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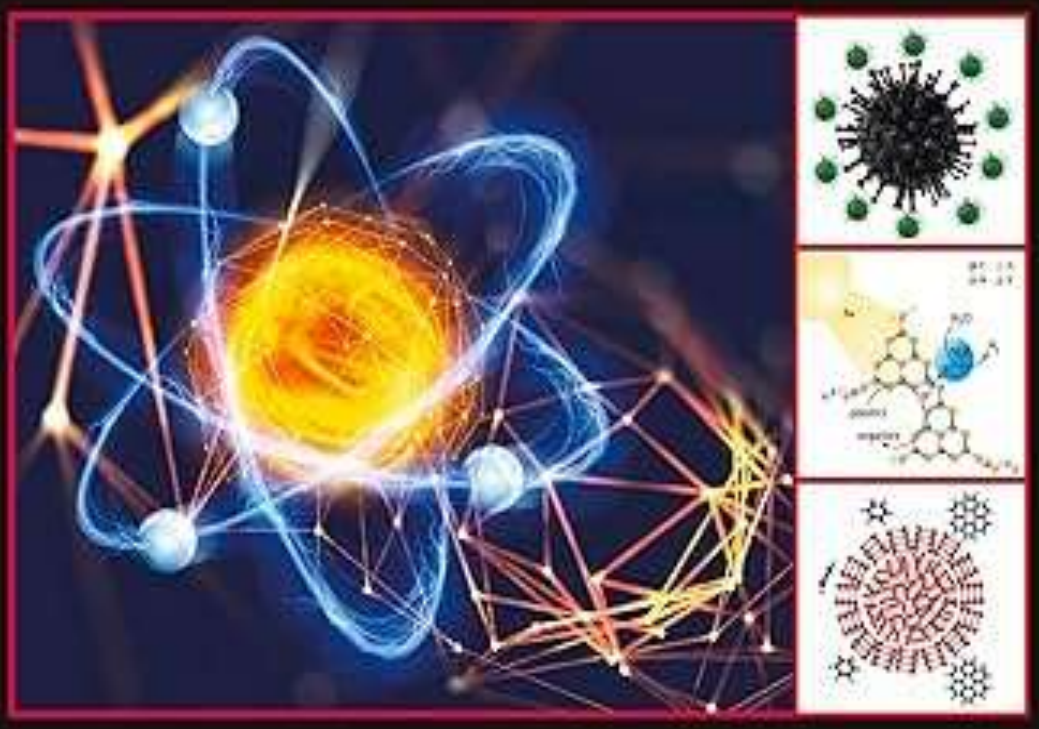

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CHAPTER 11

Application of nanoparticles as quorum quenching agent against bacterial human pathogens: a prospective therapeutic nanoweapon

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11.1 General introduction

11.1.1 Quorum sensing in bacteria

Quorum sensing means cell to cell communication between bacteria through signaling molecules called autoinducers. Microorganisms monitor and adapt to their surroundings via signaling by secreting and sensing quorum sensing molecules in the surrounding [1]. This cell-to-cell communication allows the bacterial cells to control gene expression based on cell density. With the help of quorum sensing, the bacterial cells are able to carry out processes that are energetically and metabolically steep to be performed by single bacterial cell. These processes are expressed collectively by a group of bacteria with the help of quorum sensing. Quorum sensing also helps bacteria to adapt and mutually cope with ever-changing environmental conditions [2–4].

Quorum sensing comprises of production, detection, and response to low molecular weight, extracellular signaling molecules called autoinducers. The autoinducers or the signaling molecules are synthesized and secreted outside the cells and are sensed by the bacteria present in the vicinity. Therefore, with the increase in the bacterial cell density, the concentration of autoinducers also increases in the extracellular environment. The information is perceived by bacteria with the help of cytoplasmic as well as membrane-associated receptors. Change in the bacterial cell numbers is tracked with the help of autoinducers produced. Once the critical threshold of autoinducers is attained, gene expression is altered as well as more and more autoinducers are produced [3,5–7].

The autoinducers employed in Gram-positive and Gram-negative bacteria differ in their chemical nature. Autoinducers in Gram-negative bacteria belong to N-acylated homoserine lactones (AHLs). AHLs are passively transported, i.e., are capable of freely diffusing across the cell membrane (Fig. 11.1), whereas in Gram-positive bacteria the autoinducers employed are autoinducing peptides which are not capable of freely diffusing across the membrane. The autoinducing peptides (AIPs) function through

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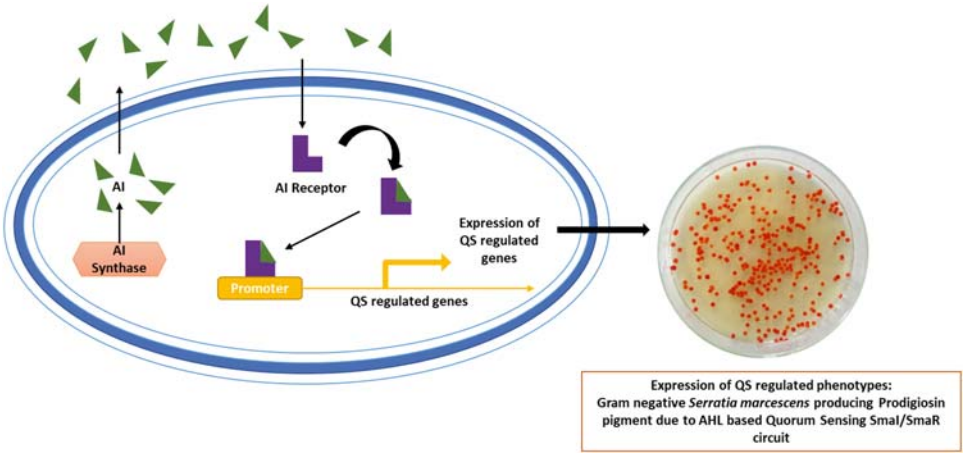

Figure 11.1 Quorum sensing system in Gram-negative bacteria. Autoinducers (AI) such as Acyl Homoserine Lactones (AHLs) are synthesized by AI synthase gene. These AIs are capable of diffusing in and out of the cell through the cell membrane. On reaching a threshold concentration of AI, it diffuses through the cell membrane and is detected and bound to cytoplasmic AI receptors. These AI receptors with bound AI then regulate the expression of quorum sensing (QS) regulated genes, e.g., pigment prodigiosin production in *Serratia marcescens*.

membrane bound receptors called sensor kinase (Fig. 11.2). AIP binds to sensor kinase which results in phosphorylation of response regulator. The phosphorylated response regulator then binds to the promoter resulting in activation of transcription and expression of genes [8,9]. However, autoinducers other than AHLs and autoinducing peptides have also been identified in bacteria. For example, 3-hydroxy palmitic acid methyl esters

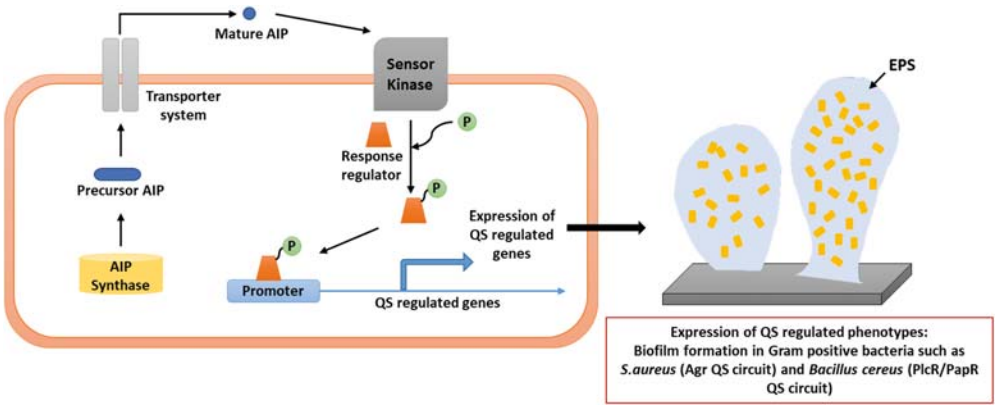

Figure 11.2 Quorum sensing system in Gram-positive bacteria. Autoinducing peptide (AIP) synthases secrete an immature form of AIPs, i.e., Precursor AIPs. These are processed into mature AIPs and are transported out of the cell by a transporter system (e.g., ABC transporters). The mature AIPs are then detected by two component sensor kinases (e.g., histidine kinase) which on getting activated transports a phosphate group to a cytoplasmic response regulator. The phosphorylated response regulator then regulates the expression of quorum sensing (QS) regulated genes, e.g., biofilm formation in *Bacillus cereus*.

in *Ralstonia solanacearum,* butyrolactone signals in *Pseudomonas aereofaciens,* AI-2 in *Vibrio harveyi* and *Salmonella enterica,* AI-3 in *E. coli*, and *Salmonella typhimurium*. In addition to these, Quinolone signals produced by *Pseudomonas aeruginosa*, Diffusible Signal Factor (DSF) synthesized by *Xanthomonas campestris* and α-hydroxyketones in *Vibrio* and *Legionella pneumophila* are signaling molecules that are distinct from typical AHLs or autoinducing peptides [10–14].

Phenotypes that are regulated by quorum sensing include biofilm formation, bioluminescence, virulence factor production, swimming, swarming and twitching motility, antibiotic production, pigment production, conjugation, sporulation. Most of the quorum sensing regulated phenotypes associated with pathogenic bacteria are required for development and progression of diseases in humans, animals, and plants and are therefore responsible for enormous health and economic impacts [5,9,15,16].

One of the primary modes for treating the bacterial infections is the usage of antibiotics. Sir Alexander Fleming discovered Penicillin in 1928 and was considered as the magic bullet as it was able to efficiently treat bacterial diseases that were regarded as incurable during the time of Second world war [17]. This led to the onset of "Golden era" of antibiotics with discovery of different antibiotics effectively treating various bacterial diseases, e.g., tuberculosis, syphilis, gonorrhea, gas gangrene, staphylococcal and streptococcal infections. However, due to excessive and indiscriminate use of antibiotics, bacteria developed resistance toward them and resulted in the emergence of Multiple Drug Resistant (MDR) bacteria. This led to the end of Golden era of antibiotics [17]. Progressively more antibiotics are being rendered ineffective in the treatment of bacterial infections due to horizontal gene transfer, thus becoming a primary concern in public health management. As a consequence, there is an urgent need to develop an alternative method for prevention of disease development and growth of pathogenic bacteria [9,18,19].

11.1.2 Quorum quenching (quorum sensing inhibition)

Quorum sensing–mediated processes are associated with characters which are not very critical for growth and development of bacteria but are associated with disease development and progression [20]. Hence, targeting quorum sensing by interfering in communication between bacteria serves as an efficient alternative strategy to prevent bacterial diseases (Fig. 11.3). Development of resistance toward quorum sensing inhibitors is less likely as they do not inhibit the growth of bacteria [19]. Thus, inhibiting intercellular communication between the bacterial cells can serve as an efficient alternative to combat the spread of MDR bacterial infectious diseases.

11.1.3 Quorum quenching strategies

There are three major strategies for inhibition of quorum sensing in bacteria, i.e., degradation or sequestration of quorum sensing signals, inhibition of detection of quorum

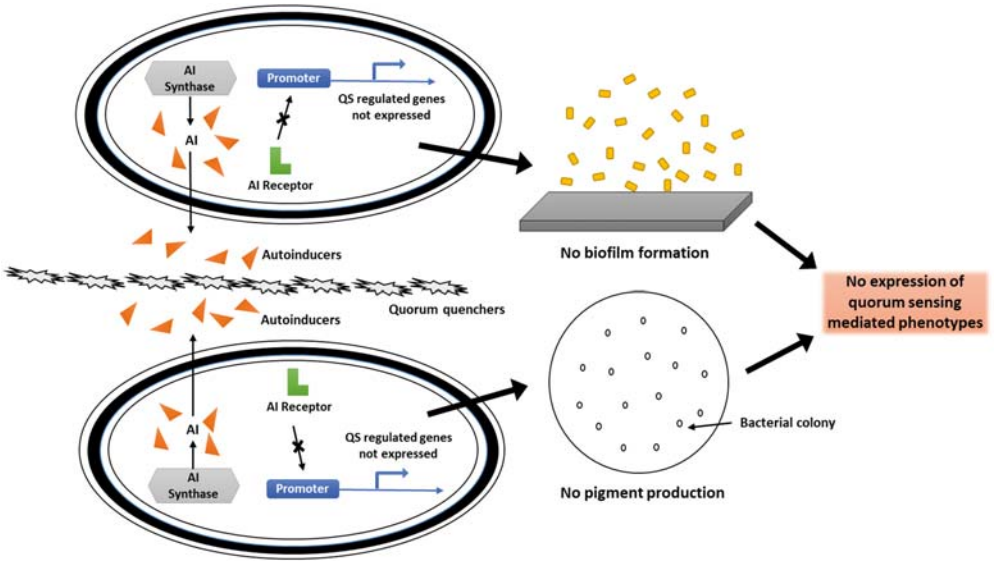

Figure 11.3 Inhibition of QS regulated phenotypes in Gram-negative bacteria by quorum quenching molecules.

sensing signals, and inhibition of synthesis of quorum sensing signals [14,20] (Fig. 11.4). In addition, other modes of quorum quenching include interference in the transport of quorum sensing signals, and development of specific antibodies that bind and block the receptors [21].

Natural and chemically synthesized compounds have been studied for quorum quenching potential. Among the natural sources are the metabolites of microbial and

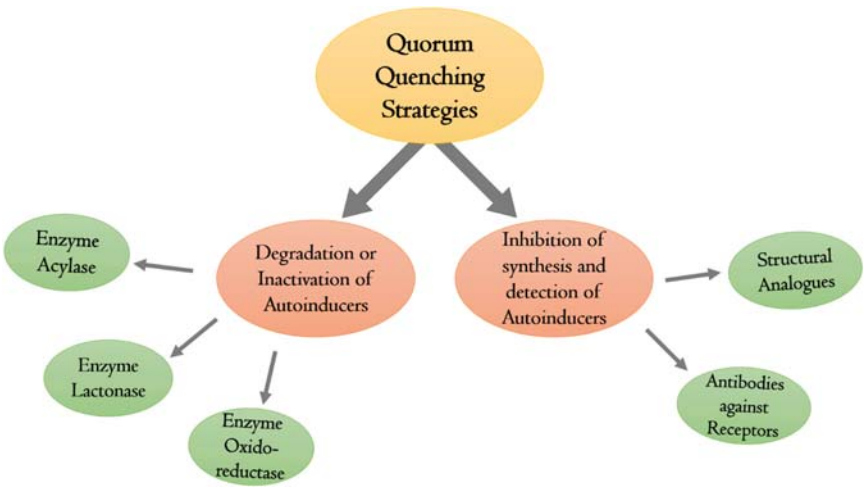

Figure 11.4 Quorum quenching strategies.

plant origin. Bacterial and fungal enzymes such as Acylase and Lactonase are identified that are capable of degrading quorum sensing signaling molecule Acyl Homoserine Lactone [7,20]. Lactonase catalyzes the hydrolysis of ester bond that results in opening of lactone ring [22]. Acylase causes degradation of acyl chain by hydrolyzing the amide bond in the acyl skeleton [23]. In addition, microorganisms and plants also produce several other metabolites that are capable of quorum quenching. For example, several plant extracts such as *Mangifera indica,* essential oils from spices (Eugenol from clove) as well as various plant essential oils are reported to inhibit quorum sensing—mediated behavior in pathogenic bacteria [24—26]. In addition, a number of microbial metabolites such as *Cis*-9-octadecanoic acid form bacteria *Stenotrophomonas maltophilia,* Xylitol from yeast *Pichia caribbica*, Melanin from edible mushroom *Auricularia auricular,* and halogenated furanone from red algae *Delisea pulchra* are shown to have quorum quenching potential [27—30]. Various chemical compounds having quorum quenching potential have been synthesized. Some of these compounds are synthesized as structural analogues as a result carrying out competitive inhibition of quorum sensing. For example, compounds like Meta-bromo-thiolactone, N-acyl cyclopentilamides, Benzothiazole derivatives, Itaconimides, Isoxazolone derivatives having quorum quenching potential in bacteria are synthesized [31—35]. Several structural analogues of Acyl Homoserine Lactones such as *N*-sulfonyl homoserine lactone as well as hydrazide, carbamate, and thiocarbamate derivatives of acyl homoserine lactone are synthesized and are shown to inhibit quorum sensing in *Chromobacterium violaceum* and *Vibrio fischeri* [36].

11.2 Nanoparticles: fundamentals and principles

Nanoparticles are an efficient link between atomic and molecular sized structures and large sized materials [37]. The size of the nanoparticles usually ranges between 1 and 100 nm [1]. According to the European Commission, the term nanomaterial is described as "a natural or a manufactured material that possesses unbound, aggregated or agglomerated particles where external dimensions are in between 1 and 100 nm size range." The United States Food and Drug Administration defines it as "materials that have at least one dimension in the range of approximately 1—100 nm and exhibit dimension-dependent phenomenon" [38]. The physical and chemical laws that are subjected to nanoparticles do not apply to particles of larger size [39]. Consequently, they have earned eminence in technological advancements due to their tunable physicochemical properties such as melting point, electrical and thermal conductivity, wettability, light absorption and scattering, catalytic activity, thus attaining superiority over their bulk counterparts [38].

Based on the materials from which nanoparticles are prepared and other physical and chemical properties, nanoparticles are grouped into various categories which include carbon-based nanoparticles, inorganic nanoparticles, organic nanoparticles, and composite-based nanoparticles. Carbon-based nanoparticles are nanomaterials made

predominantly of carbon. The two major categories of carbon-based nanoparticles are Fullerenes and Carbon nanotubes (CNTs). Fullerenes are ball shaped, hollow, cage like molecules built from carbon atoms. Carbon nanotubes are the hexagonal arrangement of carbon atoms in the form of a graphene sheet that rolls upon itself. Carbon Nanotubes can be single walled (SWNTs), double walled (DWNTs), and multiwalled (MWNTs). In addition to these, carbon-based nanoparticles also include carbon nanofibers, graphite, graphene, carbon black, and carbon onions [38,40,41]. Inorganic nanoparticles include metal based, metal oxide based, semiconductor, ceramic-based nanoparticles, and they have unique optoelectrical properties [38,40]. Organic nanoparticles are also called as Polymeric nanoparticles and are nanocapsular and nanospherical-shaped nanoparticles having loads of applications in research. Composite nanoparticles are multiphase nanoparticles. These nanoparticles are either combination of different types of nanoparticles or are combination of nanoparticles and bulk material [38,40]. In addition to these, there are lipid-based nanoparticles which have emerged in the recent times and have scores of applications in biomedical field. Lipid nanoparticles are basically solid lipid core and a matrix of soluble lipophilic molecules. Lipid core of which is stabilized by emulsifiers and surfactants [38,40,42].

Alternatively, nanoparticles can also be divided based on their dimensions. Based on that, nanoparticles are divided into 0D, 1D, 2D, and 3D. Nanomaterials in the form of nanospheres or clusters belong to 0D, whereas nanofibers, rods, and wires belong to 1D. Furthermore, 2D includes nanomaterials in the form of plates or films and the last category consist of nanomaterials in the 3D shape such as nanotubes [41,43].

11.2.1 Synthesis of nanoparticles

The methods for the synthesis of nanoparticles belong to two different approaches, i.e., Top-down approach and Bottom-up approach. In top-down approach we start with bulk molecules which are then decomposed into smaller units and later being converted into suitable nanoparticles, e.g., grinding or milling. Whereas in bottom-up approach, nanoparticles are formed from relatively smaller and simpler substances, e.g., biochemical synthesis. Consequently, the top-down method has been described as the destructive approach and bottom-up method as the building up approach [40].

Nanoparticles can be synthesized by either biological or synthetic (Physical or Chemical) method. Biological methods of nanoparticle synthesis include use of plant extracts, microbial extracts, and pure biological compounds. Natural methods of nanoparticle synthesis include synthesis by biological species. Chemical or physical synthesis or engineered methods of nanoparticle include chemical reduction, photochemical reduction, gamma irradiation, laser ablation, UV-initiated photoreduction, microwave processing, electron radiation, and microemulsion techniques. Nanoparticle synthesis also occur from grinding and milling, engine exhausts, smoke, building demolitions, and cigarette smoking [38,44].

11.2.2 Applications of nanoparticles in environmental and biomedical field

Nanoparticles also have loads of applications in environmental monitoring and pollution control. Nanoparticles play an active role in remediation of water, air, and soil. Nanoparticle-based filters, semiconductor photocatalysts, adsorbents, nanowires, as well as bioactive nanoparticles for disinfection have been developed for this purpose [45]. In addition, nanotechnology-based sensors to detect the level of pollutants such as nanocontact sensors, nanowires, and nanotube sensors, cantilever sensors are being developed. Moreover, nanotechnology has also developed biomaterial-based sensors to detect the level of exposure of human beings to the pollutants by detecting and interpreting biomarker signals [45]. Furthermore, nanoparticle-based products that prevent pollution at source are being built, e.g., use of carbon nanotubes for computer screens, development of antimicrobial coatings to prevent fouling, use of nanoemulsions instead of organic solvents in cleaning industries [39,45].

Nanoparticles also have immense applications in medical field as drug delivery and antimicrobial agents [46]. Due to their antimicrobial activity, nanoparticles are widely used in catheters, wound dressing, textile, food packaging, and water disinfection. Nanoparticles also find their applications in cancer diagnosis, cancer therapy, and as an antineoplastic. Unique optical properties of nanoparticles such as Ag and Au are also extensively exploited for manufacture of various biosensors [40]. Ag and Au nanoparticles owing to their easy production and lesser toxicity are widely exploited in the biomedical research. Nanoparticles are also used in cosmetics and sunscreens due to their antioxidant and antireflective properties [38].

11.2.3 Nanoparticles as antimicrobial agents

Nanoparticles have shown vast potential applications as an antimicrobial agent. Various metal and metal oxide nanoparticles such as silver (Ag), gold (Au), copper (Cu), selenium (Se), tellurium (Te), titanium oxide (TiO_2), zinc oxide (ZnO), calcium oxide (CaO), magnesium oxide (MgO), aluminum oxide (Al_2O_3), as well as silica and clay nanoparticles among others have been reported to possess antimicrobial activity. These nanoparticles are either synthesized by biological, chemical, or physical methods [47–49]. All the nanoparticles listed above are capable of inhibiting growth of pathogenic bacteria. Mechanisms by which nanoparticles carry out growth inhibition are different from those adopted by conventional antibiotics [1]. For example, nanoparticles enter the bacterial cells, block the transport channels, and cause structural changes in the cell membrane. Nanoparticles, predominantly, metal nanoparticles can also lead to the production of Reactive Oxygen Species (ROS) in the bacterial cells. These highly reactive oxygen species cause damage to cell membranes, peptidoglycan, ribosomes, proteins, and nuclear material. In addition, metal ions also interact with thiol groups of enzymes resulting in inhibition of enzyme function. Metal ions also attach between the purine pyrimidine base pairs as well

as with the phosphorus moieties of DNA causing interference in the DNA replication [47,50]. Owing to the multiple modes of action, nanoparticles target at different areas in the bacterial cells unlike antibiotics and therefore development of resistance toward the nanoparticles is a slow process as it requires multiple genetic changes. Additionally, nanoparticles can also act as effective carriers for various antibiotics, in this manner supporting and complementing their action [1]. Also, nanoparticles when used synergistically with antibiotics can help prevent resistance development in bacteria by hindering the working of efflux pumps by binding to its active site and obstructing the efflux of antibiotics or it may also disrupt the efflux kinetics [51].

Antifungal activity is also shown by metal nanoparticles mainly by causing disruption of cell membrane. Nanoparticles such as silver, gold, zinc oxide and titanium oxide inhibit viral attachment to the cell surface causing inhibition of viral proliferation. Furthermore, antiparasitic activity is also shown by various nanoparticles such as silver, gold, selenium, titanium oxide, zinc oxide, copper oxide, magnesium oxide, chitosan, and curcumin [47]. As a result, nanoparticles have proven to be an efficient alternative and therapeutic agent against microbial resistance and multidrug resistant varieties.

In recent times, various studies have reported the ability of nanoparticles to inhibit quorum sensing in bacteria. Owing to their unique properties, nanomaterials have found extensive applications in the biomedical sector, leading to the evolution of a new field termed as "Nanomedicine." Due to the number of advantages such as stability, efficient delivery, enhanced mucus and biofilm penetration, efficient solubility and biocompatibility, reduced toxicity toward human, researchers are targeting the application of nanoparticles as quorum quenching agents [52]. Researchers are investigating the ability of nanoparticles to target quorum sensing rather than microbial growth inhibition. Application of nanoparticles at subinhibitory concentrations can cause interference in communication between the bacterial cells consequently, inhibiting disease development and progression without the occurrence of resistance (Fig. 11.5).

11.2.4 Nanoparticles as quorum quenchers

Nanoparticles apart from its antimicrobial activity are also investigated for their quorum quenching potential [46,52]. Due to their small size and high surface area to volume ratio, silver nanoparticles have shown promising quorum quenching capabilities as compared to other metal or metalloid nanoparticles. Furthermore, nonmetal nanoparticles such as chitosan nanoparticles have also demonstrated vast potential to be exploited as quorum quenching agents.

11.3 Latest research on nanoparticles as quorum quenching agents

11.3.1 Quorum quenching by biologically synthesized nanoparticles

As summarized in Table 11.1, nanoparticles are extensively synthesized by biological methods, including plant- or microbial-based methods, and are reported to have impressive quorum quenching potential.

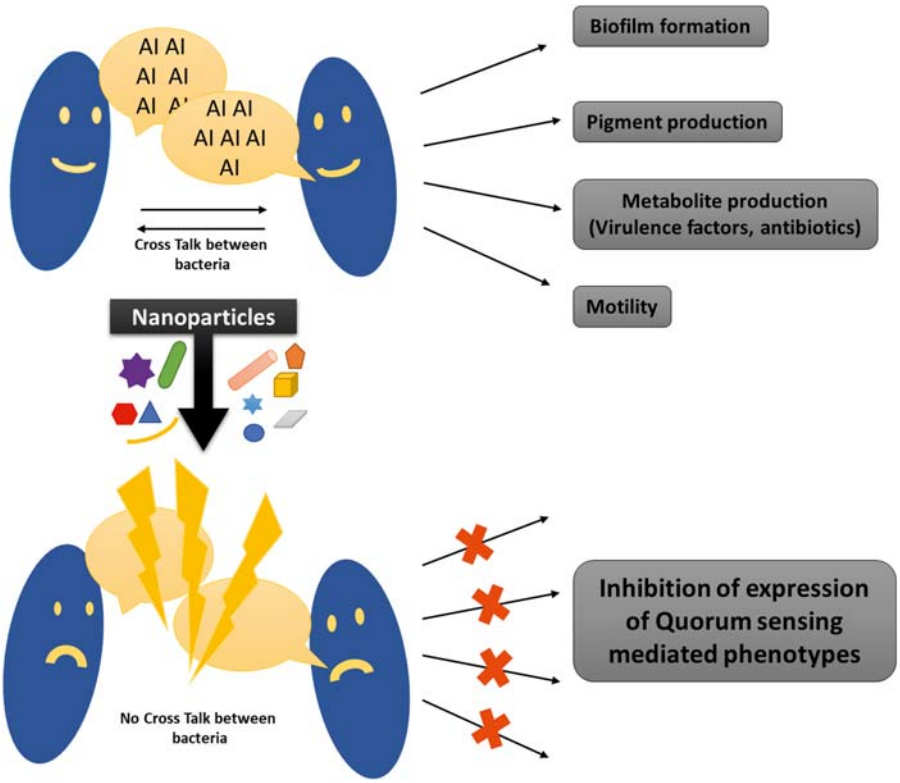

Figure 11.5 Inhibition of expression of quorum sensing—mediated phenotypes in bacteria by nanoparticles.

11.3.1.1 Quorum quenching by plant-based nanoparticles

Silver nanoparticles are extensively produced using various plant extracts and are reported to have quorum quenching potential. Shah et al. [53], reported the *Piper betle* leaves mediated synthesis of silver nanoparticles and these AgNPs were shown to inhibit the quorum sensing mediated behavior in *Pseudomonas aeruginosa*. Docking studies revealed that nanoparticles were capable of binding to the LasI and LasR proteins thereby inhibiting the biosynthesis as well as perception of the signaling molecules. These nanoparticles also inhibited the function of MvfR which is a part of Pqs quorum sensing system in *Pseudomonas aeruginosa* thus inhibiting the biofilm formation and production of virulence factors. Nanoparticles were capable of inhibiting violacein production in *Chromobacterium violaceum* 12472 and inhibition of biofilm formation, decrease in swimming and swarming motility as well as virulence factor production in *Pseudomonas aeruginosa* PAO1. Likewise, silver nanoparticles prepared using root extract of *Vetiveria zizanioides* inhibited quorum sensing mediated behavior in *Serratia marcescens* [54]. Similarly, silver nanoparticles synthesized using *Pandanus odorifer* leaf extract were capable of inhibiting violacein

Table 11.1 Quorum quenching potential of biologically synthesized nanoparticles against bacteria.

Source	Nanoparticle	Target organism	References
Plant based:			
Leaves of *Piper betle*	Silver	*Pseudomonas aeruginosa* PAO1 *Chromobacterium violaceum* 12472	[53]
Root extract of *Vetiveria zizanioides*	Silver	*Serratia marcescens*	[54]
Leaf extract of *Pandanus odorifer*	Silver	*Chromobacterium violaceum* *Pseudomonas aeruginosa* *E. coli* *Klebsiella pneumoniae* *Staphylococcus aureus*	[55]
Fruit extract of *Garcinia cambogia*	Silver	*Pseudomonas aeruginosa* *Chromobacterium violaceum*	[56]
Leaf extract of *Sargassum polyphyllum*	Silver	*Chromobacterium violaceum* MTCC 2656 *Pseudomonas aeruginosa* MTCC 2488	[57]
Fruit waste extract	Silver	*Chromobacterium violaceum* MTCC 2656	[58]
Spirulina platensis extract	Silver	*Vibrio parahaemolyticus*	[59]
Leaves of *Ochradenus baccatus*	Zinc oxide	*Pseudomonas aeruginosa* *E. coli* *Klebsiella pneumoniae* *Serratia marcescens* *Chromobacterium violaceum*	[60,61]
Nigella sativa	Zinc oxide	*Chromobacterium violaceum* *E. coli* *Listeria monocytogenes* *Pseudomonas aeruginosa*	[62]
Garcinia cambogia extract	Silver; Silver nanoparticles biofabricated with ginger extract	*Pseudomonas aeruginosa*	[56]
Aqueous extract of *Melilotus officinalis*	Silver selenide chalcogenide	*Pseudomonas aeruginosa*	[63]

Table 11.1 Quorum quenching potential of biologically synthesized nanoparticles against bacteria.—cont'd

Source	Nanoparticle	Target organism	References
Capsicum annuum extract	Gold	*Pseudomonas aeruginosa* PAO1 *Serratia marcescens* MTCC 97	[64]
Acacia arabica leaf extract	Zinc oxide	*Staphylococcus aureus* *Salmonella enterica* *E. coli*	[65]
Microbial based:			
Lysinibacillus sp. *Pseudomonas stutzeri*	Gold	*Pseudomonas aeruginosa*	[66]
Klebsiella pneumoniae MTCC 3354	Silver	*Chromobacterium violaceum*	[67]
Bacillus sp.	Silver	*Chromobacterium violaceum* ATCC 12472	[68]
Bacillus sp.	Silver; Silver nanoparticles biofabricated with ginger extract	*Pseudomonas aeruginosa*	[56]
Streptomyces sclerotialus	Silver	*Enterococcus faecalis* *Shigella flexneri* *Chromobacterium violaceum*	[69]
Biomass extract of soil fungus *Rhizopus arrhizus* BRS-07	Silver	*Chromobacterium violaceum* *Pseudomonas aeruginosa*	[70]
Mycelia of ectomycorrhiza *Laccaria fraterna* EM-1083	Gold	*Pseudomonas aeruginosa*	[71]

production in *Chromobacterium violaceum;* alginate production in *Pseudomonas aeruginosa;* EPS production, biofilm formation and swarming motility in *E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Chromobacterium violaceum*, and *Staphylococcus aureus* [55]. Silver nanoparticles were also synthesized by using *Garcinia cambogia* fruit extract which were capable of inhibiting violacein production in *Chromobacterium violaceum* and biofilm formation in *Pseudomonas aeruginosa*. Moreover, when these nanoparticles were

biofabricated with ginger extract an improved quorum quenching potential was observed against *Pseudomonas aeruginosa* through synergistic action [56]. Silver nanoparticles synthesized using *Sargassum polyphyllum* extract, ginger extract, as well as fruit waste (orange, lemon, and pomegranate peels) extract showed quorum quenching potential [57,58]. Silver nanoparticles synthesized using *Spirulina platensis* extract inhibited biofilm formation in *Vibrio parahaemolyticus* [59].

Zinc oxide nanoparticles have also been synthesized by plant extracts and reported to have quorum quenching potential. *Ochradenus baccatus* leaves mediated zinc oxide nanoparticles were capable of inhibiting biofilm formation in human pathogens such as *Pseudomonas aeruginosa, E. coli, Serratia marcescens, Klebsiella pneumoniae*, and *Chromobacterium violaceum* [60,61]. Also zinc oxide nanoparticles synthesized biologically from *Nigella sativa* inhibited quorum sensing mediated behavior in *Chromobacterium violaceum, E. coli, Listeria monocytogenes*, and *Pseudomonas aeruginosa* [62]. The zinc oxide nanoparticles were also investigated to inhibit *LasB* gene thereby causing decrease in AHL production [62]. Similarly, ZnO nanoparticles biofabricated using *Acacia arabica* extract were shown to have antibiofilm activity against food borne pathogens *Staphylococcus aureus, Salmonella enterica*, and *E. coli* [65]. The aqueous extracts of legume *Melilotus officinalis* was used to synthesize silver selenide chalcogenide (Ag_2Se) nanoparticles which showed the potential to inhibit biofilm formation in antibiotic resistant *Pseudomonas aeruginosa* [63]. Gold nanoparticles biofabricated with *Capsicum annuum* extract were also prepared which were capable of quorum quenching in *Pseudomonas aeruginosa* PAO1 and *Serratia marcescens* MTCC 97 [64].

11.3.1.2 Quorum quenching by microbially synthesized nanoparticles

The quorum quenching potential of microbially synthesized nanoparticles are not widely studied. However, there are relatively fewer reports available in literature. Gold nanoparticles synthesized by bacteria *Lysinibacillus* sp. and *Pseudomonas stutzeri* isolated from hypersaline spring Poon Bato in Botolan, Zambales, Philippines inhibited pyocyanin production in *Pseudomonas aeruginosa* PAO1 [66].

Mutant *Klebsiella pneumonia* MTCC 3354 mediated silver nanoparticles were synthesized which showed quorum quenching potential, which is evident by inhibiting violacein production inhibition in *Chromobacterium violaceum* [67]. Silver nanoparticles were also synthesized by bacteria belonging to *Bacillus* sp. which were capable of inhibiting violacein production in *Chromobacterium violaceum* and biofilm formation in *Pseudomonas aeruginosa* [56,68]. Silver nanoparticles synthesized by *Bacillus* sp. were also biofabricated with ginger extract which showed a superior quorum quenching potential in *Pseudomonas aeruginosa* [56].

Silver nanoparticles were also synthesized by using aqueous extract of biomass of the soil fungus *Rhizopus arrhizus* BRS-07. Further, silver nanoparticles mycofabricated with metabolites of soil fungus showed quorum sensing inhibitory behavior attenuating

violacein production in *Chromobacterium violaceum* as well as biofilm formation and virulence factor production in *Pseudomonas aeruginosa*. The nanoparticles were capable of significantly reducing the AHL production by *Pseudomonas aeruginosa*. Moreover, the RT PCR studies revealed that the genes in QS regulon were downregulated in the presence of the nanoparticles [70]. Silver nanoparticles were also synthesized using culture filtrate of *Streptomyces sclerotialus* and that were seen to inhibit biofilm formation in *Enterococcus faecalis* and *Shigella flexneri* as well as violacein production in *Chromobacterium violaceum* [69]. Additionally, Ref. [71] reported synthesis of gold nanoparticles intracellularly using mycelia of ectomycorrhizal fungus *Laccaria fraterna* EM-1083. These nanoparticles were capable of inhibiting biofilm formation and pyocyanin production in *Pseudomonas aeruginosa*.

11.3.2 Quorum quenching by synthetic nanoparticles

Nanoparticles produced extensively by synthetic methods, both physical as well as chemical, exhibit an impressive quorum quenching potential as summarized in Table 11.2. Ref. [72] reported the ability of silver nanowires to reduce biofilm formation and violacein production in *Pseudomonas aeruginosa* and *Chromobacterium violaceum,* respectively. Silver-coated carbon nanotubes capable of downregulating virulence genes in *Staphylococcus aureus* were also developed [73]. In addition to this, several other reports of silver nanoparticle and nanowires inhibiting quorum sensing mediated behavior in *Staphylococcus aureus, Pseudomonas aeruginosa, Pseudomonas syringae*, and *Chromobacterium violaceum* has also been published [74–76]. Molecular docking experiment has revealed the ability of silver nanoparticles to deeply embed in the active site of LasI/RhlI and LasR/RhlR proteins, resulting in the inhibition of synthesis of signaling molecules [75]. Similar, results were reported by Mishra and Mishra [77] where copper nanoparticles were capable of docking into AHL synthase LasI and RhlI and regulatory proteins LasR and RhlR hence inhibiting their activity.

Chemically synthesized zinc oxide nanospikes were also reported to have quorum sensing inhibitory potential. The nanospikes were capable of inhibiting violacein production in *Chromobacterium violaceum* 12472 and virulence factor (elastase, extracellular protease, pyocyanin) production and biofilm formation in *Pseudomonas aeruginosa*. The decrease in swarming motility of *Pseudomonas aeruginosa* was also shown in the presence zinc oxide nanospikes [78]. Zinc oxide nanoparticles were also tested by Saleh et al. (2019) for their ability to inhibit quorum sensing in *Pseudomonas aeruginosa*. The nanoparticles at subinhibitory concentrations were capable of inhibiting the production of pyocyanin, pyoverdin, rhamnolipid, hemolysin, elastases, and proteases. The RT-PCR studies revealed that at the sub-MIC concentrations of ZnO nanoparticles, the expression levels of quorum sensing regulatory genes, i.e., *LasI, LasR, PqsA, PqsR, RhlI*, and *RhlR* in *Pseudomonas aeruginosa* were significantly reduced.

Table 11.2 Quorum quenching potential of synthetic nanoparticles.

Nanoparticles	Target organism	References
Silver nanowires	*Pseudomonas aeruginosa* *Chromobacterium violaceum*	[72]
Silver-coated carbon nanotubes	*Staphylococcus aureus*	[73]
Silver	*Staphylococcus aureus*	[74]
Silver	*Pseudomonas aeruginosa*	[75]
Silver	*Pseudomonas syringae* *Pantoea stewartii*	[76]
Copper	*Pseudomonas aeruginosa*	[77]
Zinc oxide nanospikes	*Chromobacterium violaceum* *Pseudomonas aeruginosa*	[78]
Zinc oxide	*Pseudomonas aeruginosa*	Saleh et al. (2019)
Selenium Tellurium	*Chromobacterium violaceum* *Pseudomonas aeruginosa*	[46]
$AgCl-TiO_2$	*Chromobacterium violaceum*	[79]
Tin oxide hollow nanoflowers	*Chromobacterium violaceum* *Pseudomonas aeruginosa* *Serratia marcescens*	[60,61]
Chitosan	*E. coli*	[80]
Nanocurcumin	*Pseudomonas aeruginosa*	[81]
Nanoemulsions of spice essential oils	*Chromobacterium violaceum* *Klebsiella pneumoniae* *E. coli* *Salmonella typhimurium*	[82]

Ref. [46] reported the ability of chemically synthesized selenium (SeNPs) and tellurium (TeNPs) nanoparticles to inhibit violacein production in *Chromobacterium violaceum* and biofilm formation in *Pseudomonas aeruginosa*. Ref. [79] prepared $AgCl-TiO_2$ nanoparticles (ATNPs) and these were found to inhibit violacein production in *Chromobacterium violaceum*. Silver in ATNPs inhibited violacein production in a dose dependent manner, whereas TiO_2 provided a supporting matrix releasing Ag in a controlled manner. Furthermore, tin oxide (SnO_2) hollow nanoflowers were synthesized by coprecipitation method using tin chloride and ammonia precipitators. These nanoflowers were capable of inhibiting quorum sensing—mediated virulence factor production and biofilm formation in *Chromobacterium violaceum, Serratia marcescens*, and *Pseudomonas aeruginosa* [60,61].

In addition to metal nanoparticles, nonmetal nanoparticles such as chitosan (polysaccharide) nanoparticles have also been widely used. In one such report, chitosan nanoparticles were capable of inhibiting quorum sensing behavior and caused cell aggregation in *E. coli* (Qin et al., 2017). Also, Curcumin nanoparticle formulation termed as nanocurcumin showed inhibition of biofilm formation in *Pseudomonas aeruginosa* [81]. Likewise,

Venkadesaperumal et al. [82] prepared nanoemulsions of different spice essential oils by ultrasonic emulsion method. These nanoemulsions were capable of inhibiting violacein production in *Chromobacterium violaceum* CV026 as well as EPS production and biofilm formation in food-borne pathogens *Klebsiella pneumoniae, E. coli*, and *Salmonella typhimurium*.

11.3.3 Quorum quenching by nanoparticles combined with bioactive molecules or other nanomaterials

Nanoparticles are also often combined with various other compounds such as metabolites from microbial cells or plant metabolites. These microbial or plant metabolites are the ones that have quorum quenching potential and when these are combined or tagged with nanoparticles their quorum quenching potential is significantly enhanced (summarized in Table 11.3).

Ref. [83] coated gold nanoparticles with AHL Lactonase protein (AiiA) from *Bacillus licheniformis*. These nanoparticles were capable of efficiently inhibiting quorum sensing mediated behavior in *Proteus* sp. by degrading N-hexanoyl-L-homoserine Lactone. Silicon dioxide nanoparticles (SiO_2 NPs) coated with quorum quenching molecule β-cyclodextrin prepared by Ref. [84] were capable of inhibiting QS-mediated luminescence in *Vibrio fischeri*. This was due to the quenching of signaling molecules by adsorption of AHLs on β-cyclodextrin. In addition, combination nanoparticles consisting of silver and curcumin nanoparticles were also prepared which showed enhanced quorum quenching potential. These nanoparticles had the ability of inhibition of violacein

Table 11.3 Quorum quenching potential of nanoparticles in combination with bioactive molecules or nanomaterials.

Nanoparticle	Combined tag	Target organism	References
Gold	AHL Lactonase protein from *Bacillus licheniformis*	*Proteus* sp.	[83]
Silicon dioxide	β-Cyclodextrin	*Vibrio fischeri*	[84]
Silver	Curcumin nanoparticles	*Chromobacterium violaceum*	[85]
Selenium	Honey polyphenols	*Chromobacterium violaceum* *Pseudomonas aeruginosa*	[86]
Chitosan	Baicalein	*E. coli* top 10 biosensor	[87]
Chitosan triphosphate	Ferulic acid	*Pseudomonas aeruginosa* PAO1	[88]
Chitosan triphosphate	Kaempferol	*Chromobacterium violaceum* CV026	[89]
Chitosan	Quercetin	*Pseudomonas aeruginosa*	[90]
Zinc oxide/ zeolite	Chitosan hydrogel	*Streptococcus mutans*	[91]

production and biofilm formation in *Chromobacterium violaceum* and were also capable of degradation of homoserine lactones [85]. Additionally, selenium nanoparticles carrying honey polyphenols were developed by Ref. [86] which were capable inhibiting quorum sensing mediated behavior in *Chromobacterium violaceum* and *Pseudomonas aeruginosa*.

Chitosan nanoparticles are widely used in combination, where these nanoparticles or nanocapsules are capable of increasing the quorum sensing inhibitory activity of various bioactive molecules. The encapsulation of flavonoids such as baicalein by chitosan resulted in increase in their quorum sensing inhibitory potential [87]. Ref. [88] synthesized chitosan tripolyphosphate nanoparticles and encapsulated it with ferulic acid which is a phenolic compound found commonly in plants. Ferulic acid encapsulated chitosan tripolyphosphate nanoparticles attenuated pyocyanin and rhamnolipid production, biofilm formation, EPS production, Staphylolytic activity, as well as altered motility in *Pseudomonas aeruginosa* PAO1. Similarly, chitosan tripolyphosphate nanoparticles were loaded with a flavonoid Kaempferol which showed significant inhibition of violacein production in *Chromobacterium violaceum* CV026 [89]. Likewise, chitosan nanoparticles were complexed with Quercetin, a plant flavonoid. This complex was capable of inhibiting swimming motility, biofilm formation, and pyocyanin production in *Pseudomonas aeruginosa* and the inhibitory potential was superior to that of pure Quercetin [90]. Ref. [91] synthesized a zinc oxide/zeolite nanocomposite and combined it with chitosan hydrogel and the complex was reported to inhibit biofilm formation in *Streptococcus mutans*.

11.4 Mechanisms of quorum quenching by nanoparticles

Nanoparticles are being studied and extensively reported for their quorum quenching potential. However, the mechanism by which this occurs is not fully understood and very few studies are available in literature. Ref. [46] had reported the mechanism by which different nanoparticles interfere with the process of quorum sensing. Based on the study, it was noted that zinc oxide nanoparticles do not interfere with the synthesis of signaling molecules (AHLs); however, it hinders the processes associated with the perception and response to the signal. Whereas titanium dioxide and silver nanoparticles greatly affects the synthesis of autoinducers, but does not significantly disrupt signal perception and response.

Silver nanoparticles due to their unique physicochemical characters are being widely studied for their quorum sensing inhibitory potential [72]. Significant antibiofilm activity of silver nanoparticles can be attributed to their involvement in neutralization of adhesive substances hence interfering with the attachment of microbes and development of mature biofilms [1]. Nowadays, rise in multidrug resistance in bacterial pathogens is reported. There are pathogens which have developed resistance to a large number of antibiotics which makes them MDR, a potential health threat [92]. Efflux pump mediated antibiotic resistance is a main mechanism for the development of MDR bacteria. Efflux

pumps obstruct the antibiotics from accessing their targets in the microbial cells and therefore reducing intracellular concentration of antibiotics [93]. In addition, it has also been reported that efflux pumps play a role in transport of signaling molecules engaged in quorum sensing phenomenon. Quorum sensing is responsible for biofilm formation that further contributes to the development of antibiotic resistance in bacteria [51]. Several metal nanoparticles such as copper, silver, zinc oxide, and iron oxide are researched for their role as efflux pump inhibitors. The inhibition of efflux pumps by nanoparticles will not only increase the sensitivity of bacteria to antibiotics but will also inhibit the quorum sensing mechanism [51,94].

In addition, nanoparticles are also capable of docking and inhibiting the function of enzymes involved in quorum sensing. Silver and copper nanoparticles bind to AHL synthase and regulatory proteins as well as enzymes involved in the synthesis of virulence factors in pathogenic *Pseudomonas aeruginosa* thereby, inhibiting their function [75,77] [53]. In addition, blocking the diffusion of AHLs from the cytoplasm in the surrounding carried out by flavonoids loaded in nanocapsules cause interference in QS [87]. Nanoparticles are also capable of downregulating the expression of genes involved in quorum sensing. For example, silver nanoparticles and zinc oxide nanoparticles caused the downregulation of *las, rhl, pqs*, and *phzA* genes involved in QS regulon of *Pseudomonas aeruginosa* [70] (Saleh et al., 2019).

11.5 Techniques and biosensors involved in quorum quenching research of nanoparticles

Enormous applications of nanoparticles in various fields are attributable to their unique structural properties. Investigations on the structural properties of nanoparticles is very crucial and is carried out using various instrumentation techniques. Techniques such as Scanning Electron Microscopy-EDX, Transmission Electron Microscopy, Fourier Transform Infrared Analysis, X-ray Diffraction analysis, Differential Scanning Calorimetric analysis are used to perform structural characterization of nanoparticles [60,61,89]. Quorum quenching potential of nanoparticles is studied by carrying out quantification and detection of quorum sensing signaling molecules. Quorum sensing detection and quantification methods such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), Mass Spectrometry (MS), as well as combinations such as HPLC-MS, GC-MS are employed for this purpose [95].

Detection and quantification of quorum sensing signaling molecules is also executed by using several biosensors. Whole cell-based biosensors having engineered plasmids which encodes for receptors of signaling molecules and having efficient reporter systems have been developed and are widely used [95]. The example of whole cell-based biosensor includes Gram-positive QS biosensor *Streptococcus mutans* SMdC that contains

plasmid pYH2-pOMZ47 which is capable of detecting QS molecule Competence Stimulating Peptides (CSP) synthesized by *Streptococcus pneumoniae* but is incapable of producing it by itself. However, in the presence of exogenous CSP, the expression of β-galactosidase is induced, helping in the assessment of quorum sensing activity [96]. Another example of Gram-positive whole cell-based biosensor is *Staphylococcus aureus* SH1000 which contains pAH plasmid and is capable of detecting the presence of exogenous *S. aureus* quorum sensing peptides [97]. Likewise, Gram-negative whole cell-based biosensors have also been developed. These biosensors are capable of detecting Acyl Homoserine Lactone (AHL), signaling molecule in Gram-negative bacteria. *Agrobacterium tumefaciens* KYC55 with plasmids pJZ384, pJZ410, and pJZ372, *Pseudomonas aeruginosa* M71LZ with plasmid pUCP19 have LacZ/β-gal reporter system for detecting exogenous AHL production [98,99]. *E. coli* JM109 having plasmid psB1075 have a bioluminescence-based reporter system. In the presence of AHL molecules, LasR receptors on the plasmid activates Lux reporter which leads to the production of bioluminescence signal [100]. Pigment-based reporter system has been developed in *Chromobacterium violaceum,* a soil and water bacteria capable of producing violacein pigment via AHL based CviI/CviR QS circuit. A mutant *Chromobacterium violaceum* CV026 has been developed, which by itself is incapable of producing AHL, however respond to exogenous AHL by producing violacein pigment [101]. In addition, wild type *Chromobacterium violaceum* is also used to study quorum sensing inhibitory potential of quorum quenching molecules. Here inhibition of pigment violacein in the presence of quorum quenchers is examined since reduction in violacein production is directly proportional to inhibition of AHL-based quorum sensing [25]. Similarly, inhibition of prodigiosin production in *Serratia marcescens* in the presence of quorum quenchers is also examined since prodigiosin production is also mediated by AHL-based SmaI/SmaR QS circuit [102].

11.6 Summary and conclusion

The use of antibiotics is the primary mode for treating infections caused by pathogenic bacteria. However, their haphazard use has led to the development of resistance toward them and has directed the emergence of Multiple Drug Resistant (MDR) bacterial pathogens. Interference in quorum sensing (cell to cell communication) has been investigated as an effective alternative for treating these bacterial infections. Owing to the unique properties such as small size, large surface area, nanoparticles are widely used in various fields. Researchers are exploring the ability of nanoparticles to be used as quorum sensing inhibitors. Potential of various metal, metal oxide, as well as nonmetal nanoparticles synthesized by biological, chemical, and physical methods as quorum quenchers are broadly studied with silver nanoparticles being the most studied and the most efficient metal nanoparticles. In addition, biologically synthesized nanoparticles, synthesized using plant extracts as well as microorganisms are also reported to have impressive quorum

quenching potential. Accordingly, after further research and detailed studies nanoparticles can serve as excellent therapeutic agents and can be exploited in various fields to prevent disease development and economic losses caused due to various pathogenic bacteria. Nanoparticles with quorum quenching activity have high potential to substitute the use of antibiotics since there are less chances of developing resistance against nanoparticles as compared to antibiotics.

11.7 Challenges and future prospects

Preliminary studies of nanoparticles for their quorum quenching potential have been carried out broadly by using various biosensors. However, detailed studies on their mode of action have to be performed using proteomic, genomic, transcriptomic, and proteogenomic tools. In addition, several new nanomaterials having quorum quenching potential needs to be synthesized using biological, physical, or chemical methods. Studies on combining quorum quenching molecules such as acylases, lactonases, as well as novel synthetic or biological quorum quenching molecules with nanomaterials and their synergistic effects need to be carried out in detail. Development of new sensitive and specific assays to detect and quantify quorum sensing signals is also required. Further, comprehensive toxicity studies using comet assay and micronucleus test along with clinical trials have to be performed in order to exploit nanoparticles as therapeutic agents.

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