected solvent can be diversified, ensuring (i) the polymer is fully soluble in the solvent used, and (ii) the solvent is non-toxic to bacteria. The solubility properties of polymers influence the biological activity of the solvents used [131], so the selection of a solvent capable of dissolving as much of the amphiphilic polymer as possible is important to aid in antibacterial activity. Amphiphilic polymers that are antibacterial have the advantage of showing long-term antibacterial activity [132]. The physical properties of amphiphilic polymers have also been studied to obtain support for factors of antibacterial activity.

In a report by Hora et al. [107], compounds containing the ammonium functional group displayed antibacterial activity against Gram-positive bacteria. In addition, most industries have already started using products containing this functional group to kill the COVID-19 virus [134]. If this works, improvements may be made to produce antibacterial agents capable of resisting Gram-negative bacteria as well.

Enzymatic decomposition of amphiphilic polymers involves the breakdown of these polymers by specific enzymes found in biological systems. Due to their unique structure, amphiphilic polymers can be susceptible to enzyme cleavage, resulting in their deterioration into smaller fragments. This decomposition process may be influenced by factors such as the composition of the polymer (polymers with a low molecular weight are more susceptible to decomposition [135]), hydrophilic and hydrophobic segment properties, and specific enzymes found in the environment. The presence of enzymes accelerates the rate of polymer decomposition, with aliphatic polyesters being easily attacked by ester-like lipase enzymes due to their structural similarity to lipids such as glycerol [136].

The enzymatic decomposition of amphiphilic polymers can have significant implications in a variety of applications, including controlled drug release systems, tissue engineering scaffolding, and environmentally friendly materials. At the same time, the degradation products themselves may raise ecological or biomedical concerns, such as potential cytotoxicity, inflammatory responses, or accumulation in the environment. Therefore, understanding the enzymatic decomposition mechanism of these polymers is essential not only for optimizing performance but also for ensuring safety and sustainability in their practical applications.

Mechanisms of Amphiphilic Polymer Action Against ESKAPE Pathogens

Amphiphilic polymers, designed to mimic antimicrobial peptides (AMPs), offer a promising strategy to combat ESKAPE pathogens. Their mechanism of action primarily involves membrane disruption, leveraging a delicate balance between cationic and hydrophobic moieties [137, 138]. The cationic groups, such as ammonium, sulfonium, and phosphonium ions, electrostatically interact with the negatively charged bacterial membrane, facilitating polymer adsorption [139, 140]. Simultaneously, the hydrophobic regions insert into the lipid bilayer, disrupting membrane integrity and causing cell lysis through various mechanisms [141, 142]. The optimal balance between these hydrophobic and cationic components is crucial; insufficient hydrophobicity reduces antimicrobial efficacy, while excessive hydrophobicity can lead to increased haemolysis and cytotoxicity [25, 143, 144], highlighting the need for careful optimization. The presence of hydrophilic moieties like PEG can further enhance biocompatibility by reducing toxicity [102]. Studies have shown that tuning the hydrophobic-hydrophilic ratio and molecular weight with the right length and type of hydrophobic groups significantly impacts both antibacterial activity and biocompatibility [145–148].

Table 3. Variety of amphiphilic polymer systems targeting specific ESKAPE species (2015–2025).

Amphiphilic polymer system	Targeted ESKAPE species	Reference
Cationic guanidinium-based polymers	*Escherichia coli, Staphylococcus aureus*	143
Nanofiber membranes		144
Quaternized cationic polymers		99,100
Cationic copolymers		145
Geminized cationic amphiphilic polymers		146
N-halamine terpolymers		64
PEG-conjugated methacrylate polymers		147
Triblock copolypeptides		148
Fluoroamphiphilic cationic polymers	*Staphylococcus aureus, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae*	149
Methacrylate cationic nanoparticles	*Staphylococcus aureus, Enterococcus faecalis*	150
Quaternary ammonium charged naphthoic acid-containing polymers	*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Klebsiella oxytoca, Staphylococcus aureus, Acetinobacter baumnanii,*	151
Methacrylate-based copolymers	*Pseudomonas aeruginosa, Staphylococcus aureus*	152
	Escherichia coli, Staphylococcus aureus	36,137
Peptoid AMP	*Enterococcus faecium, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumnanii, Enterobacter cloacae*	153
Pseudoblock terpolymers	*Escherichia coli*	126
Cationic polycarbonates	*Escherichia coli, Staphylococcus aureus,* Methicillin-resistant *Staphylococcus aureus*	154
Amphiphilic chitosan nanoparticles	*Acetinobacter baumnanii,* Fucidin-resistant *Staphylococcus aureus,* Methicillin-susceptible *Staphylococcus aureus,* Methicillin-resistant *Staphylococcus aureus, Staphylococcus aureus Escherichia coli, Pseudomonas aeruginosa*	129
Nylon-3 polymers	*Enterococcus faecium, Staphylococcus aureus, Escherichia coli*	155
Cationic α-helical AMP	*Enterococcus faecium, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Acetinobacter baumnanii, Pseudomonas aeruginosa*	130,156
Synthetic β-Peptide Polymers	Methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa*	157
Cationic copolymer nanostructures	*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*	81
Amphiphilic ternary copolymers	*Escherichia coli, Pseudomonas aeruginosa*	103
Vancomycin encapsulated mPEG-OA	*Staphylococcus aureus,* Methicillin-resistant, *Staphylococcus aureus*	158
Functional ternary copolymers	*Escherichia coli*	159

Amphiphilic polymers, which possess both hydrophobic and hydrophilic moieties [149–151], effectively interact with bacterial outer membranes (OM) due to electrostatic interactions between the positively charged polymer and the negatively charged OM [152]. This interaction disrupts the bacterial membrane, leading to cell death [153–156]. The versatility of amphiphilic polymers extends to applications in drug delivery systems [157] and smart wound dressings [158], offering a promising platform for combating bacterial infections and promoting healing. Furthermore, adding biodegradable segments helps ease worries about long-term toxicity and harm to the environment [25, 159].

Another crucial component of amphiphilic polymer performance is efficient biofilm penetration. Biofilms provide a significant challenge to antimicrobial medications because they are shielded by an extracellular polymeric matrix [159]. Size, charge, and amphiphilicity are some of the physicochemical characteristics of polymers that influence their ability to pass through bacterial cell membranes and enter the cytoplasm [155, 160, 161]. Biofilms are more likely to be successfully disrupted by smaller polymers with a higher cationic charge density and suitable hydrophobicity [162]. Research has shown that polymers can break down mature biofilms and lower the metabolic activity of the attached bacteria, sometimes outperforming traditional antibiotics [145]. A study using cationic amphiphilic polymers by Zhou et al. [163] showed significant *in vitro* and *in vivo* activities against ESKAPE pathogens. Additionally, the molecular weight of the polymer is important; shorter polymers may be more effective against Gram-positive bacteria because they can pass through the thick peptidoglycan barrier more easily, while the impact on Gram-negative bacteria is less certain [115].

Beyond their inherent antimicrobial properties, stimuli-responsive amphiphilic polymers offer an additional layer of control and efficacy [164]. These polymers undergo conformational changes or phase transitions in response to specific environmental stimuli, such as pH, redox potential, or temperature [165, 166]. This reactivity enables targeted drug release or increased antimicrobial activity in particular situations, such as at the acidic infection site [167], thereby enhancing their efficacy [168]. For instance, pH-sensitive triblock copolymers PLA-PAE-mPEG, PAE-PLA-mPEG, and PLA-PEG-PAE have been shown to self-assemble into charge-adaptive micelles capable of penetrating and eradicating mature *Pseudomonas aeruginosa* biofilms both in vitro and in vivo. Among them, the PLA-PEG-PAE (ML-E-A) micelle exhibited superior charge-switching behaviour, stronger bacterial binding, and higher biofilm disruption efficiency, emphasizing the importance of rational copolymer architecture in maximizing antibacterial performance [169]. Similarly, redox-sensitive polymers can respond to the reducing environment of the bacterial cytoplasm, triggering a change in their conformation or activity [54]. The incorporation of temperature-sensitive moieties can also be exploited to control polymer aggregation and release, by optimizing their interaction with bacterial membranes [54]. However, the design and optimization of stimulus-responsive polymers require careful consideration of the specific stimulus, the response of the polymer, and its potential impact on both bacterial cells and host tissues to ensure enhanced antibacterial efficacy without triggering cytotoxic inflammation. Table 3 presents the variety of amphiphilic polymer systems that have been used since 2015.

Amphiphilic polymers have emerged as promising antibacterial materials due to their ability to break microbial membranes and prevent resistance formation [187]. Regardless of their potential, certain constraints must be carefully examined before clinical translation. High cationic charge density or hydrophobicity can cause cytotoxicity and haemolysis, while keeping polymers stable and useful under physiological settings remains a major challenge [188, 189]. Furthermore, large-scale synthesis is often limited by the complexity of polymer design and the biodegradation issue [190]. Thus, striking an optimal balance between antimicrobial activity, biocompatibility, and manufacturability is critical for moving these systems closer to real-world applications.

Mechanisms of antibiotic resistance in ESKAPE pathogens include target changes, enzyme inactivity, loss of porins, efflux pumps, and biofilm formation [69]. Antimicrobial resistance arises when bacteria, viruses, fungi, or parasites evolve to withstand treatment, leading to more difficult infections, higher healthcare costs, and increased morbidity and mortality [21, 191–193]. Through electrostatic and hydrophobic interactions, amphiphilic polymers break down bacterial membranes, allowing them to circumvent numerous enzyme- and target-based resistance mechanisms, in contrast to conventional antibiotics that target certain metabolic or enzymatic pathways. To improve clinical application, structural optimization, such as charge-adaptive or stimuli-responsive designs, is necessary to overcome issues like cytotoxicity, instability in physiological settings, and restricted biofilm penetration.

Conclusion and Future Perspective

This review summarizes the potential of amphiphilic polymers as a replacement for the global threat of multidrug-resistant ESKAPE pathogens. With unique features that combine both hydrophilic and hydrophobic moieties, these polymers can mimic the mechanism of action of antibacterial peptides. The presence of specific functional groups makes these polymers powerful biocides that overcome the weaknesses of natural antibacterial peptides. The cationic character of the selected polymer enables excellent adsorption of the amphiphilic polymeric

biocide onto the pathogenic cell membrane. Meanwhile, the alkyl substituent of the amphiphilic polymeric biocide with the right length enables absorption through the pathogen cell membrane, resulting in cell death. The synthesis method, the stability of the compound, and improved adsorption of the amphiphilic polymer are essential points in the fabrication of a novel antibiotic to combat ESKAPE diseases. Future developments in polymer engineering and nanotechnology should concentrate on improving the scalability, biocompatibility, and structural design of amphiphilic polymers. These advances will be key to translating their promising antimicrobial potential into clinically viable therapies against multidrug-resistant infections.

Data Availability

Not available.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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