Review article

Antibiofilm and Anti-quorum Sensing Activities of Biological Nanoparticles

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Abstract

Despite the availability of numerous antibacterial treatments, infectious diseases caused by multidrug-resistant bacteria remain a significant public health threat and are rapidly becoming the leading cause of global mortality. The emergence of multidrug resistance is due to the extensive use of high-dose antibiotics. Additionally, biofilm is another barrier to effective disease treatment because bacteria trapped in biofilm can resist antimicrobial agents. Therefore, the development of new strategies to combat multidrug-resistant bacteria and biofilm-associated infections is urgently needed. This is why special attention has been given to a recent area, "nanotechnology". Nanoparticles could be a source of hope for this problem as they can not only eliminate biofilms, but also interfere with quorum sensing (QS). Several studies have highlighted the advantages of biosynthesis over physiochemical synthesis of nanoparticles. These biologically synthesized nanoparticles demand special attention since this green technology combines energy and cost efficiency with environmental friendliness. This review summarizes the use of biological nanoparticles as biofilm and QS-inhibitors to combat biofilm-associated infections.

1. Introduction

Antimicrobial resistance is a critical global health issue that poses significant threats to mankind and animals. The Centers for Disease Control and Prevention's (CDC) 2019 report on antimicrobial resistance-related illnesses in the United States revealed that antibiotic resistant bacteria caused over 2.8 million infections each year, resulting in more than 35,000 fatalities [1]. As a result of enhanced resistance of bacteria to antibiotics and the complexity of drug discovery, a progressive decrease in

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antimicrobials development is occurring. Additionally, the World Health Organization (WHO) has listed combatting drug resistance as one of the top ten global health challenges to be monitored in 2021, as highlighted on 24 December 2020 [2].

Bacteria can develop genetic resistance to antimicrobials through frequent exposure to antibiotics. Biofilm formation is another mechanism that bacteria use to evade antibiotic exposure, posing a major health risk due to their multi-drug resistance, ability to evade host defenses, and other stress factors [3]. Biofilm bacteria's resistance to antibiotics is up to 1000 times superior to that of planktonic cells, leading to prolonged and stubborn bacterial illnesses worldwide [4]. A bacterial biofilm is a group of bacteria that can adhere to abiotic and biotic surfaces through self-produced extracellular polymeric substances (EPS) and glycocalyx [5]. Bacteria can adhere to various materials, especially on all medical implants including contact lenses, catheters, prostheses, and heart valves [6]. The capacity of bacteria to adapt to different environmental conditions and form biofilms may depend on a communication mechanism known as quorum sensing (QS) [7]. This mechanism regulates the expression of several virulence factors, including pyoverdine, pyocyanin, rhamnolipids protease, alginate, and elastase of *Pseudomonas aeruginosa*, lipase, protein A, fibronectin, enterotoxin, and hemolysins of *Staphylococcus aureus* [8, 9]. These virulence factors can create significant therapeutic problems and make treatment options very complicated. Therefore, QS inhibition is a critical drug target to combat several bacterial and fungal infections.

Several studies have shown that bacterial virulence factors can be targeted through inhibition of the QS system using either biological compounds and/or synthetic drugs [10, 11]. Combining QS inhibitors with conventional antibiotics has also shown promising preclinical benefits [12]. Nevertheless, as a result of inadequate stability, bioavailability, systemic solubility, and delivery, the implementation of these QS inhibitors in clinical trials has proved to be limited [13]. Therefore, the development of new control strategies that can effectively inhibit the QS signaling network and biofilm formation has become increasingly important as resistance to usual treatments has emerged.

The design of a new generation of nano-antimicrobials, notably QS and biofilm nano-inhibitors, has captured the attention of researchers due to their better penetration into mucus and biofilm, effective delivery, and their higher solubility [14]. Various applications of metal nanoparticles have recently been investigated in environmental, agricultural, and biomedical fields [15, 16]. In addition, nanomedicine has emerged as a new field due to the multitude of applications of nanotechnology in medicine [17]. Indeed, metal nanoparticles have been shown to be effective antimicrobial, antibiofilm, and anti- QS agents [18]. Furthermore, metal nanoparticles can replace conventional antimicrobials for inhibiting biofilm and QS and treating bacterial infections. However, the environmental contamination caused by the release of heavy metals imposes limitations on the various physiochemical methods of synthesizing these metal nanoparticles. Therefore, biological synthesis is a new trend in nanoparticle manufacturing due to its reproducibility, ease of use, nontoxicity, cost-effectiveness, and eco-friendliness [19]. Thus, this review aims to discuss the diversity of the field, starting with; a brief explanation of the biofilm lifestyle and antibiotic resistance within it, the biosynthesis of nanoparticles and the critical parameters influencing this synthesis, the various advantages of biological nanoparticles, and their antibiofilm and anti-QS activities.

2. Biofilm Formation and Drug Resistance

Biofilm formation by bacteria provides them with a protective habitat that allows them to withstand environmental conditions and accumulate vital elements [20]. It is defined as a small immobile community of microbial origin consisting of surface-attached cells integrated into a matrix of extracellular polymeric substances (EPS) [21], that offers protection against desiccation, oxidizing

agents, antibiotics, ultraviolet radiation, and host immune responses [22]. Biofilms may form on a diverse range of surfaces, including natural aquatic systems, drinking and industrial water piping, medical devices, and living tissue. Several Gram-positive and Gram-negative bacteria may build biofilm, for example, *Streptococcus viridians, S. epidermis, S. aureus, Enterococcus faecalis, Klebsiella pneumonia, P. aeruginosa, Proteus mirabilis,* and *Escherichia coli,* are all linked to life-threatening infections [23]. In addition, biofilm is the most predominant mode of growth for microorganisms on earth [24].

Biofilm resistance is widely recognized to have caused approximately 30 million fatalities and has significant economic impact [25]. The CDC estimates that 65% of bacterial infections involve biofilms, while the National Institutes of Health estimates that it is 80% [26].

The WHO has recently established a ranking of microorganisms that require careful study for the development of new antibiotics. This organization has published its first list, which distinguishes three classes of microorganisms based on priority given to the search for new antibiotics: critical, high, or medium [27]. Several new antibiotics were discovered and used in medicine from 1940 to 1960. However, some microbial strains have developed resistance to antibiotics. As a result, the effectiveness of antibiotics has decreased, necessitating the discovery of new antibacterial drugs [28]. The discovery of a novel molecule requires ten years or more, while microorganisms can develop resistance in just one to two years, highlighting the urgent need to develop alternative antimicrobial therapies [29]. Chronic bacterial infections associated with tissues and devices are not easily treated and patients are placed at high risk of recurrence [30]. Planktonic bacteria emerging from biofilm can propagate to other areas of the body or surrounding the disease site. Although a combination of antibiotics and host immune responses can destroy planktonic bacteria, there is a set of biofilm bacteria that is not eradicated through antibiotic treatment, leading to the recurrence of the infection [31].

Drug resistance in bacteria arises from mutations or swapping of antibiotic resistant genes [32]. Indeed, the sensitivity of microorganisms to antibiotics increases as they shed the biofilm, indicating that resistance to antibiotics in the biofilm is not mainly caused by mutation or gene exchange [33]. Antibiotic sensitivity decreases with biofilm maturation. For instance, in *P. aeruginosa*, bacterial resistance increased more than 4-fold in aged biofilm (day 7), compared to the new biofilm (day 1) [34]. In this review we will examine the different mechanisms by which biofilms tolerate or resist antibiotics.

2.1 Bad penetration of antibiotics

The stability of biofilm is largely influenced by the EPS matrix, which has been hypothesized to act as a barrier against several antibiotics [35]. Resistance is due to the inactivation or sequestration of antibiotics by the biofilm matrix. For example, several antibiotics of the aminoglycoside class have positive charges. They interact with the negative elements of the biofilm matrix, such as eDNA, which blocks the penetration of the antibiotic into the biofilm [20, 32]. In contrast, antimicrobial agents that do not interact with EPS constituents readily pass through biofilms, indicating that the diffusion barrier may not be the only cause leading to high antibiotic resistance in biofilms [36]. Antibiotics can be chelated by EPS matrix components by creating complexes. In addition, enzymes present in the biofilm matrix can degrade antibiotics, reducing their concentration to a level insufficient to destroy the bacteria, allowing them to survive even after exposure [20].

2.2 Changes in the microenvironment

Compared to the bacteria in the surface layer of the biofilm, the microorganisms in the deep part of the biofilm have very little or no oxygen [37]. Some antibiotics such as β-lactams, fluoroquinolones,

and aminoglycosides exhibit ineffective antibacterial action under anaerobic conditions [25]. Furthermore, this oxygen gradient in the biofilm reduces bacterial growth, which makes antibiotics less effective since most of them target the synthesis pathways of bacterial macromolecules [38]. Another agent that hinders the performance of antibiotics is the storage of toxic waste, which leads to pH alteration, substrate depletion, and reduced metabolic activity causing bacteria to enter a stationary phase. The transition is often associated with a decrease in sensitivity to a large number of antibiotics [39] since these antibiotics have lethal activity related to growth [40].

2.3 Horizontal gene transfer

Antimicrobial resistance arises through various mechanisms, including horizontal transfer of genes. Several studies have proven that bacteria in biofilms regularly swap antibiotic resistance genes [41]. These genes are usually harbored by mobile genetic elements like transposons [42], conjugative and non-conjugative plasmids [43], and bacteriophages [44]. In dual-species biofilms of *E. coli* and *P. putida*, it was found that plasmids giving antibiotic resistance were transferred by conjugation [45]. In addition, conjugation in biofilms is 700 times more efficient than in planktonic bacterial cells [46]. The eDNA present in the biofilm matrix can serve as the target of horizontal gene transfer [47].

3. Nanoparticle Synthesis

Nanotechnology has received special attention due to the specific physicochemical characteristics of nanoparticles and its intensive use in various fields. The prefix nano is taken from the Greek word *nanos*, which means "dwarf", and designates objects with a size of one billionth (10^{-9} m) of a meter. It is based on the production and modulation of nanoparticles [48]. Nanoparticles typically measure from 0.1 to 1000 nm in every spatial dimension [48]. The entirely new or improved properties of nanoparticles has allowed a rapid progression of their applications in various fields such as pharmaceutical, antimicrobial, biomedical, catalysis, and drug delivery fields, among others [49]. Nanoparticles are generally generated through two approaches: bottom-up and top-down [48]. In the bottom-up approach, nanoparticles can be produced through chemical (chemical reduction) and biological means (use of microorganisms, plants, etc.) by joining atoms to form new nuclei that develop into nanosized particles [50], In contrast, in the top-down approach, the appropriate bulk material is broken down into fine particles through size reduction using different techniques such as grinding, sputtering, milling, thermal or laser ablation [51].

At present, numerous chemical (chemical vapor deposition, galvanic displacement, wet chemical reduction, and electrochemical reduction) and physical (aerosol-assisted deposition, flame synthesis, laser ablation, and electron-beam induced reduction) methods for synthesizing nanomaterials providing a high production rate and enable precise control of nanomaterial size and shape [52]. However, the environmental pollution caused by heavy metals, the use of noxious chemicals, high bio-waste production, and energy losses limit their application [53]. Thus, there is a growing need for the development of biocompatible, cost-effective, and environmentally friendly nanomaterial manufacturing technologies. Therefore, the use of biological methods for nanoparticle synthesis offers several advantages and represents a new approach to nanomaterial synthesis. In particular, microorganisms and plants, especially, are very promising new sources for the synthesis of nanoparticles [19]. Several microorganisms, notably yeasts, fungi, and bacteria, and also plant tissues (fruit, bark, flower, stem, root, peel, leaf, etc.), have been successfully used in biological nanoparticle synthesis (Table 1).

Table 1. Biological synthesis of nanoparticles using various bioreducers

Biological Material	Temperature (°C)	Reaction Time	Types of Nanoparticles	Size (nm)	Shape	References
Microorganisms						
Bacillus licheniformis (MN900686)	37	72 h	Silver	30-46	Spherical	[54]
B. subtilis CN2	25	30 min	Silver	~21	Spherical	[55]
Kocuria sp.	54.07	13.24 h	Silver	10-200	Spherical	[56]
B. megaterium	60	72 h	Silver	3-15	Spherical	[57]
Aspergillus niger	70	72 h	Silver	1-10.5	Spherical	
Streptomyces rochei	28	8 days	Silver	5–40	Spherical	[58]
Streptomyces spiralis	28	8 days	Silver	20-60	Spherical	
Vibrio sp.	28	96 h	Silver	32.67–107.18	Spherical	[59]
Micrococcus yunnanensis	Room temperature	24 h	Gold	~54	Spherical	[60]
Vibrio alginolyticus	40	24 h	Gold	50–100	Irregular	[61]
B. zhangzhouensis	Room temperature	5 h	Magnetic iron oxide	20-70	Rhombus	[62]
P. putida	37	24 h	Zinc oxide	25 and 45	Spherical	[63]
Clostridium pasteurianum	28	4-5 h	Molybdenum	~15	Spherical	[64]
Streptomyces sp. MHM38	30-32	60 min	Copper oxide	1.72–13.49	Spherical	[65]
Monascus purpureus	28	10 days	Selenium	~48	Spherical	[66]
Biological Material	**Temperature (°C)**	**Reaction Time**	**Types of Nanoparticles**	**Size** (nm)	**Shape**	**References**
Plants						
C. sinensis	65	30 min	Silver	2- 20	Spherical	[67]
Cuminum cyminum	90	15 min	Silver	1.84-20.57	Globular	[68]
Malus domestica	90	15 min	Silver	5.46–20	Spherical	
Hypericum perforatum L	60	4-6 h	Silver	20-60	Spherical	[69]
Plantago major L	70	60 min	Silver	~10-20	Spherical	[70]
Ziziphus spina-christi	Room temperature	30 min	Silver	11.9-38.8	Spherical and hexagonal	[71]
Konjac glucomannan	90	30 min	Palladium	~6.48	Spherical	[72]
Iraqi Zahidi dates	90	20 min	Platinum	30-45	Spherical	[73]
Helianthus annuus	Room temperature	2-3 h	Zirconium oxide	6-50	Spherical	[74]
Cinnamomum tamala	60	3 h	Zinc oxide	~35	Hexagonal	[75]

3.1 Critical factors for the green production of nanoparticles

Although the biological nanoparticle synthesis approach has several advantages, the polydispersity of the formed nanoparticles is still a challenge. Therefore, it is very important to rationally develop a stable system that allows the production of nanoparticles of homogeneous morphology and size.

Many recent studies (Table 1) have attempted to establish stable systems for the biological synthesis of nanoparticles.

The pH of the solution plays a crucial role in biosynthesis of nanoparticles by affecting the shape, size, and speed of synthesis [76]. This effect may be due to the greater number of functional groups that bond and nucleate metal ions with increasing pH [77]. For example, *Garcinia mangostana* L rind extract produced many small-sized platinum nanoparticles at alkaline pH, while larger nanoparticles were observed at acidic pH [78]. Al-Radadi [79] studied the effect of pH on the synthesis of platinum nanoparticles using a range of pH solutions from 1.5 to 8.5 and found that a basic medium led to a quicker synthesis of platinum nanoparticles compared to an acidic solution. Generally, the synthesis of platinum nanoparticles is enhanced when the hydroxyl content of the medium, i.e., alkalinity, increases.

The reaction temperature is another important parameter that affects the synthesis rate, morphology, and size of nanoparticles. The synthesis of silver nanoparticles from *Camellia sinensis* extract was strongly affected by temperature conditions. At 25°C, it was observed that nanoparticles of various morphologies, such as capsule, polygonal and spherical were formed. Nevertheless, by increasing the temperature to 65°C, these nanoparticles adopted a spherical shape of varying sizes as a result of an enhanced reduction rate [67]. Another study used *Ajwa* date extract to evaluate the effect of temperature on the biosynthesis of platinum nanoparticles. This study found that the average sizes of spherical nanoparticles were 2.6 and 3.4 nm at 30 and 20°C, respectively [79]. In addition, the growth of microorganisms at the highest feasible temperature for optimal growth is advised for the production of nanoparticles with these microorganisms since the enzyme necessary for the synthesis of nanoparticles becomes increasingly active at elevated temperatures [80].

The size and shape of biosynthesized nanoparticles are also influenced by the reaction/incubation time. According to Nishanthi *et al*. [78], the most appropriate reaction time for the production of platinum nanoparticles is 10 min after addition of *G. mangostana* rind extract. The progression of nucleation increases as a function of reaction time, although no substantial spectrum shift is seen after 10 min, indicating that the synthesis was completed within a short time frame. Similarly, Bukhari *et al*. [65] reported that the formation of copper oxide nanoparticles increased over time, while their size decreased. They also showed that by adding a filtrate of *Streptomyces* to the substrate (copper oxide solution), the formation of nanoparticles became clearly visible after 60 min of incubation.

3.2 Advantages of biosynthesized nanoparticles

In recent years, significant progress has been made in the field of biological nanoparticles produced from plants and microorganisms, and their applications. There are many advantages associated with nanoparticle biosynthesis, including biocompatibility of the nanoparticles synthesized, environmentally friendly synthesis, and cost-effectiveness [81]. The presence of biologically active components on the surface of biosynthesized nanoparticles enhances their effectiveness compared to those synthesized through physicochemical methods. Medicinal plants, in particular, contain many metabolites exhibiting pharmacological activity that can bind to the synthesized nanoparticles, giving them an added advantage in improving the efficacy of the nanoparticles [82]. Biosynthesized nanoparticles also exhibit the advantage of being free from harmful contaminants that may be introduced during physicochemical production, making them especially desirable for biomedical applications [83]. Furthermore, no further stabilizing agents are required since the components of plants and microorganisms function as stabilizing and capping agents [81]. Another advantage of the biological synthesis route is that the time needed for the production of nanoparticles is very low. As an example, Nishanthi *et al*. [78] demonstrated that platinum nanoparticles could be synthesized using *G. mangostana* bark extract in just 10 min. Similarly, Arsiya *et al*. [84] reported that the

palladium ion reduction to nanoparticles was realized within 10 min after the addition of *Chlorella vulgaris*. Moreover, green synthesis of nanoparticles reduces the number of steps required, such as the fixation of certain functional groups on the nanoparticles surface to enhance their effectiveness, which is an additional stage in physicochemical synthesis [85]. Plant-based metal nanoparticles are potentially more helpful than those produced through microbial synthesis since plants or plant derivatives do not need a complex technique of preservation or maintenance, unlike microbial cultures [86]. Additionally, nanoparticles produced from fruit or plant extracts provide the advantage of preventing nanoparticle aggregation under conditions of long-term storage [87].

There is a multitude of biomedical applications for which biological nanoparticles have been used, notably antioxidant, anti-diabetic, anticholinergic [88], antifungal [89], anticancer [90], and antimicrobial [91] uses. In the following Sections, we will delve into the specific discussion of the biofilm and QS inhibition activities exhibited by nanoparticles synthesized from microorganisms and plants.

4. Biological Nanoparticles as Antibiofilm Agents

The development of non-toxic techniques for producing nanoparticles is a critical milestone in nanotechnology to make their application in nano-medicine possible. Biofilm research offers a novel avenue for the exploration of antimicrobial agents [92]. Several studies have shown that green synthesized nanoparticles are effective in preventing and eradicating biofilms (Table 2). These nanoparticles are produced by reducing a metal solution using biologically stabilizing and reducing agents [93]. The Table below provides an overview of the biological nanoparticles synthesized from plants and microorganisms that have been employed for the eradication of bacterial biofilms.

Table 2. Antibiofilm activities of nanoparticles synthesized from extract plant and microorganism against various bacteria.

Biological Material	Types of Nanoparticles	Bacterium	Reference
Cedecea sp	Silver	-*E. coli* -*P. aeruginosa*	[94]
Gmelina arborea	Silver	-*B. cereus* -*E. coli* -*P. aeruginosa* -*S. aureus*	[95]
Vibrio sp	Silver	-*P. aeruginosa* -*E. coli*	[59]
Zataria multiflora	Silver	-*S. aureus*	[96]
Foeniculum vulgare	Silver	-*S. aureus*	[97]
Trachyspermum ammi	Gold	-*S. marcescens* -*L.monocytogenes*	[98]
Tinospora cordifolia	Gold	-*P. aeruginosa*	[99]
Anthemis atropatana	Gold	-*K. pneumonia*	[100]

Table 2. Antibiofilm activities of nanoparticles synthesized from extract plant and microorganism against various bacteria (continued)

Biological Material	Types of Nanoparticles	Bacterium	Reference
Marinobacter sp	Zinc oxide	-*P. aeruginosa*	[101]
Eucalyptus globulus	Zinc oxide	-*P. aeruginosa*	[102]
Musa balbisiana	Zinc oxide	-*P. aeruginosa*	[103]
Veronica multifida	Zinc oxide	-*P. aeruginosa* -*S. aureus*	[104]
Cardiospermum halicacabum	Copper	-*S. aureus* -*P. aeruginosa* -*E. coli*	[105]
Penicillium chrysogenum	Copper oxide	-*S. aureus*	[106]
Cymbopogon citratus	Copper oxide	-*S. aureus* -*E. coli*	[107]
Acorus calamus	Cerium oxide	-*S. aureus* -*P. aeruginosa* - *E. coli*	[92]
Lysinibacillus sp	Selenium	-*P. aeruginosa*	[108]
Psidium guajava	Selenium	-*E. faecalis*	[109]
Lamii albi flos	Gold/Platinum /silver	-*E. faecium* -*E. faecalis*	[110]

4.1 Silver nanoparticles

Green-synthesized silver nanoparticles have demonstrated significant antimicrobial and antibiofilm properties against a wide range of microorganisms [111]. For example, Singh *et al*. [94] tested the antibiofilm effect of silver nanoparticles synthesized from *Cedecea* sp versus *E. coli* and *P. aeruginosa.* The inhibition of biofilm formation was found to be concentration-dependent and at a concentration below the minimum inhibitory concentration (MIC). This was caused by direct bactericidal effects or by preventing the adherence of viable bacterial cells. Then, to distinguish between these two effects, they tested the direct bactericidal ability of these nanoparticles, using mature and pre-formed biofilms of the two species by counting the number of colony-forming units to determine the viability of the biofilm cells after treatment. A substantial decrease in the viability rate of bacterial cells was shown in both types of biofilms. Furthermore, these results were confirmed by visualizing the living and dead cells under a fluorescence microscope. Similarly, Chandrasekharan *et al*. [95] demonstrated the effectiveness of silver nanoparticles biosynthesized from aqueous extracts of *Gmelina arborea* against biofilms of *Bacillus cereus, E. coli, P. aeruginosa* and *S. aureus* by inhibiting cell attachment. Furthermore, it was found that silver nanoparticles biologically synthesized by *Vibrio* sp exhibited greater efficacy against *P. aeruginosa* and *E. coli*

biofilms compared to chemically synthesized nanoparticles. Complete inhibition of biofilms caused by these pathogens was observed at concentrations of 250 and 62.5 µg/mL, respectively [59]. In another study, Barabadi *et al*. [96] revealed that silver nanoparticles produced using *Z. multiflora* appeared to be more effective than chemical silver nanoparticles against *S. aureus* biofilm at a lower concentration. Furthermore, Talank *et al*. [97] showed that silver nanoparticles produced by *F. vulgare* seed markedly reduced biofilm formation of standard and pathogenic *S. aureus*. These findings highlight the potential of biologically synthesized silver nanoparticles as viable alternatives for the eradication of bacterial biofilms.

4.2 Gold nanoparticles

Gold nanoparticles, which vary in shape, aggregation capacity, and size, are among the metal nanoparticles synthesized in an environmentally friendly manner. These nanoparticles have also been demonstrated to have bio-medical applications as they possess anti-tumor, antibacterial, and antibiofilm properties [112]. Perveen *et al*. [98] utilized seed extract of *Trachyspermum ammi* to synthesize gold nanoparticles and to investigate their antibiofilm activity against two foodborne pathogens, *S. marcescens* and *Listeria monocytogenes*. The researchers observed a reduction in biofilm development by 81% and 73% for *S. marcescens* and *L. monocytogenes*, respectively. The researchers subsequently discovered that these biologically synthesized gold nanoparticles enhanced intracellular reactive oxygen species generation in these pathogens, which can cause cell death by exceeding the antioxidant system's capability. In another study by Ali *et al*. [99], gold nanoparticles were synthesized using the medicinal plant *T. cordifolia* and then tested for their antibiofilm effect against *P. aeruginosa*. These nanoparticles, at lower doses, were found to be effective at eliminating the biofilms of *P. aeruginosa*. In addition, biologically synthesized gold nanoparticles using *Anthemis atropatana* extract were shown to significantly inhibit the biofilms formed by multi-resistant strains of *K. pneumonia* [100].

4.3 Zinc oxide nanoparticles

Biological zinc oxide nanoparticles have attracted significant research interest due to their wide range of properties, making them suitable for applications in nanomedicine and biomedical engineering [113, 114]. Indeed, Barani *et al*. [101] studied the antibiofilm activity of biological zinc oxide nanoparticles against *P. aeruginosa* and proved that 250 µg/mL of these nanoparticles could produce a 96.55% reduction of biofilm. As a result, they can be regarded as potent and efficient antibiotics. Several other investigations demonstrated that green-synthesized zinc oxide nanoparticles have antibiofilm action against *P. aeruginosa*. For example, Obeizi *et al*. [102] utilized zinc oxide nanoparticles synthesized from the essential oil of *Eucalyptus globulus* and achieved a significant inhibition rate of 85% to 97% in the biofilm formation of *P. aeruginosa*. Similarly, zinc oxide nanoparticles produced from *Musa balbisiana* Colla pseudostem biowaste showed potent antibiofilm activity against *P. aeruginosa* [103]. A plant extract of *Veronica multifida* was used to establish a greener approach to the production of zinc oxide nanoparticles. The nanoparticles expressed an antibiofilm effect against *P. aeruginosa* and *S. aureus* [104].

4.4 Copper and copper oxide nanoparticles

Biological copper nanoparticles have been the object of an important concentration of research due to their use as antibacterial and antibiofilm agents. Punniyakotti *et al*. [105] investigated the antibiofilm activity of copper nanoparticles from *Cardiospermum halicacabum* leaf extract. The results demonstrated antibiofilm activity against *S. aureus, P. aeruginosa*, and *E. coli*. In a similar

vein, Mohamed *et al*. [106] examined the antibiofilm activity of *Penicillium chrysogenum* mediated copper oxide nanoparticles against human pathogenic bacterium *S. aureus*. At doses below the MIC value, these nanoparticles have a significant effect against *S. aureus* biofilms and no effect on bacterial growth. Furthermore, copper oxide nanoparticles synthesized using *Cymbopogon citratus* leaf extract exhibited excellent antibacterial and antibiofilm properties against *S. aureus* and *E. coli* [107]. This indicated that they could be employed as potential new antimicrobial agents against pathogens.

4.5 Other nanoparticles

Numerous studies on the use of various other biological nanoparticles have shown that these nanoparticles are highly effective in disrupting or inhibiting the formation of microbial biofilms. For example, Altaf *et al*. [92] synthesized cerium oxide nanoparticles from an aqueous extract of *Acorus calamus* and tested their antibiofilm activity towards Gram-negative and Gram-positive bacteria. The treatment with cerium oxide nanoparticles reduced the biofilm formation of the tested bacteria by greater than 75%. Treatment with these nanoparticles was also able to prevent the colonization and growth of bacteria in the solid supports. Furthermore, preformed biofilms were shown to be inhibited in a dose-dependent manner. Therefore, these results may lead to the production of novel alternative antimicrobial and antibiofilm. In a separate study, Keskin *et al*. [108] synthesized selenium nanoparticles from *Lysinibacillus* sp. and used them to inhibit *P. aeruginosa* biofilm. Similarly, Miglani and Tani-Ishii [109] demonstrated that selenium nanoparticles biosynthesized using *Psidium guajava* leaves emerged as a novel antibacterial and antibiofilm agent against *E. faecalis*.

Research has demonstrated the remarkable antibiofilm properties of trimetallic nanoparticles. A notable example is the study conducted by Dlugaszewska and Dobrucka [110], who investigated the antimicrobial activity of trimetallic gold/platinum/silver nanoparticles synthesized from the extract of *Lamii albi flos.* The results revealed that these nanoparticles exhibited excellent antimicrobial activity against both planktonic and sessile strains of *Enterococcus faecium* and *E. faecalis*, highlighting their potential as effective agents against biofilm-related infections.

5. Biological Nanoparticles as Anti-QS Agents

QS refers to a microbial communication system that allows microorganisms to communicate with each other by producing and distributing molecular signals called autoinducers that can regulate a range of physiological functions [115]. These autoinducers attach to the extracellular domains of the membrane receptor histidine kinase receptor, causing autophosphorylation and a cytoplasmic reaction [116]. Through QS, microorganisms can coordinate their activities and modulate the expression of specific genes in response to population density variations [115]. This regulation of QS-dependent gene expression offers the capacity to preserve a "society-like" structure that governs some major physiological pathways and generates cooperative responses like biofilm formation, pathogenesis, biodegradation of pollutants, etc. [117]. QS allows the population to regulate gene expression in a coordinated manner [118]. It is considered to be involved in the production of virulence factors as well as in the expression of antibiotic resistance genes [119].

Pathogenic bacteria often rely on QS to regulate their virulence and pathogenicity. The difficulty of combating these bacteria requires researchers to find new solutions to fight undesirable microorganisms. One of these is quorum quenching (QQ), which obstructs microbial communication [120]. QQ is a type of process which interrupts the QS. Research on QQ has also been extended to practical fields, with the aim of developing antibacterial and anti-biofilm strategies

that effectively combat pathogens and invasive populations. While there is limited literature on the QQ potential of nanoparticles, a few studies have mentioned their direct involvement as QS-inhibitors or their capacity to serve as carriers of quorum quenchers [121]. Several approaches have been suggested for disrupting QS, including inhibition of signaling molecule synthesis, elimination/degradation of signaling molecules, inhibition of the formation of signaling molecule-receptor complexes and inhibition of the binding of signal transduction cascades [118]. Indeed, NPs can offer QQ power by applying one or more of these approaches to control drug-resistant pathogens, making the disruption of microbial communication a crucial area of focus in the development of antibacterial agents and combating multidrug resistance [122]. Notably, anti-QS agents offer a reduced risk of microbial resistance as they specifically target QS, suppressing virulence factors while allowing bacterial growth to persist [123]. Several studies have shown that biologically synthesized nanoparticles can effectively inhibit QS (Table 3). QS inhibition is therefore a new and effective strategy to eradicate biofilms and infections related to this lifestyle of bacteria.

Table 3. Anti-QS activities of nanoparticles synthesized from extract plants and microorganisms

Biological Material	Types of Nanoparticles	Activity	Phenotype	Bacterium	References
Murraya koenigii	Silver	anti-QS	-Violacein	*Chromobacterium violaceum*	[124]
			-Prodigiosin -Exoprotease activity -Swarming motility	*S. marcescens*	
			-Pyocyanin, -Rhamnolipid -Pyoverdine -Swimming motility -Elastase activity -Exoprotease activity	*P. aeruginosa*	
Koelreuteria paniculata	Silver	anti-QS	- Violacein	*C. violaceum*	[125]
Carum coptum	Silver	anti-QS	-Violacein	*C. violaceum*	[126]
			-Swimming motility -Elastase activity -Exoprotease activity -Rhamnolipid -Pyoverdin -Pyocyanin	*P. aeruginosa*	
			-Swarming motility -Exoprotease activity - Prodigiosin	*S. marcescens*	

Table 3. Anti-QS activities of nanoparticles synthesized from extract plant sand microorganisms (continued)

Biological material	Types of nanoparticles	Activity	Phenotype	Bacterium	References
Setosphaeria rostrata	Silver	anti-QS	-Pyocyanin -Swarming motility	*P. aeruginosa*	[127]
P. stutzeri	Gold	anti-QS	-Pyocyanin	*P. aeruginosa*	[128]
Capsicum annuum	Gold	anti-QS	-Swarming motility -Prodigiosin -Protease activity	*S. marcescens*	[129]
			-Pyocyanin -Pyoverdin -Rhamnolipid -Exoprotease activity -Elastase activity -Swarming motility	*P. aeruginosa*	
Laccaria fraternal	Gold	anti-QS	-Pyocyanin	*P. aeruginosa*	[130]
Ochradenus baccatus	zinc oxide	anti-QS	- Violacein	*C. violaceum*	[131]
			-Alginate	*P. aeruginosa*	
			-Prodigiosin	*S. marcescens*	
Artemisia haussknechtii	zinc oxide	anti-QS	-Pyocyanin -Swarming motility	*P. aeruginosa*	[132]
Butea monsoperma	zinc oxide	anti-QS	-Hemolysin -Protease -Pyocyanin	*P. aeruginosa*	[133]

5.1 Silver nanoparticles

Green synthesized silver nanoparticles have been shown to effectively control microbial-related diseases by inhibiting QS. Silver nanoparticles derived from *Murraya koenigii* were tested against three Gram-negative bacteria for their ability to prevent the development of biofilms and virulence factors controlled by QS. The production of violacein mediated by QS was inhibited in a remarkable way (>80%) in *C. violaceum* ATCC12472 while swimming motility was not significantly inhibited (7.22%). These nanoparticles also inhibited prodigiosin production and exoprotease activity in *S. marcescens* MTCC 97. In addition, a significant decrease (up to 90%) in swarming motility was

found at all assayed sub-MICs. Similarly, in the presence of these biological silver nanoparticles, the virulence factors of *P. aeruginosa* PAO1, such as rhamnolipid, swimming motility, elastase, pyocyanin, and pyoverdine production, and exoprotease activity also declined in a dose-dependent manner [124]. Another study demonstrated the anti-QS activity of silver nanoparticles synthesized using an aqueous extract of *Koelreuteria paniculata*, which inhibited violacein production by 80% in *C. violaceum* [125]. Qais *et al*. [126] verified the ability of silver nanoparticles synthesized from *Carum coptum* to inhibit biofilm formation and virulence factors induced by QS against three pathogens tested. They showed approximately 75% inhibition of violacein production in *C. violaceum*. The *P. aeruginosa* virulence factors including swimming motility, elastase and exoprotease activity, rhamnolipid, pyoverdin, and pyocyanin production were decreased by 89.5, 53.3, 71.1, 60.0, 49.0, and 76.9%, respectively, at sub-MIC. Furthermore, the swarming motility, exoprotease activity, and prodigiosin synthesis of *S. marcescens* were decreased by 90.7, 67.8, and 78.4%, respectively. The results of Akther *et al*. [127] confirmed that silver nanoparticles biosynthesized by the cell filtrate of *Setosphaeria rostrata* could be employed as an effective anti-QS agent because they inhibited pyocyanin production, swarming, and biofilms formation in *P. aeruginosa*. Another study showed that AgNPs exhibited strong QQ activity against *P. aeruginosa* by binding with high affinity to the active sites of a range of proteins, including LasI/RhlI synthase and LasR/RhlI (transcription regulatory proteins), as well as to their adjacent residues. This interaction led to the inhibition of LasI/RhlI synthase, consequently preventing the production of signaling molecules essential for QS. In addition, disruption of transcriptional regulatory proteins deactivated the LasR/RhlR system, eventually causing suppression of QS-regulated virulence gene expression [134]. In addition, Hayat *et al*. [118] showed that AgNPs possessed the ability to exert QQ activity by targeting genes responsible for the synthesis of signaling molecules (LasI/RhlI) or by inactivating genes involved in the production of transcriptional regulatory proteins like LasR/RhlR. A study conducted by Singh *et al*. [135] demonstrated that AgNPs synthesized from *Rhizopus arrhizus* metabolites significantly suppressed the expression of the lasA and lasB genes by 79% and 84%, respectively. Additionally, gene quantification analysis showed that at a concentration of 25 µg/mL, the lasI, rhlI, lasR, and rhlR genes were downregulated by 71%, 63%, 51%, and 36%, respectively. These findings suggest that AgNPs have potent inhibitory effects on the expression of key genes involved in QS pathways.

5.2 Gold nanoparticles

The production of gold nanoparticles using biological technologies has yielded significant positive impact in several fields. The nanoparticles have also been determined to have anti-QS potential [5]. Gold nanoparticles biosynthesized by *P. stutzeri* did not show any toxic effects against *P. aeruginosa* PA01, but their ability to inhibit the production of pyocyanin pigments increased with increasing volume of nanoparticles used [128]. Qais *et al*. [129] reported that biologically synthesized gold nanoparticles might be applied in the control of bacterial infections. They evaluated gold nanoparticles synthesized from *Capsicum annuum* extract against QS-mediated virulence factors of *S. marcescens* and *P. aeruginosa*. The virulence factors of *P. aeruginosa* were reduced in a proportion up to 90%. Likewise, it was observed that the attenuation of virulence factors of *S. marcescens* depended on the dose of gold nanoparticles used. Samanta *et al*. [130] assessed the inhibitory ability of gold nanoparticles produced from *Laccaria fraternal* mycelium on biofilm formation and QS-regulated pyocyanin production of *P. aeruginosa*. Both qualitative and quantitative data indicated that these nanoparticles effectively reduced biofilm development and pyocyanin synthesis.

5.3 Zinc oxide nanoparticles

Numerous investigations have provided evidence of the significant anti-QS properties of green-synthesized zinc oxide nanoparticles. However, the precise mechanism of their QQ capability remains to be found [118]. Al-Shabib *et al*. [131] proposed the potential use of zinc oxide nanoparticles derived from leaves of *Ochradenus baccatus* as alternative nanomaterials for combating drug-resistant bacterial infections. They showed that these nanoparticles significantly inhibited virulence factors such as prodigiosin, violacein, swarming migration, exopolysaccharide, and biofilm in many human pathogens including *S. marcescens, P. aeruginosa, C. violaceum, E. coli, L. monocytogenes,* and *K. pneumonia*. Another study demonstrated that zinc oxide nanoparticles produced using an aqueous extract of *Artemisia haussknechtii* had antibiofilm, anti-QS, antibacterial, anti-swarming motility, and antioxidant effects against multiple drug resistant bacteria [132]. In addition, Ali *et al*. [133] demonstrated a remarkable decrease in the production of *P. aeruginosa* virulence factors including hemolysin, protease, and pyocyanin by zinc oxide nanoparticles synthesized from a seed extract of *Butea monsoperma*. Furthermore, *in silico* docking analysis revealed that these zinc oxide nanoparticles acted effectively in the QS (Las/Rhl) mechanism of *P. aeruginosa* by linking to the LasI synthase catalytic cleft, RhlI synthase, and transcription receptor protein RhlR receptor and LasR receptor. As a result of the efficient interaction of zinc oxide nanoparticles with the Rhl and Las systems, autoinducers like N-acyl homoserine lactones (AHL) molecules were inactivated, resulting in the inhibition of QS and down regulation of virulence factors [136]. The current *in vitro* and *in silico* data show that biosynthesized zinc oxide nanoparticles may be effectively utilized as powerful antimicrobial agents to inhibit pathogenic drug-resistant bacteria colonization, biofilm formation, and QS-mediated virulence factors.

6. Conclusions

Understanding the fundamental principles of biofilm resistance to antibiotics is the only way to combat the development and spread of catastrophic antimicrobial resistance. Given the limited effectiveness of conventional antibiotics, biological nanoparticles possessing antibiofilm and anti-QS properties have emerged as potential therapeutic agents against bacterial pathogens. Notably, green synthesized nanoparticles have the potential to be employed as carriers for focused administration of natural and synthetic compounds that show promising antibiofilm and anti-QS activity. These nanoparticles should certainly give rise to new ways of preventing infections, particularly in the face of the increasing occurrence of multidrug resistance. These silver nanoparticles are characterized by their favorable stability and biocompatibility, broad-spectrum antimicrobial activity, and their interesting ability to disrupt QS and bacterial biofilm formation, making them promising agents for preventing biofilm-associated infections. However, it is important to take into account the potential drawbacks of these nanoparticles, such as their toxicity to human cells and the environment, as well as the risk of resistance development. Therefore, the choice of the appropriate nanoparticle will depend on the concentration used, the specific application, and the costs associated with its use. At this time, there is inadequate information on the therapeutic uses and toxicity of biological nanoparticles as biofilm and QS inhibitors and antimicrobial drug carriers. For this purpose, theoretical as well as practical aspects need to be further study at the molecular and clinical levels, and *in vivo*, *in silico* and genomic studies are necessary in order to make significant progress in the domain of "biofilm and QS nano-inhibitors".

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