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Review

Advances in Nanotechnology for Biofilm Inhibition

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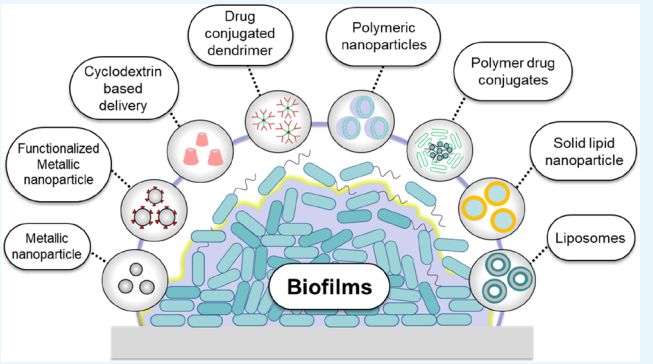
ABSTRACT: Biofilm-associated infections have emerged as a significant public health challenge due to their persistent nature and increased resistance to conventional treatment methods. The indiscriminate usage of antibiotics has made us susceptible to a range of multidrug-resistant pathogens. These pathogens show reduced susceptibility to antibiotics and increased intracellular survival. However, current methods for treating biofilms, such as smart materials and targeted drug delivery systems, have not been found effective in preventing biofilm formation. To address this challenge, nanotechnology has provided innovative solutions for preventing and treating biofilm formation by clinically relevant pathogens. Recent advances in nanotechnological strategies, including metallic nanoparticles, functionalized metallic nanoparticles, dendrimers, polymeric nanoparticles, cyclodextrin-based delivery, solid lipid nanoparticles, polymer drug conjugates, and liposomes, may provide valuable technological solutions against infectious diseases. Therefore, it is imperative to conduct a comprehensive review to summarize the recent advancements and limitations of advanced nanotechnologies. The present Review encompasses a summary of infectious agents, the mechanisms that lead to biofilm formation, and the impact of pathogens on human health. In a nutshell, this Review offers a comprehensive survey of the advanced nanotechnological solutions for managing infections. A detailed presentation has been made as to how these strategies may improve biofilm control and prevent infections. The key objective of this Review is to summarize the mechanisms, applications, and prospects of advanced nanotechnologies to provide a better understanding of their impact on biofilm formation by clinically relevant pathogens.



1. INTRODUCTION

Biofilms are complex, structurally organized microbial colonies that develop on biotic and abiotic surfaces.[1−3] The presence of extracellular polymeric substances (EPS) often protects biofilms from the hostile environmental conditions.[4,5] EPS provide protection to biofilms against food limitation,[6] antibiotic therapy,[7] and immunological responses from the host.[4] Due to their diverse genetic and phenotypic traits, biofilm cells are more resilient to destructive conditions than nonbiofilm cells or planktonic cells.[8] Moreover, the capacity of bacteria to attach to inert material, polymers, and medical devices results in the formation of mature biofilms. Biofilm formation is considered as a significant risk factor for persistent infections, especially in implant recipients.[9] The high mortality rates associated with hospital-acquired infections caused by biofilms are a worldwide public health problem.[10] Therefore, the development of materials or technologies that prevent bacterial attachment and biofilm formation is urgently needed.

Biomedical applications that have been widely employed include nanotechnology and nanomaterials, as they offer multiple advantages such as size, physicochemical characteristics, and potential to provide a maximum area−volume ratio.[11−14] Numerous review articles provide a comprehensive overview of various aspects of nanotechnology-based antibiofilm strategies. Wu et al. (2023) have reviewed latest nanotechnology-based approaches for impeding the growth cycle of biofilms.[15] The authors discussed the current nanotechnological approaches that cause interference with the bacterial biofilm formation at different stages and emphasized the significance of regulating the biofilm microenvironment. Further, a comprehensive review by Mohamad et al. (2023) discusses the connection between biofilm formation and antimicrobial resistance and also explores novel methods for combating biofilms, such as CRISPR-Cas gene editing, natural compounds, phages, and nanomediated techniques.[16] The focus of the review by Wang et al. 2023 was to provide information on enhancing the delivery of drugs to develop

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improved treatment strategies for biofilms. A number of physicochemical methods have been summarized, including charge reversal, chemical shields, and dual-corona-enhanced delivery strategies as well as electricity-, magnetism-, ultrasound-, and shock wave-based delivery of drugs.[17] In addition, an update written by Brar et al. (2023) has summarized the applications of nanotechnology-based therapeutics for developing novel antimicrobial drugs.[18] It covers recent developments regarding the purpose of silver, zinc, gold, and oxide nanoparticles (NPs) and their efficacy against multidrug-resistant bacteria. The review also highlights the potential of nanophotothermal therapy using fullerene- and antibody-functionalized nanostructures as promising strategies.[18] While several reviews have provided a comprehensive overview of nanotechnology-based anti-biofilm strategies, our Review specifically focuses on the anti-biofilm and antimicrobial activities of a range of NPs and nanomaterials, including those composed of metals, metal oxides, nanopolymers, metal-containing polymers, liposomes, and peptide nanomaterials. We also highlight recent advancements in the field, including new strategies such as CRISPR-Cas gene editing, natural compounds, phages, and advanced nanotechnological therapeutic modalities, including photothermal therapy, photodynamic therapy, chemodynamic therapy, sonodynamic therapy, and immunotherapy.

Nanomedicine is an emerging field of nanotechnology that involves a large assortment of health-related applications of nanotechnology. The synthesis of antimicrobial NPs is seen as a promising strategy for developing novel biofilm-controlling agents. In the present Review, we have surveyed the anti-biofilm activity and antimicrobial activities of NPs and nanomaterials composed of metals (silver, zinc, iron, copper, titanium, gold, and magnesium), metal oxides, nanopolymers, metal-containing polymers, liposomes, and peptide nanomaterials. In addition, there are reports that antibiotic efficacy has been enhanced using nanomaterials in combination with antibiotics for biofilm eradication. In the further sections, an attempt has been made to cover the range of recent nanotechnological advancements regarding biofilm inhibition. The objective of this Review is to examine the new antibacterial therapies that have received limited attention with regard to anti-biofilm activity and provide a summary of recent advances, emphasizing the associated challenges and potential outcomes of these technologies.

2. BIOFILM-FORMING PATHOGENS AND THEIR SIGNIFICANCE

The ESKAPE group (Figure 1) is a collection of six genera that are responsible for a range of nosocomial infections.[19] These organisms include both Gram-positive and Gram-negative bacteria. The Gram-positive group includes major nosocomial pathogens, including *Enterococcus faecium* and *Staphylococcus aureus*. *E. faecium* is a major human infectious bacteria that can cause biofilm-associated complications in patients with medical devices.[20] It has an ability to cause major infections of the bloodstream, surgical sites, urinary tract, and central nervous system. Further, *S. aureus*, another major opportunistic Gram-positive bacterium, causes persistent biofilm-associated infections in hospitalized patients.[21] The Gram-negative group of ESKAPE pathogens includes *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. *K. pneumoniae* is capable of forming complex biofilms on a variety of surfaces such as medical devices (catheters) and host

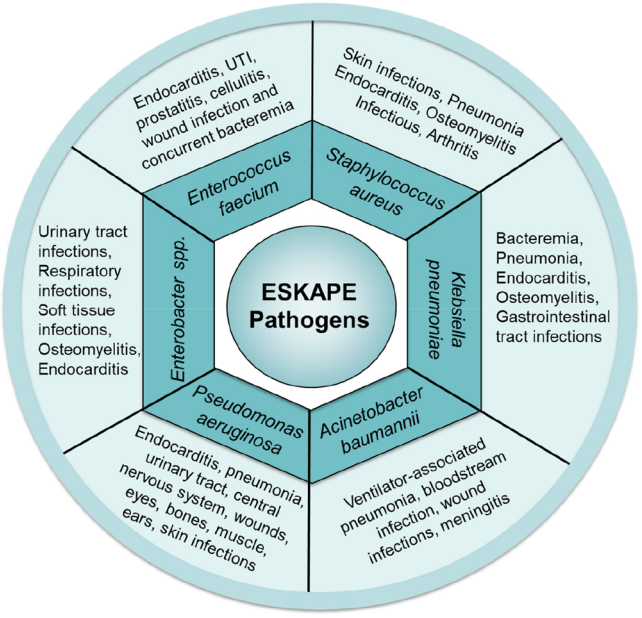

Figure 1. The ESKAPE pathogen consortium. Biofilm-associated infections caused by ESKAPE pathogens.

tissues, including gastrointestinal mucosa, the respiratory tract, and the urinary tract.[22] *A. baumannii* is an opportunistic pathogen[23] known for its ability to form complex biofilms, which play a critical role in its pathogenesis.[24] Similarly, *P. aeruginosa* is involved in chronic infections in cystic fibrosis patients.[25] *P. aeruginosa* is a well-established biofilm-forming pathogen that provides a protective environment for bacteria against host defenses and antimicrobial agents.[26] *Enterobacter* spp. is a Gram-negative bacteria usually observed in the natural environment. This bacteria can cause infections in humans, particularly in hospital settings.[27] It can lead to serious infections, including septicaemia, urinary tract infections, postsurgical peritonitis, and pneumonia.[28] Biofilms allow *Enterobacter* spp. to adhere to surfaces, resist host defenses, and tolerate antimicrobial agents.

ESKAPE pathogens have a well-established ability to form biofilms, which are protected by EPS that make the cells resistant to antimicrobial treatments, even at high concentrations.[29] The rise of MDR bacterial strains has created a significant therapeutic challenge for modern therapies, and innovative treatment techniques are urgently needed.[30] Ongoing research is focusing on the development of novel compounds that can work in conjunction with antibiotics to combat infections.[31,32] To prevent and eradicate clinically important infections, advanced strategies or innovative approaches are required, especially at the nanoscale. Overall, an understanding of the ways in which biofilms promote infection and antibiotic resistance is essential for developing effective approaches to treat infections caused by nosocomial pathogens. In the next section, the emphasis is on the molecular mechanisms associated with biofilm formation by these pathogens.

The effects conferred by biofilm formation in these bacteria are diverse, including providing protection against environmental stress, facilitation of nutrient uptake, and increased virulence. Specifically, bacteria that form biofilms exhibit more efficient nutrient and genetic material exchange, enabling them to rapidly acclimate to dynamic environmental conditions. The

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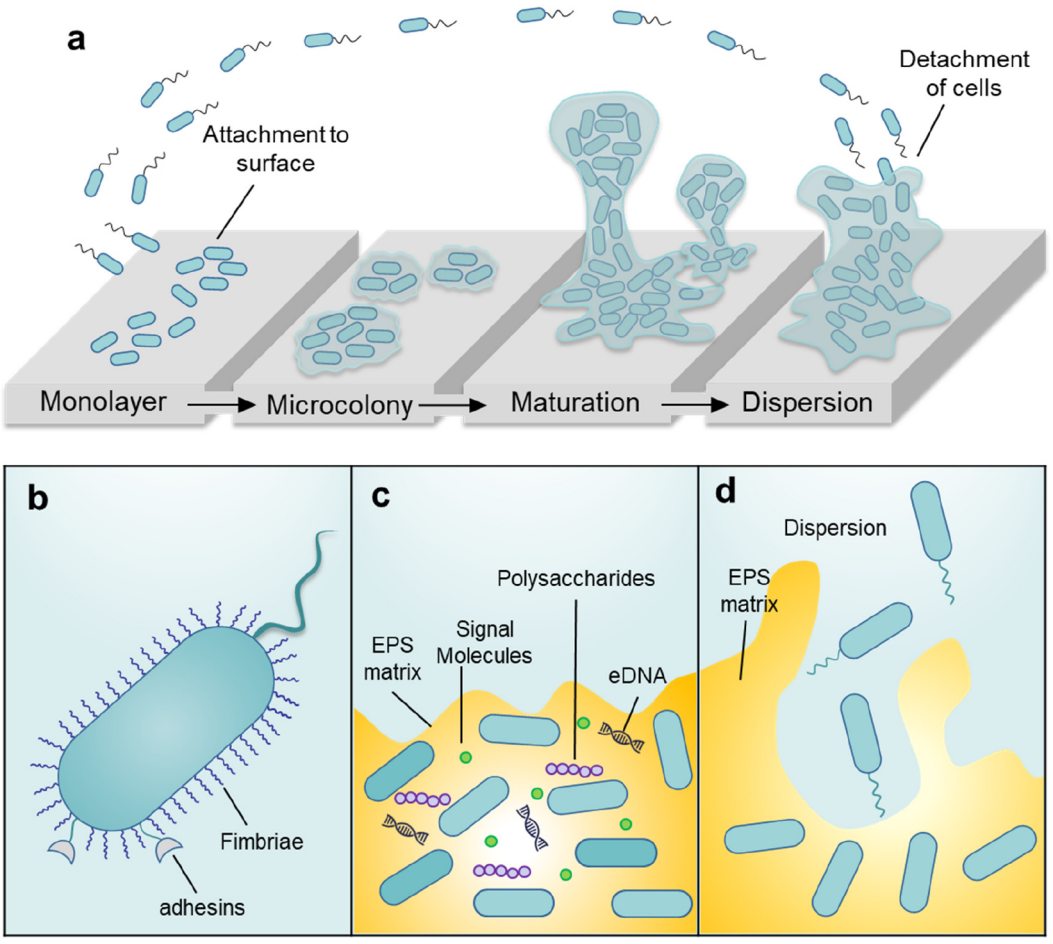

Figure 2. Biofilm formation stages and mechanism. (a) Biofilm formation stages. (b) Adhesins and fimbriae in cell attachment. (c) Role of EPS, eDNA, and polysaccharides in mature biofilms. (d) Process of dispersion in biofilms to expand the area of biofilms.

EPS matrix of biofilms additionally affords a physical defense against stressors such as antibiotics, immune cells, and other antagonistic factors, thereby promoting bacterial persistence and growth in hostile environments. Furthermore, the proximity of biofilm-associated bacteria fosters genetic material exchange, including virulence factors and antibiotic resistance genes, leading to the emergence of highly virulent and antibiotic-resistant strains. Comprehension of the molecular mechanisms governing biofilm formation and persistence is, therefore, imperative for developing innovative strategies to mitigate biofilm-associated infections. This necessitates the identification of key genes and regulatory pathways involved in biofilm formation, as well as the discovery of novel antimicrobial agents that can effectively target biofilm-associated bacteria.

3. BIOFILMS: FUNDAMENTAL PERSPECTIVE

Biofilms are complex communities of microorganisms that form on surfaces and are held together by an EPS matrix composed of polysaccharides, proteins, and nucleic acids. The matrix creates a protective environment that shields the bacteria from environmental stressors, including antibiotics and the host immune system. Biofilms exhibit distinct characteristics compared to free-living planktonic bacteria, such as increased resistance to antimicrobials, decreased growth rate, and altered gene expression patterns. The formation and maintenance of biofilms involve several stages, including attachment, microcolony formation, maturation, and detachment. During these stages, the bacteria undergo significant changes in gene expression and phenotype, resulting in a highly organized and adaptive structure. Biofilms are ubiquitous in nature and are associated with various infections, including chronic wounds, dental caries, and medical device-related infections. Understanding the fundamental microbiology of biofilms is critical in developing effective strategies to prevent and treat these infections, as biofilms pose a significant challenge to traditional antimicrobial therapies.

3.1. Biofilm Stages and Molecular Mechanism.

Bacterial biofilms are dynamic clusters of bacterial cells that are coalesced together by a self-produced EPS matrix.[33] Fungal biofilms have a high degree of similarity to bacterial biofilms in terms of their development, formation, and growth. In this Review, our primary focus is directed toward bacterial biofilms. The intricacy of the molecular processes governing the formation of biofilms necessitates the involvement of multiple factors. The environmental stimuli and phenotypic factors are crucial in the progression of biofilm formation.[34]

Biofilm formation is an ongoing process that has been subcategorized into multiple interconnected stages (Figure 2).[35] The initial stage encompasses reversible attachment of the cell to biotic and abiotic surfaces, during which cells detach from the surface and relocate.[36] This stage is distinguished by the absorption of macromolecules and the creation of a conditioning layer. The second stage involves the irreversible

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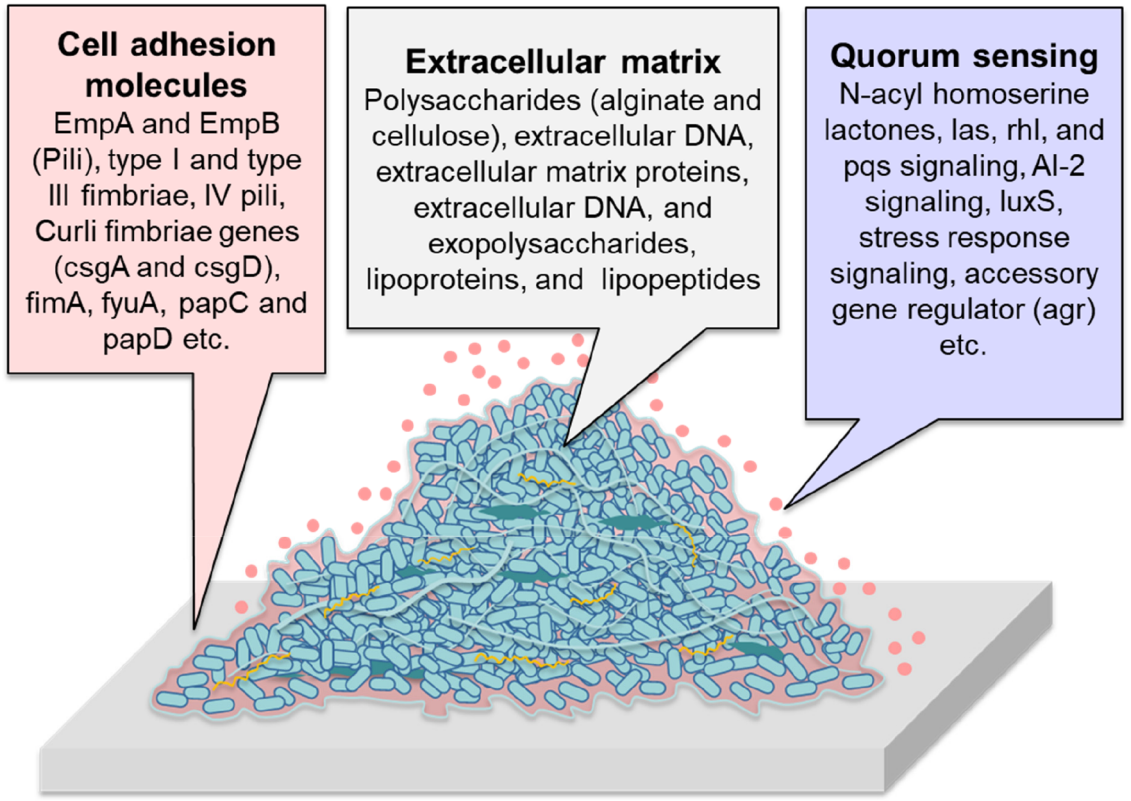

Figure 3. Major contributing factors for biofilm formation in bacteria.

phase, characterized by permanent attachment of the cell to the surface. During this stage, cells lose the ability to detach from the surface and become committed to biofilm development. Adherence of cells is further consolidated through the occurrence of robust chemical interactions and the exudation of a polysaccharide slime matrix, which fosters the accumulation of cellular detritus.[37] The third stage comprises microcolony formation, wherein microcolonies, small assemblages of cells, serve as the basis for more complex biofilm structures.[38] Owing to the nutrient-rich environmental conditions, cells demonstrate expeditious growth efficiency, culminating in biofilm formation and the construction of an intricate biofilm structure. The fourth stage is biofilm maturation; at this stage, microcolonies develop into larger-sized colonies and three-dimensional development begins; as the biofilm thickness increases, so does antibiotic resistance in the biofilms. The key reason is the failure of the antibiotics to enter into the biofilm to kill the target cells.[39] At this stage, the biofilm is resistant to antibiotic treatment, and a high dose of antibiotics may be required to treat the biofilm. The inhibition of biofilm penetration by antibiotics via EPS is caused by the binding of antimicrobial agents to EPS components, including proteins, DNA, and polysaccharides, resulting in a reduction in the effective antibiotic concentration in the biofilm matrix and the establishment of a diffusion barrier.[40] The final stage in biofilm formation is dissemination, during which cells detach from the biofilm and relocate to other sites to establish new biofilms.[39] Biofilms are characterized by a high degree of flux, with cells constantly detaching from the main biofilm structure either actively or passively and disseminating into the surrounding environment to colonize new areas. These detached cells can move in various configurations, including large cellular clusters, small groups, or as individual cells. By colonizing new areas and establishing fresh bacterial colonies, these cells facilitate the establishment of new sessile populations. The importance of cell adhesion molecules, the EPS matrix, and cell signaling in bacterial biofilms is summarized in Figure 3.

3.2. Cell Adhesion Molecules. Bacterial cells adhere to surfaces (both biotic and abiotic), leading to the production of a complex, three-dimensional biofilm.[41] Bacterial fimbriae, pili, and related adhesin factors are crucial for bacterial attachment to various surfaces, including host cells and medical devices. Fimbriae are hair-like structures composed of protein subunits that protrude from the bacterial cell surface and act as adhesion molecules.[42] Adhesin proteins, located on the bacterial cell surface, bind to specific molecules such as carbohydrates or proteins on the host cell surface. Bacterial attachment is a critical step in the pathogenesis of infection, enabling bacteria to evade immune cells, avoid being washed away by bodily fluids, and establish an infection. In addition, bacterial pili play a role in biofilm formation and disease progression of *E. faecium*.[43] Nielsen et al. (2013) showed that the sortase associated with the pilus plays an essential role in forming the pilus fiber by creating covalent isopeptide bonds between the pilin-like motif and the sortase recognition motif.[43] Research has revealed that the pilus subunits EmpA and EmpB are involved in biofilm establishment and adherence to extracellular matrix proteins. However, EmpC does not contribute to these processes. Nonetheless, it is noteworthy that all Emp pilins are essential for *E. faecium* to initiate urinary tract infections.[44,45] Two main classes of fimbriae in *K. pneumoniae* (type I and type III) are involved in adhesion, biofilm formation, and tissue invasion.[46] The *K. pneumoniae* genome contains multiple clusters of genes for chaperones and adhesin proteins for the assembly of fimbriae (*fim, ecp, mrk, kpa*, and

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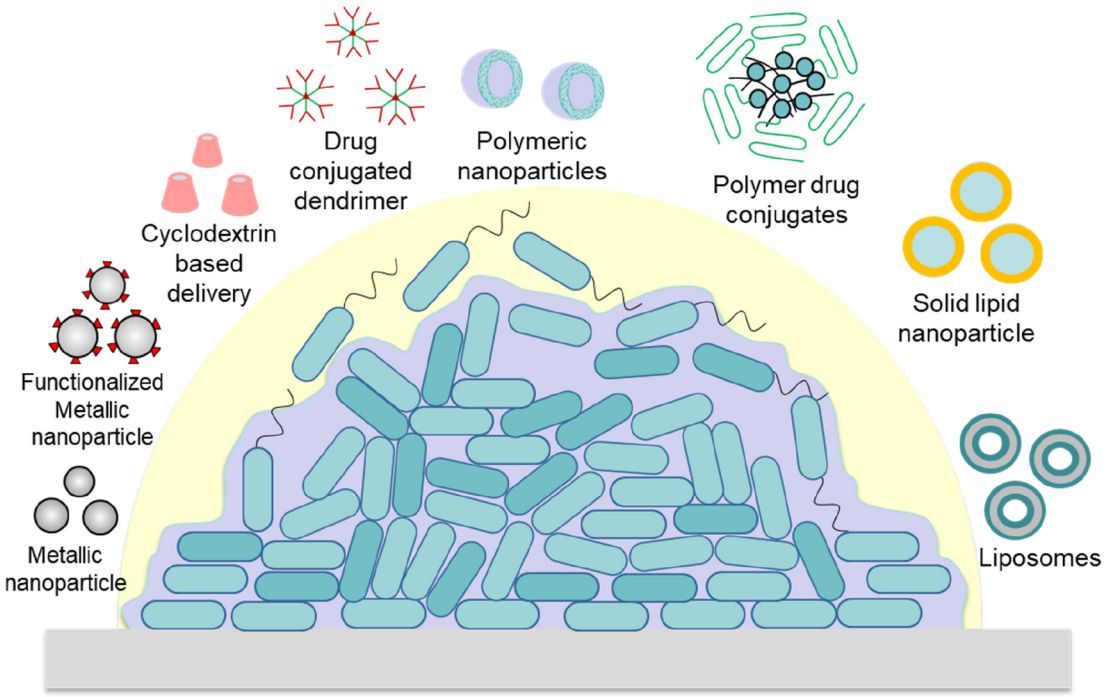

Figure 4. Advanced nanotechnological strategies to control microbial biofilms.

kpg gene clusters).[22] Biofilm formation also contributes to the persistence of *A. baumannii* in the hospital environment,[47,48] increasing the risk of cross-contamination and reinfection. Adhesion proteins help *A. baumannii* and *P. aeruginosa* cells attach to surfaces[49] and initiate biofilm formation, which includes fimbriae and type IV pili.[50−52] Moreover, studies have shown the role of curli fimbriae genes (*csgA* and *csgD*) in the biofilm formation of *Enterobacter* isolates.[53] A number of virulence-associated genes have been identified that play a key role in virulence and biofilm formation, including *fimA* (type 1 fimbriae gene),[54] *fyuA*,[55] and p pili genes (*papC* and *papD*).[54] Bacterial cell attachment with fimbriae, pili, and adhesin molecules is a crucial phase in the development of infections and biofilm formation that helps to avoid host immune responses.

3.3. Extracellular Polymeric Substances (EPS). Bacteria have the capability of forming a multilayer biofilm with an extracellular slime layer that has a complex chemical diversity.[56] The biofilm EPS matrix[57,58] is a complex network of polysaccharides and proteins.[59] Further, the extracellular DNA (eDNA) in the biofilm matrix provides structure and stability to the biofilms. In *A. baumannii,* the EPS is comprised of polysaccharides, such as alginate and cellulose, and proteins, such as pilin and exopolysaccharides.[40] Biofilm formation in *P. aeruginosa* is highly regulated and a complex process that involves multiple molecular interactions.[60] It typically begins with the attachment of individual *P. aeruginosa* cells, followed by the microcolony formation and the EPS matrix synthesis.[61] The EPS matrix is composed of polysaccharides, such as alginate, and proteins, such as extracellular DNA and exopolysaccharides.[62] According to a number of studies, polysaccharide intercellular antigen (PIA) is responsible for biofilm development, though there is additional evidence that *S. aureus* can form biofilms irrespective of PIA.[63] The *K. pneumoniae* biofilm matrix consists of proteins, DNA, exopolysaccharides, and lipopeptides.[64] Biofilm-mediated growth helps bacteria to evade the attack of immune cells and antimicrobial agents.[65] Further, research has demonstrated that eDNA (extracellular DNA) regulates biofilm development in *S. aureus*.[66,67] The eDNA is responsible for the strengthening of *S. aureus* biofilms, and DNase treatment has been shown to improve the antibiotic susceptibility of biofilms.[68]

In addition to the above-mentioned factors, the polysaccharide capsule may play a key protective role for the bacterium and be responsible for inhibiting complement deposition and evading phagocytosis and opsonization.[69] The comparative genomics and genome sequencing applications revealed 134 distinct capsule synthesis loci, also known as K-loci, in *K. pneumoniae*.[70] Notably, strains with defects in the capsule architecture have been shown to display impaired biofilm formation.[71] Encapsulation has a significant impact on biofilm formation and the survival of bacteria under harsh environmental conditions. A recent study showed that without the capsule bacteria formed stronger biofilms, which may be due to an increase in the hydrophobic nature of their surfaces.[72] In contrast, encapsulated *A. baumannii* bacteria were slightly more resistant to drying out but not to disinfectants. Apart from physical conditions, environmental factors such as light and temperature-dependent sensing also play a key role in biofilm formation. Recent research showed that light plays a crucial role in *A. baumannii* biofilm regulation. Light illumination and variable-temperature conditions can influence biofilm formation. BlsA is a protein involved in regulating bacterial behavior under different light sources.[73] Some *A. baumannii* strains lack BlsA, while light induction of blsA and BipA was observed. BlsA and BipA are required for the light-dependent expression of OmpA, a crucial factor in membrane integrity. A recent study investigated the use of riboflavin- and chlorophyllin-based photodynamic therapy as a potential treatment or prevention against *A. baumannii* biofilms.[74] The efficacy of the therapy was compared to that

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of light alone, and the role of photosensitizer type was also demonstrated.

3.4. Quorum Sensing Signaling. Quorum sensing is involved in bacteria communication, and using this system bacteria coordinate their population-wide behavior.[75] The regulation of biofilm formation and virulence in *P. aeruginosa* is governed by quorum sensing. In *P. aeruginosa*, quorum sensing molecules, such as *N*-acyl homoserine lactones,[76] are involved in the activation of virulence factors and biofilm establishment. Additionally, in *A. baumannii,* quorum sensing molecules are also involved in the regulation of biofilm formation and the activation of virulence factors.[77] *A. baumannii* can survive in challenging environments, such as those found in hospitals, due to its ability to activate stress response signaling pathways.[78] These pathways are activated in response to environmental stressors, such as antibiotics and host defenses, and help the bacteria to adapt to these conditions. Some of the stress response proteins involved in biofilm formation include the Hfq protein,[79] the oxidative stress response regulator, and the two-component regulatory system.[78] The *S. aureus* accessory gene regulator (agr) quorum-sensing system (accessory gene regulator) controls infection process, virulence, and biofilm formation.[80] It has also been shown that the staphylococcal accessory regulator (sarA)[81] and agr[82] play a crucial function in regulating gene expression to promote biofilm formation and dispersal. Another way in which *S. aureus* communicates is using autoinducing peptides (AIPs).[83] These small signaling molecules are endogenously synthesized and subsequently secreted into the extracellular environment. AIPs play a pivotal role in the coordination of gene expression in response to changes in bacterial population density.[83] This phenomenon is critical to the regulation of a diverse array of bacterial processes, including virulence, antibiotic resistance, and biofilm formation.[83,84] *K. pneumoniae* has demonstrated the presence of a homologue of *luxS*,[85] which is associated with AI-2 quorum sensing signaling pathways of *Vibrio harveyi*. Studies have also indicated that the formation of biofilms in *K. pneumoniae* is linked to the AI-2 quorum sensing.[86] Understanding these mechanisms and molecular regulators can lead to the development of new strategies to target biofilm formation and infection progression.[87]

4. NANOTECHNOLOGICAL APPROACHES FOR BIOFILM CONTROL

Advanced nanotechnology-based tools offer numerous advantages for biofilm inhibition. Nanomaterials, including NPs, have been utilized to enhance bioavailability, selectivity, and stability and reduce the toxicity of active compounds. Additionally, nanocarrier-based drug delivery offers targeted delivery and enhanced efficacy. In this section, we discuss recent advances (Figure 4 and Table.1) and the molecular mechanism of nanotechnology for biofilm control (Figure 5).

4.1. Metal and Metal Oxide Nanoparticles. Metal NPs (MNPs) consist of pure metals, metal salts, or metal oxides and vary in size from 10 to 100 nm.[88] Compared to other nanomaterials, MNPs have a high surface-to-volume ratio. They are characterized by their excellent optical characteristics[89] and substantial electric field enhancement, enabling their prospective use in bioimaging, sensors, and therapies.[90] Metal NPs have emerged as promising candidates for controlling biofilms due to their physicochemical properties.[91,92] Several studies have reported the anti-biofilm activity of metal NPs against a wide range of bacterial pathogens.[93] Silver, gold, zinc, copper, and iron NPs have been extensively investigated for their anti-biofilm potential.[94] The anti-biofilm effect of metal NPs is linked with penetration of the bacterial cell membrane/wall, disruption of the quorum sensing mechanism,[95] and interference with the EPS matrix of the biofilm.[96] The activity of reactive oxygen species on these particles is known to induce membrane damage in the target pathogen.[97] ROS-mediated oxidative stress causes the production of hydroxyl radicals, superoxide radicals, and hydrogen peroxide radicals, which induce damage to the DNA and proteins of bacteria.

Silver, gold, and zinc NPs have been widely employed as effective antibacterial agents against a variety of bacterial pathogens. Histidine-functionalized silver NPs have been used to inhibit *K. pneumoniae* biofilms and showed marked effects.[98] Singh et al. (2020) prepared AgNPs using *Solibacillus isronensis* sp. and proved the potent anti-biofilm activity against a wide range of bacteria, including *Escherichia coli*, *P. aeruginosa*, *Staphylococcus epidermidis*, and *S. aureus.*[99] Goda et al. (2022) synthesized AgNPs using pomegranate extract and showed their potent anti-biofilm activity against a range of Gram-positive (*S. epidermidis* and *S. aureus*) and Gram-negative bacteria (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *P. mirabilis*).[100] The AgNPs were immobilized on catheters and showed high activity against Gram-positive bacteria as compared to Gram-negative bacteria. The antimicrobial activity lasted for 72 h, suggesting their potential use as a prospective catheter coating to prevent biofilm formation. Further, research by Mostafa et al. (2022) also showed that chitosan-silver NPs and chitosan-gold NPs conjugates have promising broad-spectrum anti-biofilm activity against *Bacillus subtilis*, *P. aeruginosa*, *S. aureus*, and *E. coli.*[101] Silver NPs combined with a dopamine and an α-amylase coating showed the reduction of *S. aureus* biofilms on titanium surfaces.[102] AgNPs showed higher activity as compared to AuNPs. Rugaie et al. (2022) have used one-step coating AgNPs stabilized with polymeric materials (polyvinylpyrrolidone (PVP) and ethyl cellulose (EC)) and showed significant biofilm inhibition of clinical isolates on *E. coli* on urinary catheters.[103] AgNPs-PVP showed significantly higher inhibition as compared to AgNPs-EC. An interesting finding showed that the gold NPs (AuNS10 and AuNS100) can inhibit biofilm formation by *V. cholerae* (biotypes VcO395, VcN16961) in the small intestine of animals.[104] In this study, large NPs showed higher efficacy as compared to small NPs against *V. cholerae* biotypes. The gold NPs have shown significantly higher efficacy in removing the biofilm and reducing the viability of the *Staphylococcus aureus* biofilm.[105] Furthermore, studies have demonstrated the effectiveness of NPs against human fungal pathogens. The oxidation of AgNPs may occur upon exposure to oxygen in environmental and biological systems, which lead to the slow dissolution of metal ions.[106] Consequently, the toxicity AgNPs is predominantly attributed to the cytotoxic effects of Ag^+ ions on bacterial cell metabolism.

Joshi et al. (2022) have shown that the lignin-based Zn oxide NPs, including lignin−ZnO (L-ZnO), fragments of lignin−ZnO (FL-ZnO), and oxidized fragmented lignin−ZnO (OFZ-ZnO) NPs show potent anti-biofilm efficacy against *Candida albicans* biofilms. The study also showed that the ZnO targets the expression of *phr1*, *phr2*, *als3*, *als4*, *efg1*, *hwp1*, and *ras1* genes, leading to suppression of virulence factor expression.[107] The anti-biofilm capability of NPs containing

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Table 1. Recent Technological Advancements for Biofilm Inhibition by Clinically Relevant Pathogenic Organisms

nanotechnology and polymeric nanocomplexes	nanomaterial description	test surface	target organisms	size and shape	anti-biofilm efficacy	ref
metal and metal oxide NPs	AgNPs (using pomegranate extract)	AgNP-coated catheters	*S. epidermidis*, *S. aureus*, *P. aeruginosa*, *E. coli*, *P. mirabilis*, and *K. pneumoniae*	15−25 nm/spherical, elongated, mixed shapes	biofilm inhibitory effect on coated catheters (lasted for 72 h)	100
	chitosan−silver NPs and chitosan−gold NP conjugates	polystyrene plates	*P. aeruginosa*, *E. coli*, *B. subtilis*, and *S. aureus*.	AgNPs and AuNPs with sizes of : 4.5 ± 20−50.2 ± 74 and 3.47 ± 2−35.50 ± 2 nm, respectively/sphere-like	chitosan−silver NP demonstrated anti-biofilm action, chitosan−gold NP conjugates demonstrated mild anti-biofilm activity	101
	AgNPs-EC and AgNPs-PVP	urinary catheter	clinical isolate of *E. coli*	silver NPs-PVP, silver NPs-EC, and silver NPs-PEG with sizes of 163.0 ± 0.9, 122.23 ± 17.61, and 79.7 ± 8.75 nm, respectively/spherical	silver NPs-PVP impeded biofilm formation to 58.2% and 50.8%	103
	zinc oxide NPs (FL-ZnO, OFL-ZnO, and L-ZnO)	*In vitro* and *in vivo* studies	*C. albicans*	40 nm/hexagonal wurtzite structure	biofilm inhibition (more than 90% by FL-ZnO NPs)	107
	gold NPs (AuNS10 and AuNS100)	small intestinal sections of VcO395-infected mice	*V. cholerae* biotypes: classical (VcO395) and El Tor (VcN16961)	AuNS10 (10 nm) and AuNS100 (100 nm)/spherical and rod shaped	AuNS100 demonstrated high anti-biofilm efficacy for both biotypes; no effect was observed by AuNS10	104
	silver NPs from *Solibacillus isronensis* sp.	polystyrene plates	*E. coli*, *S. aureus*, *P. aeruginosa*, and *S. epidermidis*	80−120 nm/quasi-spherical shape	broad-spectrum anti-biofilm activities	99
	self-assembled azithromycin/rhamnolipid NPs	polystyrene plates	*P. aeruginosa*	121 nm/negatively charged on the surface	ability remove the polysaccharides and proteins with potent biofilm destruction	108
	silver NPs in combination with biofilm-lysing enzyme (α-amylase) and dopamine	titanium substrates	*S. aureus* biofilm	nanoparticles (20−50 nm) and nanoaggregates (80−100 nm)	*S. aureus* growth was significantly inhibited by Ag/PDA coatings	102
	gold NPs	polyethylene surface	*S. aureus* biofilm	gold NPs (0.8 and 1.4 nm as core diameters)	4:1 live/dead cells in the biofilm	105
	Zn NPs with floral extract of *Clitoria ternatea*		*Porphyromonsas gingivalis* and *Alcaligenes faecalis*	10 nm/spherical	bacterial viability was reduced by 87.89% with NP treatment	109
functionalized nanoparticles	poly-L-lysine (HBPL)-modified manganese dioxide (MnO2) nanozymes/poly(PEGMA-*co*-GMA-*co*-AAm)	*in vitro* and *in vivo* studies	*P. aeruginosa*, methicillin resistant *S. aureus* (MRSA), and *E. coli*	nanosheet (1−100 nm)	broad-spectrum anti-biofilm and antimicrobial activity	122
	quercetin (QUE) as a stable amorphous NP complex (nanoplex)	polystyrene plates	*P. aeruginosa* PAO1	roughly 150−400 nm/elongated shape	inhibition of motility and biofilm formation at 10 and 50 μg/mL were found to be 77 ± 6% and 65 ± 7%, respectively(comparable to native QUE)	119
	α-mangostin (AMG)-loaded NPs (nanoAMG)	polystyrene plates	methicillin-resistant *S. aureus* strain MRSA252	10−50 nm/shape not mentioned	biofilm inhibition by free AMG (40−44%), AMG with 24 μmol/L compound inhibits biofilm (53−62%)	120
	amphotericin B-loaded trimethyl chitosan	polystyrene plates	*C. albicans* ATCC 10231	TMC-NPs (210 ± 15 nm) and TMC NPs/AmB (365 ± 10 nm)/uniform spherical shapes with smooth surfaces	enhanced the antifungal activity of AmB (amphotericin B) against *Candida albicans* biofilms	121
cyclodextrin	loaded gellan/PVA nanofibers incorporated eucalyptol/β-cyclodextrin inclusion complex		*C. glabrata* and *C. albicans* biofilms	variable-length fibres/fiber shaped	EPNF showed inhibition up to 70% for *C. glabrata* and *C. albicans* biofilms	135
	cysteamine-substituted γ-cyclodextrin		*S. epidermidis* biofilms	nanocarriers (~30−40 nm)/toroidal shapes	cyclodextrin nanocarriers efficiently deliver antibiotics in biofilms	133
	resveratrol nano vector of 2-hydroxypropyl-β-cyclodextrins (HPβCD)	64 children between two and five years of age with plaque-induced gingivitis	oral biofilm-causing agents (*e.g.*, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Streptococcus mutans*)		significant reduction in dental plaque of patients as compared to control	134
dendrimer and dendrimer−	supramolecular dendrimer nanosystems	polystyrene plates	*P. aeruginosa*, *E. coli*, and *S. aureus*	spherical supramolecular nanomicelles ranging from 10 to 20 nm	prevention and eradication of biofilm formation by both bacteria	141

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Table 1. continued

nanotechnology and polymeric nanocomplexes	nanomaterial description	test surface	target organisms	size and shape	anti-biofilm efficacy	ref
drug conjugates	TDZ-grafted amino-ended poly (amidoamine) dendrimer (TDZ-PAMAM)	*in vitro* and *in vivo* study	methicillin-resistant *S. aureus* (MRSA)	4 and 5 nm/spherical	intensive penetration of the biofilm matrix with potent biofilm eradication activity	142
	dendritic compounds and amphotericin	polystyrene plates	*C. glabrata* biofilm		eradication of established biofilms alone and in combination with amphotericin	143
	PEGylated carbosilane dendrimers alone and in combination with phage-derived endolysin	polystyrene plates	*P. aeruginosa*		biofilm prevention and eradication activity of dendrimers alone and in combination	144
polymeric nanoparticles	amphotericin B polymer NPs show efficacy against candida species biofilms	polystyrene plates	*C. albicans* and *C. glabrata*	157 ± 3 nm	MET-AmB formulations showed activity ∼30× lower than AmB alone	148
	doxycycline-functionalized polymeric NPs inhibit *Enterococcus faecalis* biofilm formation on dentine	dentine blocks	*E. faecalis* ATCC 29212	200 nm	NPs displayed potent antimicrobial activity against *E. faecalis* biofilms	156
	dual-species bacterial biofilms are susceptible to polymeric NPs	polystyrene plates	*E. coli* (IDRL-10366, DH5α), *P. aeruginosa* (IDRL-11442, ATCC-19660), and MRSA (IDRL-6169, IDRL-12570)	∼15 nm	PNPs showed good dual-species biofilm penetration profiles (broad-spectrum antimicrobial activity)	157
	antibacterial effect of functionalized polymeric NPs on titanium surfaces using an *in vitro* subgingival biofilm model	sterile titanium discs	*Streptococcus oralis*, *Veillonella parvula*, *Actinomyces naeslundii*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*	∼150 nm	NPs induced higher biofilm mortality and reduced the bacterial load	158
polymer−drug conjugates	antimicrobial polymer−peptide conjugates		*P. aeruginosa* (ATCC 27853) and *E. coli* (ATCC 25922)		inhibits the biofilm formation and the eradication of biofilms	162
	anti-*S. aureus* α-toxin-conjugated PEG-NPs and ISMN-loaded poly-lactide-*co*-glycolide acid (PLGA)	chronic rhinosinusitis	inhibit *S. aureus* biofilms		potent bactericidal activity with low inflammatory marker expression	163
	microbubbles functionalized with AClfA1	microfluidic flow chip (glass coverslip)	*S. aureus* biofilms	micrometer-sized	∼8% increase in the dead cell number and 25% increase in biomass loss	164
	Cconjugated polymer nanostructures (CPNs) as photoactivated antimicrobial compounds	polythiophene (PEDOT) and polyaniline (PANI) material	*S. aureus* and *E. coli*	average diameter of 40 nm and length in the micrometer range	strong antimicrobial activity under UVA irradiation	165
	bchitosan−PEG−peptide conjugate (CS-PEG-LK_{13})	*in vitro* biofilm model	*P. aeruginosa* biofilms	∼100 nm	CS-PEG-LK_{13} showed high antibacterial efficiency (72.70%) as compared to LK13 peptide (15.24%) and tobramycin alone (33.57%)	166
	chitosan oligosaccharide−streptomycin conjugate (COS-Strep)	polystyrene microtiter plates	*P. aeruginosa* biofilms		COS-Strep efficiently eradicated established biofilms	167
solid lipid nanoparticle	SLNs with anacardic acid (Ana-SLNs)	polystyrene microtiter plates	*S. aureus* biofilm	50−1000 nm	significant reduction in biofilm thickness and biomass	170
	SLNs incorporated with rifampin (rifampin-SLN)	polystyrene microtiter plates	biofilm-producing *S. epidermidis*	∼100−300 nm	time- and concentration- dependent biofilm biomass reduction with rifampin-SLN	171
	cefuroxime-loaded SLNs CA-SLN	polystyrene microtiter plates	*S. aureus* biofilm		twofold higher anti-biofilm inhibition with CA-SLN	172
	white wax (Chinese) SLNs with curcumin	catheters (polyvinyl chloride)	*S. aureus* biofilms.	∼401.9 ± 21.3 nm	enhanced bioavailability of curcumin and significant inhibition of *S. aureus* biofilms	176
	nisin-loaded SLNs (SLN-nisin)	*in vitro* assay	*Treponema denticola* biofilms		oral pathogen biofilm disruption	173
	nanoencapsulated tobramycin	*in vitro* assay	*P. aeruginosa*	150 nm	high anti-biofilm potential	174
liposomes	liposomes incorporating antibiotics	96-well cell culture plate	*S. aureus* Biofilms	∼ 0.11−0.17 μm	potent interactions of liposomes with biofilms	187

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Table 1. continued

	nanomaterial description	test surface	target organisms	size and shape	anti-biofilm efficacy	ref
nanotechnology and polymeric nanocomplexes	Liposomes-in-chitosan hydrogel	polystyrene microtiter plates	*S. aureus* and *P. aeruginosa*	200–400 nm	boosts potential of chlorhexidine in biofilm eradication	188
	DNase I- and proteinase K-incorporated cationic liposomes	polystyrene microtiter plates	*Cutibacterium acnes*	95 and 150 nm	liposome penetration ~ 85% of the biofilm thickness.	189
	dual-drug-loaded liposomes	culture dish	*S. aureus* biofilms	~100 nm	potent degradation of the biofilm matrix	190

antibiotics has also been investigated. *P. aeruginosa* biofilms on polystyrene surfaces are susceptible to destruction by NPs containing azithromycin and rhamnolipids. The therapy removed the polysaccharide and protein matrix of the biofilm.[108] Further, the green synthesis of Zn NPs with floral extract of *Clitoria ternatea* showed the reduction of the biofilm formation ability of oral pathogens (*Porphyromonas gingivalis* and *Alcaligenes faecalis*).[109] Metal NPs have shown potential as viable alternatives for controlling bacterial biofilms due to their unique physicochemical properties and ability to target bacterial cells. Studies have indicated that various types of metal NPs can combat both Gram-positive and Gram-negative bacterial strains by interfering with the EPS matrix and disrupting quorum sensing mechanisms.[110]

4.2. Functionalized Nanoparticles. The presence of EPS has been shown to weaken the efficacy of antibiotics by restricting their capability to infiltrate the biofilm matrix.[111−113] Additionally, EPS provide a shielding barrier for cells residing within the microbial biofilm. To destabilize biofilms, antimicrobial compounds must permeate the surface of the biofilm. Functionalized nanoparticles (FNs) may provide an innovative solution to this challenge. NPs provide distinct surface functional and reactive molecules with a high volume-to-surface ratio for functionalization.[114,115] Therefore, NPs may function as vehicles for transporting and delivering active antimicrobial compounds. Additionally, several NPs have significant inherent anti-biofilm properties. Functionalization of NPs involves modifying their surface chemistry by attaching various molecules such as surfactants, polymers, peptides, or even antibodies.[116] This modification can improve the antibacterial action of NPs by enhancing their stability, biocompatibility, delivery, and targeting ability.[117] In addition, the anti-biofilm effect of functionalized NPs is credited to their capability to disrupt the cell wall and bacterial cell membrane and interfere with bacterial enzymes and proteins.[118]

Tran and Hadinoto (2021) produced quercetin (QUE) amorphous nanoparticle complexes (nanoplex) and showed their motility and biofilm inhibition.[119] However, the activity of a nanoplex is comparable to the QUE treatment. Nguyen et al. (2021) showed that α-mangostin (AMG) loaded NPs inhibit biofilm formation by the MRSA 252 strain. AMG-loaded NPs showed significantly higher (53−62%) biofilm inhibition as compared to the AMG alone (40−44%).[120] Further, amphotericin B (AmB) loaded trimethyl chitosan significantly inhibited biofilms of *C. albicans* ATCC 10231 better than AmB alone.[121] Recently, Tu et al. (2022) reported poly-L-lysine (HBPL) modified manganese dioxide (MnO_2) and poly(PEGMA-*co*-GMA-*co*-AAm) (PPGA) nanozyme formulations that showed biofilm inhibition against potential biofilm-forming human pathogens, including MRSA, *E. coli*, and *P. aeruginosa* biofilms.[122] Overall, functionalized NPs represent an encouraging possibility for the advancement of new antibacterial strategies with enhanced efficacy and specificity. However, more research is needed to optimize the synthesis and functionalization of NPs for antibacterial applications and to evaluate their safety and efficacy in various biological and environmental systems.

4.3. Cyclodextrin-Based Nanomaterials. Cyclodextrins are group of cyclic oligosaccharides and have proved to be useful in pharmaceuticals, cosmetics, and the food industry as drug delivery vehicles, solubilizing agents, and stabilizing agents.[123−125] Recently, cyclodextrins have been employed as anti-biofilm and antibacterial agents.[126−128] Antimicrobial and

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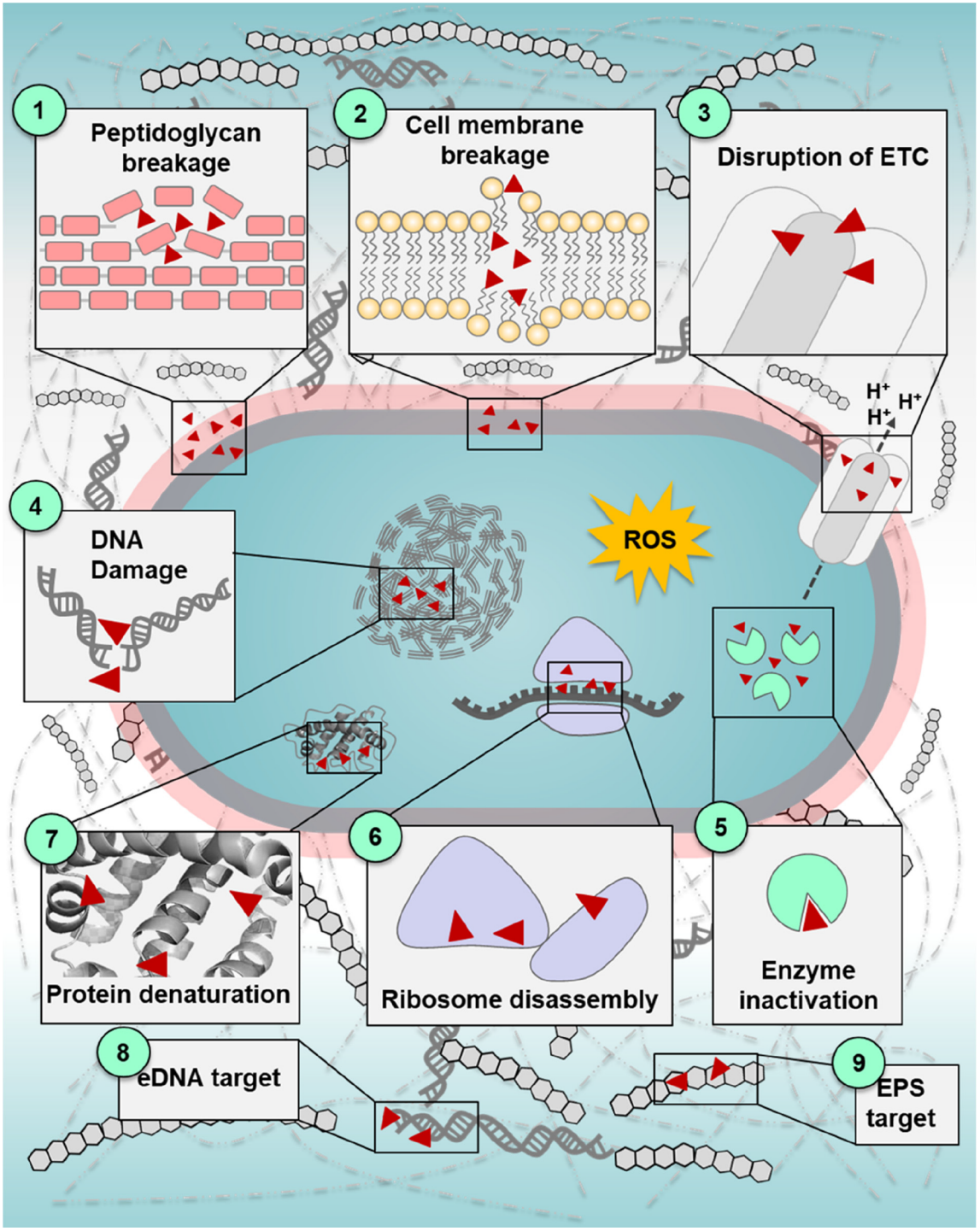

Figure 5. Molecular Mechanisms and targets of nanomaterials in biofilm inhibition: (1) Gram-positive and Gram-negative peptidoglycan breakage, (2) targeting cell membrane integrity, (3) targeting the electron transport chain, (4) bacterial DNA damage, (5) bacterial enzyme inactivation, (6) ribosome disassembly, (7) bacterial intracellular protein denaturation, (8) extracellular DNA inhibition, and (9) EPS inhibition.

anti-biofilm agents such as essential oil antibiotics or plant extracts can be conjugated with cyclodextrins to enhance their bioavailability, stability, solubility, and delivery.[129,130] Several reports have suggested the impact of cyclodextrin-based nanomaterials against a broad range of Gram-negative and Gram-positive bacteria. In recent years cyclodextrin−antibiotic conjugates, cyclodextrin−metal NPs, and cyclodextrin−essential oil complexes have been explored for their antimicrobial and anti-biofilm activity.[131,132]

Thomsen et al. (2020) showed that cysteamine-substituted γ-cyclodextrin exhibited enhanced antibiotic efficacy against the *Staphylococcus epidermidis* biofilm.[133] Cysteamine-substituted γ-cyclodextrin is a cyclodextrin molecule that has been modified with cysteamine groups. Cysteamine substitution of γ-cyclodextrin has been shown to enhance its stability and solubility. Cyclodextrin has been reported to enhance the anti-biofilm efficacy of conventional antibiotics. An oxacillin and rifampicin−cyclodextrin derivative has also shown significant

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improvement in the biofilm disruption ability of antibiotics alone. Berta et al. (2021) showed that the children aged between two and five years who received oral treatment demonstrated a significant reduction in plaque formation.[134] Further, Mishra et al. (2021) showed that a β-cyclodextrin-loaded gellan/PVA complex inhibited biofilms of *C. albicans* and *C. glabrata* (approximately 70% inhibition).[135] Cyclodextrin-based nanomaterials represent a promising approach for developing novel antibacterial and anti-biofilm agents with enhanced efficacy and reduced toxicity. However, further research is needed to optimize the synthesis and functionalization of cyclodextrin-based nanomaterials and to evaluate their safety and efficacy in various biological and environmental systems.

4.4. Dendrimer and Dendrimer−Drug Conjugates. Dendrimers are extremely branched tree-like molecules that include a well-defined structure and size.[136] Dendrimers contain a core surrounded by a series of molecular branches. Due to physiochemical and biocompatible properties, dendrimers have been used in a wide variety of functions, including gene therapy, drug delivery, diagnostics, and imaging. In addition, drug-conjugated dendrimers have been constructed with various molecules such as drugs, peptides, or imaging agents. Several studies have demonstrated the possibility of using dendrimer−drug conjugates to deliver a wide range of active compounds, including anti-inflammatory agents, chemotherapeutic agents, antimicrobial agents, and antiviral agents. Similarly, dendrimer conjugates of doxorubicin and paclitaxel have shown enhanced therapeutic efficacy and reduced systemic toxicity.[137] Dendrimers can interact with bacterial and viral membranes and disrupt their structures, leading to the inhibition of bacterial growth and viral replication.[138] Dendrimers have been reported to possess potent activity against drug-resistant bacterial strains such as MRSA and VRE.[139,140] In addition, supramolecular dendrimer nanosystems have shown potent anti-biofilm efficacy against a wide range of pathogens, including *E. coli, P. aeruginosa,* and MRSA.[141] *In vitro* and *in vivo* activity of TDZ-grafted amino-ended poly(amidoamine) dendrimer showed excellent infiltration of MRSA biofilms.[142] In addition to bacterial biofilms, fungal biofilms were also targeted with dendrimers. Amphotericin-associated dendritic compounds have shown the eradication of a *Candida* glabrate biofilm on a polystyrene surface.[143] Furthermore, antimicrobial proteins derived from bacterial viruses (bacteriophages) have also been delivered using this delivery system. Recently, it was shown that the phage-derived endolysin in combination with PEGylated carbosilane dendrimers prevented and eradicated the *P. aeruginosa* biofilms.[144] In general, dendrimers and dendrimer drug conjugates exemplify an encouraging avenue for the progress of novel drug delivery systems. However, further research is needed to optimize their formulations, synthesis, and functionalization and to evaluate their efficacy and safety in various biological systems.

4.5. Polymeric Nanoparticles. Polymeric NPs are nanosized particles composed of polymeric materials.[145] The PNPs have numerous benefits over conventional antimicrobial agents, including enhanced drug stability, bioavailability, solubility, and sustained release.[146,147] They have also been extensively investigated for their anti-biofilm and antibacterial activity.[148] Polymeric NPs can be prepared using several techniques such as solvent evaporation, emulsion, and nanoprecipitation. Key factors influencing antimicrobial and anti-biofilm activity are polymer choice and method of synthesis. These may affect the shape, size and surface properties, which in turn may influence the activity.[149] Polymeric NPs have been shown to exhibit potent antibacterial and anti-biofilm activity against Gram-positive and Gram-negative bacteria.[150] Polymeric NPs can inhibit bacterial growth, target the cell membrane biosynthesis, and prevent the formation and dispersion of biofilms.[151,152] Polymeric NPs composed of polyethylene glycol (PEG), chitosan, and poly(lactic-*co*-glycolic acid) (PLGA)[153] have been extensively explored for their antimicrobial and anti-biofilm activity.

PEGylated NPs have been shown to inhibit biofilm formation and bacterial growth of *P. aeruginosa.*[154] Furthermore, PLGA NPs have been reported to demonstrate antimicrobial activity against MRSA and VRE.[90] Further, studies have shown that drug-encapsulated chitosan NPs exhibit antibacterial activity against *S. aureus* and *E. coli.*[155] Moreover, drug-loaded chitosan NPs have also been explored to control biofilm formation by fungal pathogens. Amphotericin B (AmB) polymeric NPs showed efficacy against *Candida* biofilms on polystyrene surfaces. Results showed that the polymeric NPs were ∼30× more efficient than AmB alone.[148] Arias-Moliz and colleague showed that *E. faecalis* ATCC 29212 biofilms were inhibited by doxycycline-functionalized polymeric NPs on dentine material.[156] Furthermore, polymeric NPs have also shown efficacy against multispecies bacterial biofilms of *E. coli*, *P. aeruginosa*, and MRSA strains on polystyrene plates. The potent mutispecies biofilm eradication was linked to the broad-spectrum antibiotic activity of the polymeric NPs.[157] Functionalized polymeric NPs have also shown potent anti-biofilm efficacy against *Veillonella parvula, Streptococcus oralis, Fusobacterium nucleatum Actinomyces naeslundii, Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans* in a subgingival biofilm model.[158] In brief, polymeric NPs provide enhanced drug bioavailability, stability, solubility, and sustained release. The effectiveness of these NPs against bacterial biofilms is controlled by factors like the choice of method for synthesis and the polymer material. PNPs have shown efficacy against a variety of critical pathogens and exhibited potent anti-biofilm activity against multispecies bacterial biofilms.

4.6. Polymer−Drug Conjugates (PDCs). PDCs are formed by covalently linking a therapeutic agent to a polymeric carrier.[159] This approach enables the sustained and controlled release of the drug, leading to enhanced therapeutic efficacy and reduced toxicity. PDCs have demonstrated great potential in treating biofilm-associated infections.[160] PDCs may effectively penetrate the EPS matrix and deliver the drug directly to the site of infection.[161] In particular, PDCs with anti-biofilm activity have shown significant potential in the management of biofilms.[162] These conjugates can target either the EPS matrix or the microbial cells within the biofilm, disrupting their structure and inhibiting their growth. Additionally, PDCs can be designed to exhibit synergistic effects with traditional antibiotics, enhancing their efficacy against biofilms. Ortiz-Gómez and colleagues have developed a surface protective coating by modifying the anionic and hydrophobic peptide (2−5 kDa) and coupling it to PEG.[162] The conjugate preparation demonstrated a potent ability to eradicate established *P. aeruginosa* and *E. coli* biofilms. The study has demonstrated that conjugating the PEG polymer with a peptide of 5 kDa size was optimal for inhibiting biofilm formation in both the bacterial strains.

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S. aureus α-toxin-conjugated PEG-NPs and ISMN-loaded polylactide-*co*-glycolide acid (PLGA) showed high inhibition efficacy against *S. aureus* biofilm. Moreover, in the sheep chronic rhinosinusitis (CRS) model, the levels of IL-4, IFN-γ, and IL-8 in both blood and sinus tissues were markedly reduced, indicating ISMN-PLGA-PEG-AA is a promising therapeutic agent for the management of *S. aureus* infections.[163] Another study explored a novel method of utilizing microbubbles to attach to *S. aureus* biofilms in vitro utilizing an affimer protein called AClfA1 that specifically targets ClfA, which is responsible for cell-wall-anchored protein association. AClfA1-functionalized microbubbles showed marked biomass loss and a high dead cell count against *S. aureus* biofilms.[164]

Ghosh et al. (2021) showed that two types of conductive polymer nanofibers (CPNs) including polythiophene (PEDOT) and polyaniline (PANI) showed strong antimicrobial activity against *E. coli* and *S. aureus* biofilms.[165] The bactericidal activity of these CPNs is attributed to the generation of ROS (reactive oxygen species) induced by photostimulation, which can cause damage to the bacterial cell membranes and subsequently restrict biofilm formation.

The researchers strived to enhance the functional activity of conjugates that would effectively eradicate bacterial biofilms. Ju et al. (2020) conducted a study that revealed that the chitosan−peptide−PEG conjugate exhibited remarkable antibiofilm efficacy against *P. aeruginosa* at 8× the minimum inhibitory concentration (MIC), surpassing the effects of tobramycin and LKI3 peptide.[166] Further CS-Strep, a chitosan oligosaccharide (COS)−streptomycin conjugate, eradicated *P. aeruginosa* biofilms but had limited impact on Gram-positive biofilms. Its activity was influenced by the chitosan oligosaccharide polymerization degree and was attributed to suppression of the MexX−MexY pump system and downregulation of biofilm exopolysaccharides.[167] PDCs offer an encouraging approach for the management of biofilm infections, providing sustained and controlled release of drugs that can penetrate the EPS matrix and disrupt the structure of biofilms. With the potential for targeting both the EPS matrix and microbial cells, as well as synergistic effects with traditional antibiotics, PDCs represent a valuable tool in the management of biofilms.

4.7. Solid Lipid Nanoparticle (SLNs). Solid lipid nanoparticles (SLNs) have been used as a promising nanostrategy for inhibiting bacterial biofilms.[168] SLNs are submicrometer-sized particles consisting of lipids that possess desirable attributes, including biocompatibility, biodegradability, and a high capacity for drug loading.[169] As drug carriers, SLNs can encapsulate various types of drugs, including antibiotics, and deliver them precisely to the site of infection. Recent investigations have shown the effectiveness of SLNs in reducing the biofilm biomass, underscoring their potential as a therapeutic alternative for infections associated with biofilms.

In 2021, Anjum and colleagues (2021) reported the synthesis of SLNs containing anacardic acid (Ana) incorporated with DNase (Ana-SLNs-CH-DNase) and chitosan. These SLNs were able to considerably reduce the *S. aureus* biofilm, underscoring the promise of SLNs as viable remedial agents for infections related to biofilms.[170] The chitosan coating was intended to create positively charged SLNs that would facilitate interactions with biofilms. The hypothesis behind the DNase coating is that it is responsible for the degradation of the extracellular DNA (e-DNA) of biofilms.

SLNs have been utilized to augment the effectiveness of antibiotics against biofilms. When used alongside antibiotics, SLNs have the capability to enhance the efficacy of the antibiotics in a time- and concentration-dependent manner. Fazly and his colleagues showed rifampin-loaded SLNs can effectively reduce *Staphylococcus epidermidis* biofilm biomass in a concentration- as well as time=dependent manner.[171] In addition, SLNs loaded with cefuroxime showed twofold higher anti-biofilm activity against a *S. aureus* biofilm *in vitro*.[172]

In a recent study by Radaic and colleagues (2022), nisin-loaded SLN (SLN-Nisin) exhibited significant inhibition of *Treponema denticola* biofilms.[173] Another study evaluated the effectiveness of tobramycin-loaded SLNs against biofilms.[174] The minimum inhibitory concentration (MIC) and minimum biofilm eradication concentration (MBEC) of the nano-encapsulated tobramycin was 1−2 log lower as compared to those of drug-only groups when tested on tobramycin-susceptible isolates.

In recent years, SLNs have been used as a promising target drug delivery approach for phytochemicals against biofilm associated infections.[175] A study conducted by Luan and colleagues (2019) reported that the use of SLNs of Chinese white wax loaded with curcumin led to improved bioavailability of curcumin and significant inhibition of *S. aureus* biofilms. This study provided the clues regarding the potential of SLNs as an effective therapeutic agent for bacterial infections.[176] The use of SLNs for antimicrobial compound delivery holds immense potential as a therapeutic strategy against bacterial biofilms.

4.8. Liposomes. Liposomes are widely recognized as a conventional and highly essential delivery system within the pharmaceutical industry.[177,178] Liposomes are spherical vesicles composed of a phospholipid bilayer that can encapsulate a wide range of chemical compounds.[179] The phospholipid bilayer structure of liposomes allows the encapsulation of both hydrophilic and hydrophobic drugs,[180] making them an attractive option for drug delivery. Liposomes can also be modified to enhance their stability, circulation time, and targeting capabilities.[181,182] The manipulation of a diverse array of physical and chemical parameters confers upon liposomes the desired pharmacodynamic and pharmacokinetic characteristics.

In recent times, there has been increased interest in the use of liposomes as a drug delivery system for addressing biofilm-associated infections.[183] Liposomes have been shown to effectively penetrate the EPS and deliver the active compounds directly to the microbial cells of biofilms.[184] Furthermore, liposomes can be designed to exhibit synergistic effects with traditional antibiotics, enhancing their efficacy against biofilms.[185,186] The effective delivery of antibiotics is often hindered by the intricate and dense polysaccharide layer present in bacterial biofilms, making them resistant to antibiotic therapy. However, the utilization of liposomes may boost the antibiotic transport into the core of the biofilm, thereby potentially increasing the efficacy of the treatment. Ferreira et al. (2021) showed that the liposomes improved the delivery of antibiotics to the *S. aureus* biofilms and showed significant interaction with the biofilm matrix.[187]

Biofilm eradication is a difficult task for antimicrobial agents, primarily due to the strong adhesion of the cells to each other and to the surface. However, liposomal nanotechnology has emerged as a promising approach, offering a diverse range of strategies and solutions to eradicate biofilms. Recent studies

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have explored the potential of liposomes for eradicating biofilms. For instance, Hemmingsen et al. (2021) reported that chitosan−liposome hydrogels demonstrated a high capability for eradicating *S. aureus* and *P. aeruginosa* biofilms when combined with chlorhexidine.[188] Additionally, Fang et al. (2021) observed that cationic liposomes containing DNase I/proteinase K were able to penetrate up to 85% of the biofilm matrix and exhibited the potential to eradicate *Cutibacterium acnes* biofilms.[189] Moreover, Wang et al. (2022) demonstrated that drug-loaded liposomes facilitated the significant degradation of *S. aureus* biofilms through proton-mediated burst action.[190] These results suggest that liposomes may serve as a promising platform for developing effective strategies for controlling biofilm formation by clinically relevant pathogens.

4.9. Nanotechnology for Next-Generation Therapeutic Modalities. The synthesis of advanced multifunctional nanomaterials capable of simultaneous diagnosis and therapy has become an area of immense interest in contemporary research. Photothermally active nanomaterials are characterized by unique features such as a high surface area-to-volume ratio, adjustable physicochemical properties, and efficient optical absorption, which make them suitable for a wide range of applications. The combination of these attributes with the ability to generate heat in response to light has led to their utilization in various therapeutic applications, including antibacterial and anti-biofilm therapy. Recently, Roy et al. (2023) provided an excellent overview of critical advancements in nanotechnological approaches for antibacterial therapeutics.[191] Notably, the review highlights the incorporation of advanced therapeutic modalities such as immunotherapies, emerging immunotherapy, gene therapy, and relatively new multimodal dynamic strategies. Additionally, Chen et al. (2020) comprehensively summarized the mechanisms and details of nanomaterial-based photothermal therapy for antibacterial activity against potential bacterial pathogens.[192] Moreover, amine-functionalized aggregation-induced emission (AIE) has demonstrated the ability to eradicate bacteria such as *S. aureus* and *E. coli* by producing singlet oxygen and heat.[193] Furthermore, Zhang et al. (2020) demonstrated that chitosan (CS) encapsulated multifunctional metal−organic NPs exhibit photodynamic- and photothermal-dependent antimicrobial activity.[194] In addition to photodynamic properties, nanomaterials possess chemodynamic properties against bacteria and their biofilms. Huang et al. (2023) conducted a comprehensive survey of state-of-the-art image-guided techniques for diagnosing and treating bacterial infections, including photothermal treatment, photodynamic therapy, chemodynamic therapy, sonodynamic therapy, immunotherapy, and various other therapies.[195] Along with these advanced therapies, researchers have also focused on utilizing the physiochemical properties of NPs to release drugs through various stimuli such as sound, light, pH, electric, and magnetic fields to overcome multidrug resistance.[196] The ability to employ physiochemical properties of NPs to release drugs through stimuli shows promise for overcoming multidrug resistance. Overall, these findings pave the way for the development of novel and effective nanotheranostic strategies for the diagnosis and treatment of bacterial biofilms.

5. CONCLUSION AND FUTURE PROSPECTS

The biofilm mode of bacterial growth is a major threat to community health, as biofilms have the potential to cause persistent infections and can resist antibiotic treatment. In the fight against biofilms, nanotechnology-based approaches have emerged as promising solutions, offering several advantages over traditional antimicrobial agents. NPs and nanomaterials, such as metals, metal oxides, nanopolymers, and liposomes, have demonstrated anti-biofilm and antimicrobial activities. Furthermore, nanomaterials can enhance antibiotic efficacy and act as carriers for antibiotics. However, there are still challenges associated with the advancement of secure and efficient nanomaterials for clinical use. Future research should address these challenges and explore new antibacterial therapies that have received limited attention, such as CRISPR-Cas gene editing, natural compounds, phages, and nanomediated techniques. Innovative strategies aimed at effectively combating bacterial biofilms include emerging methods for the efficient delivery of antimicrobial compounds into the biofilm, targeting motility phenotypes, limiting attachment stages, reducing the secretion of the EPS matrix using nanoenzymes, and restricting nutrient flow. In addition, applying nanotechnology-based techniques to increase stress and induce damage to the biofilm architecture shows considerable potential to solve this persistent problem. Scientists will continue to depend on cell lines and related model systems to evaluate the safety of NPs for human use. *In vitro* studies may include evaluating the effect of nanotechnologies on the cell, viability, gene expression, and proliferation. Further, *in vivo* studies may include evaluating the effect of nanobased material delivery on animals and monitoring toxicity, metabolism, and distribution. Nanotechnology holds promise for combating biofilms and improving public health, and continued research is necessary to achieve these advancements.

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