Insights into Antibiofilm Mode of Actions of Natural and Synthetic Polymers: A Mini Review

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Abstract. Pathogenic biofilms, which are organized and structured communities of microorganisms that adhere to surfaces and are enveloped in a polysaccharide and stringent extra-polymeric matrix, represent a challenging medical and industrial problem because of their remarkable recalcitrance towards conventional therapies. Natural and synthetic polymers offer promising strategies for biofilm control. This mini review discusses the antibiofilm efficacy of chitosan, β-peptides, polyhexamethylene biguanide, hyaluronic acid, alginate, poly(3,4-ethylenedioxythiophene), polyethylenimine, and epsilon-polylysine. These polymers inhibit biofilm formation by interfering with protein synthesis, altering mRNA expression, causing cell permeabilization, inducing DNA/RNA damage, interfering with negatively charged components of the biofilm matrix, and through chemodynamic and photothermal activities. These diverse mechanisms highlight the multifaceted approach required to combat biofilms effectively. The integration of these polymers into biofilm mitigation strategies holds significant promise for applications across healthcare, water treatment, and industrial maintenance, offering a robust solution to a persistent problem.

Keywords: Antibiofilm, Biofilm, Natural Polymers, Synthetic Polymers.

1.0 Introduction

Microbial biofilms are communities of microorganisms, such as bacteria, fungi, and algae, that adhere to surfaces and are embedded in a self-produced extracellular matrix [1]. These biofilms exhibit increased resistance to antimicrobial agents, making them difficult to treat with existing antibiotics [2]. The extracellular matrix acts as a protective barrier, shielding the microbes from the host's immune system and antibiotics (Figure 1). Biofilms can cause persistent infections in various parts of the human body, including wounds, medical implants, respiratory system, and urinary tract. They can lead to chronic infections, such as cystic fibrosis lung infections, endocarditis (heart valve infection), and prosthetic joint infections, which are challenging to treat due to

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their resistance to antibiotics and the immune system. According to Moscoso et al. [3], nearly 80% of biofilm-related infections do not respond to antibiotic treatment. It is estimated that biofilm infections cost nearly $100 billion annually to the United States healthcare system and cause more than 500,000 deaths in the United States alone [4]. In order to effectively combat biofilm infections, it is necessary to employ a multimodal approach that makes use of antibiotics, antifungals, disinfectants, natural products, nanoparticles; and combined antimicrobials [5-11].

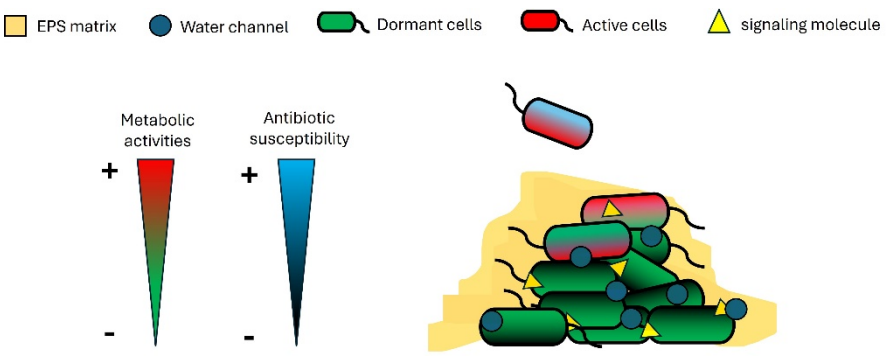

Fig. 1. Biofilm structure.

A range of natural and synthetic polymers have been explored for their antibiofilm properties. Banerjee et al. [12] highlights the potential of cationic and charge-switchable macromolecules, conjugated polymers, polymeric metal nanocomposites, hydrogels, and supramolecular polymers in inhibiting or eradicating bacterial biofilms. Polysaccharide-based coatings, such as those using ulvan and chitosan, have also shown promise in impeding biofilm formation [13]. Jansen and Kohnen [14] suggest that modification of polymer surfaces, such as through glow discharge treatment and surface coupling of antimicrobials, can effectively prevent bacterial biofilm formation. These studies collectively underscore the potential of both natural and synthetic polymers in combating biofilm-related infections. This review summarizes the antibiofilm mode of action of chitosan, β-peptides, polyhexamethylene biguanide, hyaluronic acid, alginate, poly(3,4-ethylenedioxythiophene), polyethylenimine and epsilon-polylysine.

1.1 Chitosan

Chitosan is a natural polysaccharide derived from chitin. It features amino groups along its backbone, which can form hydrogen bonds and ionic interactions, giving it antimicrobial properties. Chitosan is biocompatible, biodegradable, and used

in medical applications, water treatment, and agriculture for its ability to form films and gels. Derived from chitin, chitosan has intrinsic antimicrobial properties due to its cationic nature, which disrupts bacterial cell membranes. It is highly effective against a broad range of bacteria and is used in wound dressings and coatings to prevent biofilm formation [15, 16]. The anti-biofilm impact of chitosan is primarily influenced by the levels of N-deacetylation [17] and molecular weights [18], which are widely acknowledged. The polycationic properties enables higher anti-biofilm and bactericidal capacities for biopolymer-antibiotic combinations, such as gentamicin/chitosan and gentamicin/ poly-l-lysine [19]. According to Carlson [20], chitosan coatings hinder biofilm formation by permeabilizing microbial cells as they contact the surface.

1.2 β-peptide

β-peptides are synthetic peptides that mimic the structure and function of natural peptides but with a backbone extension at the β-carbon. This modification grants β-peptides to increase stability against enzymatic degradation and diverse bioactivity, including antimicrobial properties. They are commonly used in the development of drugs due to their stability and ability to resist enzymatic degradation. β-peptides are synthetic analogs of natural peptides that can mimic their antimicrobial activity. Hydrophobicity of β-peptides is an important design parameter for preventing biofilm formation, with β-peptides having greater hydrophobicity being more effective in preventing *Candida albicans* biofilm formation [21]. In 2009, Karlsson et al. [22] demonstrated that β -peptides penetrated the cell membrane and accumulated in the cytoplasm of both planktonic and biofilm fractions *of C. albicans*. The labelled peptide was detected only in metabolically inactive cells, suggesting that peptide entry is correlated with cell death. The positively charged peptides often associate with negatively charged microbial membranes, which causes the peptides to adopt a globally amphiphilic helical conformation at the membrane–water interface [23]. Furthermore, researchers also proposed other different mechanisms of antimicrobial peptides such as the attack of DNA and RNA, the inhibition of the synthesis of protein and cell wall [24].

1.3 Polyhexamethylene biguanide

Polyhexamethylene biguanide (PHMB) consists of repeating biguanide units linked by hexamethylene chains. It has a molecular weight of approximately 1415 and a polydispersity index (PDI) of 4.7, indicating a broad molecular weight distribution. PHMB is chemically stable, making it suitable for use in various environments and formulations. It does not degrade easily under normal conditions. It is widely used as a disinfectant and antiseptic in wound care products and contact lens solutions. The antibiofilm efficacy of PHMB against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Candida albicans* has been reported by Gryson et al. [25]. PHMB has the ability to penetrate bacteria and hinder cell division by directly

interacting with DNA, causing the condensation of bacterial chromosomes [26]. Upon binding to DNA, PHMB will compact the DNA to generate nanoparticles, potentially due to the electrostatic attraction between the cationic PHMB and anionic DNA molecules. Kamaruzzaman et al. [27] suggested that PHMB interacted with extracellular matrix containing extracellular DNA to disrupt biofilm structure.

1.4 Hyaluronic acid

Hyaluronic acid (HA) is a polyanionic natural polymer that exists as a linear polysaccharide made up of glucuronic acid and N-acetylglucosamine units connected by a β-1,4 linkage. It is the most adaptable macromolecule found in the connective tissues of all vertebrates. Hyaluronic acid possesses a diverse array of uses because of its exceptional physicochemical characteristics, including biodegradability, biocompatibility, nontoxicity, and non-immunogenicity. It is commonly used in skincare products for its moisturizing properties. Drago et al. [28] studied the anti-adhesive and antibiofilm activity of HA towards bacterial species commonly isolated from respiratory infections. HA has been shown to significantly reduce the biofilm formation of *Porphyromonas gingivalis* by reducing the expression of fimA, mfa1, hagA, rgpA, and kgp genes, which are related to the adhesion of *P. gingivalis* [29, 30]. HA-based nanogels have also been investigated as carriers for several other AMPs such as the synthetic antimicrobial and antibiofilm peptides SAAP-148 and Ab-Cath [31].

1.5 Alginate

Alginate is another natural polysaccharide extracted from brown seaweed. It is composed of mannuronic and guluronic acid units, which can form gels in the presence of divalent cations like calcium. Alginate's biocompatibility, gel-forming ability, and mild processing conditions make it suitable for wound dressings, drug delivery, and food applications. Alginate, a polysaccharide extracted from brown algae, is often used to create hydrogels that can be loaded with antimicrobial. Alginate hydrogels are used in medical applications such as wound dressings. Antibiofilm efficacy of alginate against *Staphylococcus epidermidis* has previously been reported [32]. Alginate is also one of main polysaccharides used in antibiofilm coatings [13]. While alginate itself is not well studied for its antibiofilm efficacy, it is frequently combined with other antimicrobial agents to enhance overall effectiveness in combating bacterial biofilms. Porter et al. [33] produced AgNP/Alginate nanocomposite hydrogel and demonstrated species-dependent cell death of biofilm-forming bacteria due to slow silver ion release. Nanogels based on alginates have been extensively studied for chemodynamic therapy (CDT) and photothermal therapy (PTT) for biofilm control [34]. CDT uses high H2O2 content in the bacterial microenvironment to produce toxic hydroxyl radicals (˙OH) via Fenton or Fenton-like reactions while PTT converts near-infrared (NIR) light to the thermal energy. Both CDT and PPT are useful for biofilm eradication and wound disinfection [35].

1.6 Poly(3,4-ethylenedioxythiophene)

Poly(3,4-ethylenedioxythiophene) (PEDOT) is a conductive polymer blend known for its high electrical conductivity, transparency, and flexibility. PEDOT is used in electronic applications such as organic solar cells and flexible displays due to its stability and ease of processing. This conductive polymer is known for its electronic properties but can also be functionalized to possess antimicrobial activity [36]. Its ability to be combined with various antimicrobial agents enhances its utility in biomedical applications. Reduced PEDOT films are known to express antibacterial effects, most probably due to the electron-saturation of the surface preventing bacterial electron transfer [37]. Studies have shown that PEDOT and its derivatives can effectively convert near-infrared (NIR) laser irradiation into heat, making them suitable for photothermal therapy (PTT) applications [38]. The photothermal activity of PEDOT could be useful for biofilm inhibition [39]. In addition, Hsu et al. [40] demonstrated excellent antibiofilm activity of PEDOT/PSS and PEDOT/GO nanohybrid coatings. Only 0.1% of bacteria can be adhered on the surface due to the lower surface roughness and negative charge surface by PEDOT/PSS and PEDOT/GO modification.

1.7 Polyethyleneimine

Polyethyleneimine (PEI) is a polymer characterized by its repeating units composed of amine groups connected by two carbon aliphatic spacers (CH_2CH_2). PEI can exist in two main structural forms: linear and branched. The presence of multiple amine groups allows PEI to carry a positive charge, especially in acidic conditions, making it useful for applications such as gene delivery and water treatment. PEI is generally soluble in water and various organic solvents, enhancing its versatility in different applications. Polyethyleneimine (PEI) has been extensively studied for its antibiofilm and antimicrobial activity against various bacterial and yeast species in recent years. Research has shown that PEI can inhibit biofilm formation and disrupt pre-formed biofilms, making it an interesting compound for potential therapeutic applications [41]. The antibiofilm activity of PEI is attributed to its high positive charge density, which allows it to interact with the negatively charged components of the biofilm matrix, leading to its disruption [42].

1.8 Epsilon-polylysine

Epsilon-polylysine (ε-PL) is a biopolymer composed of 25-35 lysine residues linked by isopeptide bonds formed through dehydration condensation, resulting in a polymer with a highly cationic nature due to the numerous amine groups along its backbone. It is a water-soluble compound with a melting point of 142.2 °C and is notable for its use in food preservation and biomedical applications due to its non-toxic and biodegradable characteristics. Fang et al. [43] demonstrated that ε-PL significantly inhibited the Listeria monocytogenes biofilm, exopolysaccharide production, and cell adhesion, which were consistent with the reduction of swimming and AI-2 activity. ε-

PL also showed inhibitory effects against *P. aeruginosa* and *K. pneumoniae* biofilms [44]. The antibiofilm mechanism of ε-PL may involve its electrostatic interaction with bacterial cell surface and the removal of phospholipids from supported lipid bilayers [45].

1.9 Summary of antibiofilm mode of actions

Natural and synthetic polymers combat biofilms through multiple mechanisms (Figure 2). They interfere with protein synthesis, disrupting essential cellular functions and bacterial growth. Altering mRNA expression involves modifications at the transcriptional level, hindering the proper production of proteins necessary for biofilm maintenance. Cell permeabilization, often achieved by disrupting the cell membrane, allows antimicrobial agents to penetrate and destroy bacterial cells. Inducing DNA/RNA damage directly impacts the genetic material, leading to cell death or impaired replication. Polymers can also target the biofilm matrix by electrostatically interacting with its negatively charged components, weakening the structural integrity of the biofilm. Additionally, some polymers exhibit photothermal activities, where they convert light into heat upon exposure to near-infrared (NIR) light, effectively killing bacteria through localized thermal effects.

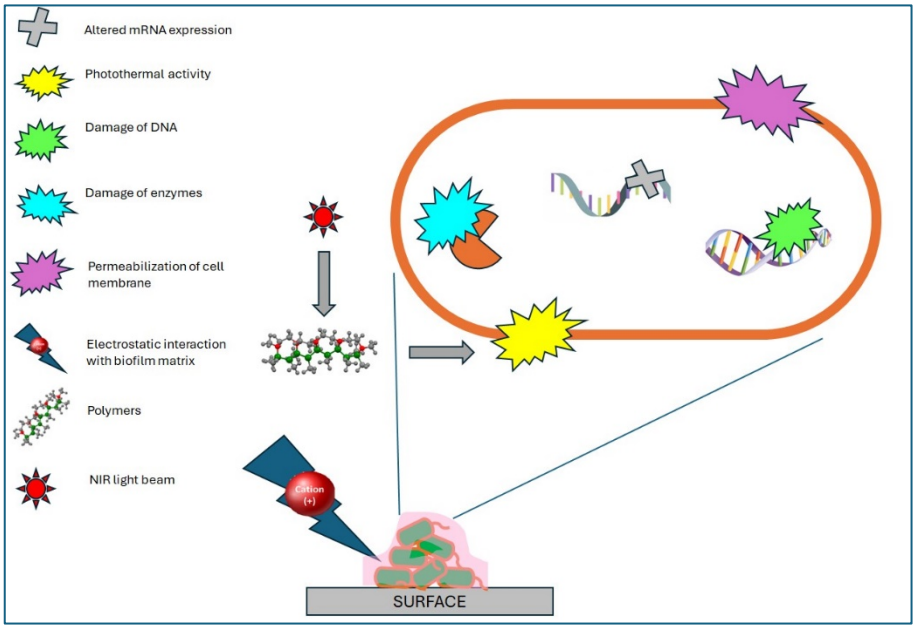

Fig. 2. Natural and synthetic polymers combat biofilms through multiple mechanisms.

2.0 Conclusion

The antibiofilm potential of various polymers is significant due to their ability to disrupt biofilm formation and persistence through multiple mechanisms. Chitosan, β-peptides, polyhexamethylene biguanide, hyaluronic acid, alginate, poly(3,4-ethylenedioxythiophene), polyethylenimine, and epsilon-polylysine exhibit efficacy by interfering with protein synthesis, altering mRNA expression, causing cell permeabilization, inducing DNA/RNA damage, and disrupting negatively charged components of the biofilm matrix. Additionally, some polymers employ chemodynamic and photothermal activities. These multifaceted strategies demonstrate the polymers' effectiveness in combating biofilms, making them promising candidates for integration into biofilm control applications across healthcare, water treatment, and industrial maintenance.

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Conflict of Interest. The authors have no competing interests to declare that are relevant to the content of this article.

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