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Cationic Compounds in Antimicrobial Therapy: Structure–Activity Relationships and Emerging Technologies

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ABSTRACT

The phenomenon of antibiotic resistance is one of the most pressing challenges of our modern age. The development of multidrug-resistant bacteria poses a serious threat to public health. Therefore, it is necessary to develop new therapeutic strategies that are a viable alternative to conventional antibiotics and, at the same time, effectively and concretely overcome their current limitations. The most promising synthetic approaches are oriented towards the use of cationic compounds, which have a physicochemical mechanism of action based on electrostatic interactions with bacterial membranes; targeting this mechanism reduces the possibility of resistance developing. Cationic compounds include antimicrobial peptides, cationic polymers, quaternary ammonium and quaternary phosphonium salts, and Gemini surfactants. This review offers a comprehensive summary of recent advancements in cationic antimicrobial platforms, highlighting the structure-activity relationships, mechanisms of action, and design strategies, illustrating how these molecules can achieve enhanced efficacy and biocompatibility for humans. Natural AMPs and their synthetic analogues have facilitated the creation of novel polymer topologies and self-assembling systems exhibiting rapid, multi-target efficacy. Cationic polymers serve as the foundation for the creation of "contact-active" antibacterial coatings and anti-biofilm materials by adjusting their charge and hydrophobicity. finally, Gemini surfactants and cationic systems create structural synergy by integrating antibacterial efficacy, biodegradability, and potential theranostic applications. Furthermore, the issues concerning environmental sustainability, biocompatibility, and the incorporation of intelligent and stimulus-responsive systems are also addressed. Developing novel antimicrobial compounds that are effective, selective, and sustainable necessitates a multidisciplinary collaboration among chemistry, materials science, and microbiology.

Keywords: Cationic antimicrobials; Antimicrobial peptides; Quaternary ammonium-phosphonium salts; Gemini surfactants; Antimicrobial resistance; Structure–activity relationships.

1. Introduction

1.1. Antibiotic resistance: global overview and limitations of traditional therapies

One of the greatest threats to global public health is associated with the worrying increase in infections caused by multi-drug resistant (MDR) bacteria. According to a well-known assessment commissioned by the British government, antimicrobial resistance es expected to cause more than 10 million deaths per year by 2050, with a severe economic impact on global health systems [1]. The socio-economic consequences of antibiotic resistance are substantial, including increased treatment costs, longer hospital admissions, and mortality related to this phenomenon [2].

This occurrence is intensified by a combination of biological and anthropogenic factors. The main molecular mechanisms underlying the emergence, spread, and transmission of resistance genes among bacteria are mainly due to genetic mutations in the bacteria themselves and horizontal gene transfer through plasmids and transposons [3,4]. Another emerging factor influencing the selection of resistant strains is, alongside environmental dispersion, the improper use of antibiotics in both medical and agricultural contexts [5].

1.2. Biofilm and microbial persistence

Biofilms are crucial to the persistence of bacterial infections. Biofilms are three-dimensional structures consisting of microbial communities embedded in an extracellular matrix. This

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extracellular matrix serves as a physical and chemical barrier against pharmaceuticals and the host's immune responses. This results in resistance to antimicrobial treatment, rendering it ineffective and increasing the chance of relapse following traditional treatment. Biofilms are implicated in various infections and have been shown to play a critical role in the chronicity of human diseases. The onset of biofilm-related infections is not only responsible for an increase in severe symptoms but also has a significant impact on related mortality [6,7].

1.3. Cationic molecules: a new frontier in antimicrobials

The ineffectiveness of conventional drugs has directed research towards the study of novel strategies and antimicrobial agents capable of overcoming the resistance mechanisms of multi-resistant bacteria. Among the emerging strategies, particular attention is being paid to cationic compounds, which include antimicrobial peptides, cationic polymers, quaternary ammonium salts, phosphonium and gemini surfactants. The distinguishing characteristic of these compounds is the presence of positive charges, which promote interaction with negatively charged bacterial membranes, particularly anionic lipids, lipopolysaccharides and teichoic acids [8]. The electrostatic interaction between these compounds and the membranes causes destabilisation of the phospholipid bilayer, loss of membrane potential, and consequent cell death. In contrast with traditional antibiotics that target specific molecular sites, cationic agents exert a multifaceted physicochemical mechanism that is challenging to evade through mere point mutations. Furthermore, they have fast kinetics of action and provide significant efficacy against bacteria resistant to conventional antibiotics [9,10]. Simultaneously, materials engineering has enabled the incorporation of these antimicrobial compounds into advanced controlled-release systems on surfaces, rendering them antibacterial. These are employed to prevent of hospital-acquired infections. Cationic coatings for catheters and implantable devices have demonstrated efficacy in reducing biofilm formation, even in complex clinical conditions [11]. All this has paved the way for a new multifunctional approach to fighting infections. The aim of this review is to provide the first comprehensive and up-to-date overview (2022-2025) of the principal cationic antibacterial platforms, including quaternary ammonium compounds (QACs), cationic polymers, antimicrobial peptides (AMPs) and gemini surfactant systems. Unlike recent reviews available today, which all focus on individual cationic classes such as QACs [12,13], cationic polymers [14], AMPs [15,16] or gemini surfactants [17], this work offers a cross-sectional view of the entire landscape of cationic antibacterial materials. The review highlights the main common mechanisms of action and structure activity relationship (SAR) studies, integrating approaches usually carried out separately and demonstrating the interdisciplinarity and connection between them in guiding new design strategies. Recent advancements, together with a direct comparison of structural variations, stimulus-responsive materials and novel synthetic methodologies, enable the enhancement and acceleration of the synthesis of new antimicrobial agents. Overall, this review fills a gap in the current landscape, offering a broad and comparative analysis of cationic platforms, which is essential for accelerating the design of compounds capable of addressing the problem of antibiotic resistance. A comparative summary of the main cationic systems analysed is reported in **Figure 1.**

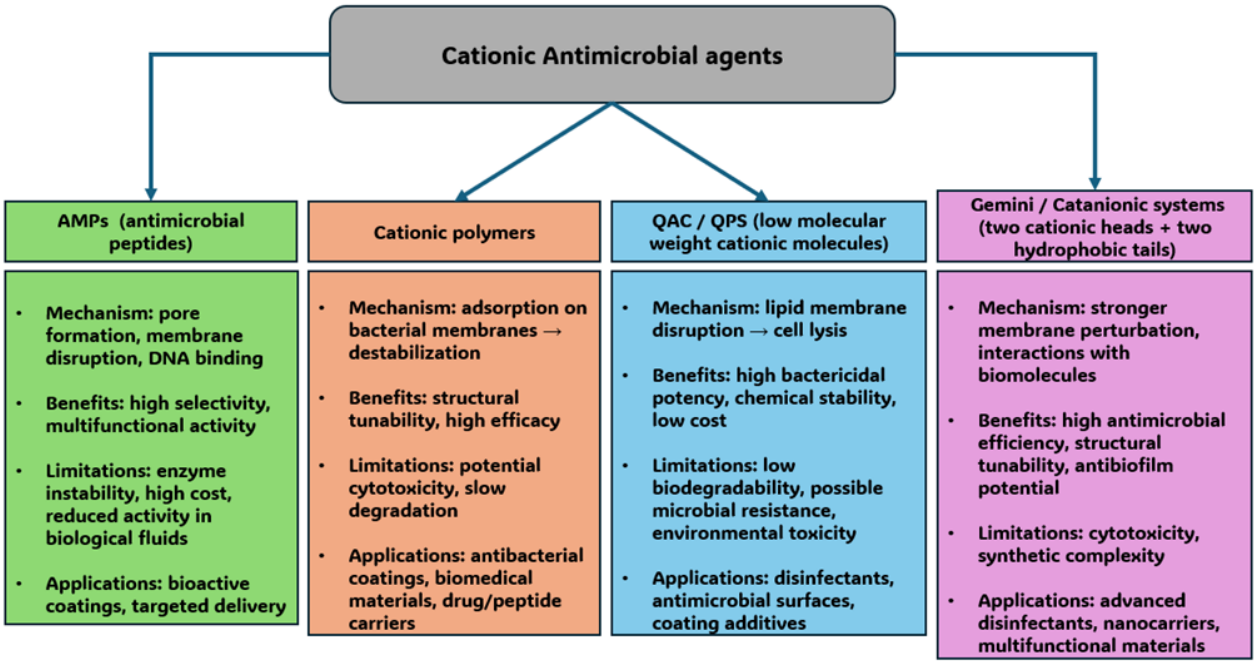

Figure 1 | Comparison of the main classes of cationic antimicrobial compounds.

2. Antimicrobial Peptides (AMPs)

Antimicrobial peptides are naturally produced by several species, including humans, and are essential to the innate immune system. The first antimicrobial peptide, gramicidin, was discovered in 1939 by microbiologist Renè Dubos in a strain of Bacillus with anti-pneumococcal properties [18]. To date, the APD (Antimicrobial Peptide Database) contains over 5 000 AMPs, of which 3 000 are isolated from animal eukaryotes. These peptides are produced in response to bacterial infections and are capable of neutralising various pathogens [16,19–21]. Their adaptability mostly stems from their amphipathic structure, characterized by a net positive charge, and their ability to selectively recognise and interact with bacterial membranes, which are abundant in anionic phospholipids.

2.1 Mechanism of action and selectivity towards bacterial cells

The primary characteristic that has shifted attention towards AMPs as therapeutic agents is their physical and multimodal mechanism of action (**Figure 2**). Their mechanism involves electrostatic interactions with negatively charged bacterial membranes, leading to destabilisation through the insertion of hydrophobic portions, resulting in loss of membrane integrity and subsequent cell lysis. Secondary structures, such as α-helices and β-sheets, help form amphipathic regions that can induce pore formation (barrel-stave or toroidal) and membrane destabilization. This rapid, non-target-specific physical mechanism is responsible for their effectiveness against resistant strains and reduced the likelihood of resistance to development [22,23]. Numerous studies indicate that AMPs do not only target the membrane. In addition to causing physical damage to the phospholipid bilayer, certain peptides are able to penetrate the microbial cells and interfere with essential processes such as DNA, RNA and protein synthesis, as well as key enzyme activity and oxidative homeostasis. This multifunctionality broadens their therapeutic profile, making them a model of inspiration for the development of new synthetic cationic compounds capable of targeting multiple microbial targets simultaneously, while maintaining a low propensity for resistance [15]. The design of antimicrobial peptides exhibiting high bactericidal activity while maintaining low cytotoxicity towards human cells, characterized by good selectivity, can be achieved by modulating peptide length, overall hydrophobicity and charge distribution. These principles form the basis for the development of formulations and polymeric conjugates that increase their stability, bioavailability and specific targeting, while maintaining safety and compatibility with the host [23].

2.2 Synthetic peptides and mimetics: rational design and self-assembly

The clinical application of natural AMPs is severely limited due to high costs, metabolic instability and protein degradation. These factors have stimulated research and development into the synthesis of cationic peptidomimetics capable of preserving antimicrobial activity while improving stability characteristics [24–26]. To increase resistance to proteolysis, the most effective approach is to insert D-amino acids and the reinforcement of stability through stabilised cyclic or β-turn structures. Finally, interaction with membranes is promoted by the introduction of aromatic cationic units. Recent studies indicate that the strategic substitution of specific amino acids allows the modulation of key properties, such as positive charge and amphipathicity, thereby improving antimicrobial activity while minimizing cytotoxicity towards human cells. Peptides designed in this manner exhibit self-

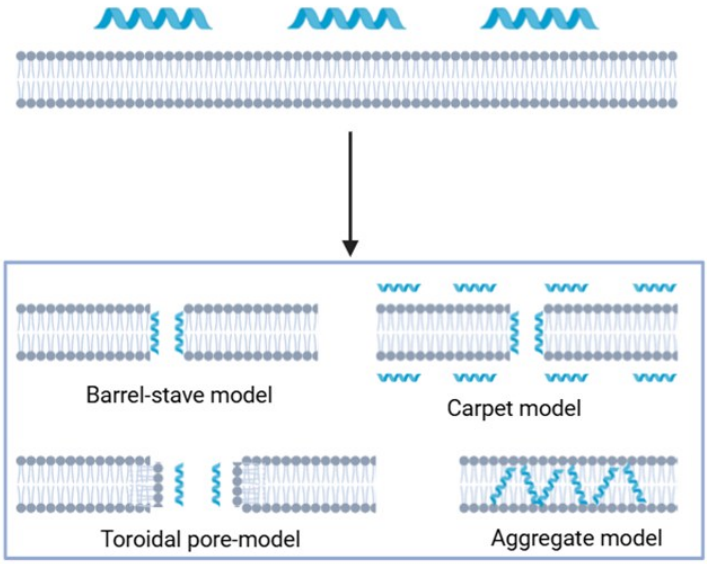

Figure 2 | Main mechanisms of action of AMPs against bacterial membranes. After initial adsorption on the phospholipid surface, these molecules can destabilise the membrane through different mechanisms; Barrel stave, carpet model, toroidal pore model and aggregate model.

assembling in nanoparticles, promoting rapid destabilisation of bacterial membranes and exhibiting strong efficacy both *in vivo* and *in vitro* against multi-resistant Gram-negative pathogens. This highlights how rational design based on the study of the structural and physicochemical characteristics of AMPs can be a valuable guide for the discovery and synthesis of new peptidomimetics that are safe and effective [27]. Li *et al.* have recently developed new bis-pyridine cationic mimetics of antimicrobial peptides (**Figure 3**), demonstrating significant antibacterial activity against both Gram-positive and Gram-negative strains while exhibiting low haemolytic toxicity. These compounds are stable in complex body fluids, with rapid bactericidal activity, a prolonged post-antibiotic effect and a rapid reduction in *S. aureus* load. Furthermore, the bacteria showed a low propensity to develop resistance. Finally, these compounds also shown excellent anti-biofilm properties, effectively preventing biofilm formation and degrading established biofilms. These characteristics confirm the potential of these compounds as new antimicrobial agents mimicking AMPs [28].

2.3 Nanostructured delivery systems

A notable area of investigation involves the encapsulation of antimicrobial peptides in nanoparticles or polymeric vesicles. This strategy not only protects the peptides from proteolytic degradation and facilitates a more controlled release of these compounds. The optimisation of AMPs administration can be enhanced through the use of delivery systems based on biodegradable nanoparticles. Ali et al. have demonstrated in their studies that encapsulating antimicrobial peptides in poly(lactic-co-glycolic acid) (PLGA) nanoparticles reduces the MIC (Minimal Inhibitory Concentration) value by approximately 50% compared to the free peptide, significantly improves penetration and therefore effectiveness against biofilms, and preserves excellent biocompatibility of the compound. In complex infectious models, these systems have resulted in a reduction exceeding 95% in bacterial load, thereby confirming their effectiveness in more realistic biological systems. This demonstrates how the combined approach based on amino acid modification of peptides and encapsulation in nanoparticles represents an innovative and promising strategy to overcome the limitations of natural AMPs, improving, stability, antimicrobial activity and safety [29]. Another method entails the integration of quaternary ammonium and phosphonium groups into antimicrobial peptides. These provide the ability to enhance antimicrobial activity via multiple mechanisms of action. Cationic compounds exhibit selective interactions with bacterial membranes. Their activity is mainly attributed to the induction of respiratory dysfunction through the generation of reactive oxygen species and damage to intracellular biomolecules. These synergistic mechanisms are essential and promising for combating bacterial infections, especially those caused by antibiotic-resistant pathogens. Recent studies have shown how this combination of antimicrobial peptides with antibiotics can exert a synergistic action against S. suis through membrane disruption, ROS (Reactive Oxygen Species) induction and biofilm formation inhibition [30]. This multimodality and synergy pave the way for therapies that can be combined and used in tandem to target bacteria on multiple fronts simultaneously, improving treatment efficacy.

2.4 Biomedical applications and functionalised surfaces

An effective strategy for preventing bacterial colonisation and biofilm formation on medical devices is the immobilisation of antimicrobial peptides on biomedical surfaces. Unlike traditional therapeutic formulations, AMPs immobilised on surfaces provide extended local activity, reducing the risk of resistance and ensuring long-lasting efficacy. Recent studies have shown that the covalent immobilisation of antimicrobial peptides on the surfaces of catheters and orthopaedic implants surfaces can significantly reduce biofilm formation, hence enhancing the functionality and safety of these devices. A review conducted by Nicolas et al. analysed various techniques for immobilisation on biomedical devices surfaces, highlighting the mechanisms of action by which they prevent bacterial adhesion and biofilm formation. The authors, analysing immobilisation techniques on various materials in the biomedical field, emphasised the importance of maintaining the antimicrobial activity of AMPs during the immobilisation process [31]. The self-assembling properties, structural versatility and modular synthesis of AMPs have established them as one of the most promising antimicrobial platforms for tackling the global emergency of antibiotic resistance. The study of the properties of natural peptides has inspired and driven research towards the design of new synthetic cationic molecules capable of replicating their effectiveness but with greater stability and safety.

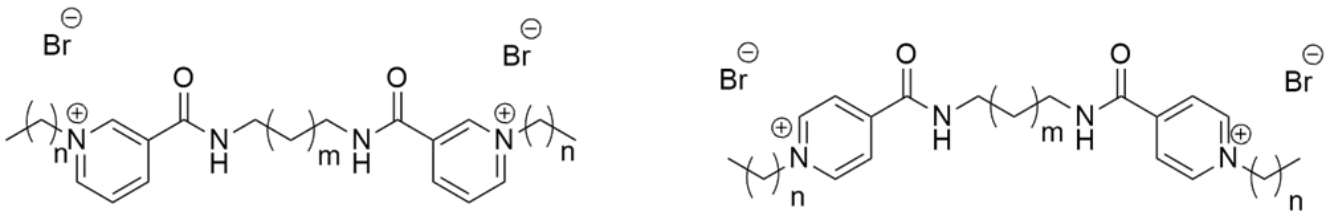

Figure 3 | General structure of bis-pyridine cationic compounds [26].

3. Cationic polymers and salts

3.1 Cationic polymers: molecular design and advanced architectures

In recent years, numerous studies on cationic polymers have demonstrated their potential as effective antibacterial compounds against both Gram-positive and Gram-negative strains, exhibiting rapid action and a low likelihood of resistance development. Unlike traditional antibiotics, their target is the bacterial membrane; they act through electrostatic interactions between the positive charges along the polymer chain and the negatively charged bacterial surfaces [11]. An important feature of cationic polymers lies in their modularity, which permits the modification of their structural features through changes in their chemical and physical attributes. Recent studies have highlighted and identified three main parameters that influence the activity and selectivity of these compounds: cationic charge density, the balance between hydrophobicity and hydrophilicity, and polymer architecture. Excessive cationic charge increases the risk of haemolysis and cytotoxicity, while reduced hydrophobic content reduces affinity for the bacterial membrane, effectively compromising its antimicrobial activity [32]. Tyagi *et al.* conducted studies that demonstrated how varying the degree of polymerisation and the distribution of hydrophobic and cationic groups along the polymer chain leads to polymers with high antibacterial activity and low toxicity to human cells. The research emphasizes that the ability to interact with the bacterial membrane and the formation of pores is influenced by the architecture, which can be linear or branched. This provides supplementary tools for the rational synthesis of novel antimicrobial materials. Precise modification of chemical-structural parameters is therefore essential for developing effective and safe cationic polymers capable of acting against multi-resistant bacteria [33].

3.2 Miktoarm, star and imidazole copolymer architectures

An advanced approach to the design of antimicrobial agents is represented by core-cross-linked (CCS) cationic star polymers. Recently, Laroque *et al.* developed and conducted studies on diblock and miktoarm polymers, combining non-polar and cationic arms to modulate charge exposure. *In vitro* investigation demonstrated that miktoarms with cationic units more accessible to the bacterial membrane exhibit superior antibacterial activity against *Staphylococcus aureus*, while diblock polymers with partially shielded cationic units display reduced efficacy. In conclusion, these studies have shown how the miktoarm type can optimise interaction with the bacterial membrane, highlighting how crucial the balance between the number and length of cationic arms is to maximise antimicrobial efficacy with lower cytotoxicity [34]. Liu *et al.* developed imidazole-based cationic copolymers (**Figure 4**), which exhibited high bactericidal activity against *MRSA (Methicillin-Resistant Staphylococcus aureus)*, *S. aureus*, *E. faecalis*, *E. coli*, and *P. aeruginosa*. These compounds were associated with high biocompatibility with erythrocytes and mammalian cells. The antibacterial action was attributed to electrostatic interactions between these compounds and the membranes, along with the insertion of hydrophobic segments, resulting in membrane permeabilisation and depolarisation. Furthermore, they were determined to be highly effective in eradicating biofilms. An additional significant feature is their ability not to induce bacterial resistance after repeated exposure, thus highlighting their potential as safe and selective antibacterial agents for clinical applications, including medical coatings [35]. Similar research was conducted by Zhoung *et al.* on cationic main chain polymers containing imidazole units and adjusted hydrophobicity. These compounds showed good antibacterial activity against Gram-positive and Gram -negative pathogens, including resistant strains and mycobacteria. These polymers are absorbed by the cell in a manner dependent on the membrane potential ($\Delta\Psi$), and their effectiveness is maintained on actively growing bacteria but is limited on bacteria in the stationary phase. Furthermore, the polymers exhibit significant selectivity, minimal toxicity to mammalian cells, and do not induce resistance in non-fermentative bacteria. Finally, research using animal models has validated the therapeutic effectiveness against systemic skin infections, once again highlighting the potential of these copolymers as antibacterial agents [36].

3.3 Multifunctional and photoactive materials

Biofilms provide a significant challenge in hospital environments, prompting research into polymers capable of self-assembling or function as active vectors. Nabawy *et al.* have developed cationic alternating poly (phenylene ethynylene) (PPE) copolymers (CP_Cn_TMA) (**Figure 5**) with variable alkyl side chain lengths achieving a balance between hydrophobic groups and positive charges that effectively eradicate both Gram-positive and Gram-negative bacteria. They are efficient against multi-resistant clinical isolates due to their ability to penetrate biofilm and reduce more than 80% of extracellular biomass without inducing resistance and keeping low toxicity towards fibroblasts and red blood cells. Furthermore, they have also demonstrated efficacy in mouse models of skin infections [37].

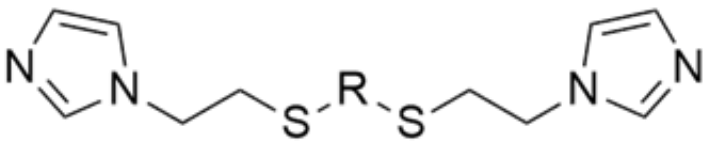

Figure 4 | General structure of bi-imidazole monomer [33].

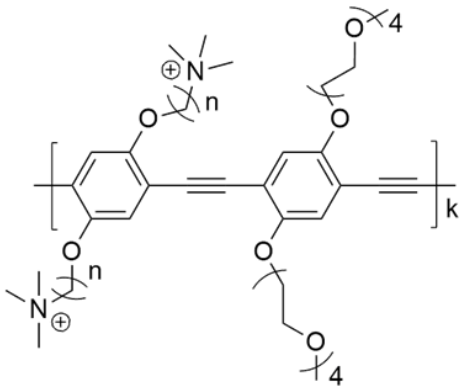

Figure 5 | General structure of CP_Cn_TMA alternating copolymers [37].

Other studies have integrated photoactive groups into polymers to produce photodynamic materials capable of generating ROS under light, thereby increasing efficacy without increasing systemic toxicity. Ma *et al.* developed D–A type BPDS-COFs (Covalent Organic Frameworks based on 4,4'-bipyridine-2,2'-disulfonate) functionalised with pyridine (PY) and quaternary ammonium (QA) groups, effectively combining photoelectric and antibacterial activity. The material synthesised exhibits excellent crystallinity and porosity, along with enhanced hydrophilicity and chemical stability. This configuration promotes the separation of photo-induced electrons and the generation of active oxygen species capable of damaging bacterial membranes, proteins and nucleic acids. These systems achieve sterilisation rates of over 99% with low cytotoxicity towards fibroblasts, showing high antibacterial efficacy against *E. coli*, *S. aureus* and *P. gingivalis*, both in the absence and presence of visible light [38]. These systems push towards a new generation of intelligent and selective therapeutic agents.

3.4 Versatility of cationic units: ammonium, sulphonium and phosphonium

Recent studies have been conducted comparing the properties of polymers containing ammonium, sulfonium and phosphonium cations highlighting crucial differences. Compounds containing quaternary ammonium have been extensively researched due to their significant antibacterial activity; nonetheless, aromatic derivates pose environmental concerns mainly related to their persistence and toxicity. Polymers containing the imidazolium group, on the other hand, are characterised by greater rigidity and π -π interaction potential with membranes, resulting in a more rigid structure that increases their affinity for bacterial surfaces. Polymers containing the sulfonium group, on the other hand, show less haemolysis and better reactivity compared to their ammonium analogues, attributable to a different electronic distribution, which reduces interaction with eukaryotic membranes. Finally, polymers containing the phosphonium group offer superior chemical stability and a wider therapeutic window. These polymers exhibit enhanced antimicrobial activity compared to QACs, demonstrating increased efficacy against Gram-negative bacteria, hence positioning them as a promising strategy for clinical applications [39,40]. This difference is mainly related to the difference in electronegativity between nitrogen and carbon compared to phosphorus and carbon. This difference affects the electrostatic interactions that occur with bacterial membranes, improving the effectiveness of the polymer. In addition, the chemical stability of phosphonium groups contributes to a longer duration of antimicrobial activity [41]. Another extensively explored class is 1,4 Diazabicyclo[2,2,2]octane (DABCO)-based systems (**Figure 6**), which combine a highly cationic rigid core with excellent thermal and chemical stability.

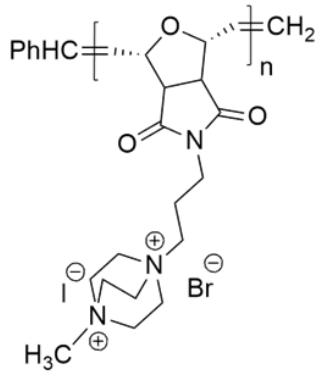

Figure 6 | General structure of DABCO-based homopolymer [42].

Temur *et al.* conducted studies on these materials and found an effective balance between antimicrobial activity and biocompatibility. Experimental data showed minimal haemolysis and IC_{50} higher than the efficient concentrations. These systems exhibited stability in PBS and physiological solution, without any loss of activity over 28 days. SEM (Scanning Electron Microscope) and TEM (Transmission Electron Microscope) investigation verified that polymer activity induces bacterial membrane degradation through vacuole formation and intracellular content depletion, aligning with a "carpet" mechanism. Furthermore, the results obtained indicate that these polymers are selective, stable and highly promising for biocompatible antimicrobial applications with high activity even against multi-resistant bacteria [42].

3.5 Smart surfaces and devices

Cationic polymers are used to coat medical devices, particularly intravascular catheters, orthopaedic implants and implantable cardiovascular systems. The antibacterial contact activity enables the prevention of microbial adherence and biofilm formation on surfaces, hence combating the onset of device-associated illnesses. Moreover, they provide durable coatings due to their structural stability and the possibility of covalent anchoring to surfaces, which minimises the uncontrolled release of the active ingredient, preserving its long-term effectiveness [43].

3.6 Antibacterial coatings and biomedical surfaces

Recent research has concentrated on employing cationic polymers as coatings for hospital surfaces and implantable devices as a major preventative technique, functioning either as bactericidal surfaces or anti-adhesion surfaces (**Figure 7**) [44]. Materials functionalised with quaternary ammonium salts, derivatised ammonium or polymeric cationic groups can act as antimicrobial barrier, limiting microbial adhesion and therefore biofilm formation. The strategy most used today exploits the positive charge immobilised on the surface, so that it can interact with the bacterial membrane, generating local destabilisation and leading to the loss of cell integrity. This mechanism is called "contact-active" and is particularly advantageous compared to materials that release antibiotics, as it avoids resistance phenomena associated with the diffusion of bioactive molecules in the microenvironment [45]. Emerging technologies are based on bio-inspired polymers, cationic hydrogels, amphiphilic copolymers and polymeric nanocapsules. Wolf-Brandstetter *et al.* have investigated cationic amphiphilic copolymers capable of adsorbing onto surfaces like titanium, yielding a sustained antimicrobial effect with high biocompatibility. These materials are particularly suitable for applications in prostheses and catheters, as they combine "contact-active" antibacterial activity with compatibility with human cells and reduce the risk of microbial resistance [46]. Zeng *et al.* have developed cationic polymeric nanocapsules. These nanocapsules are based on pyridine quaternary ammonium salts, possess a hollow architecture, high surface charge density, and the ability to exert effective "contact-active" antimicrobial activity against Gram-negative pathogens by breaking down the membrane through electrostatic interaction with anionic phospholipids, eliminating the necessity for cell membrane penetration [47]. Recent research tends to replace contact-active coatings with smart antibacterial materials overcoming static effect with "on-demand" response to physiological stimuli (pH, enzymes, ROS), or by integrating multi-target anti-biofilm strategies, or by combining with advanced nanotechnologies that merge theranostic and antimicrobial functions [48,49]. These innovations could revolutionise the control of medical device-related infections, offering better and more durable solutions. Concurrently, low molecular weight cationic structures, such as quaternary ammonium and phosphonium salts, still represent the simplest and most historically established part of cationic polymers, providing a basic model for comparing structure -activity relationships.

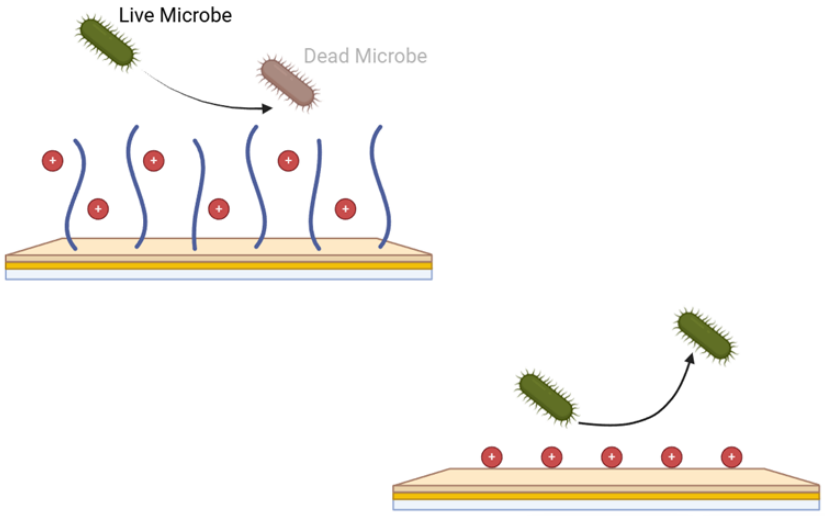

Figure 7 | Schematic representation of the main mechanisms of action of surfaces functionalised with cationic molecules or cationic polymers. At the top, the bactericidal mechanism; at the bottom, the anti-adhesion mechanism.

3.7 Quaternary ammonium and phosphonic salts

Quaternary ammonium salts (QACs) are well-established and versatile classes of compounds used to eredicate bacteria. They were originally employed as disinfectants, antiseptics, and antibacterial agents in industrial and cosmetic contexts. Their antibacterial capacity and activity lie in their simple yet effective mechanism of action. Quaternary ammonium salts interact with bacterial cell membranes thanks to the presence of a permanent cationic structure, which promotes a strong electrostatic bond with negatively charged bacterial surfaces. This interaction is followed by the insertion of the hydrophobic portion of the compound into the phospholipid bilayer, resulting in the the physical-chemical destabilisation of the membrane, the dissipation of membrane electrical potential, concurrent the leakage of intracellular components and, finally, cell lysis. Quaternary ammonium salts differ from traditional antibiotics because in the latter act on specific enzymatic targets or metabolic pathways, while QACs exert a direct mechanical action that reduces the chances of resistance developing in the conventional manner. Despite their advantages, the use of quaternary ammonium salts poses some limitations. Effective antimicrobial properties necessitate a balance between the density of the cationic charge, the hydrophobic portion of the molecule, and the ability to diffuse within the bacterial membrane without damaging eukaryotic cells, hence ensuring adequate selectivity. A further issue lies in the environmental persistence of some compounds and their potential toxicity at elevated concentrations. Thanks to further studies on antimicrobial polymers and ionic liquids, QACs have been re-proposed as adjustable antimicrobials. These molecules allow for minor structural modifications from a basic structure to enhance their properties, including selectivity, stability and biological compatibility [50–52].

3.8 Structure-activity: the balance between hydrophobicity and charge

The antibacterial properties of quaternary ammonium salts depend on the structure of the molecule, mainly on the length of the alkyl chain, the nature and number of cationic heads, and the presence of aromatic groups or heterocycles. Recent studies on cationic amphiphilic AIEgens (Aggregaton-Induced Emssion luminogens) by Deng *et al.* have confirmed the importance of these parameters, showing how alkyl chain length and charge density directly influence the antibacterial activity of these compounds and their selectivity towards bacterial cells. The article demonstrates how molecules with intermediate chains (C8-C12) are more effective against Gram-positive bacteria by directly disrupting the cell membrane without involving specific enzymatic targets, while maintaining low cytotoxicity towards human cells. Analyses were conducted using SEM/TEM, Z-potential measurements, membrane depolarisation, and molecular simulations, which demonstrated how these molecules interact directly and optimally with the bacterial phospholipid bilayer, inducing perturbations and disorganisation of the phospholipids themselves. Finally, in vivo results confirmed the efficacy and biocompatibility of these compounds. These results provide an insight for the design of new-generation quaternary ammonium compounds that can also be used as antimicrobial coatings for medical devices [53]. Simultaneously, additional research has demonstrated that in the production of mono- and bi-cationic pyridine compounds (**Figure 8**), the length of the alkyl chains and the presence of bi-cationic units can increase antibacterial activity even against resistant clinical strains and limit biofilm formation [54]. The properties of quaternary ammonium salts are additionally influenced by their conformational structure and self-assembling capabilities. Particularly effective QACs exhibited greater conformational flexibility, attributed to the presence of aromatic rings that allowed π-π interactions with bacterial membranes. On the other hand, self-assembly phenomena in micelles or functional nanostructures increased the density of cationic and hydrophobic units, improving their stability and affinity for the bacterial membrane. These characteristics increase antimicrobial efficacy, selectivity towards bacterial cells and stability in solution [55]. The findings presented above support the concept of a fundamental structure that can be modified and modulated by varying both its chemical composition and structure to design selective, powerful compounds with good biocompatibility.

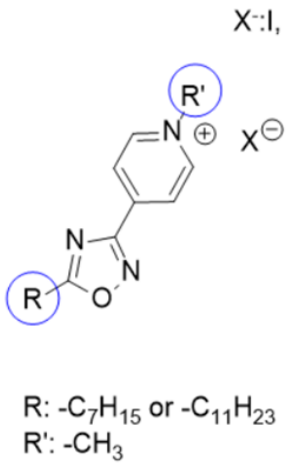

Figure 8 | General structure of mono-cationic pyridine compound [52].

3.9 From chemistry to biomedicine: QACs as smart materials

Recently, the use of quaternary ammonium salts has evolved far beyond their traditional application. These compounds have been incorporated into various advanced platforms to increase their effectiveness, durability and selectivity. Examples of these platforms include functionalised polymers, which combine cationic charges and hydrophobic groups to optimise antibacterial activity and biocompatibility, as well as durable antibacterial coatings for medical devices that can prevent bacterial colonisation and biofilm formation without releasing the active ingredient. Finally, other platforms include nanocapsules for controlled release, which allow the concentration of the QAC released to be modulated, thereby improving antibacterial efficacy and reducing cytotoxicity towards eukaryotic cells [47]. Santoro and Izzo have demonstrated how the covalent anchoring of quaternary ammonium groups to polymeric surfaces allows materials with intrinsic and non-leaching antimicrobial activity to be obtained, which is a fundamental requirement for use in medical devices [56]. Recent experimental research have confirmed the effectiveness of this approach. Surfaces and nanocomposites containing functionalised quaternary ammonium salts have good antimicrobial properties without releasing the active ingredient and are also capable of reducing biofilm formation and bacterial colonisation on implantable substrates [57]. Other systems are based on DABCO, which fall into the category of cationic antimicrobial materials. Temur *et al.* demonstrated that cationic polymers derived from DABCO are active against multi-resistant strains, have good thermal and chemical stability, and a very low haemolysis profile. These polymers are obtained by ROMP (Ring Opening Metathesis Polymerisation), with different molecular lengths [42]. These results therefore confirm that the design of cationic molecules with defined structures represents a way to generate bacterial agents.

3.10 Emerging resistance and environmental impact

The extensive use of quaternary ammonium salts, especially during the SARS-CoV-2 pandemic, has heightened selective pressure on pathogens, causing the emergence of strains tolerant to these biocides. Kuznetsova *et al.* have reported in their studies that nosocomial bacteria such as *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *S. aureus* already show reduced sensitivity to chlorhexidine and benzalkonium chloride-based disinfectants, alongside a significant prevalence of genes associated with efflux pump transduction. These bacteria employ adaptive strategies such as membrane remodelling or the formation of structured biofilms capable of circumventing the activities of these biocides [58]. These mechanisms, frequently concomitant with the onset of antibiotic resistance, indicate that disproportionate use of QACs can also contribute to the spread of multi-resistant bacteria. Besides the problems related with the emergence of antibiotic resistance, another concern relates to the negative environmental impact of excessive use of quaternary ammonium salts. A monitoring research was conducted in three German rivers revealed an increase in quaternary ammonium salts in sediments during and after the pandemic, with concentrations exceeding the ecotoxicological no-effect thresholds for long-chain compounds prior to 2020 [59]. This has raised concerns about the chronic effects they will have on aquatic ecosystems, as incomplete removal in treatment plants contributes to their large-scale accumulation.

3.10 Posphonium salts (QPSs): a more sustainable alternative

In light of these issues, research is shifting towards the discovery of new compounds. Alfei *et al.* studied phosphonium salt compounds [60], (**Figure 9**) these are quaternary compounds comprising triphenylalkylphosphonium derivatives. These compounds have shown promising properties against biofilm proliferation in vitro, greater chemical stability than QACs, and a wider therapeutic window. The modulation of QPS synthesis, which is simple and versatile, is aimed at obtaining compounds that can develop less resistance. Phosphonium salts constitute a significant approach for addressing chronic infections, also associated with medical devices that are consequential to the colonisation of multi-resistant biofilm -producing bacteria; moreover, they exhibit reduced environmental persistence, thereby mitigating he ecotoxicological risks associated with QACs [61]. Innovative approaches are implemented to obtain more degradable molecules that exhibit less environmental persistence and possess targeted and modifiable activity over time. Thus, the evolution and future research of quaternary ammonium salts cannot be exempt from a risk assessment including antimicrobial resistance, ecotoxicity and sustainability in applications. Future research should focus on harmonizing chemical innovation with environmental sustainability to develop compounds that effectively combat microbes while minimizing ecological damage. One of the main objectives is to limit the indiscriminate use of quaternary ammonium salts, thus avoiding selective pressures that favour the onset of resistance, and to develop hybrid and synergistic systems combining both QACs and QPSs with polymers, peptides or other antimicrobial molecules to increase efficacy at reduced dosages. Finally, integrating nanotechnological strategies using nanoparticles or functionalised coatings that optimise the release and penetration of molecules within biofilms. The challenge will be to balance the antimicrobial potency, safety and sustainability of these compounds; however, further studies are needed to achieve therapeutic efficiency while minimising environmental and clinical costs. **Table 1** illustrates the structure-activity relationships of the compounds discussed above. The correlation is based on characteristics such as charge density, hydrophobicity and molecular topology, and can be extended to other complex amphiphilic systems such as gemini and catanionic compounds, which will be discussed in the next section.

4. Gemini surfactants and catanionic systems

4.1 Gemini surfactants

Gemini surfactants are compounds characterised by the presence of two polar cationic heads and two hydrophobic chains connected by a spacer that is modular and confers more favourable chemical-physical properties, including greater surface efficiency and enhanced antimicrobial activity. These structures represent an

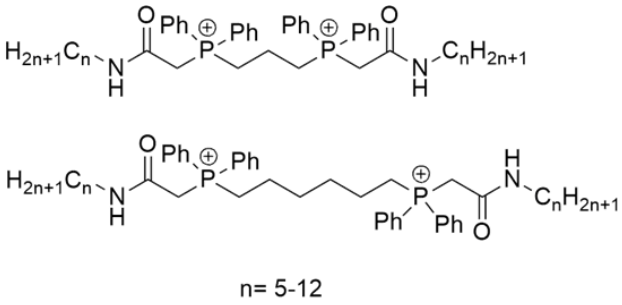

Figure 9 | General structure of phosphonium salt compounds [59].

Table 1 | Structure–activity relationship (SAR) trends of cationic systems.

Parameter	Structural variable (from examples in text)	Effect on antimicrobial activity	Effect on cytotoxicity	Qualitative trend (as described)
Cationic charge density	Number and type of charged groups (ammonium, imidazolium, pyridinium)	Increases binding to bacterial membranes and killing efficiency	Excessive charge density increases haemolysis and toxicity	Optimal balance between electrostatic attraction and selectivity is required
Hydrophobicity	Alkyl chain length, aromatic substituents, backbone rigidity	Enhances membrane insertion and biofilm penetration	High hydrophobicity reduces selectivity and solubility	Moderate amphiphilicity gives best antimicrobial-toxicity balance
Molecular topology	Linear vs. branched vs. star-shaped architectures	Multivalent interactions increase surface coverage and activity	Branched or dense systems may reduce biocompatibility	Topology tuning can improve selectivity and membrane affinity
Spacer length (gemini surfactants)	Number of methylene units connecting cationic heads	Affects membrane insertion and CMC; moderate length improves synergy	Long spacers increase lipophilicity and cytotoxicity	6–8 carbons often give optimal efficiency/toxicity ratio

evolution from conventional cationic surfactants. The modularity of these compounds lies in the ability to make structural changes in terms of the nature or length of the hydrophobic unit and the spacer. These changes optimise the interaction of these compounds with biological membranes. Numerous cationic Gemini systems based on quaternary ammonium (**Figure 10**), pyridinium, imidazolium and amide structures have been developed, increasing and broadening the spectrum of activities and versatility compared to traditional monocationic surfactants [17]. These structures have a lower CMC (critical micelle concentration) than their monocationic analogues. Recent studies have confirmed that this characteristic promotes antibacterial activity. For example, Gemini with optimised chain lengths show both efficient micellisation at low concentrations and reduced MICs against Gram-positive and Gram-negative bacteria [62,63]. However, it should be emphasised that the reduction in CMC is not the only indicator of the antimicrobial efficacy of these compounds. Additional considerations, as previously noted, include the length of the hydrophobic chain, the nature of the spacer and the presence of heterocyclic functionalities. The spacer, a structural component linking the two cationic heads, plays a crucial role in the design of Gemini surfactants. The choice of one spacer over another modulates the conformational flexibility of the molecule, the charge density and electrostatic interaction with bacterial phospholipids, membrane penetration and disorganisation, as well as selectivity for eukaryotic cells. Studies by Bao *et al.* indicates that an aliphatic spacer of intermediate length achieves the best compromise between antimicrobial activity and biosafety; specifically, heterocyclic Gemini with dodecyl chains and short spacers show high antibacterial activity against *S. aureus* (up to ~100% inhibition), enhanced surfactant properties with diminished surface tension, lower micellisation concentration, and adequate biocompatibility for both medical and industrial applications. These results highlight the predominant role of the spacer within these compounds, as it can increase their antimicrobial efficacy while reducing undesirable effects. Finally, the introduction of aromatic units can enhance their action thanks to π-π interaction with lipid and protein components [64]. Gemini surfactants are employed in diverse sophisticated biological applications thanks to their self-assembling properties and ability to modulate their amphiphilic qualities. Their bicationic structure allows synergistic interaction with biological membranes, enhancing the eradication of resistant biofilms and the development of highly adhesive antibacterial coatings, beneficial in medical devices and hospital surfaces [65]. Thanks to their self-assembling properties in micelles, vesicles or nanocapsules, they serve as excellent carriers for anti-cancer drugs, increasing their availability and selectivity towards neoplastic cells. Recent studies have shown that nanoparticles formulated with Gemini surfactants, encapsulating curcumin and tamoxifen, can significantly improve selective cytotoxicity towards breast cancer cells [66]. He *et al.* have recently developed peptides conjugated to quaternary ammonium Gemini moieties. These structures are capable of self-assembling into cationic nanoparticles with good antimicrobial activity and low cytotoxicity. Antimicrobial efficiency relies on a multimodal mechanism of action that includes both the physical disruption of the bacterial membrane and the suppression of ribosomal protein synthesis, ensuring high efficacy even against multi-resistant strains. Furthermore, these nanomaterials have demonstrated activity in vivo, preventing systemic skin infections and surpassing the efficacy of vancomycin, thus highlighting the potential of these Gemini-based peptides [67]. Hafidi *et al.* studied and developed systems consisting of arginine-based Gemini surfactants (**Figure 11**). These compounds consisted of two cationic arginine heads connected to two hydrophobic chains of different lengths, and they showed strong antimicrobial activity against clinically relevant bacteria and fungi. They also demonstrated the ability to eradicate mature biofilms of MRSA, *C. albicans* and *C. tropicalis* at low concentrations. Their efficacy is dictated by their hydrophobic content, while their physiologically compatible cationic structure ensures low cytotoxicity and reduced hemolysis, making them promising for pharmacological applications [68].

4.2. Catanionic systems: synergy and reduced toxicity

Other systems combine a cationic and an anionic surfactant. This combination results in supramolecular aggregates with adjustable charge; through structural variations, their affinity for bacterial membranes can be modulated, thereby improving their selectivity, reducing cytotoxicity and increasing stability in physiological

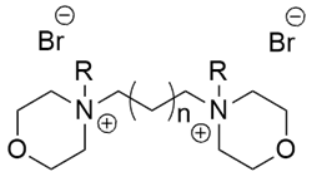

Figure 10 | Example of structure of cationic Gemini compound based on quaternary ammonium [15].

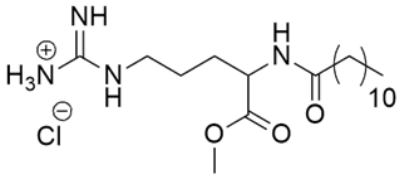

Figure 11 | Structure of arginine-based surfactants [66].

fluids. Studies have been conducted on the influence of variations in the cationic/anionic ratio on antimicrobial efficacy. Investigations conducted on cationic vesicles with arginine-based surfactants have demonstrated that these modifications significantly influence surface charge, aggregation, and toxicity, while maintaining good antimicrobial efficacy [69]. Kowalczyk *et al.* conducted studies on mixtures of monomeric cationic surfactants and Gemini/dimer surfactants with varying molar ratios of the cationic to the anionic portion. The results indicated that minor increments of anionic surfactant effectively preserve the antibacterial activity of these systems [70]. Furthermore, these systems can also be used for the delivery of bioactive molecules [71]; for example, they can be adapted for anti-tumor applications, through drug delivery, or for environmental sensing systems, exploiting their ability to incorporate functional molecules that are able to respond to specific environmental stimuli. Surfactants have demonstrated significant capabilities in combining antibacterial efficacy, biological safety and multifunctionality, opening innovative opportunities for the design and further investigation of these substances.

4.3. Biodegradability and sustainability

To overcome the environmental problems caused by the excessive use of quaternary ammonium salts, recent research is also focusing on the sustainability of these compounds. Research is being conducted on the redesign of surfactants in accordance with the principles of green chemistry. New synthesis strategies aim to introduce biodegradable hydrophobic chains that decompose swiftly without environmental accumulation, integrate cationic heads inspired by natural amino acids (such as histidine, arginine or tryptophan) to improve biological compatibility, and use clean, low-environmental-impact synthesis methods, reducing the use of toxic solvents. For example, recent studies conducted on histidine-based cationic surfactants have shown excellent biodegradability and low cytotoxicity of these compounds, making them promising for pharmaceutical applications while also being sustainable [72]. The characteristics of surface efficiency, self-assembling capacity and structural versatility make these Gemini and catanionic systems one of the most promising classes in the antimicrobial field.

5. Applications and perspectives

The significant versatility of cationic organic compounds allows their application in several fields where both antibacterial characteristics and surfactant properties are required. These substances have been studied in surface antibacterial coatings to prevent the aggregation of bacterial colonies for the formation of biofilms and also for the development of new macromolecules that have higher biological tolerability and a lower capacity to develop resistance. Their characteristics and properties are based on the mechanisms mentioned above and are influenced by positive charge density, structure and hydrophobicity. These parameters regulate the interactions of these compounds with microbial membranes. **Table 2** provides an overview of the main applications and current research directions and summarizes the representative systems described in this review, together with the type of application or surface, their antimicrobial mechanism and the main observations or limitations highlighted in recent studies. Current research focuses on increasing specificity of action and reducing toxicity to host cells, as well as developing more sustainable and biodegradable formulations. Future activities should continue to integrate microbial efficacy with environmental and biological compatibility, while enabling practical and safe applications of these cationic materials in medical and industrial contexts.

5.1 Sustainability perspective

From a sustainability standpont, the rational design of novel cationic antimicrobial systems should prioritize environmental safety alongside antimicrobial activity. Essential design principles include the development of biodegradable or cleavable cationic strcutures, the reduction of long-term environmental persistence, and the modulation of charge density and hydrophobicity to minimize ecotoxicity while maintaining activity [73]. The use of renewable or bio-based building blocks, as well as stimuli-responsive or degradable formulations that limit unnecessary release, represents an additional strategy to minimize environmental impact [74,75]. Integrating life-cycle considerations at the early phases of material design will be essential to ensure effective, safe, and sustainable cationic antimicrobial systems for widespread medical and industrial applications.

Concluding Remarks

The spread of antibiotic-resistant strains is one of the global health emergencies that poses a serious threat to our society. The use of cationic compounds such as antimicrobial peptides, cationic polymers, quaternary ammonium salts and Gemini surfactants represents innovative therapeutic strategies that can offer significant help in combating and curbing this threat. Their physical mechanism of action, which targets bacterial membranes, is advantageous compared to that of traditional antibiotics, as it presents a reduced likelihood of resistance development. Among these systems, cationic polymers and QACs stand out for their structural tunability and synthetic scalability, making them particularly suitable for industrial translation, including antimicrobial coating, medical device surfaces, and water-treatment technologies. Their adaptability in hydrophilic/lipophilic balance enables optimization for selectivity and cytotoxicity, facilitating compliance with regulatory requirement for biomedical and consumer application. Gemini surfactants, thanks to their bicationic structure, achieve high efficacy at low concentrations, represent attractive candidates for biofilm-resistant material, advanced surface treatments, and long-lasting antimicrobial coating. Their efficiency at reduced dosages is especially relevant from both toxicological and sustainability perspectives, supporting potential large-scale development. Antimicrobial peptides remain highly promising due to their broad-spectrum activity and functional versatility, particularly for clinical and therapeutic applications. However, challenges related to stability, cost-effective synthesis, and regulatory approval remain key barriers that must be

Table 2 | Representative applications and perspectives of cationic organic systems, summarizing the main functional categories, mechanisms, and remarks on performance.

Application / Focus Area	Example Systems (mentioned in the review)	Mechanism / Functionality	Performance Notes / Perspectives
Antibacterial coatings	Cationic polymers; QACs; DABCO-based	Contact-active antibacterial action through electrostatic interaction	Reduction of E. coli and S. aureus adhesion; suitable for medical devices; minimal leaching
Biofilm inhibition / prevention of adhesion	Polyimidazolium polymers; cationic copolymers; pyridinium-based nanocapsules	Membrane destabilisation or electrostatic repulsion	Active against resistant strains; some systems disrupt early-stage biofilms
Nanostructure delivery systems	Self-assembling cationic polymers, nanoparticles carriers with AMPs	Enhanced penetration into biofilms; controlled release;	Lower MIC values than free agents; improved biocompatibility
Gemini surfactants and catanionic systems	Gemini ammonium/ pyridinium, amphiphilic surfactants	Dual-head cationic interaction with membranes; self-assembly into micelles/ vesicles	High antibacterial and antibiofilm efficiency; good selectivity and tunability;
Cationic peptides and peptide mimics	Natural AMPs; bis-pyridyl AMP mimetics; AMP-functionalized surfaces	Membrane disruption, intracellular targeting, ROS induction, multimodal action	High selectivity; activity against MDR bacteria and persisters; limitations: stability and synthesis costs
Sustainability-oriented and next-generation materials	Biodegradable cationic polymers; quaternary phosphonium salts (QPSs)	Membranolytic action with less environmental impact	Greater biocompatibility, reduced toxicity, alternatives to QACs

addressed before widespread clinical adoption. To facilitate the transition to the clinical application of these compounds toward real-word applications, future research should focus on studying possible solutions to increase biocompatibility and reduce systemic toxicity. Defining structure-activity relationships will guide the synthesis of new compounds, thoroughly evaluating the field of environmental persistence and degradation by-products. Developing smart formulations with modulable and multifunctional activities and conducting standardized and comparable preclinical and clinical tests will be achieved as final goals. Equal attention should be devoted to environmental persistence, biodegradability, and degradation by-products, especially for materials intended for long-term or large-scale use. Thanks to the integration of knowledge from various fields such as chemistry, biology, nanotechnology and materials engineering, cationic molecules could truly represent promising platforms for therapeutic innovation in the treatment of infections and constitute an effective weapon against bacterial resistance.

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