CODEN: WJAPAC Impact Factor: 5.48 ISSN: 3049-3013

World Journal of Advance Pharmaceutical Sciences

Volume 3, Issue 8, Page: 1-7 Review Article www.wjaps.com

ANTIMICROBIAL POLYMERS IN CONTEMPORARY MEDICINE – A REVIEW

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How to cite this Article: Mahalakshmi S.[1]*, Priscilla Pharkari S.[2], Selvi S.[3], Guna Priya D.[4], Banu Priya D.[5], Dhanesh Kumar M. R.[6], Dr. Sathish A.[7]. (2026). ANTIMICROBIAL POLYMERS IN CONTEMPORARY MEDICINE – A REVIEW. World Journal of Advance Pharmaceutical Sciences, 3(8), 1-7.

Article Info

Article Received: 27 May 2026,

Article Revised: 17 June 2026,

Article Accepted: 07 July 2026.

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DOI: https://doi.org/10.5281/zenodo.21706283

ABSTRACT

Antimicrobial polymers present a promising alternative to antibiotic therapies, particularly as traditional methods become increasingly ineffective due to antimicrobial resistance and antibiotic persistence. This review aims to provide a comprehensive overview of both natural and synthetic antimicrobial polymers, detailing their formulation in pharmaceutical applications and preparation techniques. It critically assesses the advantages and limitations of these polymers, focusing on their clinical relevance, safety profiles, and the potential to combat antimicrobial resistance. Additionally, the review identifies key challenges and future directions for the clinical implementation of antimicrobial polymer-based systems, emphasizing the importance of safety, scalability, and effectiveness in addressing public health concerns related to antimicrobial resistance.

KEYWORDS: Antimicrobial, Polymers, Antimicrobial Resistance, Drug Delivery.

INTRODUCTION

Antimicrobial resistance (AMR) refers to the ability of pathogens such as viruses, bacteria, fungi, and parasites to withstand antibiotic treatment, allowing them to survive within host cells. Resistance is observed when the minimum inhibitory concentration (MIC) of an antibiotic is insufficient to inhibit a previously susceptible micro-organism. Additionally, antimicrobial tolerance may occur, where a higher minimum duration of killing (MDK) is required for tolerant strains. The misuse and over-prescription of antibiotics contribute significantly to AMR, with studies indicating inappropriate prescriptions in 30% to 50% of cases. Non-therapeutic use in viral infections and conditions like asthma also exacerbates the issue. Furthermore, the overuse of antibiotics in livestock farming—accounting for about 80% of antibiotic sales in the U.S.—is a major driver of AMR, posing severe health and environmental risks as resistant bacteria can transfer to humans through the food supply.[1-3]

Four primary processes account for bacterial resistance to antimicrobials: target alteration, restricted uptake, active efflux, and antibiotic inactivation. Antibiotics can be rendered inactive by chemical changes or enzymatic breakdown, such as the synthesis of β-lactamases. Bacterial alterations that evade antibiotic processes, such as decreasing affinity for penicillin-binding proteins, are

referred to as target modification. Reducing porin expression leads to limited absorption, whereas overexpressing efflux pumps causes active efflux. Horizontal gene transfer (HGT), which makes it easier for new resistance traits to be incorporated into bacterial DNA, and spontaneous mutations are two genetic transfer methods that give rise to these resistance features.[4-6]

Antimicrobial resistance (AMR) poses a significant threat to human health, complicating the treatment of infections caused by pathogenic microorganisms. The emergence of multidrug-resistant strains limits therapeutic options and raises morbidity, mortality, and healthcare costs. This urgency has prompted interest in alternative therapeutic approaches, including host-directed therapies, engineered biological systems, and advanced biomaterials aimed at overcoming existing resistance mechanisms.[7, 8]

The increase of antimicrobial resistance (AMR) in the face of novel antimicrobial compounds presents current treatment problems. Developing antimicrobial peptides, bacteriophages, nanoparticles, synthetic bacteria, host-directed immunotherapies, and antimicrobial polymers as alternatives to antibiotics for bacterial infections is essential for modern medicine. Although thorough analyses of their processes, design approaches, and therapeutic uses are still needed, antimicrobial polymers' adaptability and multifunctional qualities—such as membrane rupture and controlled drug release—make them promise against AMR. In addition to discussing present issues and anticipated future developments, this review gives a general overview of antimicrobial polymers, including their classification, structure–function relationships, action against resistant microorganisms, and potential in biomedical and environmental contexts.[9, 10]

ANTIMICROBIAL POLYMERS

Cornell R. J. *et al.* initially presented antimicrobial polymers in 1965, concentrating on the production of homo- and copolymers from 2-methacryloxytropolones.[1] Their study showed the antibacterial qualities of these polymers against a range of pathogenic bacteria, with recorded inhibition zones showing efficient action. Since then, a number of criteria have been used to classify and comprehend antimicrobial polymers. The main features of polymers are described in this document, with particular attention to: (I) their origin, with a distinction between natural and synthetic types; (II) mechanisms of antimicrobial action, such as membrane disruption and inhibition of intracellular targets; (III) types of antimicrobial functionality, such as cationic polymers, metal-containing polymers (such as silver, copper, and zinc), antibiotic-loaded systems, and polymer–drug conjugates; (IV) biodegradability, comparing biodegradable and non-biodegradable systems; and (V) application fields, including biomedical uses, food packaging, textile engineering, and water purification.

Table 1: Classification of antimicrobial polymers.

Origin	Polymer	Pharmaceutical Use	Known Targets
Natural	Chitosan[11]	Drug delivery systems in forms like hydrogels, Nanoparticles, coated liposomes.	*Escherichia coli* *Candida albicans* *Staphylococcus aureus* *Candida tropicalis*
	Epsilon-poly-L-lysine[12]	Drug and gene delivery systems, hydrogels.	*Lysteria monocitogenes* *Pseudomonas aeruginosa* *Proteus vulgaris* *Aerobacter aerogenes* *Corynebacterium xerosis* *Micrococcus lysodeikticus* *Staphylococcus aureus*
Synthetic	Zwitterionic polymers (Phosphorylcholine, Poly(sulfobetaine methacrylate), Carboxybetaine)[13]	Drug delivery systems, surface coatings, wound dressing.	*Pseudomonas aeuroginosa* *Staphylococcus epidermidis* *Pseudomonas aeuroginosa*
	Polyguanidines[14]	Wound dressing.	*Bacillus subtilis* *Staphylococcus aureus* *Escherichia coli*
	Polyethylenimine[15]	Drug and gene delivery.	*Staphylococcus aureus (selective)* *Escherichia coli*

Natural Polymers

(i) Chitosan

Chitosan, discovered in 1859 and named in 1894, is a linear mucopolysaccharide resulting from chitin deacetylation, characterized by β-(1→4) glycosidic bonds of N-acetyl-d-glucosamine units. It is biodegradable, low-toxicity, and biocompatible, exhibiting antimicrobial and fungicidal properties. Its

antimicrobial activity is affected by factors such as pH, molecular weight, and degree of deacetylation. At pH below pKa, electrostatic interaction with bacterial cell walls occurs through amino group protonation; above pKa, hydrophobic interactions and chelation take effect without significant protonation.[16, 17]

Chitosan's antibacterial activity is determined by its molecular weight (MW). Low MW chitosan (≤50 kDa) penetrates bacterial cell walls to prevent DNA transcription, but high MW chitosan inhibits microbial growth extracellularly by chelating metals. According to research, its efficacy varies depending on the kind of bacteria: it is more effective against Gram-positive bacteria with higher MW and Gram-negative bacteria with lower MW. For example, low-MW chitosan decreased development of *P. aeruginosa* by 72.52%, compared to 64.57% by high-MW chitosan. Furthermore, *Streptococcus* mutans on tooth surfaces is inhibited by low-MW chitosan. Additionally, the effectiveness is pH-dependent; in acidic environments, chitosan interacts with negatively charged Gram-negative bacteria more successfully. Its antimicrobial qualities, charge density, and binding to lipopolysaccharides (LPS) are all impacted by deacetylation.[18, 19]

Synthetic Polymers

(i) Zwitterionic Polymers

Zwitterionic polymers are macromolecules with both positive and negative charges, resulting in high polarity. Examples include phosphorylcholine, carboxybetaine, and sulfobetaine, which are hydrophilic and biocompatible, making them alternatives to polyethylene glycol in drug delivery and surface coatings. These polymers bond to nanoparticles, like SB-siloxane bonded to silica particles, demonstrating high stability under varying temperatures and salt concentrations. They inhibit biofilm formation by creating a hydrophilic layer that repels bacteria, enhancing hemocompatibility in medical devices. Studies show that poly(sulfobetaine methacrylate) effectively reduces biofilm formation in *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, while poly(carboxybetaine methacrylate) significantly decreases biofilm presence for these bacteria over extended periods and resists protein adsorption from human plasma.[20, 21]

(ii) Polymeric Ionic Liquids (PILs)

Ionic liquid (IL) monomers are polymerized to create solid materials known as polymeric ionic liquids (PILs), which were first introduced in 1998. Some PILs have antibacterial qualities against a variety of bacteria and fungi, especially those based on quaternary ammonium, pyridinium, and imidazolium. PILs exhibit increased antibacterial efficacy when paired with silver nanoparticles. Cationic ILs, which damage bacterial cell walls through adsorption, are the main topic of the text. According to a study, longer alkyl chains in ILs based on imidazolium and pyrrolidinium lower minimum inhibitory concentrations (MICs). Methylpyrrolidinium bromide, for example, significantly reduced MIC against *E. coli* with longer alkyl chains.[22, 23]

(iii) Polyguanidines

Polyguanidines are antimicrobial polymers first described in 1984 as novel polymeric biocides. They can be prepared through various methods, including polymerization in solution, using sodium or zinc dicyanimide with diamine salts or water, and reacting diamines with chlorine cyan in organic solvents. Their antimicrobial properties stem from acrylate monomers with pendant biguanide groups, which interact electrostatically with bacterial cell membranes. Polyguanidines demonstrate higher antibacterial activity against Gram-positive bacteria due to their simpler cell wall structure, facilitating penetration by high molecular weight polymers. Their mechanism of action involves absorption to negatively charged bacterial membranes, leading to damage and leakage of inner components.[24, 25]

ANTIMICROBIAL POLYMER-BASED FORMULATIONS

Nanoparticles

The evolution of nanoparticle (NP) drug delivery systems predates the formal establishment of nanotechnology, a concept theorized by Richard Feynman. Initial references to colloidal transport systems emerged in 1961, with significant advancements noted by R.C. Oppenheim in 1978 and the patenting of lipid solid microspheres in the early 1990s. The overarching aim of NP drug delivery systems is to ensure chemical stability, solubility, controlled release, biocompatibility, and targeted delivery. NPs are categorized into seven types: liposomes, emulsions, ceramic NPs, metallic particles, gold-shell NPs, quantum dots, and polymeric/lipidic NPs. Polymeric NPs offer advantages such as versatile cargo encapsulation and potential antimicrobial properties, presenting a promising alternative for treating infectious diseases.[26, 27]

A notable example of antimicrobial nanoparticles (NPs) is chitosan-based NPs, utilized in wound dressings and tissue engineering due to their wound healing properties and protective barrier against infections. Another type, cationic NPs like PEI NPs, can disrupt bacterial cell walls and biofilms, offering advantages over traditional antibiotics that often fail against biofilm-resistant bacteria. Chitosan NP activity has been tested against *E. coli* O157 and L. monocytogenes, revealing that SA1 NPs (with a molecular weight of 50–190 KDa) produced consistent results, showing a minimum inhibitory concentration (MIC) of 1.2 mg/mL for *E. coli* and 0.04 mg/mL for *L. monocytogenes*. In contrast, SA2 NPs (90–190 KDa) yielded variable results. Additionally, NPs made of ε-PL have shown efficacy against S. aureus and C. albicans with an MIC of 400 μg/mL for both species.[28, 29]

Hydrogels

Hydrogels are networks of water that are frequently cross-linked with polymers. They are useful substitutes for drug delivery systems, especially when it comes to encasing hydrophilic medications. Their ability to absorb water gives them suppleness and elasticity. Composed of natural, synthetic, or semi-synthetic polymers like cellulose and collagen, hydrogels may also comprise antibacterial polymers, offering further benefits. Despite its modest mechanical strength, chitosan is a well-known antibacterial polymer utilized in bioink compositions. Another ingredient, PL, is renowned for its antibacterial qualities in hydrogel formulations that have been trademarked.[30, 31]

Polymeric Micelles

Polymeric micelles are amphiphilic structures that form nanocarriers by self-aggregating in aqueous environments, with hydrophobic components creating a stable core and hydrophilic elements forming a protective shell. They are considered promising for delivering antimicrobial medicines due to enhanced bioavailability, targeting, and controlled release, addressing issues of low bioavailability and rapid degradation. Recent advancements have led to multifunctional micelles responsive to stimuli, improving drug delivery to infection sites and combating antibiotic resistance. A study demonstrated that PEG-PLGA micelles loaded with piperacillin/tazobactam reduced the minimum inhibitory concentration (MIC) against multidrug-resistant Pseudomonas aeruginosa. Stancheva R. *et al.'s* investigation of mixed polymeric micelles loaded with ciprofloxacin demonstrates the diverse modes of action of polymeric micelles. Their research revealed a twofold synergistic effect: the antibiotic's increased solubility and bioavailability combined with the micelles' cationic crowns' inherent antibacterial activity. This activity enhances electrostatic interactions with Gram-negative bacterial membranes, leading to growth inhibition.[32-34]

Dendrimers

Dendrimers are branched polymer macromolecules with a central core and protruding branches, allowing for numerous functional groups on their surface. This structure enhances their application in medicine, particularly for treating microbial infections, due to their ability to self-assemble and act as effective drug delivery systems. Dendrimers can encapsulate hydrophobic antimicrobials, protecting them from degradation and increasing retention. Polymethacrylates, which may contain cationic groups, exhibit antimicrobial properties by disrupting bacterial membranes and promoting cell lysis, making them effective against both Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains. A study by Holmes A.M. *et al.* demonstrated that the antibacterial efficacy of PAMAM dendrimers increases with generation, with G5 showing a minimum inhibitory concentration (MIC) of 2.9 µg/mL against *S. aureus*, compared to 26.8 µg/mL for G2, highlighting the role of electrostatic interactions in their bactericidal action.[35, 36]

Medical Composites

Biomedical engineers are becoming more interested in antimicrobial polymers and composites because of their capacity to combine antibacterial properties with mechanical strength. Recent advancements use antibacterial nanoparticles like zinc and silver in combination with matrix polymers like polylactic acid (PLA) to create such composites without sacrificing mechanical characteristics. Innovations include natural antimicrobial peptides combined with bioresorbable polymers like poly(ε-caprolactone) (PCL) to prevent infections while biodegrading after usage. These biocomposites are good substitutes for synthetic polymers in regenerative medicine because they can prevent bacterial development and biofilm. By generating reactive oxygen species (ROS) and interacting with nucleic acids, silver nanoparticles (AgNPs) aid in the disintegration of bacterial membranes. A study found that PCL/PLA composites containing 50 µg/mL AgNPs and Thymus vulgaris essential oil effectively reduced *E. coli* and *S. aureus* loads within 8 hours.[37, 38]

Biosensor Coatings

The research highlights the expanding role of biosensor coatings in the biomedical field, particularly through the use of antimicrobial polymers like chitosan. Chitosan-based coatings significantly reduce bacterial adhesion and biofilm formation on implantable medical devices, with reductions of 70–95%, effectively inhibiting pathogens such as *Staphylococcus aureus* and *Escherichia coli* while ensuring cytocompatibility. Additionally, chitosan membranes for wound therapy have demonstrated broad-spectrum antibacterial action and controlled release of antimicrobial agents, enhancing treatment efficacy and minimizing inflammatory responses.

Zwitterionic polymers, including carboxibetaines, phosphorylcholine, and sulfobetaines, demonstrate high hydrophilicity and strong surface hydration, leading to reduced protein adsorption, biofilm formation, and cellular activation on blood-contacting medical devices. Research by Moayedi *et al.* indicates that antifouling coatings made from these polymers, through grafting or surface coating, achieve a 90% decrease in protein adsorption and significantly lower bacterial adhesion and macrophage activation. Innovative coating strategies utilizing these polymers show efficacy in minimizing bacterial and protein adhesion on metal implants *in vitro*.[39, 40]

Because PEI and polyguanidines interact with microbial membranes, they are used as cationic polymers in medical device composites. In order to treat wounds, Yue *et al.'s* research created composite sponges made of chitosan, PVA, and polyguanidines (PHMG). These

sponges showed good bactericidal qualities against both Gram-positive and Gram-negative bacteria, which improved wound healing and decreased inflammation *in vivo*. Furthermore, developments in biodegradable and antibacterial polymer composites have resulted in the creation of antibiofilm biocomposites, which improve polymer surfaces to reduce microbial adhesion after implantation.[41]

FUTURE PERSPECTIVE

Despite development, clinical translation and application of antimicrobial polymers confront hurdles, such as the requirement for consistent material characterisation, especially for natural polymers like chitosan. To ensure reproducibility, key parameters such as molecular weight and charge density must be established methodologically. Polymers should be designed with greater selectivity and efficacy against biofilm-associated bacteria and multidrug-resistant strains, while decreasing toxicity. Although antimicrobial polymers reduce the possibility of antibiotic resistance, adaptive bacterial responses must be studied throughout time. Furthermore, standardized biofilm models are required for more practical *in vitro* systems. The regulatory categorization process is complex, demanding an understanding of clinical development needs. Scalability and cost-effectiveness, which include reproducible manufacturing and sterilization stability, are critical for industrial applications.

CONCLUSIONS

Formulations of antimicrobial polymers are adaptable substances with substantial infection control potential. The combination of intrinsic antimicrobial activity and adjustable physicochemical characteristics, which offer several mechanisms of action such as membrane rupture and surface-mediated anti-adhesive effects, is their primary advantage. Antimicrobial polymers provide more structural variety, enhanced chemical stability, and flexible functional characteristics as compared to traditional antibiotics. These characteristics make them appropriate for use in medication delivery systems, biomedical coatings, and wound care. Environmental factors, molecular architecture, and polymer makeup all have a significant impact on their antibacterial efficacy. In particular, their effectiveness can be greatly diminished by complex biological settings such biofilms and polymicrobial diseases. A promising class of materials for the creation of supplemental and alternative infection control methods is antimicrobial polymers.

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