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ASSESSING LONG-TERM SAFETY AND TOXICITY OF NANOPARTICLE-BASED ANTIMICROBIAL PEPTIDES FOR BIOFILM TREATMENT

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ABSTRACT This article thoroughly examines the significance of biofilms concerning microbial resistance and the challenges they create for infection control. Structured communities of microorganisms, known as biofilms, are shielded from host immune responses and antimicrobial agents by an extracellular matrix that they produce themselves. Their formation and persistence are linked to increased pathogenicity, especially in chronic infections involving tissues and medical equipment. One promising strategy to combat biofilms involves developing nanotechnology, particularly nanoparticles like polymer-based nanomaterials, silver, and gold. Nanoparticles possess unique physicochemical properties that enable them to penetrate biofilms and disrupt microbial communication, thereby enhancing antimicrobial effectiveness. However, concerns about the toxicity of nanoparticles and their environmental impact remain. This paper discusses the mechanisms of nanoparticle toxicity to ensure their safe use in biomedical applications. Future research should focus on creating sustainable methods, optimizing particle size and surface features, and thoroughly evaluating the biocompatibility of nanoparticles. Managing biofilm-associated infections could be improved by combining nanotechnology with traditional antimicrobial approaches, although the clinical implementation of these advances still depends on safety and toxicity evaluations.

Keywords: *Antimicrobial peptides, Nanoparticles, Biofilm, EPS matrix, Quorum sensing.*

INTRODUCTION

Biofilms and their clinical significance

Biofilms are a group of microbial cells that self-produce a matrix of polymers, which enable their attachment to surfaces and prevent the host defense systems(Koo et al., 2017). The EPS matrix is essential for maintaining biofilm structure, allowing bacteria to endure harsh environments, antibiotics, and physical challenges. Biofilms can develop on vast surfaces that include both organic materials and living organisms, like tissue and cells (Ghazay et al., 2020). Biofilms generally have a thickness ranging from millimeters to micrometers, found on living tissues, medical devices, and aquatic environments. Biofilms that include different microbial species living together are called multispecies biofilms (D'Acunto et al., 2015). Organisms like bacteria and fungi can produce biofilms on various surfaces. The morphology of these cells can be varied, including filamentous, spiral, and rod shapes (Mohanta et al., 2023). Nutrient availability, pH, and temperature play a key role in determining biofilm formation (Vatansever & Turetgen, 2018). Bacteria that form biofilm exhibit different traits, as shown in Figure 1 also:

- Bacterial communication uses signaling molecules to manage biofilm formation and help to communicate among cells.
- Secondary messengers like cyclic nucleotides control bacterial movement, attachment, and extracellular polymeric substance production.
- Proteins that are linked with the matrix increase biofilm stability and integrity (Zhao et al., 2017).

Biofilms represent considerable challenges for public health and can lead to economic repercussions (Roque-Borda et al., 2025a). 60-80% of bacterial infections are linked with biofilm and can develop on human tissues such as skin, eyes, and gastrointestinal tract, or on medical devices like catheters, pacemakers, and contact lenses (Perry & Tan, 2023). Biofilm-related infections are connected to long-term health conditions (such as cystic fibrosis, persistent wounds, and osteomyelitis), malfunctions of medical devices, and higher healthcare expenses resulting from extended treatment durations and complications. The financial impact goes beyond healthcare, affecting sectors such as the water distribution system, where biofilm leads to plumbing blockages and contamination, further increasing expenses. Dealing with biofilm-associated resistance is important for public health and also for minimizing loss across various sectors (Muhammad et al., 2020).

Antibiotic resistance to biofilms

Importantly unique structure and adaptive strategies of biofilms protect antimicrobial agents, making them important factors in antimicrobial resistance. Key factors such as bacterial cell density, quorum-sensing interactions, and genetic adaptations like the activation of efflux pumps and mutations enhance their toughness, complicating treatment efforts (Rao et al., 2021). The arrangement of biofilm acts as a shield against antibiotics, and the quorum-sensing process increases bacterial communication by regulating the genes that are linked with the defense and survival of biofilm (Huang et al., 2022). Biofilms exhibit an extraordinary capacity to swiftly adjust to antibiotics, even in minimal concentrations. This underscores the significant selective force imposed by antimicrobial substances, propelling the rapid development of resistance strategies. Such an impressive level of flexibility presents a considerable obstacle for medical intervention (Caballero-Díaz et al., 2013). Furthermore, the biofilm is rich in proteins, and extracellular DNA increases resistance through binding to antimicrobial agents and reducing their efficacy. Bacterial cells are protected by this composition and lessen the effectiveness of antibiotics that are intended to fight biofilms (Yamabe et al., 2022). Cells that are situated across the membrane struggle to access them, diminishing their effectiveness and permitting the safeguarded inner population to endure and multiply (Charles, 2019). Biofilm matrix works as a physical barrier that enhances physiological changes in bacteria and results in increased resistance. For example, the matrix reacts with sublethal levels of antibiotics by altering its synthesis. This responsive behavior fortifies the biofilm composition and advances the rapid development of resistance tactics among the microbial communities (Awashra & Młynarz, 2023). Infrared spectroscopy result shows that the rate at which the antibiotic ciprofloxacin moves to a colonized surface is reduced in comparison to an aseptic surface (Uruén et al., 2021). The use of different antimicrobial substances may result in cellular dormancy, which triggers an antitoxin for cell deactivation under conditions of elevated antimicrobial stress. It can also lead to a state of metabolic inactivity that may counteract the dormancy. Since numerous antibiotics target cells that are metabolically active and divide quickly, potentially leading to the resistance of biofilms to antibiotics after being subjected to stressors, and also influences the slow growth condition of inactive cells (Khan et al., 2021).

Antimicrobial peptides (AMPs) to combat biofilm resistance

AMPs are small biological molecules that are structurally diverse and are found in insects, mammals, and fungi (Polinário et al., 2023). Antimicrobial peptides exhibit significant selectivity, strong potency, effectiveness, minimal toxicity, and limited tissue accumulation. They also face challenges, including instability, low bioavailability, and difficulty in crossing membranes (Silveira et al., 2021). The most prevalent antimicrobial peptides (AMPs) found in nature are those with an α-helical structure, which permits alternation such as addition or deletion of amino acids. These modifications enhance their amphipathic properties, aiding the infiltration of bacterial cell membranes and enhancing their selectivity for different membrane receptors (Roque-Borda et al., 2022). It is well-known that the regions with positive charge of antimicrobial peptides (AMPs) adhere electrostatically to bacterial cell membranes that have negatively charged phospholipids that gather on their surfaces. Once the essential concentration is reached, the hydrophobic areas of peptides infiltrate the phospholipid bilayer of the membrane, leading to a change in its structure and function. This results in an irregularity in ion exchange, a decrease in membrane potential, interference with cellular metabolism, and eventually leads to cell death. The selectivity of AMPs arises from their electrostatic interactions with bacterial cells rather than host cells, which result from their unique composition: certain phospholipids (Such as cardiolipin, phosphatidylglycerol, and phosphatidylserine) are solely present in bacteria, whereas mammalian cells are chiefly made up of different components such as phosphatidylcholine and phosphatidylethanolamine (Roque-Borda et al., 2025b).

Nanoparticle-based delivery of antimicrobial peptides

Nanotechnology methods hold significant promise for providing efficient strategies for the management and prevention of biofilm as they manipulate materials at the atomic and molecular scale that possess elevated surface-to-volume ratios and high atomic activation energy. It serves as a valuable platform to create potent antimicrobial agents by fine-tuning the physicochemical attributes of metals. While metal oxides can be toxic and damaging to natural environments, their physicochemical properties transform at the nanoscale. Additionally, the capacity of nanoparticles to infiltrate biofilms also prevents the biofilms from developing (Mohanta et al., 2023). During the interaction between biofilms and nanoparticles, three phases can be identified: the transportation of NPs near the biofilm, surface attachment of nanoparticles to biofilm, and the NPs movement within biofilms. Various factors, such as the surrounding environment, extracellular polymeric matrix (EPM), and the NPs' physicochemical characteristics, affect the occurrence of each of these phases (Shkodenko et al., 2020). Nanoparticles have metal oxides and cationic surfactants that serve as anti-biofilm properties (Sadekuzzaman et al., 2015). Their area-to-mass ratio, significant responsiveness, and the ability to modify their surfaces have provided them with unique characteristics that facilitate the effective elimination of biofilms. Nanoparticles function as anti-quorum-sensing agents by disrupting bacterial cell-to-cell pathways. This interruption will result in the prevention of the formation of the receptor complex and the synthesis of signaling molecules. The capacity of metallic nanoparticles to demonstrate quorum quenching activity has been especially emphasized (Lahiri et al., 2021).

Nanoparticles made of metal and their oxides

Metal and metal oxide nanoparticles, typically 1-100 nanometers in size, are composed of metallic elements or their compounds and exhibit unique physicochemical properties distinct from their bulk counterparts. These nanoscale materials demonstrate potent antimicrobial activity through mechanisms specific to

each type. Commonly researched NPs include silver (Ag), gold (Au), zinc(Zn), copper (Cu), and zinc oxide (ZnO), each offering distinct modes of microbial inhibition. These various functionalities make them an efficient tool to control bacterial infections and other pathogenic threats (Wang et al., 2017; Akintelu et al., 2021). Moreover, metal-based thin film coatings are seeking attention for antimicrobial stewardship. Applied to medical devices, wound dressings, and healthcare settings, these films are often composed of metals like silver or copper that release ions gradually, ensuring sustained antibacterial action. Their ability to prevent microbial attachment and biofilm development is pivotal for reducing healthcare-associated infections and extending device longevity. Ongoing research into these coatings plays a key role in tackling antibiotic-resistant pathogens (Ashhari et al., 2023; Finina & Mersha, 2024).

Lipid nanoparticles

These nanoparticles are nano-sized carriers made mainly of lipids, which are molecules known for their biocompatibility and biodegradability. These nanoparticles have attracted considerable interest in antimicrobial applications because of their effectiveness in entrapping and transporting antimicrobial agents. Their distinctive characteristics, such as controlled drug release, improved cellular uptake, and minimized toxicity, render them suitable for addressing bacterial infections, particularly those caused by strains resistant to antibiotics (Zeng et al., 2023) (Finina & Mersha, 2024).

Polymeric nanoparticles

Polymeric nanoparticles are particles primarily constructed from polymers that are large molecules made up of repeating units known as monomers. Ranging typically from several dozen to several hundred nanometers in size, these nanostructures are highly adaptable and are employed across a wide array of applications. They can be either natural or artificial polymers. Frequently used synthetic polymers include polyethylene, polyvinyl chloride (PVC), and polystyrene, while widely utilized biopolymers in nanoparticle fabrication include chitosan, alginate, and cellulose (Perumal, 2022). The distinctive properties of nanoparticles provide numerous benefits compared to conventional antibiotics, such as a lower chance of resistance formation due to their multifunctional strategies, which complicate the process for bacteria to acquire resistance (Zhu et al., 2024; Xu et al., 2023). Moreover, nanoparticles facilitate targeted delivery that permits lower antibiotic dosages while preserving therapeutic effectiveness. This can aid in minimizing side effects and lowering the selective pressure on bacteria to develop resistance (Gao et al., 2018). Despite the urgent need for new antibiotics, the discovery and development of novel antibacterial agents have dramatically declined. Creating these drugs is a costly and time-consuming process, yielding few approvals in recent decades. This inactivation is increased by bacteria's rapid resistance mechanisms and a lack of groundbreaking candidates in the pipeline. Although broad-spectrum antibiotics can combat various pathogens, they often disturb helpful microbiota, triggering side effects and secondary infections. Moreover, limited profitability due to short treatment duration and diminishing returns from resistance discourages pharmaceutical investment, especially when compared to more lucrative long-term therapies for chronic conditions (Ahmed et al., 2024; Ho et al., 2025).

Nanoparticles' safety and toxicity evaluation

The composition of nanomaterials is important for their toxicity as it affects key characteristics such as miscibility, redox behaviors, ion release, and interplay with biomolecules. These traits together define their toxicological profile and contribute to understanding how nanomaterials might cause negative biological impacts (Havelikar et al., 2024). Certain nanomaterials, including copper oxide, silver nanoparticles, and quantum dots, may present toxicity hazards as a result of the release of dangerous metal ions (Sukhanova et al., 2018). In contrast, gold nanoparticles show much better biocompatibility (Yang et al., 2019). The particle size also affects the interaction between nanoparticles and biological systems (Dhawan & Sharma, 2010). The optimal nanoparticle size for biomedical uses typically falls between 10 and 100 nm, with approximately 50 nm often being preferred for drug delivery because of its effective absorption and beneficial pharmacokinetic properties. Size is crucial in determining both systemic and organ-specific reactions. For example, nanoparticles sized between 10 and 50 nm can be efficiently eliminated by the kidneys while larger particles tend to accumulate in organs such as the liver, spleen, or lungs (Calé et al., 2025). Silver nanoparticles (Ag NPs) are commonly incorporated into numerous products due to their antibacterial capabilities; however, research indicated they may be harmful to mammalian cells. It is essential to comprehend the mechanisms of toxicity to ensure their safe application in the future (Jaswal & Gupta, 2023). Recent research on silver nanoparticles has highlighted their antimicrobial, antiviral, and anticancer potential. Nevertheless, apprehensions about their possible harmful effects still remain. Although Ag NPs are incorporated into a variety of products from medical devices to consumer goods, ensuring their safety remains a critical issue. Research highlights the necessity for more environmentally friendly synthesis techniques and the assessment of their biocompatibility and cytotoxic effects. Thorough investigation is crucial to guarantee their safe application in therapeutic contexts (Noga et al., 2023). Silver nanoparticles and their released Ag+ ions exert cytotoxic effects by disrupting cell membranes, producing reactive oxygen species (ROS) and including protein oxidation, mitochondrial dysfunction, DNA fragmentation, and suppressed cell growth. Their interaction with sulfur-rich biomolecules contributes to this toxicity. Due to their strong antibacterial activity and ability to penetrate membranes, Ag NPs accumulate in cytoplasm, triggering oxidative stress and apoptosis in mammalian cells (Tortella et al., 2020; Sati et al., 2025) as shown in Figure. 2 (Calé et al., 2025).

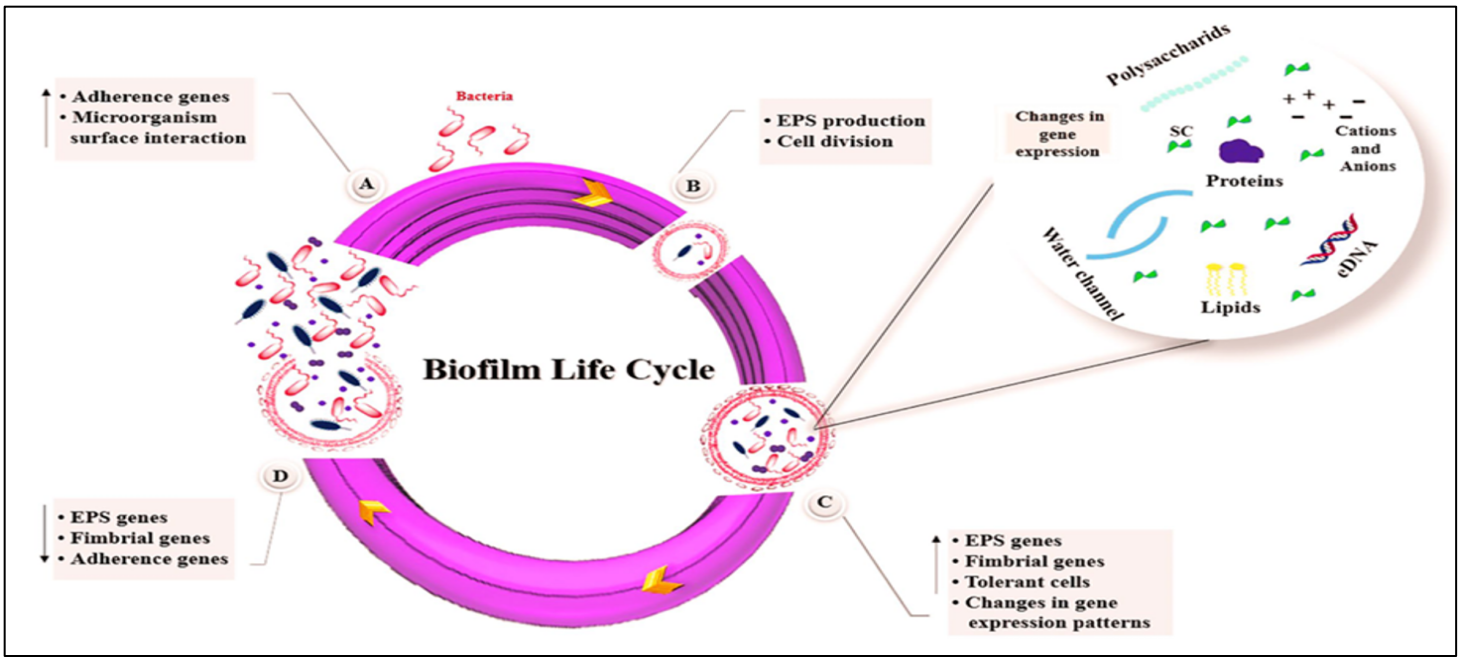

Figure 1: Depicting the biofilm (A) Bacterial attachment, (B) Microcolony formation, (C) Biofilm maturation, (D) Biofilm dispersal. SC, signaling compounds; eDNA, extracellular DNA; EPS, exopolysaccharides (Afrasiabi & Partoazar, 2024)

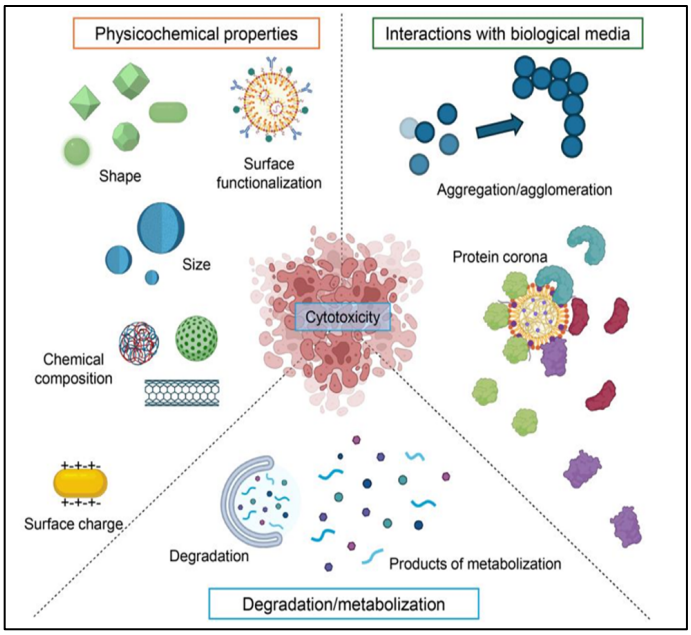

Figure 2: Factors that affect nanoparticles' biocompatibility and their safety.

CONCLUSION

This article offers essential insights into biofilm complexity, its formation process, and the factors driving its resistance to antimicrobial agents. Biofilms can be more difficult to treat than other planktonic microbes that live freely. Some specific mechanisms within biofilms make them resistant to treatment and lead to chronic infections. The emerging use of nanoparticles based on antimicrobial peptides holds great potential for penetrating biofilms and disrupting microbial communities. However, ensuring the safety and toxicity of nanoparticles is a key element for their successful application. Overall, while this innovative technology is bringing change to the diagnostic world, ongoing research must address its toxicity and safety to develop a sustainable and human-friendly solution against resilient biofilms. Combining scientific advancements with careful safety assessments will be key to overcoming the persistent threat of biofilm-associated infections.

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