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Revolutionizing Antimicrobial Therapies Through Biofilm-Targeted Nanomedicine

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Abstract

Revolutionizing Antimicrobial Therapies Through Biofilm-Targeted Nanomedicine. Biofilm-associated infections pose significant challenges to traditional antimicrobial therapies due to their inherent resistance mechanisms and protective extracellular matrix. Nanomedicine offers transformative solutions by providing innovative strategies to target, penetrate, and disrupt biofilms effectively. Recent advancements in nanotechnology have enabled the development of multifunctional nanocarriers, hybrid nanoparticles, and stimuli-responsive systems designed to enhance drug delivery and reduce bacterial resistance. These systems facilitate precise targeting of biofilms, leveraging mechanisms such as enzyme-mediated degradation, quorum-sensing inhibition, and environment-responsive drug release. Furthermore, personalized medicine approaches, integrating pathogen-specific diagnostics and AI-driven optimization, hold promise for tailoring treatments to individual patient needs. Despite these breakthroughs, challenges such as toxicity concerns, scalability, and regulatory hurdles remain. Overcoming these barriers through interdisciplinary collaboration and continued research is essential to translate nanomedicine from laboratory success to clinical application. This paradigm shift in antimicrobial therapy has the potential to revolutionize the treatment of biofilm-related infections, significantly reducing global healthcare burdens and improving patient outcomes.

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1. Introduction

The discovery of antibacterials was a watershed point in human history, revolutionizing medicine and saving many lives. However, overuse and misuse of antibacterials has resulted in the creation of multidrug-resistant (MDR) bacteria or "superbugs," which reduces their efficacy. The increase of antimicrobial resistance (AMR) has made treating chronic illnesses more challenging. [1]. The 2017 World Health Organization (WHO) Global Antimicrobial Surveillance System study identified antimicrobial resistance (AMR) as a global hazard to health, life expectancy, and food production. According to 2018 modeling research conducted by the Organisation for Economic Cooperation and Development (OECD), AMR is responsible for 4.95 million deaths worldwide and a $3.5 billion economic impact annually. As of December 2021, there were more than 620 million verified COVID-19 cases and around 6.5 million confirmed deaths worldwide. In contrast, if antimicrobial resistance (AMR) is not tackled, it might cause around 10 million deaths per year by 2050, with economic consequences potentially as severe as the 2008/2009 financial crisis. While global efforts have mostly focused on finding new antibiotic medications to tackle AMR, progress has been slow due to poor profitability, with no new antibiotic classes authorized since the late 1980s. Additional scientific and translational challenges, including as efflux, low permeability, and rapid

resistance development, exacerbate gaps in the antimicrobial development pipeline [2]. The majority of microorganisms are found in biofilms, where they either develop slowly or dormantly, which is thought to improve tolerance. The ability of a bacterial population to rapidly withstand deadly antibiotic dosages is known as tolerance to antimicrobials. This may be because the bacteria slow down their essential functions [3]. In general, antibiotic efficacy is defined mostly by the drug's ability to reach its target within bacterial cells at adequate levels [4]. Antibiotic concentrations are insufficient in biofilms because the EPS matrix prevents antibiotic penetration. Furthermore, the slow development of bacteria in biofilms limits the availability of bacterial targets. Unlike tolerance, antimicrobial resistance (AMR) is not transitory; it remains even after biofilm breakdown and is caused by bacterial genome changes or the acquisition of AMR components via horizontal gene transfer. Furthermore, bacteria communicate through quorum sensing, which regulates their metabolism and promotes biofilm development and pathogenicity [5].

Antibiotics are still the principal treatment option for both planktonic and biofilm infections. They target critical bacterial activities such cell wall and membrane synthesis, as well as DNA, RNA, and protein biosynthesis. Traditional antimicrobial therapies are clearly ineffectual against localized and persistent infections, with biofilm-associated infections being up to 1000 times less susceptible than planktonic infections [6]. Aminoglycosides (such as gentamicin, amikacin, and tobramycin) cannot penetrate the EPS due to their molecular size and electrostatic interactions with the matrix, which anchor them to the biofilm surface and reduce their effectiveness against bacteria within biofilms. As a result, medication concentrations within biofilms are frequently subtherapeutic, resulting in a considerable loss in efficacy and encouraging the development of antimicrobial resistance. The development of biofilms on surfaces such as mucosal tissues and medical equipment, as well as free-floating biofilm-like clusters, is clinically significant [7]. While there is insufficient clinical evidence for effective biofilm eradication, persistent infections are routinely treated with large doses of antibiotics, which are frequently coupled with various medications for extended periods of time, or by surgical removal of the biofilm when possible. These approaches raise serious concerns about increased toxicity and problems for patients. As a result, there is an urgent need for novel anti-biofilm therapy techniques to address this essential issue and improve clinical results [8].

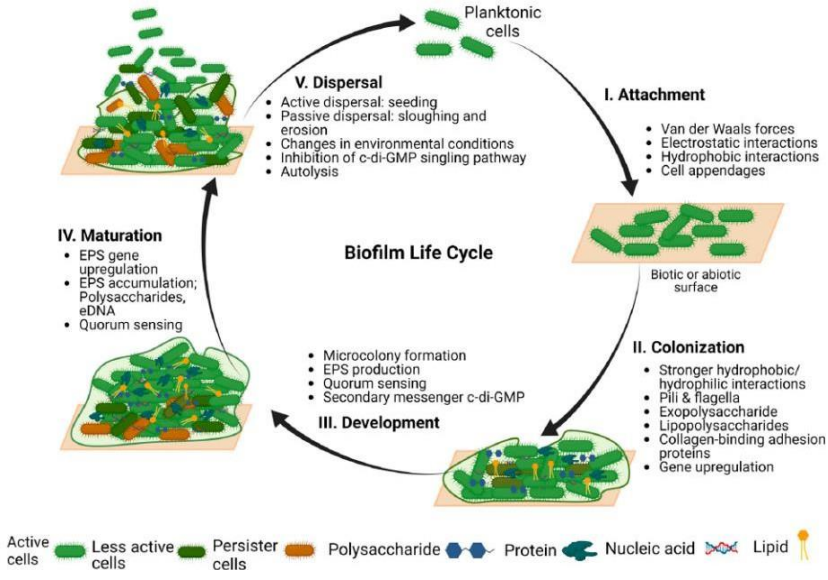

Figure 1: The biofilm formation process comprises five key stages: I) attachment, II) colonization, III) maturation, IV) development, and V) dispersal.

Due to the time and cost required to discover novel compounds, combination medication therapy have been successfully used in clinical practice. When used in conjunction with other treatments, the addition of non-antibiotic chemicals and antibiotic adjuvants can boost a drug's efficacy, particularly in tackling bacterial resistance [9]. The field of "antimicrobial adjuvants" has recently gained popularity. This paper

discusses EPS-degrading enzymes and quorum sensing inhibitors (QSIs) as potential antibacterial adjuvants that target two essential components of bacterial biofilms: the EPS matrix and the QS system. These strategies usher in a new age of combined antibiotic and antimicrobial adjuvant/anti-biofilm therapy [10]. A lack of targeted distribution and the potential for the compound to degrade or be removed before reaching its intended site are two common disadvantages of administering antimicrobial medicines in their free form. Additionally, when high concentrations of therapeutic chemicals are utilized to target biofilms, traditional drug delivery modalities (such as oral, inhalation, or injection) raise the risk of systemic toxicity [11]. Researchers are looking into a number of approaches to deal with these issues. These include using nanoparticle methods to deliver drugs to biofilms, using small compounds to interfere with bacterial signaling and communication, and inhibiting or degrading the EPS matrix. Co-delivery of many antimicrobial drugs, antibiotics, and/or antimicrobial adjuvants inside a single nanocarrier system is another noteworthy benefit. This might result in a synergistic therapeutic effect and perhaps increase antimicrobial activity [12]. To deliver various antimicrobial treatments, a range of nanocarriers have been used, including hydrogels, dendrimers, lipid nanoparticles, polymeric nanoparticles, and mesoporous silica nanoparticles. Because of their versatility and biocompatibility, lipid nanocarriers (LNCs) are thought to be one of the most promising antimicrobial delivery technologies. They have also been demonstrated to increase the potency of currently available antibiotics [13]. As biomimetic and biocompatible drug delivery methods, LNCs can assist in overcoming the different chemical, biological, and physical hurdles that bacteria present. They increase the efficacy and decrease the toxicity of antimicrobial drugs by improving absorption, permeability, bioavailability, and biofilm targeting. In order to increase overall antimicrobial efficiency, LNCs also help antibiotics pass through chemical and physical barriers, combine with bacterial cell membranes, allow for stimuli-responsive release, and work in concert with adjuvants and integrated antibiotics [14]. In order to treat biofilms, this study highlights the utilization of lipid nanocarrier-enabled delivery methods for antibiotics and antimicrobial adjuvants. The fact that this subject has never been studied before emphasizes how special this study is. Examples from current research are used to support the discussion of LNCs' function as an anti-biofilm treatment [15]. A thorough analysis is conducted of the mechanisms behind the creation of biofilms and the difficulties in eliminating them, which lead to insufficient therapeutic therapy. A summary of current developments in the use of potential anti-biofilm agents is provided, along with in-depth information on the many kinds of LNCs used to administer antibiotics and antimicrobial adjuvants [16].

1.2 Overview of Biofilm-Associated Infections and Their Clinical Challenges

Biofilm-associated infections occur when microbial communities form biofilms on surfaces within the body or on medical devices. Biofilms are consisting of microorganisms encased in an extracellular polymeric substance (EPS) matrix that provides structural support and protection. This complex structure enables microbes to survive in hostile environments and evade antimicrobial agents. Biofilms are implicated in a broad range of infections, posing significant challenges to treatment [17]. Chronic wound infections, including those found in diabetic ulcers, venous stasis ulcers, and pressure sores, are often caused by biofilm-forming bacteria that resist conventional antimicrobial therapies. Similarly, implant-associated infections are common on devices such as catheters, prosthetic joints, heart valves, and stents, where biofilms form and protect bacteria from immune response and antibiotics. Pulmonary infections, particularly in cystic fibrosis patients, are frequently caused by Pseudomonas aeruginosa, which forms biofilms in the lungs, complicating treatment [18]. Dental infections, such as periodontitis and dental plaque-associated caries, are also linked to biofilms, making them difficult to treat with standard oral hygiene practices alone. Additionally, recurrent urinary tract infections (UTIs) are often associated with biofilm formation in the urinary tract, further complicating management and treatment. These infections emphasize the necessity for more efficient strategies to hinder or disrupt biofilm formation in clinical environments [19].

Biofilm-embedded microorganisms exhibit a significantly higher resistance to antimicrobial agents—up to thousand-fold greater than their planktonic counterparts—due to several factors. The EPS matrix in biofilms limits drug penetration, while slower microbial growth rates within the biofilm hinder the effectiveness of antibiotics that target active processes. Additionally, the presence of persister cells within the biofilm contributes to antibiotic tolerance [20]. Biofilm infections often become chronic, evading both antimicrobial treatments and the host immune system, leading to

frequent recurrence even after aggressive treatment. The formation of biofilms on medical devices, such as prosthetic joints, pacemakers, and vascular grafts, can result in device failure and severe complications, often necessitating surgical removal or replacement. Moreover, biofilms shield microorganisms from immune responses like phagocytosis and the action of antimicrobial peptides, exacerbating inflammation and tissue damage, which further contributes to chronic infection. Microorganisms within biofilms can also periodically disperse, causing the infection to spread to other parts of the body, as seen in conditions like endocarditis or bloodstream infections [21]. Additionally, biofilms promote horizontal gene transfer, accelerating the development of MDR pathogens. Diagnosing of biofilm-associated infections is difficult, as they are often underdiagnosed due to their resistance to standard culture-based diagnostic methods and their polymicrobial nature. The economic and healthcare burden of biofilm infections is considerable, with prolonged hospital stays, repeated treatments, and the need for surgical interventions or device replacements, leading to increased healthcare costs [22].

1.3 Limitations of Conventional Antimicrobial Therapies in Addressing Biofilms

Biofilms present significant challenges to conventional antimicrobial therapies due to their unique structural, biochemical, and physiological characteristics. One of the main limitations is reduced antibiotic penetration. The EPS matrix of biofilms serves as both physical and chemical barrier, blocking antibiotics from reaching the deeper layers where a large portion of microbial cells reside, leaving them unaffected. Additionally, within biofilms, microbial cells exhibit altered physiology, including a shift to a metabolically dormant state [23]. These dormant cells, often referred to as persister cells, are highly tolerant to antibiotics that target active cellular processes, such as protein synthesis or cell wall assembly. Biofilms also protect microbes from the host immune response, shielding them from defenses like phagocytosis and antimicrobial peptides, which further hinders the immune system's ability to eradicate infections. Furthermore, the biofilm matrix can bind and sequester antimicrobial agents, reducing their bioavailability, and certain components of the matrix, such as polysaccharides or enzymes like β-lactamases, can even inactivate antibiotics. The biofilm environment also promotes horizontal gene transfer, facilitating the spread of AMR genes among microbial cells and accelerating the development of resistance mechanisms [24]. Chronic and recurrent infections are another concern, as residual persister cells or subpopulations of microbes can regrow after antibiotic treatment, leading to repeated infections, particularly in medical device-associated infections like those involving catheters or prosthetic joints. Additionally, achieving the high concentrations of antibiotics required to penetrate biofilms often leads to systemic toxicity, and prolonged use of high-dose antibiotics can damage host tissues and promote further resistance. Conventional antibiotics also lack specificity, often affecting both biofilm-forming bacteria and surrounding healthy microbiota, which can lead to dysbiosis and secondary infections [25].

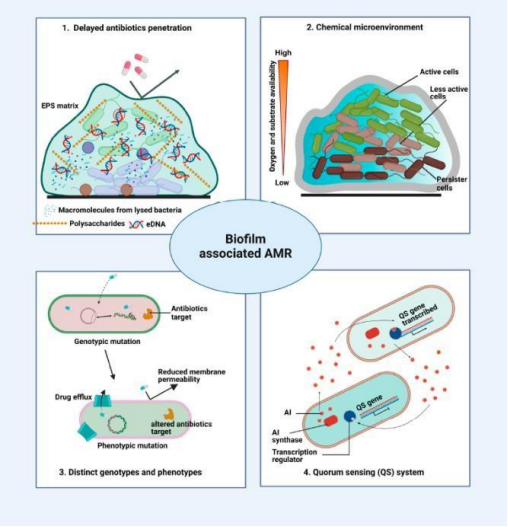

Figure 2: An example of the several ways that biofilm-mediated resistance to antibiotics works

1.4 The Need for Innovative Therapeutic Strategies

Biofilm related infection is a growing challenge in medicine, significantly contributing to AMR and the burden of chronic diseases. The limitations of conventional therapies underscore the need for innovative approaches to effectively target biofilms and mitigate their clinical and societal impacts [26]. The architecture of biofilms, with their EPS matrix, acts as a physical and chemical barrier that prevents effective antibiotic penetration, allowing microbial cells to survive even in the presence of high antimicrobial concentrations. This intrinsic resistance necessitates novel strategies to bypass or disrupt the biofilm barrier. Additionally, the phenotypic heterogeneity within biofilms, including the presence of dormant persister cells, makes it difficult for traditional therapies, which primarily target actively dividing cells, to eradicate these infections, leading to chronic and recurrent issues. Moreover, biofilms accelerate the development of AMR through horizontal gene transfer, further complicating treatment efforts. The high clinical and economic burden of biofilm infections, due to challenges in diagnosis and the need for prolonged hospital stays or invasive surgical interventions, highlights the urgent demand for more effective, less invasive therapies [27].

To address these challenges, several innovative therapeutic strategies are emerging. Nanomedicine, particularly biofilm-disrupting nanoparticles (NPs), offers promising solutions. Engineered NPs can penetrate the biofilm matrix, deliver drugs to microbial cells, and disrupt the structural integrity of the biofilm [28]. These nanoparticles can be functionalized for targeted delivery, combined with matrix-disrupting agents, or made stimuli-responsive to release drugs in response to specific environmental triggers within the biofilm. Combination therapies, such as pairing traditional antibiotics with biofilm-targeting agents, can enhance therapeutic efficacy. For example, using antibiotics in conjunction with biofilm-disrupting enzymes like DNase or proteases or employing quorum-sensing inhibitors (QSIs) to prevent biofilm formation can significantly improve outcomes. Quorum sensing, a microbial communication system that regulates biofilm formation, can be targeted with QSIs to both prevent biofilm development and enhance the susceptibility of biofilm cells to antibiotics [29].

Additionally, antimicrobial peptides (AMPs) are being explored for their ability to penetrate biofilms, disrupt microbial membranes, and modulate immune responses. Phage therapy, which uses bacteriophages to target specific pathogens within biofilms, is another promising approach, as some phages produce enzymes that degrade the biofilm matrix, enhancing their ability to eliminate biofilm-associated microbes [30]. Photodynamic therapy (PDT) offers a non-invasive and targeted treatment option, using light-activated compounds to generate ROS that kill microorganisms and disrupt biofilm structures. Host-directed therapies, including immunomodulatory agents and vaccines targeting biofilm-forming pathogens, can complement antimicrobial therapies by boosting the host‘s immune response. Finally, the development of advanced biomaterials, such as biofilm-resistant coatings for medical devices, aims to prevent biofilm formation at the source, reducing the risk of device-associated infections and the need for therapeutic interventions. These innovative approaches are paving the way for more effective and individualized therapies for illnesses linked to biofilms [31].

1.5 Nanomedicine: A Paradigm Shift in Antimicrobial Therapies

Nanomedicine represents a transformative approach in the field of medicine, particularly in the realm of antimicrobial therapies. By leveraging nanoscale materials and technologies, nanomedicine offers innovative solutions to overcome the limitations of conventional treatments, especially for biofilm-associated infections. Nanoparticles (NPs), which are designed at the nanometer scale (one-hundred nm), possess distinctive physical, chemical, and biological properties that are not achievable with bulk materials [32]. These properties make nanomedicine a promising platform for revolutionizing antimicrobial treatments. One key advantage is the ability to target delivery, where NPs can be functionalized with ligands or surface modifications that specifically bind to microbial cells or biofilm components. This minimizes toxicity and reduces off-target effects by ensuring precise delivery of antimicrobial medicines to the infection site. Additionally, because of their tiny size, nanoparticles can pass through the thick EPS matrix of biofilms and deliver therapeutic chemicals to normally inaccessible parts of the biofilm [33].

Nanomedicine also offers multifunctional capabilities, enabling the integration of various therapeutic strategies into a single platform. For example, nanoparticles can combine antimicrobial agents with biofilm-disrupting enzymes and imaging agents for both treatment and diagnostic purposes.

Furthermore, nanoparticles can be engineered to be stimuli-responsive, releasing their payload in response to specific environmental triggers such as changes in pH, enzymatic activity, or redox potential [34]. This ensures that drugs are released in a controlled manner, targeting the biofilm environment precisely. Another significant advantage is the reduction in resistance development. By delivering high local concentrations of antimicrobials directly to biofilm-associated microbes, nanomedicine reduces the likelihood of sublethal exposure that often contributes to resistance development [35].

Applications of nanomedicine in antimicrobial therapies are diverse. Metallic nanoparticles such as silver, gold, and zinc oxide possess inherent antimicrobial properties, often through mechanisms like membrane disruption and reactive oxygen species (ROS) generation. Polymeric nanoparticles, such as those made from biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), can encapsulate drugs, providing sustained and controlled release. Nanoparticles can also deliver matrix-degrading enzymes (e.g., DNase, proteases) to weaken the structural integrity of biofilms, while liposomal formulations improve the solubility and bioavailability of poorly soluble antimicrobial agents [36]. Quorum-sensing inhibitors (QSIs) delivered by nanoparticles can disrupt microbial communication, preventing biofilm formation and enhancing susceptibility to antibiotics. Photothermal and photodynamic therapies (PTT and PDT) using nanoparticles, such as gold or porphyrin-loaded nanoparticles, generate heat or ROS under light activation, effectively killing microbes and disrupting biofilms without systemic toxicity. Additionally, immunomodulatory nanocarriers can deliver agents that enhance the host immune response against biofilm-associated infections [37].

Recent advances in nanomedicine for antimicrobial therapies include the use of silver nanoparticles, known for their potent antimicrobial activity against MDR pathogens and biofilm-associated infections, and chitosan nanoparticles, which are biodegradable, biocompatible, and show strong antimicrobial and biofilm-disrupting properties [38]. Lipid-based nanocarriers, including liposomes and solid lipid nanoparticles, have also shown promise in enhancing the delivery of hydrophobic antibiotics like amphotericin B. Despite these advances, several challenges remain for the widespread clinical adoption of nanomedicine. These include concerns about safety and biocompatibility, as the potential toxicity and long-term effects of nanoparticles must be carefully evaluated. Additionally, the scalability and cost of producing nanomedicines at a clinical scale must be addressed, and standardized regulatory protocols are needed to streamline approval processes. Nevertheless, nanomedicine holds immense potential in combating biofilm-associated infections, reducing AMR, and improving patient outcomes in the fight against chronic and MDR infections [39].

1.6 Scope and Objectives of the Review

The scope of this review is to explore the challenges posed by biofilm-associated infections and the limitations of conventional antimicrobial therapies in addressing these persistent infections. It focuses on emerging and innovative strategies, particularly biofilm-targeted nanomedicine, as a promising solution to these challenges. The review includes an in-depth analysis of the mechanisms of biofilm resistance, the structural and functional characteristics that contribute to the biofilm‘s resilience against traditional therapies, and the potential of nanomedicine-based approaches to transform the landscape of antimicrobial treatment. By evaluating how nanomedicine can target and disrupt biofilms more effectively than conventional drugs, this review aims to highlight the breakthroughs in addressing biofilm-related infections [40].

The primary objectives of this review are to first identify and highlight the limitations of traditional antimicrobial therapies in managing biofilm-associated infections. The review further delves into the structural and functional mechanisms that make biofilms resistant to treatment, such as reduced drug penetration and the presence of persistent microbial cells [41]. Additionally, it examines the innovations in biofilm-targeted nanomedicine and other emerging strategies, assessing their potential in overcoming the limitations posed by conventional therapies. The review also summarizes recent preclinical and clinical developments, showcasing the advancements made in antimicrobial therapies, particularly those focused on biofilm disruption and eradication. Finally, it proposes future directions for research, discussing the challenges, opportunities, and the translational potential of nanomedicine and other innovative therapies in combating biofilm-associated infections, with the goal of improving patient outcomes and addressing the global health threat of AMR [42].

2. Biofilms: Structure, Function, and Challenges, Biofilm Formation and Dynamics

Biofilms are intricate, three-dimensional microbial communities that form on various surfaces and are encased in a self-produced EPS matrix. The EPS, composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA), plays a crucial role in providing structural integrity, protecting the cells, and facilitating intercellular communication. Within the biofilm, there is a spatial organization that results in gradients of nutrients, oxygen, and metabolites [43]. These gradients influence microbial activity and survival, with cells at the biofilm's periphery being metabolically active, while those in the core may adopt a dormant state, becoming persister cells that contribute to the biofilm‘s resilience. This structural and functional diversity within the biofilm leads to significant challenges in addressing biofilm-associated infections. Biofilms serve several essential functions for microorganisms. The EPS matrix acts as a protective barrier, shielding the microbes from environmental stressors, including antimicrobial agents and host immune responses. Furthermore, the biofilm structure enhances resource efficiency by facilitating nutrient retention, waste removal, and metabolic cooperation among the cells. However, biofilms also promote resistance development by enabling horizontal gene transfer, which accelerates the spread of AMR genes among microbial populations [44].

The challenges of biofilm-related infections are multifaceted. Biofilms exhibit resistance to antimicrobial agents that is up to 1,000 times greater than that of planktonic cells, making conventional therapies largely ineffective. The EPS matrix and phenotypic diversity within biofilms hinder the host immune system‘s ability to clear infections, while the presence of dormant cells in the core of the biofilm contributes to chronic and recurrent infections. In medical settings, biofilm formation on medical devices, such as catheters and implants, often necessitates their removal or replacement, further complicating treatment [45].

Biofilm formation is a highly regulated and dynamic process, occurring in several distinct stages. The process begins with initial adhesion, where microorganisms attach to surfaces through weak van der Waals forces and hydrophobic interactions. The surface properties, such as roughness and charge, as well as environmental factors like pH and nutrient availability, influence this attachment. Once attached, bacterial cells produce adhesion molecules and secrete EPS components, cementing their attachment to the surface, marking the stage of irreversible attachment [46]. As microorganisms proliferate, they form microcolonies surrounded by the developing EPS matrix, entering the early biofilm formation stage. Quorum sensing, a cell-to-cell communication mechanism, plays a key role in regulating biofilm maturation and coordinating group behavior. As the biofilm matures, it develops a complex three-dimensional structure, including water channels that allow for nutrient and waste exchange, and phenotypic heterogeneity emerges, with varying levels of metabolic activity throughout the biofilm. Finally, in response to environmental cues, microbial cells or aggregates disperse from the biofilm, enabling the spread of the infection to new surfaces and perpetuating the infection cycle [47].

2.1 Stages of Biofilm Development

Biofilm development is a dynamic, multi-step process characterized by microbial attachment, growth, and eventual dispersion. It begins with the initial attachment of microorganisms to a surface through weak, reversible interactions, including van der Waals forces, electrostatic forces, and hydrophobic interactions. The surface properties, such as roughness, hydrophobicity, and charge, as well as environmental conditions like pH, nutrient levels, and flow rates, significantly influence this early stage. Once attached, bacterial cells anchor more firmly using specialized structures such as adhesins, pili, fimbriae, and flagella [48]. During this stage, the production of EPS begins, providing a scaffold for further microbial adherence and enhancing the stability of the attachment. As the biofilm matures, microorganisms proliferate, forming microcolonies that are surrounded by the self-produced EPS matrix, which is composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA). This matrix not only provides structural stability but also mediates adhesion and forms protective barriers against environmental threats. The biofilm develops into a complex three-dimensional structure with water channels that facilitate the exchange of nutrients, oxygen, and waste products. Within this structure, cells exhibit metabolic gradients, with actively growing cells on the periphery and dormant persister cells in the core, contributing to phenotypic diversity. Quorum sensing, a cell-density-dependent signaling mechanism, regulates gene expression, biofilm maturation, and cooperative behaviors such as

virulence and resistance, further enhancing the biofilm's resilience. In the final stage, dispersion, environmental cues such as changes in nutrient availability, oxygen levels, pH, or mechanical stress trigger the release of microbial cells or aggregates from the biofilm [49]. Dispersion can also be induced by internal factors like enzymatic degradation of the EPS matrix. Once released, the microbial cells revert to the planktonic state, enhancing their motility and potential for colonizing new surfaces, which facilitates the spread of infection and contributes to the chronicity of biofilm-associated diseases. A key feature of biofilms is the EPS, which serves as the structural foundation and protective environment for microbial cells. The EPS matrix is composed of polysaccharides, proteins, lipids, and extracellular DNA (eDNA), and it plays several critical functions. It provides structural integrity, forms a barrier against the penetration of antibiotics and immune cells, supports nutrient retention, and facilitates cell communication through quorum sensing and genetic exchange. Biofilms exhibit significantly higher resistance to antimicrobials compared to planktonic cells [50]. This resistance is driven by multiple mechanisms, including the physical barriers created by the EPS matrix, which impede the diffusion of antimicrobial agents and result in sublethal concentrations within the biofilm. Additionally, biofilm cells exhibit metabolic heterogeneity, with dormant or slow-growing cells in the biofilm core (persister cells) being inherently less susceptible to antibiotics that target active growth. Biofilm cells also upregulate stress-response genes, enhancing their survival under antimicrobial pressure. The close proximity of cells within biofilms facilitates horizontal gene transfer, promoting the spread of resistance genes. Moreover, biofilm cells can exhibit transient phenotypic states that reduce susceptibility to antibiotics, even without genetic resistance, contributing to their overall resilience [51].

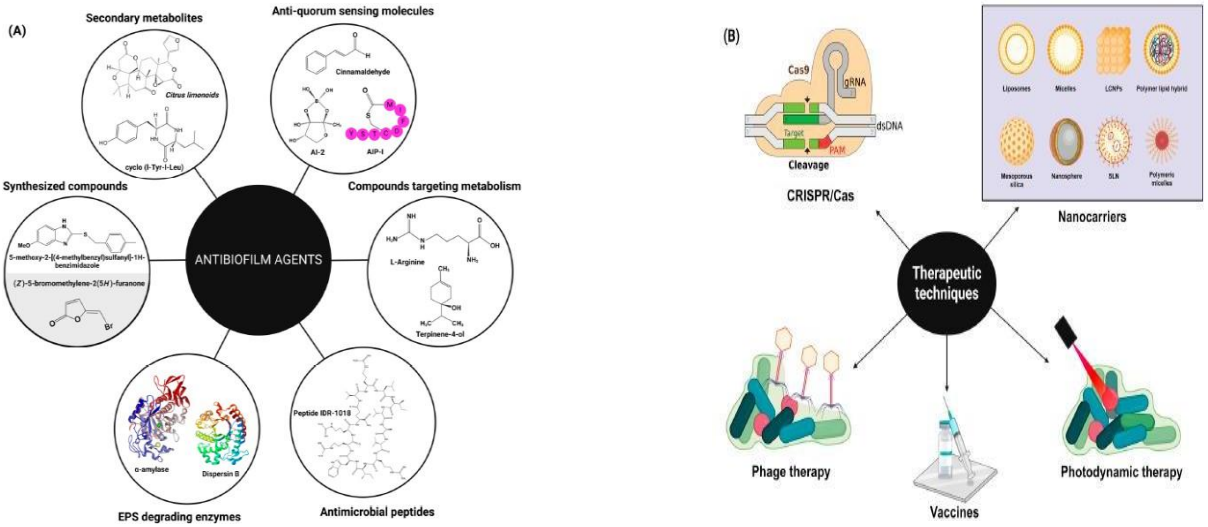

Figure 3: An example of the several antibiofilm agents that target the various substances that cause biofilm development

2.3 Clinical Implications of Biofilms

Biofilms are a major contributor to chronic and recurrent infections, significantly complicating medical treatments and increasing healthcare burdens. Their ability to adhere to surfaces, resist conventional therapies, and evade the immune system makes them a critical concern in clinical settings. Biofilm formation is implicated in several chronic infections, including respiratory infections such as cystic fibrosis, where Pseudomonas aeruginosa biofilms dominate the airway, and chronic wounds, such as diabetic ulcers and pressure sores, where biofilms delay healing and increase the risk of systemic infections [52].

In addition to chronic infections, biofilms are a common cause of device-associated infections. Medical devices such as catheters and implants are particularly vulnerable to biofilm formation. For example, urinary and central venous catheters can develop biofilms that lead to bloodstream infections, while orthopedic prostheses, heart valves, and pacemakers are susceptible to biofilm-associated

infections that often require device removal or replacement [53].

Biofilm-associated cells exhibit significantly higher resistance to antibiotics than planktonic cells, with resistance levels up to 1,000 times greater. This AMR prolongs treatment courses, increases the need for high-dose antibiotics, and raises the risk of adverse effects. Additionally, biofilms shield microbes from immune recognition, reducing phagocytosis and antibody-mediated responses, which leads to persistent infections. These chronic biofilm infections often result in ongoing inflammation, tissue damage, and systemic complications [54].

The healthcare burden of biofilm-related infections is substantial. These infections often require prolonged hospitalizations, repeated surgical interventions, and higher healthcare costs, all of which contribute to significant patient morbidity and decreased quality of life. Moreover, biofilms contribute to the global AMR crisis by serving as reservoirs for resistant pathogens and facilitating the spread of resistance genes, further compounding the challenge of managing these infections [55].

2.4 Common Biofilm-Associated Infections

Infections linked to biofilms are common in clinical settings and are essential for chronic illnesses and treatment resistance. These infections, which frequently need intensive or specific therapies to cure, arise when biofilms form on biological tissues or medical equipment. Biofilm-associated infections are most frequently seen in chronic wounds, including pressure sores, diabetic foot ulcers, and venous leg ulcers. Biofilms in these wounds impede the healing process, raise the risk of systemic infections such as osteomyelitis, and lead to antibiotic resistance, both systemic and topical. These infections are frequently linked to pathogens such as Streptococcus species, Pseudomonas aeruginosa, and Staphylococcus aureus [56].

Biofilms also commonly colonize medical devices, making infections difficult to treat and often requiring the removal or replacement of the devices. These include urinary catheters (causing catheter-associated UTIs), central venous catheters (leading to bloodstream infections), orthopedic implants (responsible for prosthetic joint infections), cardiovascular devices (such as pacemakers, which may lead to endocarditis), and endotracheal tubes (causing ventilator-associated pneumonia). Pathogens like Escherichia coli, Klebsiella pneumoniae, Candida species, and Staphylococcus epidermidis are often responsible for these infections [57].

In the respiratory system, biofilm formation in the airways contributes to chronic infections and poor therapeutic outcomes. In cystic fibrosis, Pseudomonas aeruginosa biofilms dominate the airway, exacerbating the condition, while in chronic obstructive pulmonary disease (COPD), biofilms exacerbate infections and inflammation. Additionally, Mycobacterium tuberculosis forms biofilms in lung lesions, which contribute to its drug tolerance [58].

Oral and periodontal infections are another common consequence of biofilm formation. Dental caries, periodontitis, and peri-implantitis are often caused by biofilms in the oral cavity, particularly by pathogens such as Streptococcus mutans and Porphyromonas gingivalis. These infections can lead to chronic inflammation, bone loss, and an increased risk of systemic conditions like cardiovascular disease [59].

Biofilms are also prevalent in the ear, nose, and throat regions, contributing to chronic otolaryngological conditions such as otitis media, sinusitis, and tonsillitis. These infections are frequently caused by pathogens such as Moraxella catarrhalis, Streptococcus pneumoniae, and Haemophilus influenzae. Similarly, biofilms in the urinary system, which are frequently brought on by Proteus mirabilis and uropathogenic Escherichia coli (UPEC), lead to recurrent and chronic UTIs, including pyelonephritis and recurrent bladder infections [60]. Finally, biofilms can form in skin and soft tissue infections, such as folliculitis and hidradenitis suppurativa, leading to chronic inflammation and poor therapeutic outcomes. Staphylococcus aureus, including methicillin-resistant strains (MRSA), is frequently involved in these skin infections [61].

2.5 Challenges in Treatment and Increased Resistance to Conventional Antibiotics

Biofilm-associated infections present significant challenges in treatment due to their unique structural and physiological characteristics, which enable them to evade conventional antimicrobial therapies. One of the primary obstacles is the protective EPS matrix that encases the biofilm. This matrix acts as a physical barrier, limiting the penetration of antibiotics and immune cells, which results in sublethal drug concentrations within the biofilm. Additionally, microbial cells within biofilms exhibit phenotypic

heterogeneity, with some cells in dormant or slow-growing states (persister cells) that are highly tolerant to antibiotics, making conventional therapies, which typically target actively dividing cells, ineffective. Biofilm cells also display altered microbial physiology, including unique stress responses and metabolic adaptations that enhance their survival under antimicrobial pressure, further complicating treatment efforts [62].

The chronicity and recurrence of biofilm-associated infections are another challenge, as biofilms serve as reservoirs for persistent and recurrent infections. Dormant cells within the biofilm can reactivate after treatment, leading to relapses and the persistence of the infection. Biofilm-associated bacteria are also highly resistant to conventional antibiotics. Several factors contribute to this resistance, including limited antibiotic penetration due to the dense EPS matrix, microenvironmental gradients that create zones of reduced metabolic activity, and adaptive resistance mechanisms that alter gene expression to withstand antimicrobial agents. Furthermore, the close proximity of cells within biofilms facilitates horizontal gene transfer, promoting the spread of resistance genes among microbial populations, while evolutionary pressure from incomplete antibiotic penetration fosters the selection of resistant strains [63].

Therapeutic challenges in treating biofilm-related infections are compounded by the limited efficacy of monotherapies, which often fail to eradicate biofilms. This necessitates the use of combination therapies or alternative approaches, which may require higher doses or prolonged use of antibiotics, increasing the risk of toxicity and adverse effects. Additionally, biofilm formation on medical devices frequently requires their removal or replacement, a process that can be invasive and costly. The immune system's inability to effectively clear biofilm-associated infections due to the EPS matrix further prolongs infection and complicates treatment [64].

Biofilm-associated infections have important wider ramifications, including longer hospital stays, greater morbidity rates, and higher healthcare expenses. Biofilms also play a key role in the global AMR crisis by acting as reservoirs for resistant pathogens, which exacerbate the problem and limit the effectiveness of current antibiotics. This underscores the urgency of developing novel strategies to combat biofilm-related infections and address the growing threat of AMR [65].

3. Nanotechnology in Antimicrobial Therapies

Nanotechnology in antimicrobial therapies utilizes nanoscale materials, such as nanoparticles and nanomaterials, to enhance the efficacy of treatments against infections, especially those involving biofilms. These technologies enable targeted drug delivery, improve biofilm penetration, and reduce AMR. By leveraging the unique properties of nanoparticles, such as high surface area and bioactivity, nanotechnology offers a promising solution to combat chronic and MDR infections more effectively. Nanotechnology in healthcare involves the use of nanomaterials and nanoscale devices to diagnose, treat, and prevent diseases. It enhances drug delivery, allows precise targeting of tissues, and improves imaging techniques. By manipulating materials at the atomic and molecular scale, nanotechnology enables the development of more effective therapies, reduces side effects, and offers innovative solutions for difficult-to-treat conditions, including cancer, infections, and chronic diseases [23].

Nanomaterials represent a diverse class of engineered materials designed at the nanoscale, each offering unique properties tailored for various biomedical applications. These include solid structures called nanoparticles, which are usually between 1 and 100 nanometers in size and are composed of ceramics, polymers, or metals like gold and silver. Their high surface area enables efficient drug loading and targeted delivery to specific sites. Conversely, liposomes are spherical vesicles made of lipid bilayers that may hold both hydrophilic and hydrophobic medications. They facilitate controlled drug release and enhance bioavailability, making them a popular choice for drug delivery and gene therapy [66]. Dendrimers, with their highly branched and tree-like structures, offer extensive surface areas for drug attachment and provide precise control over drug release, making them suitable for targeted therapies and diagnostics. Nanogels, composed of cross-linked polymer networks, exhibit the ability to swell or shrink in response to environmental stimuli such as pH or temperature, enabling controlled drug release to specific tissues or cells. Each of these nanomaterials brings distinct advantages, offering innovative approaches to disease treatment, including applications in antimicrobial therapies and cancer treatment [67].

Compared to conventional medication delivery methods, nanomaterials provide a number of benefits.

They improve bioavailability, which facilitates improved medication distribution and absorption. Because of their tiny size, they may be delivered precisely to particular tissues or cells, which minimizes adverse effects and enhances therapeutic results. Nanomaterials can be engineered for controlled and sustained drug release, minimizing the need for frequent dosing. Additionally, their high surface area enables the encapsulation of both hydrophobic and hydrophilic drugs, offering versatility in treatment options. Overall, nanotechnology provides more efficient, precise, and safer drug delivery compared to conventional methods [68].

3.1 Mechanisms of Action in Antimicrobial Nanomedicine

Antimicrobial nanomedicine harnesses the unique properties of nanomaterials to disrupt microbial cells, offering enhanced efficacy in combating infections, including biofilm-associated ones [69]. Several mechanisms contribute to the antimicrobial action of nanomaterials:

3.3.1. Physical Disruption of Microbial Membranes

Significant harm and microbiological mortality may result from NPs' interactions with microbial cell membranes. They may attach to and pass through cell membranes due to their tiny size and huge surface area, which physically disrupts the membrane and allows intracellular contents to flow out. Furthermore, by breaching the microbial membranes, nanoparticles with sharp edges or a high surface charge can cause mechanical harm that might lead to cell lysis or death. These processes demonstrate the strong antibacterial qualities of nanoparticles and their possible uses in the fight against microbial illnesses [70].

3.3.2. Generation of Reactive Oxygen Species (ROS)

Nanomaterials, such as silver, copper, and zinc oxide nanoparticles, can induce oxidative stress in microbial cells by generating reactive oxygen species (ROS) during their interactions. These ROS cause extensive damage to essential cellular components, including proteins, lipids, and DNA, compromising the structural and functional integrity of the cells. Furthermore, ROS disrupt critical cellular processes, such as respiration and DNA replication, ultimately inhibiting vital functions and leading to microbial cell death. This dual mechanism of oxidative stress and functional inhibition underscores the effectiveness of these nanomaterials as antimicrobial agents [71].

3.3.3. Metal Ion Release

Certain nanoparticles, such as silver and copper, exhibit antimicrobial properties through ion leaching, where they release metal ions into their environment. These ions disrupt bacterial cell walls, interfere with enzyme functions, and inhibit cell division, effectively impairing microbial survival. Once inside the microbial cells, the metal ions interact with intracellular components, causing further damage to critical structures, including the cell membrane and DNA. This combination of external and internal toxicity highlights the potent antimicrobial effects of these nanoparticles and their potential applications in controlling microbial infections [72].

3.3.4. Biofilm Disruption

Nanoparticles offer significant advantages in combating biofilms, which are often resistant to traditional antibiotics. Their small size and ability to interact with the biofilm matrix enable nanoparticles to penetrate biofilms more effectively, reaching the embedded microbial communities. Additionally, some nanomaterials are engineered to release enzymes or small molecules that degrade the EPS matrix of biofilms. This enzymatic disruption weakens the structural integrity of the biofilm, exposing the microbes and making them more susceptible to antimicrobial treatments. These properties highlight the potential of nanoparticles as powerful tools for addressing biofilm-associated infections [73].

3.3.5. Targeted Drug Delivery

Therapeutic drugs can be precisely delivered to the site of infection by functionalizing nanoparticles with particular ligands that attach to specific receptors on microbial cells. By concentrating the antimicrobial medicines where they are most required, this focused method increases their efficacy. Furthermore, by concentrating the therapy on microbial cells, the harm to healthy cells is reduced, which greatly lowers the toxicity and adverse consequences that are frequently linked to traditional antimicrobial treatments. The potential of nanoparticles to increase the accuracy and effectiveness of antimicrobial therapies is highlighted by this combination of specificity and safety [74].

3.3.6. Antimicrobial Peptide Mimicry

Certain nanomaterials, especially those with cationic surfaces, exhibit peptide-like behavior by mimicking the activity of antimicrobial peptides (AMPs). These

nanoparticles interact with microbial membranes, disrupting their structure and leading to bacterial death, much like the mechanism employed by AMPs. They also have broad-spectrum antibacterial action, which allows them to efficiently battle both Gram-positive and Gram-negative bacteria by targeting a variety of microbial membranes. This dual functionality highlights their potential as versatile and powerful agents in the fight against a wide range of microbial infections [75].

Table 1: Nanomedicine Formulations for Biofilm-Targeted Therapy

S. No.	Nanomedicine Formulation Name	Drug	Method of Preparation	Application	References
1	Lipid-based Nanoparticles	Vancomycin	Solvent evaporation or thin-film hydration	Deep biofilm penetration in prosthetic joint infections	[76], [77]
2	Nitric Oxide-Releasing Nanocarriers	Ciprofloxacin	Co-delivery with nitric oxide donors	Biofilm dispersion and increased bacterial susceptibility	[78]
3	Enzyme-Functionalized Nanoparticles	Rifampin	Conjugation with enzymes (e.g., DNase, alginate lyase)	Enhanced biofilm disruption and bacterial killing	[79], [80]
4	Cationic Nanoparticles	-	Electrostatic assembly with positively charged polymers	Improved penetration into biofilms formed by P. aeruginosa and S. aureus	[81]
5	pH-sensitive Liposomes	Antibiotics	Lipid film hydration with pH-responsive polymer coating	Selective drug release in acidic biofilm environments	[82]
6	Silver Nanoparticle Coatings	-	Chemical reduction of silver salts onto medical device surfaces	Preventing biofilm formation on medical devices like catheters and stents	[83]
7	PEGylated Nanoparticles	-	Surface modification with polyethylene glycol (PEG)	Anti-adhesive coating for preventing bacterial adhesion	[84]
8	Gold Nanoparticles for Photothermal Therapy	-	Reduction of gold salts in the presence of reducing agents	Light-activated biofilm eradication in chronic wound models	[85], [86]
9	Magnetic Nanoparticles	-	Coating with magnetic nanoparticles for targeted delivery	Biofilm disruption under magnetic guidance in catheter-associated infections	[87], [88]
10	Hybrid Nanocarriers	Vancomycin & Rifampin	Co-encapsulation in liposomes or polymeric nanoparticles	Dual drug delivery and enhanced biofilm disruption	[89]
11	Nitric Oxide-loaded Liposomes	Ciprofloxacin	Loading of nitric oxide donors into liposomal structures	Biofilm dispersal and increased drug sensitivity	[90]
12	Dendrimers for Antibiotic Delivery	Gentamicin	Synthesis via divergent or convergent methods	Targeted drug delivery and enhanced bacterial killing	[91]
13	Polymeric Nanoparticles	Amoxicillin	Emulsion-solvent evaporation or nanoprecipitation	Targeted therapy for biofilm-related infections	
14	Carbon Nanotubes	-	Functionalization with antimicrobial agents	Biofilm disruption and targeted treatment	[92], [93]
15	Mesoporous Silica Nanoparticles	Doxycycline	Sol-gel or surfactant-assisted synthesis	Controlled drug release for biofilm-associated infections	[94]

16	Chitosan Nanoparticles	Tetracycline	Ionic gelation or spray-drying	Biofilm eradication and enhanced antimicrobial effects	[95], [96]
17	Polyethylenimine (PEI) Nanoparticles	-	Electrostatic assembly and polymer modification	Targeted drug delivery to biofilm-forming bacteria	[97]
18	Liposome-encapsulated Enzymes	-	Lipid film hydration followed by enzyme encapsulation	Enzyme-based biofilm matrix degradation	[98]
19	Zinc Oxide Nanoparticles	-	Sol-gel method or chemical vapor deposition	Antibacterial and biofilm-inhibiting effects	[99]
20	Pheromone-based Nanocarriers	-	Coating with bacterial pheromones	Disruption of bacterial communication and biofilm prevention	[100]
21	Alginate Nanoparticles	-	Cross-linking of alginate with antimicrobial agents	Biofilm penetration and treatment	[101], [102]
22	Poly(lactic-co-glycolic acid) (PLGA) Nanoparticles	-	Solvent evaporation or nanoprecipitation	Drug delivery for biofilm-related infections	[103]
23	Curcumin-loaded Nanoparticles	Curcumin	Solvent evaporation or co-precipitation with surfactants	Anti-biofilm activity and bacterial inhibition	[104]
24	Self-assembled Peptide Nanoparticles	-	Peptide self-assembly in solution	Biofilm penetration and antimicrobial effects	[105]
25	Hydrogels with Antimicrobial Nanoparticles	-	Cross-linking of antimicrobial nanoparticles with hydrogels	Controlled release for biofilm-targeted therapy	[106]

4. Biofilm-Targeted Nanomedicine Strategies Targeting Mechanisms

Biofilm-targeted nanomedicine strategies are designed to deliver therapeutic agents that effectively disrupt, prevent, or penetrate microbial biofilms by leveraging specific targeting mechanisms. These approaches include passive targeting, which exploits the natural characteristics of biofilms, such as their porous EPS matrix and microenvironmental features like acidic pH, hypoxic zones, or oxidative stress gradients. Enhanced Permeability and Retention (EPR) effects and stimuli-responsive systems further improve penetration and drug delivery by responding to biofilm-specific cues such as pH, oxidative stress, or biofilm enzymes [107]. Active targeting employs functionalized nanocarriers that bind directly to biofilm components, such as polysaccharides, proteins, or DNA, while inhibitors of adhesion molecules and quorum sensing disrupt biofilm formation and bacterial communication, respectively. Enzyme-based strategies utilize matrix-degrading enzymes, such as DNase, proteases, or alginate lyase, to degrade the EPS matrix and enhance penetration, while enzyme release can be triggered by biofilm-specific stimuli. Immune modulation strategies focus on reprogramming macrophages to a pro-inflammatory M1 phenotype or delivering immune-stimulating molecules like cytokines to boost the host‘s innate response against biofilms. Additionally, physical or mechanical targeting methods, including the use of magnetic nanoparticles, ultrasound-responsive systems, and light-activated systems, apply external forces to disrupt biofilm structures or enhance drug penetration through mechanisms like sonication, magnetic control, or photodynamic and photothermal effects. Together, these multifaceted strategies provide innovative and effective approaches to addressing biofilm-associated infections [108].

5. Advances In Biofilm-Targeted Nanomedicine: In Vitro And In Vivo Studies

Advances in biofilm-targeted nanomedicine have been validated through in vitro and in vivo studies, showcasing innovative nanocarrier designs and therapeutic strategies for combating biofilm-associated infections. In vitro studies provide a controlled environment to explore interactions between nanomedicines and biofilms. Notable advancements include the design of nanoparticles functionalized with EPS-degrading enzymes, such as DNase or alginate lyase, which significantly reduce

biofilm biomass and enhance bacterial eradication by breaking down the biofilm matrix. Cationic nanoparticles, with their positive charge, interact electrostatically with negatively charged biofilm components, improving penetration into dense biofilms formed by pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus* [107]. Quorum-sensing inhibitor-loaded nanoparticles, such as those carrying furanone derivatives, suppress biofilm maturation and reduce bacterial resistance. Stimuli-responsive systems, such as pH-sensitive liposomes, selectively release antibiotics within acidic biofilm niches, increasing localized activity while minimizing off-target effects. Combination therapies co-loading antibiotics and biofilm-dispersing agents, like nitric oxide donors, exhibit synergistic effects by disrupting biofilms and killing bacteria in multi-species biofilm models. In vivo studies further assess the efficacy, safety, and pharmacokinetics of these nanomedicines [109]. For instance, silver nanoparticles embedded in hydrogel coatings for orthopedic implants prevent biofilm formation and promote wound healing in rodent models. Lipid-based nanoparticles delivering vancomycin target biofilms in prosthetic joint infections, achieving higher antibiotic concentrations at infection sites and reducing biofilm burden in rabbit osteomyelitis models. Photothermal and photodynamic therapies, such as gold nanoparticles activated by light, demonstrate localized bacterial eradication with minimal tissue damage in mouse chronic wound models. Immune-modulating nanocarriers carrying cytokines enhance macrophage recruitment and biofilm clearance in murine cystic fibrosis lung infection models. Multifunctional systems, like magnetic nanoparticles for biofilm disruption coupled with antibiotic delivery, effectively remove biofilms under magnetic guidance and reduce bacterial loads in catheter-associated infections in rat models. These advancements underscore the transformative potential of nanomedicine in addressing complex biofilm-associated infections [110].

6. Synergistic Approaches

Synergistic approaches in biofilm-targeted nanomedicine involve combining nanomedicine with traditional antibiotics and employing strategies to prevent biofilm formation. By leveraging synergistic effects, nanocarriers improve antibiotic delivery, enhance penetration into biofilms, and reduce the required drug doses, thereby overcoming resistance. Co-delivery systems disrupt biofilm structures and bacterial defenses, increasing antibiotic efficacy against resistant strains. Examples include lipid-based nanoparticles delivering vancomycin for deep biofilm penetration in prosthetic joint infections, nitric oxide-releasing nanocarriers combined with ciprofloxacin to disperse biofilms and increase bacterial susceptibility, and enzyme-functionalized gold nanoparticles paired with rifampin, which enhance biofilm disruption and bacterial killing [111]. Prevention strategies focus on coating medical devices with nanoparticles, such as silver nanoparticles that release antimicrobial agents to prevent biofilm formation on catheters, stents, and implants, and zinc oxide or copper nanoparticles that offer additional antibacterial properties. Anti-adhesive and anti-quorum sensing strategies further combat biofilm formation, with PEGylated and hydrophilic coatings preventing bacterial adhesion, the initial step in biofilm development, and nanocarriers delivering quorum-sensing inhibitors like furanones or autoinducer analogs to block bacterial communication and biofilm maturation. These synergistic approaches offer powerful solutions to mitigate biofilm-associated infections and enhance treatment outcomes [112].

7. Future Perspectives and Directions in Biofilm-Targeted Nanomedicine

The future of biofilm-targeted nanomedicine holds promising advancements, with emerging trends and innovative approaches poised to revolutionize the treatment of biofilm-associated infections. One key area of progress is the development of biofilm-responsive nanocarriers designed for selective drug release in specific biofilm microenvironments, such as those that are acidic or rich in enzymes. The incorporation of advanced stimuli-responsive systems, such as light, ultrasound, or magnetic fields, is also gaining attention for their potential to enhance biofilm disruption and targeted therapy. Additionally, the creation of multi-functional and hybrid nanoparticles is gaining momentum, with combinations of antimicrobial agents, biofilm-dispersing enzymes, and immune modulators integrated into a single nanocarrier. Hybrid systems, such as liposome-gold nanostructures, offer enhanced efficacy by combining the advantages of organic and inorganic materials [110].

Another exciting direction is the application of personalized medicine in biofilm therapies, where precision nanomedicine can be tailored to specific infections, pathogens, and patient profiles. This includes the use of customizable nanoparticles optimized for individual patients, with the integration

of AI and machine learning to improve nanocarrier design and treatment outcomes. However, several translational challenges remain, including regulatory hurdles for nanomedicine approval, scalability, and cost-effectiveness while maintaining high-quality standards. On the other hand, opportunities abound in the form of advancements in nanomanufacturing technologies, the potential for multidisciplinary collaborations among researchers, clinicians, and industry, and increasing funding and regulatory support for biofilm-targeted therapies. As these innovations continue to unfold, collaborative efforts are essential to overcome existing barriers and translate these advancements into clinical applications, ultimately enhancing the effectiveness of nanomedicine in combating biofilm-associated infections [113].

Conclusion

Biofilm-targeted nanomedicine holds transformative potential to revolutionize antimicrobial therapies. By leveraging advanced nanotechnology, these strategies offer enhanced penetration, targeted delivery, and effective disruption of resilient biofilm structures that are often impervious to conventional treatments. The integration of multifunctional and hybrid nanoparticles, along with personalized medicine approaches, underscores the versatility and efficacy of nanomedicine in combating biofilm-associated infections. However, realizing this potential necessitates sustained research efforts and robust multidisciplinary collaboration. Bridging the gaps between nanotechnology, microbiology, clinical medicine, and regulatory science is crucial to address existing challenges such as toxicity, scalability, and regulatory approval. Continued innovation, coupled with collaborative endeavors, will drive the development of safe, effective, and accessible nanomedicine-based therapies. Ultimately, the advancement of biofilm-targeted nanomedicine promises not only to enhance current antimicrobial strategies but also to pave the way for novel treatments that can effectively manage and prevent persistent and chronic infections, thereby significantly impacting global health outcomes.

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Author Contributions

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The authors declare that there is no conflict of interest.

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