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Antibacterial cationic polymers: A novel approach for combating bacterial infections

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Abstract

Bacterial resistance is a growing global health problem that is impeding effective disease treatment. The emergence of multidrug-resistant bacteria threatens the viability of conventional antibiotics. Bacterial adhesion and biofilm formation are critical parameters for establishment of infection in the host. Antimicrobial cationic polymers have emerged as a promising tool for combatting bacterial infections due to their potential to inhibit bacterial adhesion, biofilm formation and growth. Cationic polymers have broad-spectrum antibacterial activity against a variety of bacteria, including strains that are resistant to antibiotics. Optimizing polymer efficacy, reducing potential toxicity, and improving stability remain important research areas. Several nanopolymers (nanoparticle conjugated polymers) naturally have antibacterial properties. They can be utilized by health care institutions to make antimicrobial coatings for surfaces or medical devices, thus lowering the risk of healthcare-associated infections. This review highlights an update on recent advances in the synthesis of cationic polymers and their formulations with minimal host side effects and maximum antibacterial efficacy.

Keywords: Cationic polymer; Antibacterial activity; Nanocomposite; Quaternary Ammonium Compounds

1. Introduction

Antibiotic-resistant bacteria have been identified as a major concern for public health and clinical practice by the World Health Organization (WHO) [1]. The rise of bacterial resistance to traditional antibiotics has spurred researchers to look for novel antimicrobial strategies. Among these tactics, cationic polymers have gotten a lot of attention because of their unique antibacterial properties and potential to combat the growing risk of antibiotic resistance. Cationic polymers, which have positively charged molecular structures, have shown exceptional antibacterial effectiveness against a wide range of bacterial infections. Their primary mechanism of action involves electrostatic interactions with negatively charged bacterial cell membranes, resulting in membrane breakdown, permeabilization, and cell death. Unlike conventional antibiotics, which target specific cellular processes, cationic polymers adopt a diverse approach, making it difficult for bacteria to develop resistance quickly [2].

Cationic polymers have two major functional groups: positively charged and hydrophobic groups. These groups work in synergy to impart antibacterial activities to the polymer. Positively charged atoms, such as quaternary ammonium ions (NR4+), pyridinium ions (N+), or guanidinium ions (NH2+), make up the positive end of cationic groups, which bind to negatively charged bacterial membranes. The polymer's hydrophobic groups are typically nonpolar and capable of repelling water. These groups have the ability to enter the lipid bilayer of the membrane of the microbial cell. This includes their ability to combat both Gram-positive and Gram-negative bacteria, the latter of which can be difficult to eradicate due to impermeable outer membranes [3]. Furthermore, when used with conventional antibiotics, cationic polymers have shown synergistic benefits, increased overall antibacterial activity and perhaps lowered antibiotic dosage [4]. The rupture of bacterial membranes by the polymer allows antibiotics to permeate the cells more efficiently

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and overcome resistance mechanisms [5,6]. Cationic polymers are biocompatible with mammalian cells to variable degrees, making them useful for medical purposes. Their possible applications include wound dressings, catheters, medical implants, and medical device coating [7]. This study promises to provide significant insights into the future of antimicrobial tactics by examining the mechanisms of action, exploring the implications for bacterial resistance, and reviewing current research, paving the way for the creation of innovative therapeutic approaches.

2. Antimicrobial cationic polymers

Cationic polymers are a class of synthetic macromolecules that possess positively charged groups along their polymer chains. These positively charged groups are often in the form of ammonium ions or other quaternary amine structures. Due to their cationic nature, these polymers exhibit unique properties and have found diverse applications in various fields. Cationic polymers carry positive charges, which makes them interact with negatively charged molecules such as DNA, RNA, proteins, and other biomolecules, leading to applications in gene delivery and drug delivery. These polymers can electrostatically adsorb onto surfaces, making them useful for coatings, adsorbents, and membranes. Some cationic polymers are pH-sensitive, meaning their charge density can change with variations in pH, offering responsive behavior for specific applications. Many cationic polymers are biocompatible and have been explored for biomedical and pharmaceutical applications. Cationic polymers with tailored structures can be incorporated into various products via surface grafting, wet-end addition, blending, or reactive extrusion, effectively addressing the dilemma of improving substrate properties and bacterial growth. Antimicrobial cationic polymers are classified into two groups i.e., natural antimicrobial cationic polymers and synthetic antimicrobial cationic polymers.

2.1. Natural antimicrobial cationic polymers

These are polymers derived from natural sources that have intrinsic antibacterial properties due to their positive charge (cationic). These polymers have a wide range of applications in medicine, food preservation, and biological research. Cationic polymers and their formulations have been extensively studied for their antimicrobial properties. Here are several efficient natural antibacterial cationic polymers.

Chitin (β-(1–4)-poly-N-acetyl-D-glucosamine), the second-most prevalent biopolymer on Earth, has a number of applications in the biomedical and pharmaceutical industries due to its deacetylated derivative, chitosan. Currently, the exoskeleton of crustaceans serves as the primary source of chitin. Chitosan's chemical qualities molecular weight and degree of deacetylation (MW and DD), and physiological factors like temperature and pH, may affect its properties, including antibacterial activity. The simplest mode of action includes electrostatic interactions between the negatively charged membranes of microorganisms and the positively charged NH3+ sites of chitosan. This interaction changes the microbial cell's permeability, resulting in the release of intracellular substances. According to Chung et al., the binding of chitosan to microbial enzymes and nucleotides causes cell disruption in *Escherichia coli* (E. coli) and *Staphylococcus aureus* (S. aureus) [8]. Chitosan has a well-known antibacterial effect on a range of bacteria, but this effect is also constrained by its low solubility [9], which is explained by its stiff crystalline structure [10]. In contrast, the availability of free amino groups makes it possible to derivatives chitosan through a variety of regulated chemical processes and produce more soluble molecules. Solubility is raised through structural alterations like quaternization and hydrophilic substitution. A number of studies that have shown antibacterial efficacy against different bacteria, including S. aureus, *Bacillus subtilis* (B. subtilis), E. coli, and *Pseudomonas aeruginosa* (P. aeruginosa), have included chitosan guanidilate derivatives, chitosan galactosylate, etc. At pH 7, all of these derivatives display substantially more activity than the original chitosan. It is found that the Minimum Inhibitory Concentration (MIC) value of chitosan for Gram-positive bacteria B. aureus at pH 6.0 is 80-2000 μg/ml, whereas a slightly decreased pH of 5.5 drove down the MIC value to 60 μg/ml. 2-53 μg/ml of chitosan is required to inhibit the growth of Gram-negative bacteria like *Vibrio cholera* (V. cholera) [11]. Artan et al. demonstrated that a chitosan-oligosaccharide (3-5 kDa) reduced HIV-1 replication at nontoxic quantities by preventing the development of HIV-1-induced syncytia and decreasing the generation of p24 antigen. This oligosaccharide also prevented viral entrance and virus-cell fusion, offering a potential new option for the creation of fresh anti-HIV medications [12]. Additionally, the MT4 cell line was used to study the anti-HIV activity of a chitosan-conjugate and the corresponding nanoparticles. The results showed that chitosan-conjugate nanoparticles may be used as a targeting and sustained polymeric prodrug, improving treatment efficacy and reducing side effects in antiretroviral treatment. Intranasal delivery of chitosan is effective in preventing influenza A H7N9 infection, according to a study by Zheng et al. using a mouse model. The mechanism suggested is connected to the stimulation of the innate immune system [13]. Recently, Sharma et al. hypothesized the possibility of employing chitosan as a possible antiviral chemical against the SARS-Cov-2 virus. The method outlined in their hypotheses involved focusing on CD 147 receptors, a unique route for virus invasion into cells [14]. Significant attention was given to the antifungal activity of chitosan when combined with antifungal medications used in clinical practice, although the outcomes were inconsistent. Low molecular weight chitosan, which has a molecular weight of 70 kDa and a deacetylation degree of about 75%, had

promising anti-Candida efficacy, but it did not work synergistically when combined with fluconazole [15]. When combined with other antifungals such as fluconazole, voriconazole, miconazole, and amphotericin B, chitosan-oligosaccharide with a molecular weight of 15 kD showed excellent synergistic effects against Candida spp. Lo et al. investigated the synergistic interactions between fluconazole, amphotericin B, and caspofungin as well as the antifungal efficacy of chitosan with various molecular weights and deacetylation degrees against drug-resistant Candida strains [16]. The combination of chitosan and fluconazole produced impressive synergistic effects, while other antifungal drugs had no effect. Additionally, chitosan and fluconazole worked well together to treat drug-resistant types of bacteria. The study also emphasizes the impact of chitosan's molecular weight and degree of deacetylation on its antifungal action. It is generally believed that the polycationic nature of chitosan, communicated by the positively charged NH3+ groups of glucosamine, may be a key factor contributing to its interaction with negatively charged surface elements of many fungi and bacteria and ultimately impairing vital bacterial activities.

A typical natural polypeptide called epsilon-poly-l-lysine (EPL) includes homopolypeptides of L-lysine with roughly 25–35 repeat units. EPL has broad antibacterial effects due to its natural antimicrobial nature. Biosynthesized EPL is described as having a peptide bond between carboxyl groups and -amino groups of L-lysine residues rather than the conventional peptide bonds linking -poly-L-lysine. The number of repeating L-lysine residues is known to be a significant factor in the antimicrobial activity of EPL, and it has been demonstrated that >10 residues are necessary for EPL to achieve adequate antibacterial activity. It has drawn interest because of its antibacterial capabilities and prospective industrial uses. Gram-positive and Gram-negative bacteria, as well as some fungi, are all susceptible to EPL's broad spectrum of antimicrobial activity. To increase the shelf life of many food products, cosmetics, and personal care items, EPL is frequently used as a natural preservative. It assists in preventing the growth of bacteria, molds, and yeasts that cause deterioration, which can result in increased freshness and less rotting. It might be applied to medical device coatings, wound dressings, and other items where limiting bacterial growth is essential to avoiding infections. EPL at the MIC showed a biocidal action that caused a 2 to 3-log reduction in colony forming unit (CFU) during incubation. After 8 hours of incubation, no CFU was present, indicating a >5.5-log decrease, which was accelerated by increasing the EPL concentration to 2X MIC [17]. E. coli and *Listeria innocua* (L. innocua) cells permeabilized in a dose-dependent manner in response to rising EPL concentrations. The quantity of E. coli cells with a damaged membrane was comparable to the control sample's heat-killed cell count at the MIC. However, in L. innocua, the effect on membrane permeability was less pronounced. Despite exposure to EPL at concentrations that resulted in a 4-log drop in the number of viable cells, 30% of L. innocua cells still had an unbroken membrane. This finding suggests that EPL interacts with additional targets that cause cell death in L. innocua, even when cell membrane integrity is preserved. EPL's MIC ranged from 80 g/ml to 400 g/ml to 600 g/ml for *Ralstonia solanacearum* (R. solanacearum) and *Xanthomonas euvesicatoria* (X. euvesicatoria), respectively, to suppress the growth of X. citri [18]. For B. strains, the effect of EPL on spore germination was also studied. *Geobacillus stearothermophilus*, B. coagulans, and B. subtilis each had inhibitory concentrations of 2.5, 12.5 and 12.5 g/ml for spore germination [19]. Bacteriophages with a long tail, non-contractile, and double-stranded DNA were considerably inactivated in the presence of 500 g EPL/ml, with survival rates ranging from 0 to 27%. Similarly, Polyethylenimine (PEI) polymer has multiple uses, including antibacterial and anti-biofilm characteristics. The capacity of PEI to attach to surfaces may inhibit biofilm formation, which is important in bacterial resistance and persistent illnesses. Bacteria had a polyethylenimine (PEI) MIC of 400 mg/l, while yeast had a value of 50 mg/l. The results for PEI's minimal lethal concentrations (MLC) were in line with the MIC values, demonstrating the substance's potent fungicidal properties [20]. The results for the ATCC and clinical strains were comparable.

2.2. Synthetic antimicrobial cationic polymers

These are man-made polymers, designed to have cationic properties that allow them to bind with and destabilize negatively charged bacterial membranes. They are non-toxic, ease of synthesis, inexpensive, and easy to formulate with drugs and nanomaterials. Several synthetic cationic polymers and their nanocomposite have been developed in recent years. Researchers are interested in these polymers because of their potential applications in a range of fields, including health, materials science, and industrial contexts. Here we highlight the antibacterial activity of several potent synthetic cationic polymers (Table 1).

Polyamidoamine (PAMAM) dendrimers are highly branching and well-defined macromolecules, used in a variety of applications such as antibacterial agents, medication delivery, gene therapy, imaging, and nanotechnology. It has been studied for its antibacterial properties, notably in terms of disrupting bacterial cell membranes weakening the biofilm formation and making the bacteria more treatable. PAMAM dendrimers and their derivatives were tested for antibacterial efficacy against the common eye infections. The MICs for unmodified third and fifth-generation (G3 and G5) amino-terminated dendrimers for P. aeruginosa and S. aureus were in the range of 6.3-12.5 g/mL, which was comparable to the control antimicrobial peptide LL-37 (1.3-12.5 g/mL), and within the broad range of 0.047-128 g/mL for fluoroquinolone antibiotics [21].

Poly(beta-amino esters) (PBAEs) are a type of synthetic polymer that has gotten a lot of attention because of their prospective applications in medical sciences. Because of their ease of synthesis, low cost, and outstanding biocompatibility, PBAEs have received a lot of attention in recent years. PBAEs containing oligopeptide chains have been identified as a strong tool for inducing cell-specific transfection, with a ten-fold improvement in transfection effectiveness over commercial controls in vitro [22]. Various Poly(-amino ester)s (PAE) derivatives of polytrimethylenimines exhibit effective antibacterial activity against clinical isolates resistant to conventional antibiotics. According to Julita Pachla et al., greater MWs and nonmodified polymers can have MIC values as low as 4 g/mL [23] . *Acinetobacter baumannii* (A. baumannii), a multidrug-resistant pathogen that is responsible for the majority of nosocomial infections. Glycol Chitosan is reported to be capable of inhibiting S. aureus around 90% and does not lose this activity with time. Glycol chitosan is a natural biopolymer derived from chitin found in crustacean shells such as shrimp and crab. Glycol chitosan is created by chemically modifying chitosan with glycol groups, altering its properties and making it soluble over a larger pH range. Because of its unique structure, glycol chitosan has been studied for a variety of uses, including its potential antibacterial effect. Chitosan is well-known for its distinct features, which include biocompatibility, biodegradability, and the ability to interact with biological systems. Glycol chitosan inhibits the development of E. coli, S. aureus, and S. enteritidis (MICs: 4 g/mL, 32 g/mL, and 0.5 g/mL, respectively [24]

Poly(N-isopropylacrylamide) (PNIPAM) is a synthetic polymer that has gained popularity due to its unusual temperature-responsive characteristics. This means that the polymer is hydrophilic and water-soluble below approximately 32°C, but hydrophobic and precipitates out of solution above this temperature. Unless combined with antibacterial agents such as silver nanoparticles, metal ions, or antimicrobial peptides, PNIPAM has no antibacterial activity. It has been demonstrated that this polymer is efficient against Gram-positive bacteria and fungi by adding dimethylaminoethyl methacrylate (DMAEMA), a water-soluble monomer containing a tertiary amine group, MICs can be reduced to 2.5 mg/ml. Gram-negative bacteria, on the other hand, are unaffected [25].

Poly(diallyldimethylammonium chloride), often abbreviated as PolyDADMAC, is a water-soluble synthetic cationic polymer that belongs to the class of polymeric quaternary ammonium compounds. DADMAC is generated by reacting two equivalents of allyl chloride with dimethylamine. Then radical polymerization of DADMAC produced PolyDADMAC with an organic peroxide. At very low doses, PolyDADMAC alone demonstrated a strong microbicidal activity against each strain examined namely P. aeruginosa MDR, *Klebsiella pneumoniae* KPC+ MRSA. The resistant fungus C. albicans fluconazole R is the most delicate strain, and it may be killed with just 0.8 µg/mL of poly(diallyldimethylammonium) chloride (PDDA). It's strange that the Gram-positive MRSA required the highest PDDA concentration to be killed—5 and 8 g/mL PDDA alone or with the NPs, respectively [26].

Polyhexamethylene biguanide (PHMB) is typically produced via a polymerization reaction involving hexamethylene diamine and chlorhexidine digluconate. This process results in the creation of a polymer chain composed of alternating biguanide units. It has both antibacterial and antiviral properties. It is widely accepted that its ability to pierce the bacterial phospholipid membrane and eventually kill it accounts for its antibacterial activity. Recently, the antibacterial efficacy of PHMB and PHMB coupled nanoparticles (NP) against mastitis-causing S. aureus was investigated. The MIC90 of S. aureus was determined using a microdilution assay. PHMB NP had the lowest MIC value (0.03 g/mL) to inhibit 90% of S. aureus followed by chlorhexidine digluconate (0.25 g/mL) and PHMB (0.5 g/mL) [27]. Anti-biofilm activities were investigated in another investigation by treating S. aureus biofilms and assessing the impact on biofilm mass in vitro. PHMB coupled with FITC (i.e., a fluorescent tag used as a tracking agent) colocalized with intracellular S. aureus, indicating its direct binding with the bacterium inside the host cells. PHMB at 15 mg/L reduced 28 to 37% of mass of biofilms. The half-maximal inhibitory concentrations (IC50) for PHMB were 21 ± 2 mg/L in a cytotoxicity assay, showing the potential use of PHMB in mastitis therapy [28].

Polymeric Quaternary Ammonium Compounds (QACs) are a class of polymers that contain quaternary ammonium groups within their structure. Polymeric QACs are known for their broad-spectrum antimicrobial, antistatic, and conditioning properties, which make them useful in various industrial and consumer applications including personal care and cosmetic products. Number of commercial antibacterial chemicals such as polyhexamethylene biguanide (PHMB) and/or polyquaternium-1 (PQ-1) are used in multipurpose solutions. PHMB and PQ-1 interactions with various model biomembranes demonstrated that they were intercalated into the biomembranes [29]. Polyethyleneimine (PEI) is a polymer with a high positive charge density because it contains amino groups (-NH2) in its backbone. PEI in conjugation of metallic nanoparticles become more efficient to enhance their efficiency and functionality for various applications. These nanoparticles are typically composed of PEI molecules that have been modified with quaternary ammonium groups (QA-PEI). Small quantities of QA-PEI nanoparticles, from 0.5 to 2 wt.%, led to efficient and long-lasting antibacterial effects. QA-PEI nanoparticles were originally designed to provide dental materials with antibacterial activity against oral bacteria [30].

Poly(α-amino acids), β-peptides, and polycarbonates are classes of synthetic polymers with distinct structures and properties. They can be designed to be biocompatible and biodegradable, which makes them suitable for medical applications. Poly(α-amino acids) are polymers that are derived from naturally occurring α-amino acids, such as glycine, alanine, and others, through their amino and carboxylic acid functional groups. β-Peptides are a class of synthetic peptides in which the peptide backbone contains β-amino acid residues instead of the more common α-amino acids found in natural peptides and proteins. Polycarbonates are a class of synthetic polymers that are formed by the polymerization of cyclic carbonate monomers. poly-l-arginine (PLA) showed antibacterial activity against *E. coli* O157:H7 and *S. aureus* and the inhibitory effect increased with increasing PLA concentration ([31,32]. Minami et al. showed that glycine has antibacterial activity against *Helicobacter pylori in* a concentration-dependent manner and increases the inhibitory effect of amoxicillin ([32]. The cationic antimicrobial peptides can be divided into α-helical peptides and β-sheet peptides. There are a number of α-helical peptides that can bind to lipopolysaccharides, such as the lipopolysaccharide-binding protein CAP18. The β-sheet peptides have more complicated structures. The β-sheet degrees are extremely different among the different peptides such as proline-rich antibacterial peptides. Polycarbonates themselves are not inherently known for their antibacterial activity. Polycarbonates may be functionalized with antimicrobial agents such as QACs, antibiotic or silver nanoparticles to provide antibacterial activities. Silver nanoparticle is known for its broad-spectrum antibacterial activity and has been used in various applications to inhibit the growth of bacteria. These nanoparticles incorporated polycarbonates kill bacteria more effectively with increased concentration, giving low MICs (4.3–10.8 μM) against B. subtilis, S. aureus, methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis* (*E. faecalis*) and *Cryptococcus neoformans*.

Main-chain cationic polymers (MCCP), similar to other cationic polymers, usually consist of hydrophobic parts, like alkyl chains, and a cationic center consisting of ammonium, guanidine, or imidazolium groups. Linear polyethyleneimine (LPEI) and PHMB are two commercial antimicrobials of this group. These polymers showed excellent broad-spectrum antimicrobial activity with MICs in the range of 4–8 μg ml−1 against both Gram-negative and Gram-positive bacteria [33]. Interestingly, Poly[2-(dimethylamino)ethyl methacrylate] (pDMAEMA) is a pH sensitive synthetic polymer that belong to poly(alkyl amino methacrylate) family. Its properties and charge distribution change as the pH changes. According to L-AB Rawlinson et al. (2010), the antibacterial impact may vary, depending on the type of bacterium being targeted. The MIC of pDMAEMA against Gram-negative bacteria was reported to be between 0.1 to 1 mg/ml [34], however, it varies substantially in case of Gram-positive. Stawski et al. (2022) effectively deposited pDMAEMA on fabrics [35]. They show that in dynamic contact situations, samples with external pDMAEMA coatings are particularly efficient against S. aureus.

Table 1 The natural and synthetic antimicrobial cationic polymers and their applications

Cationic polymers	Name of polymer	Applications	References
Natural	Chitosan	Targets microbial enzymes and nucleotides to disrupt the cells. Nanoparticle-conjugated Chitosan is used for bacterial decontamination of water. Effective antiviral and antifungal agent	[8,11–13,16]
	Poly-L-lysine	Most commonly used in food preservation. Other applications include biomedicines like drug or vaccine carriers. Inhibit the growth of phytopathogenic bacteria.	[18,36,37]
	Polyethyleneimine (PEI):	Inhibits biofilm formation and is also a potent fungicide.	[20]
	Polyamidoamine (PAMAM) Dendrimers	Has substantial antibacterial efficacy against the common eye infections P. aeruginosa and S. aureus.	[21]
	Poly (beta-amino esters)	Propagation of bacteria resistant to common antibiotics can be mitigated	[23]
	Glycol Chitosan	Better control over Gram-negative bacteria than the Gram-positive bacteria.	[38]
	Poly(N-isopropylacrylamide) (PNIPAM)	Does not exhibit antimicrobial activity by alone. The addition of dimethylaminoethyl methacrylate (DMAEMA) makes it an inhibitor of gram-positive bacteria and fungi. Gram-negative bacteria are unaffected.	[25]

Synthetic	Poly(diallyl dimethyl ammonium chloride) (PolyDADMAC)	Exhibits a strong microcidal activity against quite a few drug-resistant microbes namely P. aeruginosa MDR, K. pneumoniae KPC+ MRSA, C. albicans fluconazole R	[26]
	Polyethylene glycol (PEG) Polymers	PEG alone has very poor antibacterial activity while attachment of heat-resistant polylactic acid improves the MIC values.	[39]
	Poly(vinylamine) (PVAm)	The antimicrobial effects can be attributed to the high positive charge. Alkyl chain length C6 is the most effective against S. aureus, while B. subtilis. It is more sensitive to PVAm C8.	[40]
	Poly(allylamine) (PAA)	Considered as effective as Chitosan for both Gram-positive and Gram-negative bacteria.	[41]
	Polyhexamethylene Biguanide (PHMB)	PHMB-coupled nanoparticles have an impressive MIC90 of 0.03 g/mL while PHMB alone has a value of 0.5 g/mL in controlling S. aureus infection. Effective Anti-biofilm activity requires a concentration of 15 mg/L	[27,28]
	Polymeric Quaternary Ammonium Compounds (QACs)	By quaternary ammonium group modification of polyethyleneimine (PEI) nanoparticles, efficient and long-lasting antibacterial effects can be achieved especially in the case of oral bacteria	[29,30]
	Guanidine-Containing Polymers	The guanidine-containing polyurethanes (PU-TMGs) are strong contact-killing but non-leaching compounds against both gram-positive and gram-negative bacteria	[42]
	poly(α-amino acids), β-peptides, polycarbonates	The inhibitory effect of poly-l-arginine (PLA) against *E. coli* O157:H7 and S. aureus *is reported as* concentration-dependent. Glycine has a synergistic antibacterial activity with amoxicillin against *Helicobacter pylori*. The self-assembled nanoparticles of triblock polycarbonates kill bacteria more effectively than individual polymer chains due to increased local charge concentration, giving low MICs (4.3–10.8 μM) against B. subtilis, S. aureus, methicillin-resistant *S. aureus* (MRSA), E. faecalis and *Cryptococcus neoformans.*	[31,32,43]
	Main-chain cationic polymers (MCCP) eg Main-chain aromatic imidazolium oligomers (IBN-1)	Strong broad-spectrum antimicrobial potency (MIC 4–8 μg ml−1) against both Gram-positive and Gram-negative bacteria.	[33]
	poly[2-(dimethylamino)ethyl metha-crylate] (PDMAEMA)	PDMAEMA actively inhibits Gram-positive bacteria around its pKa and at lower pH values, while for Gram-negative bacteria its activity was found around its pKa and at higher pH values. External PDMAEMA coatings are particularly efficient against S. aureus.	[34,35]

It's important to note that while these cationic polymers have shown antimicrobial activity in laboratory settings, their effectiveness can vary depending on factors such as the type of microorganism, polymer concentration, and application method.

3. Cationic polymer conjugates with metallic nanoparticles

Nanoparticles with antibacterial activity have gained significant attention due to their potential to combat bacterial infections and address the challenge of antibiotic resistance. Silver nanoparticles are one of the most well-known examples of nanoparticles with strong antibacterial properties. Other than that gold, iron oxide and copper

nanoparticles also have potential antibacterial activity. Researchers continue to study the optimal size, concentration, toxicity and methods of incorporating nanoparticles into various materials including cationic polymer for safe and effective biomedical and antibacterial applications. Nanoparticle-polymer composites, often referred to as nanoparticle-polymer hybrids or nanocomposites, combine the unique properties of nanoparticles with the versatility and engineering capabilities of polymers. These hybrid materials have a wide range of applications across various fields due to their enhanced properties and tailored functionalities. Nanoparticle-polymer composites are typically prepared by dispersing nanoparticles within a polymer matrix. Various techniques are used for synthesis, including in-situ polymerization, solution mixing, melt blending, and electrospinning. Various types of nanoparticles can be incorporated into polymer matrices, including silver, gold, and copper nanoparticles that are commonly used for their unique optical, electrical, and antimicrobial properties. A polymer matrix, such as chitosan or polyethyleneimine (PEI), is used to stabilize and disperse the silver nanoparticles. Chitosan is a natural cationic polymer derived from chitin, while PEI is a synthetic cationic polymer.

Quaternized poly (N, N-dimethyl aminoethyl methacrylate), or qPDMAEMA, is a cationic polymer that is often synthesized through the quaternization of poly(N, N-dimethyl aminoethyl methacrylate) (PDMAEMA). The quaternization process involves introducing quaternary ammonium groups, which give the polymer a permanent positive charge. Nanoparticles such as Fe3O4 nanoparticles, polymer nanoparticles, or inorganic nanoparticles, can be modified by coating or conjugating them with qPDMAEMA polymers. qPDMAEMA-modified nanoparticles have been investigated for their potential antibacterial and biofilm-related applications. These modified nanoparticles leverage the positive charge of qPDMAEMA to interact with bacterial membranes and biofilm matrices, offering a multifaceted approach to combating bacterial infections and inhibiting biofilm formation. Shatan et al prepared cationic polymer-coated magnetic nanoparticles possessing potential bactericidal properties against both *E. coli* and *S. aureus*. Here, cationic polymers i.e., PDMAEMA and poly[2-(dimethylamino) ethyl methacrylate-*co*-2-*tert*-butylaminoethyl methacrylate] [P(DMAEMA-TBAEMA)] were grafted on the surface of Sipomer PAM-200-coated Fe3O4 particles (MNP@S). The P(DMAEMA-TBAEMA)-coated magnetite particles possessed superior biocidal properties against both *E. coli* and *S. aureus* compared to those of P(DMAEMA)-coated one [44]. The effectiveness of coated MNP@S magnetite particles depended on the type of microorganism, dose of particles, solvent and their coating.

Similarly, polystyrene nanoparticles are widely used as model systems in biomedical research, such as drug delivery, imaging, and targeted therapy. They can be functionalized with ligands, antibodies, or other molecules for specific interactions with cells or tissues. Polystyrene nanoparticles (PSt-NPs) are synthesized by using cationic initiator, ADIP (2,2′-azobis-[2-(1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium-2-yl)] propane triflate and comonomers, VBTMAC ((vinylbenzyl)trimethylammonium chloride). In vitro assay showed that the PSt nanoparticles have antibacterial activity against *Staphylococcus epidermidis*, with a MIC of about 0.69 mg/mL. Using polydiacetylene vesicles as a model membrane system, PSt-NPs damaged the bilayer structure of the model membrane, suggesting it a potential antibacterial agent. Likewise, poly(N-isopropylacrylamide)-co-poly (glutamic acid) (PNIPAm-co-PGA) coated superparamagnetic iron oxide nanoparticles (SPIONs) with a MnFe2O4 composition can potentially exhibit antibacterial properties due to the combination of the polymer and magnetic nanoparticle characteristics. These polymer-coated NPs showed a strong antibacterial activity against E. coli with MIC of 20 μg/mL [45]. The PNIPAm-co-PGA coating can interact with bacterial cell membranes due to the presence of glutamic acid residues. The positive charge from the glutamic acid and small-size poly-SPIONs may disrupt the negatively charged bacterial membrane and subsequent interactions with cellular DNA, and enzymes causing bacterial cell death. Mei et al developed a nontoxic nanocomposite PDMAEMA-C4-AgNPs that exhibited a strong antimicrobial activity against *P. aeruginosa* and *S. aureus* with almost no bacterial resistance. Notably, the same therapeutic effect was seen in a diabetic rat model, demonstrating the effectiveness of AgNPs@ PDMAEMA-C4 as an antimicrobial agent with the potential to treat bacteria-induced infections in individuals with impaired immunity [46]

4. Antibacterial mechanism of cationic polymer and their challenges

Cationic polymers have antibacterial efficacy by targeting bacterial cell membranes, which are made up of lipids, proteins, and other components [47,48]. The average charge on the outer surface of the bacterial cell membrane is negative. These polymers are attracted to negatively charge bacterial cell surfaces due to their positively charged groups. This early electrostatic interaction promotes bacterial membrane adsorption. Polymer molecules intercalate between the membranes of bacterial cells. The hydrophobic portion of the polymer promotes insertion into the lipid bilayer, whereas the cationic groups stay oriented toward the bacterium's surface [49,50].

The introduction of cationic polymers disrupts the lipid pattern within the membrane. According to Chen et al. (2019), this disturbance can result in the formation of transient pores or defects in the lipid bilayer. The pores and defects in the membrane cause increased permeability. The loss of ions, metabolites, and other biological components disrupts

the bacterium's equilibrium. The breakdown of the membrane's lipid bilayer and the resulting ion leaks induce the loss of membrane potential and ion gradients across the bacterial cell membrane. Increased permeability and ion imbalances interfere with critical cellular activities. Cellular component leakage exposes critical processes such as energy production and nutrition intake. Bacterial cell death is caused by the cumulative consequences of membrane rupture, increased permeability, ion imbalances, and cellular content leakage. The bacterium cannot survive without an intact membrane and functional cellular processes. The antibacterial efficacy of cationic polymers conjugated with metallic nanoparticles is enhanced because the nanoparticles improve their stability, dispersion, and targeted delivery to bacterial cells. Polymers can also serve as carriers for these nanoparticles, increasing their efficiency. Both gold and silver nanoparticles can emit ions into their surroundings (gold ions and silver ions, respectively). By interfering with biological functions, these ions can further destabilize bacterial cells. Silver nanoparticles can cause oxidation and damage to key biomolecules within the bacterial cell, including proteins and DNA. This has the potential to disrupt critical cellular processes and result in cell death. Metallic nanoparticle-conjugated polymers have shown potential in antibacterial applications, however, there are a number of issues and factors to take into account. One major obstacle is the potential cytotoxicity of gold and silver nanoparticles in human cells. These nanoparticles might affect human cells in addition to germs. In particular, when thinking about medical applications, striking a balance between antibacterial activity and biocompatibility is crucial [51]. Similar to antibiotic resistance, bacteria can gradually develop a resistance to nanoparticles. Overuse of antibacterial drugs can result in the formation of resistant strains, which is a serious concern [52]. The antibacterial activity of nanoparticles is greatly influenced by their size and structure. It can be difficult to achieve the appropriate size and form to enhance effectiveness while limiting cytotoxicity [53]. It is also difficult to regulate the dosage and exposure of nanoparticles in real-world applications, such as medical equipment or consumer goods. It's crucial to guarantee an exposure level that is both safe and effective [54].

5. Conclusion

Due to their distinct characteristics, such as a positive charge that permits interactions with negatively charged bacterial cell membranes, cationic polymers have emerged as viable possibilities for treating bacterial infections. The broad-spectrum antibacterial action of cationic polymers affects both Gram-positive and Gram-negative bacteria. Due to their adaptability, they are useful for a variety of uses, including antimicrobial coatings, medical equipment, and wound dressings. A possible route for antibacterial action is represented by polymers coupled with metallic nanoparticles. Through a number of methods, including membrane rupture, the production of reactive oxygen species (ROS), and ion release, these compounds have proven their efficacy against bacteria. Their antibacterial qualities make them especially desirable for use in medical equipment, wound dressings, coatings, and other situations where preventing bacterial colonization is crucial. It can be difficult to regulate the dosage and exposure of nanoparticles in real-world applications, such as medical equipment or consumer goods. A safe and effective exposure level must be ensured. A multidisciplinary strategy combining skills in materials science, biology, toxicity, and regulatory issues is necessary to meet these challenges. While taking these complications into account, ongoing research attempts to create safer and more effective nanoparticle-based antibacterial treatments.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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