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Article *in* Current Pharmaceutical Biotechnology · April 2023

DOI: 10.2174/1389201024666230428121122

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Antibacterial Effects of Nanocomposites on Efflux Pump Expression and Biofilm Production in *Pseudomonas aeruginosa*: A Systematic Review

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Abstract

Background: *Pseudomonas aeruginosa* is an opportunistic gram-negative pathogen with multiple mechanisms of resistance to antibiotics. This systematic review aimed to study the antibacterial effects of nanocomposites on efflux pump expression and biofilm production in *P. aeruginosa*.

Methods: The search was conducted from January 1, 2000, to May 30, 2022, using terms such as (P. aeruginosa) AND (biofilm) AND (antibiofilm activity) AND (anti-Efflux Pump Expression activity) AND (nanoparticles) AND (Efflux Pump Expression) AND (Solid Lipid NPS) AND (Nano Lipid Carriers). Many databases are included in the collection, including Science Direct, PubMed, Scopus, Ovid, and Cochrane.

Results: A list of selected articles was retrieved by using the relevant keywords. A total of 323 published papers were selected and imported into the Endnote library (version X9). Following the removal of duplicates, 240 were selected for further processing. Based on the titles and abstracts of the articles, 54 irrelevant studies were excluded. Among the remaining 186 articles, 54 were included in the analysis because their full texts were accessible. Ultimately, 74 studies were selected based on inclusion/exclusion criteria.

Conclusion: Recent studies regarding the impact of NPs on drug resistance in *P. aeruginosa* found that various nanostructures were developed with different antimicrobial properties. The results of our study suggest that NPs may be a feasible alternative for combating microbial resistance in *P. aeruginosa* by blocking flux pumps and inhibiting biofilm formation.

Keywords: Efflux Pump; Anti-biofilm activity; *Pseudomonas aeruginosa;* Systematic Review; Nanoparticles

1. INTRODUCTION

Bacterial biofilm consists of a complex assemblage of bacteria enclosed in a glycocalyx coating that adheres to mucosae and other surfaces, such as catheters, prostheses, and contact lenses. Several types of bacteria can form biofilms, including *P. aeruginosa*, *Acinetobacter*, *Staphylococcus*, and *Bacillus* spp [1, 2]. *P. aeruginosa* is an opportunistic pathogen that causes nosocomial pneumonia, urinary tract infections, sepsis, bacteremia, and surgical wound infections [3]. This bacterium is a gram-negative, facultative anaerobe, motile, and non-fermentative. Biofilm formation by pathogens can increase their resistance to antibiotics up to 1,000-fold over planktonic forms. Thus, the biofilm matrix prevents antimicrobials from entering the cell and contributes to therapeutic agents' resistance [4].

Hence, current antibiotics fail to treat biofilm-producing *P. aeruginosa* infections, leading to serious problems in hospital management and the medical community [5]. Recently, NPs have been considered for treating pathogenic bacteria to address biofilms and the fact that *P. aeruginosa* antibiotics are highly resistant to common antibiotics [6]. Various nanoparticle types are promising pharmaceutical agents with properties such as antimicrobial activity, biofilm inhibition, anticancer activity, and antioxidant activity [7]. Moreover, the emergence of antibiotic resistance among *P. aeruginosa* isolates can be attributed to an increased expression of efflux systems, which are important for developing innate and acquired antibiotic resistance to cephalosporins and carbapenems [8-10]. Figure 1 illustrates possible mechanisms of nano-bioactive materials against biofilm formation stages. Various studies show that NBMs could affect biofilm formation by 5 pathways. The whole genome or biofilm-associated genes of *P. aeruginosa* might undergo mutation by some metal nanostructures such as palladium, copper and Ag NPs [11, 12]. According to Singh et al. (2019), RNA-sequencing of *P. aeruginosa* isolates treated with Ag NPs significantly reduced the expression of biofilm genes and made antibiotic-resistant bacteria more susceptible [13].

Further, biofilm inhibition was reported at mRNA or protein levels responsible for biofilm production in P. aeruginosa infections [14]. Scientists have demonstrated that bacteria create biofilms primarily due to quorum sensing between bacteria. Therefore, NPs play an important role in halting biofilm formation by interfering with the quorum signaling mechanism in bacteria populations [15, 16].

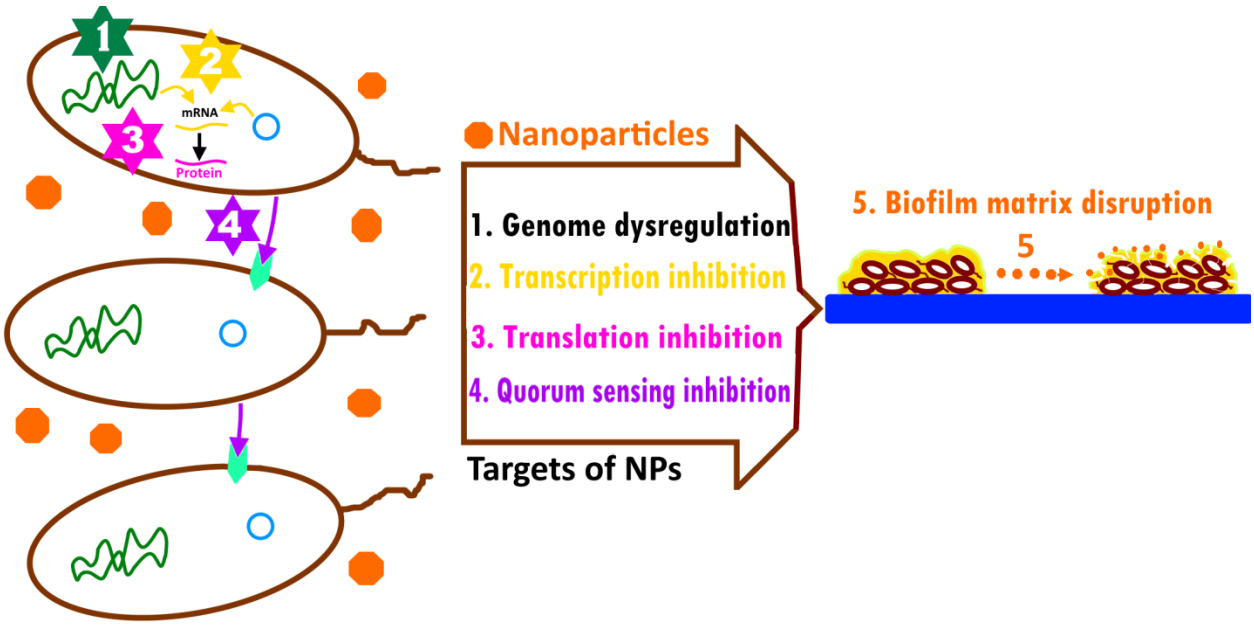

Fig. 1. Schematic mechanisms for bacterial biofilms targeted by NPs in various ways.

Antimicrobial efflux pumps not only inactivate antimicrobial agents but also reduce their concentration, which leads to the accumulation of resistance mutations due to drug excretion. Recently, there has been an increase in the search for new efflux inhibitors [94]. There are 12 types of Multidrug efflux systems (MEX) in P. aeruginosa, which are members of the Resistance Nodulation-Cell division (RND) family and responsible for their innate resistance. Among these, 5 pumps MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexXY-OprM, and MexGH- OpmD are the most important factors of antibiotic resistance [11]. The most important factors related to antibiotic resistance are MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexXY-OprM, and MexGH-OprD. P. aeruginosa is inherently resistant to antibiotics because MexAB-OprM is the only secretory pump present [12]. Efflux pumps prevent drugs from interfering with bacterial growth and protect bacteria against harmful substances. MEX family members facilitate the removal of antimicrobial compounds from cells by using the proton-stimulating force of the membrane [14, 15]. Unlike antibiotics targeting MEX systems, NPs may interfere with their functionality by inhibiting gene expression or physically disrupting their components [17]. There is evidence that NPs may disrupt P. aeruginosa's MEX system by attacking multiple targets at once [18].

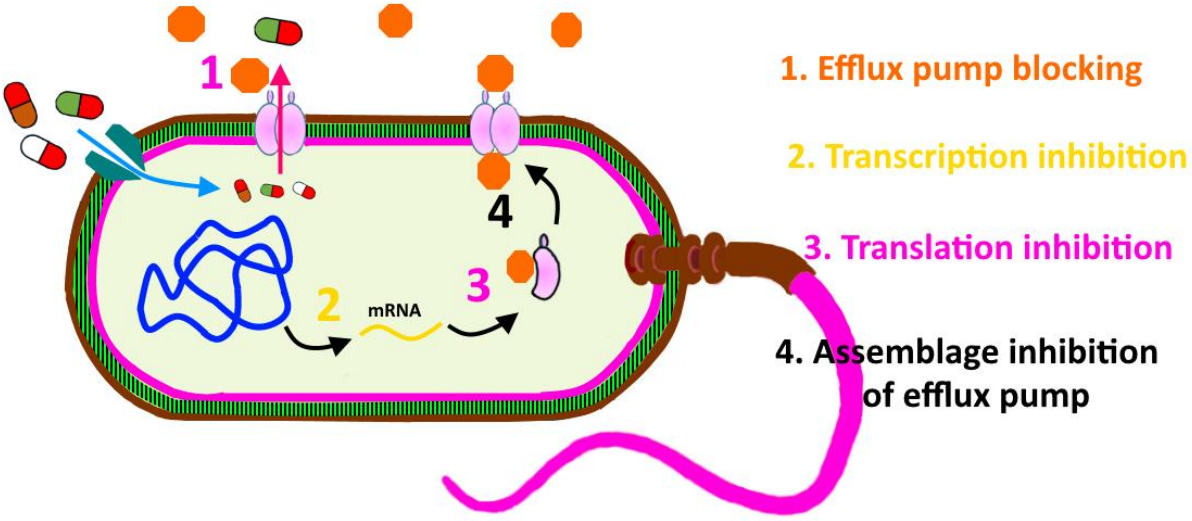

Fig. 2. Schematic of the possible mechanisms targeted by various metal nanoparticles.

As stated in the literature, nanostructures offer numerous benefits when eliminating the resistance function associated with pumps and physical barriers, such as microbial biofilms. Researchers have recently turned their attention to nanostructures to find new ways of eliminating microbial drug resistance.Various physical and chemical methods are available for synthesizing NPs, including chemical reduction, laser and microwave technology, and electrochemical synthesis [16]. Numerous researchers have examined various NPs' anti-biofilm and anti-efflux pump properties, including gold, copper, and Ag NPs. According to their assertion, NPs can be used as an alternative to antibiotics to inhibit the growth of biofilms and the expression of efflux pumps in bacteria [17, 18]. In this systematic review, the effect of different nanostructures, especially metal-based nanomaterials and their derivatives, on the expression of efflux pumps in P. aeruginosa and biofilm formation in the bacterium were discussed.

2. METHODOLOGY

This systematic review focused on literature available online in both English and Persian between January 1, 2000 and May 30, 2022. The search was conducted in English databases such as Science Direct, PubMed, Scopus, Ovid, and Cochrane. The Persian databases were included Magiran, Iranmedex, Irandoc and SID. Our search was focused mainly on *Pseudomonas aeruginosa* (*P. aeruginosa*) AND (biofilm) AND (antibiofilm activity) AND (Efflux Pump Expression) AND (anti-Efflux Pump Expression activity) AND (nanoparticles) AND (Solid Lipid NPS) AND (Nano Lipid Carriers). Two authors evaluated the articles independently, and discrepancies were resolved through discussion.

Studies selected for inclusion evaluated the effect of NPs on the biofilm and the expression of efflux pump genes in P. aeruginosa. These studies were published in both Farsi and English, and they were published in reputable journals. These were studies that had clear, detailed results; they were studies that were accessible in full text. Among the studies excluded from consideration were case reports, case series, and systematic reviews, summaries of presentations at seminars and conferences, and studies that needed more clarity. Data retrieved from papers were tabulated as follows: Author, year, type of nanoparticle, nanoparticle impact site, and concentration of NPs.

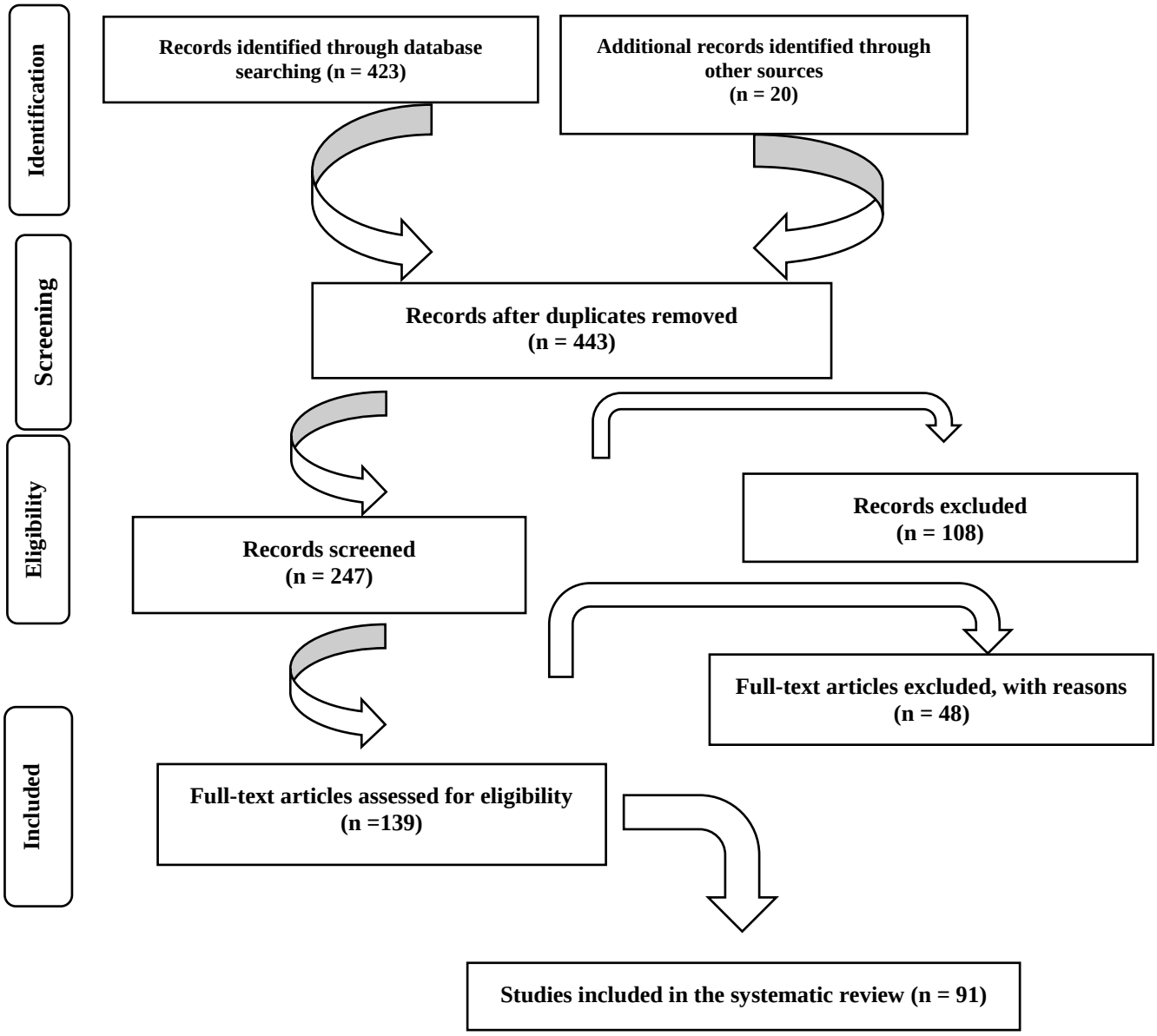

Figure 3. The PRISMA denrogram for selecting articles and incorporating them into the study**.**

3. RESULTS AND DISCUSSION

The selected articles were entered into Endnote X9 based on keywords and after, they were subjected to inclusion and exclusion criteria. The initial retrieval of all databases yielded 443 studies. However, only 247 studies were chosen for the next step after removing duplicates. According to the titles and abstracts of the articles, 108 studies were deemed irrelevant. Among the remaining 139 articles, 91 contained full text for eligibility. Finally, 91 studies were selected for comparative and conceptual discussion based on the standard systematic inclusion and exclusion criteria. Table 1 provides details of the author, year, nanoparticle type, nanoparticle impact site, and concentration of NPs.

Table1. Included publications of a survey on the efficacy and activity of NPs used against *P. aeruginosa*

Author	Year	Formulation details	Active therapeutic compartment	Effective treatment dose	Therapeutic mechanism	Ref
Liu	2019	(4-nitropyridine N-oxide)-Ag-NPs	4NPO and Ag-NPs	Ag(50 mg/l)+4NPO(6.25 mg/l)	Quorum sensing inhibitor Antibiofilm	[19]
LewisOscar	2021	Bio@Ag-NPs	Ag-NPs	100 µg/ml	Antibiofilm	[24]
Targhi	2021	Niosomal-Curcumin-Cu and Ag NPs	NS-Cur-Ag and NS-Cur-Cu	25 µg/mL	Antibiofilm	[60]
Paunova-Krasteva	2020	micelles@Ag NPs	M@Ag-NPs	500 µg/mL	Antibiofilm	[88]
Patel	2019	Chitosan-SLN@Silver sulfadiazine	Silver sulfadiazine	18.75 µg/ml	Antibiofilm	[23]
Madhi	2020	Chitosan–Ag NPs-Ciprofloxacin and Chitosan–Ag NPs-Ciprofloxacin	Ag-NPs, Cip and Gen	(Ag-Cip) 0.3 mg/ml and (Ag-Gen)1mg/ml	Efflux pump inhibition	[32]
Mohammad	2021	chem@Ag NPs	Ag-NPs	250 µg/mL	Efflux pump	[43]
Silva Santos	2016	Bio@Ag NPs	Ag-NPs	24 µg silver-500mg nanocomposite	Antibiofilm	[53]
Campo-Beleño	2022	Bio@Ag NPs	Ag-NPs	100 µg/mL	Antibiofilm	[84]

Kumar	2022	Bio@ Ag NPs	Ag-NPs	15 µg/mL	Antibiofilm	[85]
Saeki	2021	Bio@Ag NPs	Ag-NPs	7.81–31.25 µg/mL	Antibiofilm	[37]
Bhargava	2018	Fucose-Ag NPs	Ag-NPs	30 µg	Antibiofilm	[34]
El-Deeb	2020	Polysaccharides-Ag NPs	Ag-NPs	0.5–1µg/mL	Antibiofilm	[36]
Guo	2019	D-maltose@Ag NPs	Ag-NPs	18 µg/mL	Antibiofilm	[62]
Korzekwa	2022	Glucose@SiO2/Ag0 and Glucose@ TiO2/Ag0	SiO2/Ag0 and TiO2/Ag0	256 µg/mL and 512 µg/mL	Antibiofilm	[63]
Mirzaei	2021	Bio@Silver selenide-NPs	Ag2Se NPs	50 µg/mL	Antibiofilm	[40]
Shahbandeh	2020	Ag NPs and Ag NPs-imipenem	Ag-NPs and Ag- IMI NPs	0.5–1024 µg/ mL	Efflux pumps inhibition	[54]
Abdolhosseini	2019	Ag NPs-thiosemicarbazide	Ag-NPS and Cip	64 µg/mL	Efflux pumps	[59]
Al-Obaidi	2018	Ag NPs-ciprofloxacin (Cip)	Ag-NPs@Cip	200 µg/mL	Antibiofilm	[68]
Singh	2018	Bio@Au NPs and Ag NPs	Au-NPs and Ag-NPs	1.6–100 µg/mL	Antibiofilm	[42]
Slavin	2021	Lignin@Ag NPs	Li-Ag NPs	10 µg/mL	Antibiofilm	[74]
Yang	2015	Polyvinylpyrrolidone-Ag NPs	Ag-NPs	21.6 µg/ml	Biofilm stimulator	[56]
de Lacerda	2020	chem@Ag NPs	Ag-NPs	200 µg/mL	Antibiofilm	[80]
Dorri	2022	Chem-Ag NPs	Ag-NPs	different	Efflux pump	[18]
Parasuraman	2020	Methylene blue@Ag NPs	Ag NPs	512 µg/mL	Photodynamic antibiofilm therapy	[64]
Ding	2018	11- amino-1-undecanethiol (AUT) – Ag NPs	Ag NPs	0.6 µg/mL	Efflux pumps inhinition	[58]
Gondil	2019	Seabuckthorn@Ag NPs	SBT@Ag NPs	128 µg/mL	Antibiofilm via QS interruption	[76]

Hůlková	2020	Branched polyethylenimine-Ag NPs	PEI-Ag NPs	150 mg/mL	Antibiofilm	[77]
Chakraborty	2021	Tetrazine@Ag NPs-thymoquinone (TQ)	Ag NPs and TQ	Ag NPs(5 µg/mL) and TQ (10 µg/mL)	Antibiofilm	[67]
Qureshi	2021	Chem@Ag NPs	Ag NPs	2000 µg/mL	Efflux pump or biofilm inhibition	[78]
Pompilio	2018	chem@Ag NPs	Ag NPs	8.48 µg/mL	Antibiofilm	[86]
Aziz	2022	chem@Ag NPs	Ag NPs	200-1000 µg/mL	Antibiofilm	[89]
El-Telbany	2022	Commercial-Ag NPs	Ag NPs	200 µg/mL	Antibiofilm	[82]
Ugalde-Arbizu	2022	Mesoporous Silica NPs (MSNs)-nicotinic-AgCl+ phenytoin	SN-Ag and SN-Ag@Ph	3.5 µg /mL and 3.20 µg /mL	Antibiofilm	[91]
Hemmati	2020	chitosan-Zinc oxide-gentamicin nanocomposite	ZnO NPs-Gen	128 µg/mL	Antibiofilm	[39]
Madhi	2020	Chitosan-ZnO NPs-Gentamicin (Gen) and Chitosan-ZnO NPs-ciprofloxacin (Cip)	ZnO-Gen and ZnO-Cip	ZnNPs+ Gen (16 µg/ml) and ZnNPs-Cip (128 µg/ml)	Efflux pump inhibition	[21]
Badawya	2020	Chitosan-ZnO NPs	ZnO-NPs	Different in various isolates	Anti-Quorum sensing and Antibiofilm	[22]
Abdelraheem	2021	Chem@ZnO NPs	ZnO-NPs	16 and 32µg/ml	Antibiofilm	[27]
García-Lara	2015	Chem@ZnO NPs	ZnO NPs	different	Antibiofilm via QS interruption	[73]
Fadwa	2021	Chem@ZnO NPs	ZnO NPs	2 µg/ml	Antibiofilm	[51]
El-Shounya	2019	Chem@ZnO NPs	ZnO NPs	500 µg/mL	Antibiofilm	[65]
Eleftheriadou	2021	Chem@CuO, ZnO, or CuZn NPs	Cocktail	50 µg/mL	Efflux pump inhibition	[35]
Rahmati	2022	Chem@Au NPs and ZnO NPs	Au-NPs and ZnO-NPs	500 µg /mL	Antibiofilm	[49]
Khan	2021	Phloroglucinol@Au	Phg@Au NPs and	1024 µg/mL	Antibiofilm	[50]

		NPs and ZnO NPs	Phg@ZnO NPs			
Mirzaei	2021	Bio@Zinc selenide-NPs	ZnSe NPs	50 μg/mL	Antibiofilm	[41]
Aswathanarayan	2017	Chem@ZnO and CuO NPS	ZnO and CuO NPS	3.125 μg/ ml and 6.25 μg/mL	Antibiofilm	[83]
Mubdir	2021	Chem@Au-NPs-Curcumin	Au-NPs and Cur	7.8-250 μg/mL	Antibiofilm	[47]
Arya	2019	Vanillin-Au NPs-Meropenem and Vanillin-Au NPs-trimethoprim	Au-Mer and Au-Trm	Au(50 μg/ml), Mer (3.1 μg/ml) and Cip (25 μg/ml)	Efflux pump inhibition	[20]
Ali	2022	Bio@Au NPs	Au NPs	50 μg/mL	Antibiofilm	[70]
Qais	2021	Bio@Au NPs	Au NPs	200 μg/mL	Antibiofilm via QS interruption	[71]
Habimana	2018	Citrate@Au-NPs	Au-NPs	5.9 μg/mL	Antibiofilm	[38]
Syed	2016	Bio@Au NPs	Au NPs	10 mg/ml	Antibiofilm	[92]
Zhang	2020	Glycoconjugate-Au NPs@ceftazidim (CAZ)	Galactose-Au-NPs-CAZ and Fucose-Au NPs-CAZ	2 μg/mL	Antibiofilm	[75]
Khare	2021	Chitosan-Embelin-Au-NPs	Au-NPs and Ciprofloxacin	2 μg mL	Efflux pumps	[44]
Rajkumari	2017	Baicalein@Au NPs	Bcl@Au NPs	100 μg/mL	Antibiofilm	[79]
Armijo	2020	Sodium alginate (ALG)- Fe3O4-Tobramycin (TOB)	Fe3O4-ALG NPs Fe3O4-ALG@TOBRA NPs	30 μg/ml	Antibiofilm	[25]
Pham	2019	Chem@FeOOH NPs	FeOOH NPs	1.35 mM	Antibiofilm	[28]
Sharif	2019	Bio@FeO NPs	FeO NPs	different	Antibiofilm	[57]
Baig	2020	Chem@Cu–TiO_2 NPs	Cu NPs and TiO_2 NPs	2.5 mg/mL	Antibiofilm	[33]
Singh	2019	Chem@Cu NPs	Cu NPs	300 μg/ ml	Efflux pumps and Biofilm inhibition	[45]
Li	2018	Ag, Fe, ZnO, TiO2, SiO2, Fe2O3-single-	Ag- SWCNTs-GO	100 μg L	Antibiofilm	[46]

		wall carbon nanotubes (SWCNTs)-graphene oxide (GO)	Fe-SWCNTs-GO TiO2-SWCNTs-GO SiO2- SWCNTs-GO			
Hiebner	2020	Chem@SiO2 NPs	SiO2 NPs	-	Antibiofilm	[48]
Memar	2021	chem@SiO2-meropenem	(Meso-SiO_2)-Mer	1–1024 mg/mL	Antibiofilm	[52]
Nsayef Muslim	2020	Chem@SiO2-lectin	SiO_2 NPs	Different	Antibiofilm	[17]
Shakibaiea	2015	Bio@Selenium NPs	Se NPs	16 µg/mL	Antibiofilm	[61]
Singh	2017	SeNPs@Hony phytochemicals	Se-NPs@HP	4.5 µg/mL	Antibiofilm via QS interruption	[69]
Jegel	2022	Polycarbonate@CeO2 nanozymes	CeO2	1.6 µg/mL	Antibiofilm	[66]
Xu	2018	chem@CeO2-NPs	CeO2-NPs	0.1 mg/L and 1 mg/ L	Biofilm	[30]
Zubair	2021	Bio@TiO2	TiO2	250 µg/mL	Antibiofilm	[72]
Rajkumari	2019	Bio@TiO2	TiO2	31.25 µg/ml	Antibiofilm	[81]
Ahmed	2021	Chem@TiO_2-NPs	TiO_2-NPs	4 µg/ml	Efflux Pump and Biofilm inhibition	[31]
Darabpour	2018	Fullerene@sulfur	Sulfur-NPs	2 and 4 mg/mL	Antibiofilm	[29]
Kher	2022	Chem@Sulfur-NPs	Sulfur-NPs	233.3 µg/mL	Antibiofilm	[93]
Maruthupandy	2020	Chem@Nickel NPs	NiO NPs	60 µg/mL	Antibiofilm	[87]
Alvares	2021	Bio@Tellurium NPs	Tellurium NPs	50 µg/ mL	Antibiofilm	[90]

*Ag-NPs: silver NPs, Au-NPs: Gold nanoparticles, ZnO-NPs: Zinc oxide nanoparticles, Cu-NPs: Copper nanoparticles, CeO2-NPs: Cerium oxide nanoparticles, TDN: Titanium dioxide nanoparticles. FeO-NPs: Iron oxide nanoparticles

Among all metal nanostructures evaluated for Pseudomonas biofilms and efflux pumps, silver accounted for 42.7% (38 studies), zinc for 12.36% (11 studies), and gold for 11.23% (10 studies). Other metals are less used in this study (Figure 4A). In all the studies, chemically synthesized nanomaterials made up the largest proportion of the total nanomaterials used to evaluate antibiofilm inhibitory and efflux pump activities. However, chitosan-based NPs

accounted for 8.8% of the total amount of NPs synthesized in this study. Furthermore, mono- and oligosaccharides such as fucose, maltose, glucose, and galactose were applied as capping agents for metal NPs (Figure 4B).

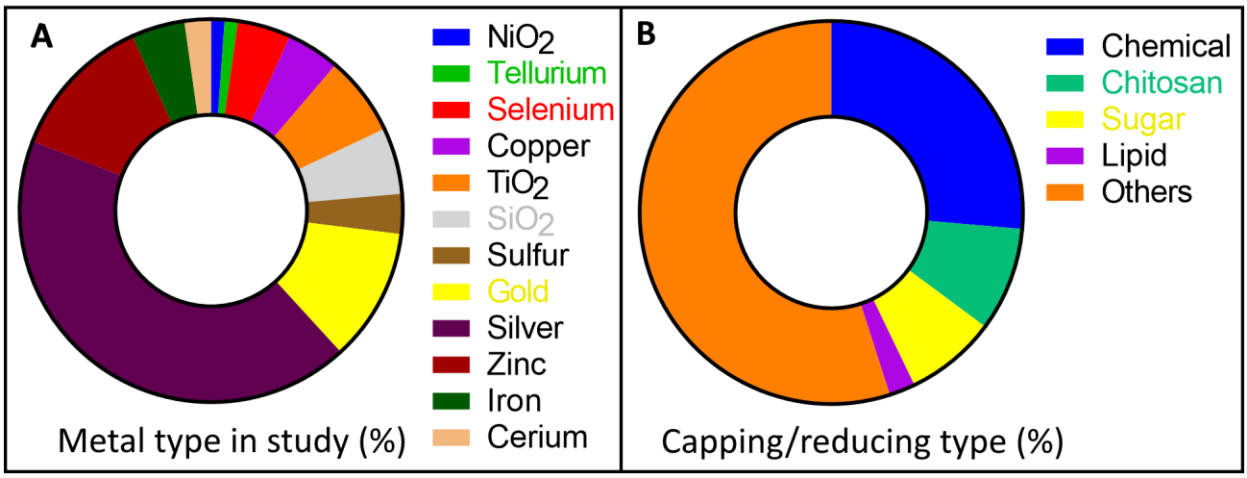

Fig. 4. The most applicable of nanoparticles in terms of the latest studies on P. aeuginosa biofilm and Efflux pump inhibition.

Metal role in nanomaterials and antibiofilm and Efflux pump inhibitory potency

According to various literature, metals have been documented to affect a range of biological molecules and metabolic pathways within living organisms. Furthermore, the way NPs are synthesized can also affect their bioactive properties, particularly important in treating pathogens when used as drugs. Two groups of metal NPs can be distinguished: metal elements and metal oxides. The synthesis of NPs can be accomplished in several ways based on physical techniques (top-down) and chemical processes (bottom-up). The chemical synthesis of NPs can be achieved using metal salts, such as nitrates, sulfates, and metal chlorides.

Furthermore, some reactants, such as sodium citrate and ascorbic acid, serve as reducing agents in the reaction. Occasionally, NPs are coated and stabilized with bioactive molecules such as polymers, citrate, and thiol. For the green synthesis of NPs, pure biomolecules or metabolites extracted from plants, bacteria, fungi, algae, lichens, yeasts, and viruses are used as reducing and capping agents. In this systematic review, metal-based NPs were evaluated for their effectiveness as antibiofilm and efflux pump inhibitors against *P. aeruginosa* strains.

Based on the study's findings in Figure 5, the most effective dose of metal NPs was determined to be less than 100 µg/ml. However, few studies reported that silver and titanium NPs had been used at doses up to 1000 µg/ml.

In this regard, research has shown that the consumption of metal NPs in high doses can cause liver and kidney toxicity. The toxicity of metal NPs has been demonstrated in some cases, even at low doses, especially when they are produced via non-biological methods. Consequently, NPs

derived from biological sources are more advantageous for treatment purposes. In this section, recent studies are reviewed in order of the number of studies conducted on nanometallic hybrids.

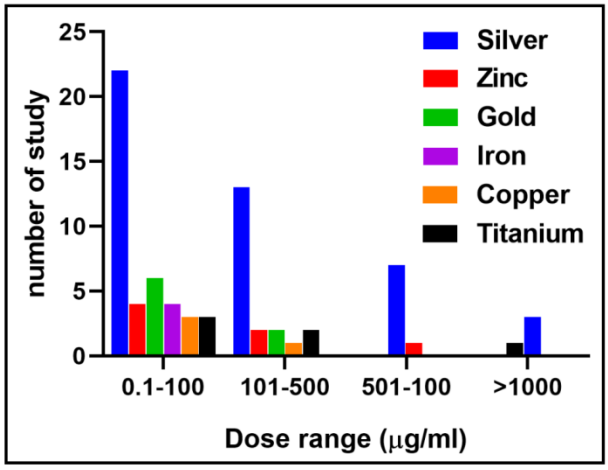

Fig. 5. the percentage of studies arranged based on NPs types against P. aeruginisa Sp.

Silver nanoparticles

Silver has been used as an antimicrobial agent in ancient medicine throughout history. AgNPs are mostly used in medical devices, food additives, packaging materials, electronics, and agricultural products. The antimicrobial properties of silver are attributed to silver ions' formation from its salt. The silver ions disrupt the homeostatic balance of the cell by damaging the membrane and causing macromolecules to leak out. Further, Ag+ ions can interfere with gene expression and inhibit microbial enzymes by interacting with amino acid or nucleic acid units in proteins and DNA. As a result of the presence of Ag NPs, free oxygen radicals can be produced, such as hydroxyl radicals (OH), hydrogen peroxides (H2O2), and superoxides (O2). In many studies, Ag NPs are documented to have broad antimicrobial effects on bacteria that resist antibiotics. Ag NPs have the potential to reduce bacterial resistance by inhibiting Efflux pumps and the formation of biofilms. In the analyses of data from Table 1, Ag NPs and their hybrids were mostly used for studying antibiofilm and efflux pump inhibition activities in *P. aeruginosa* strains. This study found that Ag NPs were more antimicrobial effective at lower concentrations and least cytotoxic to host cells than other metal NPs. Various methods exist for synthesizing Ag NPs of various shapes and sizes. Literature demonstrated metallic NPs have different biological properties depending on their physiochemical features. In many studies, biomolecules capped Ag NPs were reported to inhibit MDR efflux pumps in various pathogens, including *P. aeruginosa* strains.

Here are some highlights of the studies reviewed. According to Liu et al., Ag NPs combined with 4NPO inhibited quorum sensing and thereby reduced biofilm formation. They concluded that combination treatment with 50 mg/l Ag-NP and 6.25 mg/l 4NPO significantly inhibited the formation of biofilms in P. aeruginosa. In a recent study, Patel et al. (2019) synthesized a nanocomposite consisting of chitosan to encapsulate solid lipid-silver sulfadiazine NPs to improve the therapeutic effectiveness and biocompatibility of the particles. In their study, this

combination increased antibiofilm efficacy at a treatment dose of 18.75 mg/ml. A Niosomal formulation of Curcumin-Copper and silver was developed by Targhi et al. (2012) to enhance antibiofilm activity against P. aeruginosa. Their findings showed that lipid-based NPs exhibited significantly greater antimicrobial activity than free metallic NPs.

As mentioned in table 1, Ag NPs synthesized by biological methods, such as plants or bacteria, exhibited significant antibiofilm and MDR efflux pump inhibitory activity at concentrations below 500 μg/mL. However, some chemically synthesized Ag NPs proved more effective than biologically synthesized ones. Considering this, it is noteworthy that chemical NPs were more toxic for use in living organisms. Silva Santose et al. (2016) synthesized silver nanocomposite coated with xanthan derived from Xanthomonas campestris with a spherical shape and size of fewer than 10 nm. Approximately 500 mg of nanocomposite containing 24.62 g of Ag NPs could inhibit biofilm formation in P. aeruginosa and other pathogens. The NPs could have different antimicrobial properties based on the type of bio-reducing agent used in green silver nanoparticle synthesis. Accordingly, Campo-Beleno et al. prepared two biogenic Ag NPs derived from fungal species and plants using Aspergillus flavus and Citrus latifolia tan, which displayed differential antimicrobial activity. They demonstrated that Ag NPs derived from fungi, combined with antibacterial agents such as meropenem and levofloxacin, had synergistic antibacterial effects in some clinical strains, mainly P. aeruginosa.

In contrast, Ag NPs derived from plants were not synergistic. In another study, Madhi et al. (2020) found that using Ag NPs combined with gentamicin and ciprofloxacin against P. aeruginosa PAO1 increased MIC values by 4 folds. Their study found that combining metal NPs with antibiotics might adversely affect each other's antimicrobial potential. Researchers found that Ag NPs synthesized by green synthesis were more effective at reducing biofilms, especially when coated with biomolecules such as carbohydrate compounds. Meanwhile, metal NPs synthesized using synthetic polymers such as ionic macromolecules such as polyethyleneimine, although possessing good antimicrobial properties had more severe adverse side effects. As the majority of studies on metal NPs' influence on biofilm formation and drug resistance pumps in Pseudomonas have focused on Ag NPs, there is no doubt that there is a great deal of diversity in the studies associated with them.

Zinc nanoparticles

Zinc metal occurs widely in nature as zinc oxide (ZnO), mainly used as an antibacterial, antifungal, and antibiofilm agent in pharmaceutical and cosmetic products (such as antiseptic powders, shampoos, and ointments). [210,211]. Due to the decreased toxicity, the US Food and Drug Administration (US FDA) has deemed ZnO a Generally Recognized As Safe or GRAS substance (21CFR182.8991). Consequently, this makes it safe to be used on humans. A green and environmentally friendly synthetic route to prepare biocompatible ZnO NPs has been developed to reduce the toxicity of synthetically produced ZnO. One of the most valuable and widely used forms in medicine is using ZnO NPs through methods based on green resources.

Also, the use of hybrid nanocomposites through the combination of zinc with biomaterials and other metals has improved its medicinal and therapeutic properties. ZnO NPs have shown very effective antimicrobial properties against many microorganisms. The mechanism of antimicrobial action of ZnO NPs is through the electrostatic binding of NPs to the bacterial coating [26, 63].

One of the most important ways of creating the antimicrobial effect of NPs on the production of reactive oxygen species (ROS) is due to the creation of a reactive band with a wide band gap of 3.37 eV. Studies have shown that the release of Zn2+ ions causes the creation of ROS on the surface of bacterial cell membranes. They also display good protein adsorption properties and can therefore be used in the metabolism of human body systems, cytotoxicity regulation, and other cellular responses. ZnO NPs exhibited the potential of antibacterial activity via inhibition of biofilm formation in various pathogens. Here, some of the related studies focused on P. aeruginosa biofilm inhibition by ZnO NPs have been reviewed. Several studies have demonstrated that ZnO NPs prevent the formation of biofilms by disrupting the quorum sensing signals. Garcia*Lara et al. (2015) found that chemically synthesized ZnO NPs can disrupt quorum-sensing signaling depending on the biofilm formation in six clinical strains of P. aeruginosa isolated from cystic fibrosis patients. According to Fadwa et al. (2021), chemical-based ZnO NPs exhibit anti-biofilm functionality at concentrations as low as 2 µg/ml.

Further, researchers developed zinc oxide nanocomposites stabilized with chitosan nanocomposites, inhibiting drug resistance pumps when used at 10 to 1000 µg/ml concentrations. Medhi et al. (2020) observed synergistic effects of ZnO NPs emasculated in chitosan in combination with gentamycin and ciprofloxacin against P. aeruginosa MDR strains at 16 and 128 µg/ml. Similarly, Hemati et al. (2020) found that ZnO NPs encapsulated in chitosan provided synergistic effects with gentamicin at 128 µg/mL. According to several studies, ZnO NPs inhibit their efflux pump and biofilm-related genes from exerting their antibacterial activity. Abdelraheem et al. (2021) reported that treatment with ZnO-NPs significantly reduced the amount of biofilm expression in clinical isolates of P. aeruginosa. Rahmati et al. assessed the effects of Au-NPs and ZnO-NPs on the expression level of the MexAB-OprM efflux pump genes in clinical isolates of P. aeruginosa. Based on their findings, Au-NPs and ZnO-NPs failed to inhibit the efflux pump in the isolates studied [49]. This means some strains of P. aeruginosa developed their ways of tolerating ZnO NPs' antimicrobial properties. In such a scenario, combination therapies might be able to remove the pathogens' resistance strategies. For instance, Eleftheriadou et al. (2021) demonstrated that CuO, ZnO or CuZn NPs in combination with ciprofloxacin inhibit the efflux pump and can be used as potential sources of efflux pump inhibitors in P. aeruginosa [35].

Gold nanoparticles

The element gold is symbolized by the atomic number 79 and has the Latin name aurum (Au). The use of gold for therapeutic purposes dates back to the 1920s when Robert Koch used gold

cyanide salt to kill tuberculosis bacilli. Today, many diseases are treated with gold compounds, including rheumatoid arthritis, palindromic rheumatism, lupus erythematosus, and cancer [84]. A major application of Au NPs is the diagnosis of diseases and their imaging of them. Due to the coherent vibrations of open electrons on the surfaces of Au NPs, they may show intense assimilation of light in their visible area. Surface plasmon resonance (SPR) has recently been demonstrated in Au NPs, allowing the development of optical biosensors. During photothermal therapy, Au NPs' electrons are vibrated from their conduction band to their transition band (d to sp), producing local heat to destroy cancerous tissues and cells. The photothermal properties and bioconjugation potential of Au NPs make them ideal antibacterial agents against MDR pathogens. Therefore, combining Au NPs and antibiotics is an effective treatment for MDR pathogens. In a recent study by Arya et al. (2019), vanillin-capped Au NPs were synthesized with sizes of 35 nm in various polymorphs and hexagonal, triangle and spherical forms. Synergistic effects were found by combining Au NPs (50 g/ml) with meropenem or trimethoprim, with a 10 and 14 folds reduction in MIC values for meropenem antibiotics, respectively.

Additionally, Au NPs at a concentration of 50 g/ml significantly inhibited the Efflux pump activity of the XDR Pseudomonas aeruginusa strain [20]. Zhang et al. (2020) conjugated AuNPs with fucose and galactose to create core-shell AuNPs capable of loading Ceftazidime (CAZ). Fuc-AuNP@CAZ and Gal-AuNP@CAZ were highly potent for effective photo/chemotherapeutics to eradicate *P. aeruginosa* biofilms formed on clinically relevant surfaces (glass slides and steel surfaces).

Mubdir et al. (2021) synthesized chemically Au NPs and coated them with curcumin (cur) to improve their stability and biocompatibility. Compared with uncoated AuNPs, Cur-coated AuNPs significantly enhanced anti-biofilm activity against pathogenic P. aeruginosa isolated from various tissues in hospitalized patients. It has been established that quorum sensing is a necessary signal for forming biofilms by microbial populations. Hence, suppressing quorum-sensing can assist in preventing bacteria's resistance to antibiotics. According to Qais et al. (2021) study, biogenic AuNPs synthesized using capsicum annuum extract could significantly disrupt quorum sensing signals in P. aeruginosa PAO1. According to several studies, quorum sensing by microbial populations is a signal that enables them to form biofilms. Hence, suppressing quorum-sensing can assist in preventing bacteria's resistance to antibiotics. In a study by Khare et al. (2021), Embelin-loaded chitosan Au-NPs inhibited the expression of some genes associated with efflux pumps in P. aeruginosa (MexA, MexB, and OprM). Similarly, Dorri et al. (2022) approved that Au-NPs significantly decreased the expression of mexA and mexB efflux pump genes in P. aeruginosa [18].

Copper nanoparticles

Among the alloying applications, copper (Cu) has traditionally been used as an antimicrobial agent to combat microbes in the industry […..]. The use of copper in homes dates back to ancient

times due to its broad antimicrobial properties against various human pathogens. CuO NPs are typically used in applications such as solar cells, sensors, color catalysts for decomposition, and biomolecule detection. Copper is an essential component in biological metabolic pathways. Some enzymes require copper as a cofactor, including superoxide dismutase, tyrosine kinase, cytochrome-C oxidase, etc. They generate cellular energy through mitochondrial respiration by participating in enzymatic activities. According to studies, copper is highly effective in combating specific human pathogens, particularly Gram-negative bacteria. Cu NPs are small and have plasmonic properties, meaning they exhibit a high plasmonic resonance characteristic known as surface plasmonic resonance (SPR). As such, they can interact with bacterial membranes and, ultimately, destroy them by lysis of the cells. Cu NPs may function by producing released Cu2+ ions in the bacterial cell membrane and penetrating it.

A recent study has shown that NPs can penetrate biofilms and destroy them—furthermore, copper acts by inactivating the enzymes involved in biofilm synthesis to inhibit its formation. Targhi et al. (2021) developed a liposomal formulation containing curcumin-capped Cu NPs encapsulated in chitosan hydrogel and evaluated its antibiofilm-eradicating effects against Staphylococcus aureus and P. aeruginosa. They concluded that Cur-CuNPs@Ch enclosed significantly greater antibiofilm activity than each alone. Aswathanarayan et al. (2017) demonstrated that some metal NPs, copper oxide, iron, zinc oxide, and Au NPs could significantly inhibit biofilm formation in MDR pathogens, especially P. aeruginosa PA01. Their results elucidated that copper oxide NPs had a MIC value of 6.25 μg/ml against P. aeruginosa PA01. As reported by Singh et al. (2019), polyacrylic acid-coated CuNPs were synthesized and examined for their ability to inhibit the Efflux pump and antibiofilm activities against P. aeruginosa MTCC 3541. In contrast to the literature, P. aeruginosa MTCC 3541 displayed high resistance to both CuNPs and Cu2+ (MIC 300 g/ml and >600 g/ml). Although CuNPs and Cu2+ exposure significantly decreased genes associated with Efflux pump activity and biofilm formation, the physical disruption of biofilm by CuNPs is thought to be the main mechanism for their anti-biofilm activities.

Chalcogenide nanoparticles

As the name implies, chalcogenides are chemical compounds that contain at least one chalcogen, including oxygen, sulfur, selenium, tellurium, polonium and an element, which may be an anion or a cation. Among chalcogens, both S and Se have reported medicinal uses and the potential to control several biological applications. In ancient times, sulfur and selenium compounds have been used to treat and prevent microorganism-caused infections. Several biological activities are attributed to sulfur and selenium in these compounds, including antimicrobial, antioxidant, and anticancer properties. However, the low water solubility of bare sulfur prevents it from being used in biological applications [95]. Kher et al. (2022) examined chemically synthesized Sulfur NPs against MDR Staphylococcus pseudintermedius (SP) and P. aeruginosa (PA) isolated from canine skin explants in both the planktonic and biofilm state […..]. The authors found that sulfur NPs could inhibit 7 of 10 MDR-SP isolates at the concentration of 233.3 g/mL in their study. In

contrast, 6 out of 10 isolates were inhibited in the biofilm state at a concentration range of 233.33 to 1866.7 g/ml.

Several biological properties are associated with silver, copper, and zinc salts in chalcogenide NPs. These salts are widely used in photography, chemotherapy, and biosensors. Additionally, sulfur NPs have strong catalytic properties that can remove environmental toxins. Among the elements in the chalcogen group, selenium has strong antioxidant properties. In recent studies, copper, zinc, and silver selenide have been found to have antimicrobial and anticancer properties [40,41, 69, 29, 93]. Multichalcogen NPs have also been developed, which can act synergistically with different treatments. According to Shakibaie et al. (2015), biogenic Se NPs and selenium dioxide were evaluated for their anti-biofilm activity against clinical isolates of P. aeruginosa. According to their findings, biofilm Se NPs inhibited P. aeruginosa biofilms 34.3% more efficiently than untreated samples [61].

Singh et al. (2017) produced Se NPs by a biological method, which inhibited the quorum sensing signaling pathway's genes and ultimately prevented biofilm formation in P. aeruginosa bacteria [69]. Mirzaei et al. (2021) produced silver selenide and zinc selenide by biological method from extracts of the plant, *Melilotus officinalis* and seaweed *Gracilaria corticata* [40, 41]. They reported that these NPs could inhibit biofilm in many bacteria, especially P. aeruginosa. Darabpour (2018) produced sulfur NPs coated with Fullerene. They showed that at a concentration of 2 to 4 mg/liter, it inhibited P. aeruginosa biofilm. The only study included in this review of tellurium NPs was by Alvares et al. (2021), who produced tellurium nanorods with an average size of 40 nm using cell lysates of Haloferax alexandrinus GUSF-1 (KF796625). Their findings showed that these tellurium nanorods showed a 75.03% reduction in P. aeruginosa ATCC 9027 biofilms at a concentration of 50 µg/ml [90].

Titanium nanoparticles

Among the most widely used metal NPs for photocatalysis, TiO2 NPs have been used in various synthesis reactions as catalysts. Among the many applications of titanium, tissue engineering and implants are particularly important due to their high biocompatibility. Generally, titanium oxide is found in three different crystal forms: rutile, anatase, and brookite. Among these crystalline forms, anatase is most interesting for its biological activity. Photocatalytic reactions are triggered when these NPs are exposed to UV rays (UV-A, B, and C), which cause electrons to be released from nanoparticle electron holes. Titanium NPs are also antimicrobial because their valence layer releases electrons, which cause destructive reactions in biomolecules. TiO2 NPs doped with other metals are preferable for antimicrobial applications to TiO2 NPs alone. Titanium NPs are usually modified using carbon-based materials such as carbon nanotubes, graphene, or carbon dots. Numerous studies have been conducted on the effects of titanium NPs on inhibiting biofilms or efflux pumps, most of which included pathogenic bacteria other than Pseudomonas. In this case, Ahmad examined the effects of titanium dioxide NPs (TiO2) on the expression of the efflux pump in MDR P. aeruginosa. They concluded that TiO2 NPs reduced biofilm

formation by 96% due to reducing the efflux pump's expression. In addition, using TiO2 alone and in combination with antibiotics led to a decrease in the expression of the efflux pump genes MexY, MexB, and MexA [31].

Iron nanoparticles

Iron-based, especially magnetic NPs, are one of the most widely used NPs in medicine. These NPs have been used in various applications as carriers for drugs and drugs to be delivered directly to specific areas of the body. Additionally, evidence suggests that iron NPs possess an antimicrobial effect. Sharif et al. examined the effect of FeO-NPs on the expression of the MexAB-OprM efflux pump gene against resistant isolates of P. aeruginosa. According to this study, this nanoparticle has a weak potential to inhibit MexAB-OprM efflux pump function. According to Pham et al. (2019), iron NPs (FeOOH-NP) inhibit biofilm formation and disrupt biofilm structure in a concentration-dependent manner [28].
Armijo et al. (2020) assessed the antibacterial activity of iron oxide, iron nitride, and tobramycin-conjugated NPs against *P. aeruginosa* biofilm. The results showed complete inhibition for all NPs except PEG-capped NPs at 17.5 mg/ml. Therefore, no susceptibility was found to PEG-capped NPs, suggesting the capping agents contributed significantly to the nanocomposite's bactericidal properties [25].

Silica nanoparticles

According to studies, SiO2 NPs function as microporous and mesoporous carriers for various drugs. Consequently, few studies have focused solely on SiO2 NPs' biological effects. Various studies have indicated that Silica has a synergetic effect on the biological system when combined with other metals. A recent study by Hiebner et al. (2020) examined the antibiofilm effect and affinity of SiO2 NPs in the structure of an extracellular polymeric substance matrix. It indicated that a confocal laser scanning microscopy (CLSM) technique could clarify biofilm-nanoparticle interactions, which is more efficient when controlling biofilms based on nanoparticle systems [48]. Various methods, including doping SiO2 NPs with other metals, have been used in some studies. Li et al. (2018) functionalized several metallic NPs, including Silica, with single-wall carbon nanotubes (SWCNTs), C60, or graphene oxide (GO). They found that Ag, Fe, ZnO, TiO2-SWCNTs, C60, and GO-based nanocomposites were potent against quorum sensing genes of P. aeruginosa PAO1. However, SiO2-SWCNTs, C60 and GO-based nanocomposites had no significant antibiofilm or anti-QS activity in P. aeruginosa PAO1. Memar et al. (2021) synthesized mesoporous SiO2 NPs (MSNs) loaded with meropenem to examine antibiofilm activity against carbapenem-resistant P. aeruginosa. According to the findings, Mer-SiO2 NPs demonstrated antibacterial and biofilm inhibition activities on all isolates at levels lower than MICs for meropenem alone. According to Nsayef Muslim et al., after investigating the anti-biofilm effects of silica-conjugated lectin NPs against P. aeruginosa, pure lectin is about 70%

effective against biofilms. In contrast, gold, platinum, SnO2, and SiO2 NPs inhibit biofilms by 94% and 91%, respectively reported at 89% and 86% [17].

Multi-metal nanoparticles and their combinations

As the development of NPs proceeds, combining different materials may be effective in emerging new properties. The biological activity of metal NPs is directly affected by their surface coating and the compounds involved in their synthesis. Various studies have demonstrated that combining several metal NPs or doping metals during their synthesis stage can increase their biological activity or yield new properties. Several metals can be used in the structure of NPs, along with polymers and macromolecules. Several metals are combined into metal nanocomposites for redox and photocatalytic reactions. According to studies, NPs doped with some antimicrobial agents are more effective than others. Among the studies that demonstrated the importance of double NPs over single NPs, Elfetriado et al. 2021 showed that polyol-CuZn NPs, combined with ciprofloxacin and meropenem, were more effective than CuO, ZnO NPs at inhibiting the efflux pump and reducing resistance in MDR P. aeruginosa [35]. Additionally, they demonstrated that a cocktail of all NPs was the most effective treatment for inhibiting efflux pumps.

It is important to consider the composition of each component in formulating multimetal NPs. The biological properties of nanocomposite materials can be altered by modifying the ratios of their constituent components. Baig et al. studied the anti-biofilm activity of copper oxide-titanium dioxide nanocomposites against drug-resistant P. aeruginosa. It was found that increasing the amount of CuO in nanocomposites significantly reduced the biomass of P. aeruginosa. In addition, the maximum inhibition of biofilm formation compared to pure TiO2, α-CuO@TiO2, and β-CuO@TiO2 was related to γ-CuO@TiO2 [33].

Other Nanoparticles

A systematic analysis included 74 studies, two of which studied cerium oxide NPs and one of which studied nickel NPs. Among the most promising nanomaterials, cerium oxide NPs (CeO2 NPs) are used for polishing materials, fuel additives, and other applications. The Cerium oxide NPs (CeO2 NPs) are known to have antibacterial properties due to the relatively low toxicity and unique mechanism of action that these NPs possess. The antimicrobial activity of CeO2 NPs is attributed to the reversible transition between Ce(III)/Ce(IV) valence states that act as a catalyst in biological pathways. Accordingly, Xu et al. studied the effect of cerium oxide NPs (CeO2-NPs) on P. aeruginosa biofilm formation, rhlI-rhlR, rhlAB, and pqsR-pqsA genes associated with biofilm formation. Cerium oxide NPs were found to reduce biofilm formation by interfering with the QS system and generating reactive oxygen species (ROS) [30]. Several studies have shown that coatings based on CeO2 NPs are an effective barrier to the attachment of microbes to non-living surfaces. Due to their antimicrobial properties, CeO2 NPs prevent bacteria from surviving on surfaces. In this regard, Jegel et al. (2022) constructed highly transparent CeO2-polycarbonate

(PC) surfaces with anti-adhesive properties against bacterial biofilms. They were highly efficient functional mimics of haloperoxidases due to their high catalytic activity in halogenation reactions. Various studies have shown that these enzymes prevent biofilm formation by halogenating quorum-sensing molecules that interfere with cell-to-cell communication in bacteria. In the present study, NiO NPs had the least contribution among the NPs studied. Numerous studies have demonstrated the antimicrobial properties of NiO NPs. According to our criteria, only one study demonstrated the effect of NiO NPs on P. aeruginosa biofilms and efflux pumps in this study. Maruthupandy et al. (2020) chemically fabricated nickel NPs with potassium hydroxide in alkaline conditions. These NPs were characterized as rod shapes with 3 nm in width. As NiO NPs were applied at a dose range, biofilms were inhibited in a dose-dependent manner at 60 µg/ml.

Conclusion

The emergence of antimicrobial resistance based on biofilm mats is one of the most important strategies for prolonging the life of pathogens in the body and the environment. The presence of microbial biofilms on the surfaces of objects in hospitals can spread infection. Additionally, microbial resistance is a consequence of signaling between microbial populations collectively resisting antimicrobials. Here, some antimicrobial compounds can alter the physical structure of microbial biofilms, leading to eliminating resistance flows. Additionally, inhibiting signaling currents before biofilm formation is essential in combating microbial resistance. The multidimensional nature of NPs allows them to exert various effects on bacterial resistance. The presence of drug efflux pumps in pathogenic bacteria is another form of resistance to antibiotics. Microbial resistance may occur naturally or through cross-infection with other strains of pathogens, so broad-spectrum medicinal compounds may be effective in removing both specific and nonspecific forms of resistance. Therefore, NPs can inhibit microbial pathogenicity by interrupting resistance gene expression through their specific functions. A tripartite system of efflux pumps exists in P. aeruginosa, which is responsible for removing antimicrobial substances from the cell. Various NPs with various antimicrobial properties have been evaluated in this study by antibiofilm and efflux inhibition methods based on their potential to inhibit bacterial growth. According to these studies, NPs have the potential to serve as powerful antimicrobial agents for drug development against microbial resistance. Still, it is important to consider their safety for host cells and biocompatibility under physiological conditions. Taken together, recent studies have shown that further study is needed to achieve an effective formulation that meets the criteria of a standard drug for anti-biofilm drugs or efflux pump inhibitors. Further, it appears as though a broad range of more extensive studies on this trial are necessary to eliminate microbial resistance in vivo under physiological conditions.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Not Applicable

ACKNOWLEDGEMENTS

The authors appreciated the Vice Chancellor for Research and Technology of Lorestan University of Medical Sciences.

THE STANDARD FOR REPORTING:

PRISMA guidelines and methodology were followed.
PRISMA checklist is available on the publisher's website.

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