Chapter 11
Nanoparticles as Quorum Sensing Inhibitor: Prospects and Limitations

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Abstract The emergence and worldwide spread of multi-drug resistant bacterial pathogens and slow pace of drug discovery with novel mode of action has necessitated search for alternative or new strategies to combat bacterial infection. Targeting virulence and pathogenicity of pathogens controlled by quorum sensing (QS) is considered as a promising anti-infective drug target. Several molecules both natural and synthetic were reported to interfere quorum sensing and are potential candidates for anti-infective drugs. The inhibition of QS might successfully attenuate and eradicate the microbial pathogens in combination with host immune system. It is expected that QS inhibition will exert less selection pressure for development of resistance among pathogenic bacteria. The recent progress in nanobiotechnology have given a greater hope for the development of novel anti-QS agents/formulations with improved therapeutic potential, enhanced targeted delivery with lesser toxicity to host system. The improved action of nano-formulations is a fascinating ability compared to their bulk. Recently, nanoparticles such as metal nanoparticles are reported to exhibit promising anti-QS activity both *in vitro* and *in vivo*. Nanomaterials are also been tested as vehicle for targeted delivery of conventionally used antimicrobial agents. There is greater scope of manipulation in nano-based formulations according to desired needs making such therapeutic strategies more efficient. Of note, the risks associated with the application of nanoparticles in drug delivery, diagnostics, production of improved biocompatible material or preventing biofilm formation on medical devices, *etc.* are needed to be scrutinized. In this article, we have made an attempt to review the recent advancements in nanoparticle as anti-QS agents and progress made on nano-based formulations with promising prospects and limitations.

Keywords Quorum sensing · Nanoparticles · Anti-QS agents · Drug delivery · Bacterial infection · Multi-drug resistance

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Abbreviations

AgNPs	Silver nanoparticles
AHL	Acylhomoserine lactone
CNTs	Carbon nanotubes
QS	Quorum sensing
QSI	Quorum sensing inhibitor
HSL	Homoserine lactone
SLNs	Solid lipid nanoparticles
MDR	Multi-drug resistance

11.1 Introduction

Microbial cell to cell communication is used in microbial system that helps in adaption and monitoring of their surroundings via chemical signalling, contact base chemical exchanges and electric signalling (Galloway et al. 2010; Phelan et al. 2012; Shrestha et al. 2013). One of such system is quorum sensing (QS) in which bacteria examines its local population by monitoring the amount of autoinducers, small chemical signal molecules. For the first time, QS was discovered in *Vibrio fischeri*, a marine bacterium, by Nealson and co-workers (Nealson et al. 1970). The term "quorum sensing" was coined by Fuqua and his group that referred to acylated homoserine lactone (AHL)-mediated luxR/luxI regulated system (Fuqua et al. 1994). In bacteria harbouring QS system, autoinducers interact with transcriptional regulators altering the genetic expression profiles, once their concentration reaches the certain threshold limit (Schaefer et al. 2013; Zhang and Li 2015; Ahmad et al. 2017). Autoinducers also bind to the extracellular domains of histidine kinase receptor, a membrane receptor, leading to autophosphorylation and causes a cognate cytoplasmic response (Ke et al. 2015). Regulation of expression of QS-dependent genes in a population by autoinducers provides an ability to maintain a "society" like structure that controls certain important physiological pathways and produce "co-operative" response such as biofilm formation, pathogenesis, pollutant biodegradation etc. (Ren et al. 2013; Husain et al. 2015; Yong et al. 2015). Recently, considerable amount of literature and reviews are available that highlights the importance of disruption of QS system as a promising strategy for disease control, water treatment systems and biodegradation (Bhardwaj et al. 2013; Díaz et al. 2013; Rampioni et al. 2014; Siddiqui et al. 2015).

In QS, the expression of virulence factors and other proteins are also controlled which are involved in primary metabolic process (Husain et al. 2016; Rajamanikandan et al. 2017). A remarkable portion of bacterial genome *i.e.* 4–10% and more than 20% of bacterial proteome system is influenced by this communication system (Sifri 2008). Apart from above mentioned processes, many other responses are also controlled by QS that includes competence, motility, secretion of virulence factors, sporulation, bioluminescence, and antibiotic production (Roux et al. 2009). Another

problem with conventional antimicrobial agents (mainly antibiotics) is that its subjudicious use had led to the emergence of multi-drug resistant (MDR) strains or "superbugs" (Maheshwari et al. 2016). Virulence and pathogenicity in large number of pathogenic bacteria are regulated by QS. Therefore, it is now considered that disruption of this microbial communication may prove to be an important target for the development of novel anti-infective agents and combating problem of multidrug resistance (Al-Shabib et al. 2017). It is expected that QS inhibitors may successfully eradicate the microbial infections in combination with host immune system without having any harmful effect on human tissues (Defoirdt et al. 2013). Moreover, microbes are less likely to develop resistance against anti-QS agents since it mainly targets the virulence factors without inhibiting the growth of microorganisms (Hentzer and Givskov 2003; Ahmad and Husain 2014).

Recent advances in nanotechnology have opened new hope for researchers as it has gained much attention due to its application in medicine, diagnostics, bioremediation, agriculture etc. (Valcárcel and López-Lorente 2016). The underlying reason of nanoparticle's better action compared to their bulk form is their fascinating properties which are superior to those of bulk materials (Wagh et al. 2013). This advancement has attracted the attention of researchers to develop novel antibacterial agents in the form of nanomedicine (Khan et al. 2016). Anticipated application of nanotechnology in healthcare include diagnostics, drug delivery, preventing biofilm formation on medical devices, production of improved biocompatible material *etc.* (Zia et al. 2010). However, risks associated with the application of nanoparticles in medicine is also subject to scrutiny. In this chapter, we have briefly summarised the fundamental concept of nanoparticles, its application in medicine, its current status of knowledge on application of nanoparticles as anti-QS agents and in delivery of anti-QS agents.

11.2 Nanoparticles: Characteristics and Their Interaction with Bacteria

Recently, there has been enormous growth in nanotechnology that has found its vital applications in basic and applied research of biological, chemical, physical and earth sciences (Fernandez-Garcia et al. 2004; Rodríguez and Fernández-García 2007; Raghunath and Perumal 2017). Nanoparticles are usually in the range of 1–100 nm having great versatility in their shapes and size that possess unique chemical and physical characteristics. Till date, nanoparticles have found their application in diagnosis, catalysis, drug delivery, sensing, semiconductors and solid oxide fuel cells (Haddad and Seabra 2012; Corr 2013). Various reports have been found on the application of nanomaterials as antimicrobial agents (Jones et al. 2008; Mahapatra et al. 2008; Tran et al. 2010). The unique chemical and physical properties of nanoparticles compared to their bulk material enable them to differently interact with biological systems and contribute to antimicrobial activity (Singh and Nalwa 2011). The alkaline nature of metal nanoparticles such as magnesium oxide and calcium oxide nanoparticles is the significant component that confers to

antimicrobial activity (Sawai et al. 2005). These alkali metal nanoparticles are relatively more soluble that contributes in alkalinity of the medium which is not found in semiconductor metal nanoparticles such as zinc oxide nanoparticles (Zhang et al. 2007). The electrostatic nature of positively charged nanoparticles such as cerium oxide nanoparticles also determines their bacteriostatic and bactericidal property (Thill et al. 2006). Titanium nanoparticles are semiconductor photocatalysts which inhibit the growth of even desiccation tolerant and ultraviolet radiation-resistant bacteria (Sadiq et al. 2010).

Nanoparticles exhibit wide range of action that can serve as broad spectrum antimicrobial agents against micro-organisms including those of multi-drug resistant strains. Different nanoparticles with diverse functional and physicochemical properties makes them good antimicrobial agent and an alternative to the conventionally used antibiotics. Nanoparticles of desired properties can be made as anti-infective agents owing to their high novel electrical, chemical, magnetic, mechanical and optical properties and high surface area-to-volume ratio (Whitesides 2005). The antimicrobial efficacy of nanoparticles is mainly governed by the solubility in aqueous medium, particle size and release of metal ions (Raghunath and Perumal 2017). The mode of action of nanoparticles is quite different from conventional antibiotics that include destruction of enzyme and nucleic acid pathway and alterations of the cell wall (Zhu et al. 2013). Due to limited site of action of antibiotics, bacteria develop resistance against one or more antibiotics. On the other hand, nanoparticle exhibited completely different mode of action including membrane damage and alteration of cellular processes both at molecular and biochemical levels (Kumar et al. 2011a,b). Antibacterial efficacy of nanoparticles is also due to induction of oxidative stress, release of metal ions and non-oxidative stress (Nagy et al. 2011; Gurunathan et al. 2012; Leung et al. 2014). The multiple mode actions require multiple simultaneous genetic changes in bacterial cell to develop antibacterial resistance against nanoparticles (Zaidi et al. 2017) which makes difficult to emergence of early resistance to nanoparticle. Moreover, use of nanomaterials as vehicle for antibiotics for targeted delivery can support and complement traditional antibiotics. The nanomaterials as delivery systems include concurrent delivery of multiple drugs, enhanced drug solubility and prolonged systemic circulation as reported earlier (Davis and Shin 2008; Chetoni et al. 2016). The promising results at research level have endorsed the use of nanoparticles for the treatment of infectious diseases and delivery of vaccines in which many formulations are under various phases of pre-clinical and clinical tests (Raghunath and Perumal 2017; Zaidi et al. 2017).

11.3 Nanoparticles as Anti-QS Agents

In search for novel quorum sensing inhibitors, researchers have tested diverse group of compounds including, phytocompounds and synthetic compounds (Asfour 2017). In recent years, efforts have been made to evaluate various nanoparticles as

antimicrobial agents against a number of pathogenic microorganims (Zaidi et al. 2017). Search for novel activities in nanoparticles such as anti-QS properties and QS mediated inhibition of virulence and biofilm have been recently documented (Radzig et al. 2013; Chaudhari et al. 2015; García-Lara et al. 2015; Miller et al. 2015). Some of the relevant literature reports are summarized in Table 11.1. Since most of the studies in this direction are directed towards metallic nanoparticle such as silver nanoparticle. A survey of literature is briefly described below.

11.3.1 Silver Nanoparticles

Silver nanoparticles are nanoscale clusters of silver atoms (Ag^0). The silver nanoparticles is most commonly synthesised by chemical reduction of silver ions with reducing agents (Iravani et al. 2014). However, green synthesis of nanoparticles has now become more common. Various combinations of silver nanoparticles with other metal is used to enhance the availability and activity of metal nanoparticles (Janczak and Aspinwall 2012). Antimicrobial property of silver nanoparticles has been well documented in literature (Agnihotri et al. 2014; Ahmed et al. 2016; Zou et al. 2017). The mechanism of action of silver nanoparticles is not yet fully explored but involves three most common mechanisms:

(i) Free silver ions uptake followed by interruption of ATP production and DNA replication.
(ii) Production of reactive oxygen species(ROS)
(iii) Damage to cytoplasmic membrane.

Silver nanoparticles (AgNPs), one of the most widely studied metal nanoparticles, have been found to inhibit QS controlled virulence factors in both Gram-positive and Gram-negative bacteria (Wagh et al. 2013). A brief study on green synthesized silver nanoparticles from *Cymbopogan citratus* leaf extract demonstrated quorum quenching action and prevented biofilms formation by *Staphylococcus aureus* which was also demonstrated by microscopic data (Masurkar et al. 2012). The research found that silver nanoparticles might be involved in neutralisation of adhesive substances which are required for the initial attachment of microbes and for maintenance of biofilm strength.

A detailed study conducted by Singh and co-workers demonstrated that biosynthesized AgNPs inhibited the violacein production approximately by 100% at 25 μg/ml in *Chromobacterium violaceum* 12472. Furthermore, they examined the effect of AgNPs on *C. violaceum* CV026 and *Pseudomonas aeruginosa* PAO1 both at toxic and non-toxic concentrations. The results demonstrated that AgNPs interfered QS *via* attenuation of AHL production not by its toxic effect. Many QS mediated virulence factors of PAO1 were inhibited by AgNPs such as Las a protease activity (15–86% inhibition), LasB elastase (22–86% inhibition), pyocyanin (18–96% suppression), pyoverdine (14–95% suppression), pyochelin (10–92% suppression) and rhamnolipid (10–70% inhibition) at non-toxic concentrations. The

Table 11.1 Nanoparticles demonstrating anti-QS activity and their mode of action

S. No.	Nanoparticles	Activities found	Test organism	References
1.	Silver nanoparticle	Quorum quenching against *S. aureus* biofilm	*S. aureus*	Masurkar et al. (2012)
2.	Silver nanoparticle	Inhibition of violacein of *C. violaceum*, inhibition of virulence factors such as protease activity, elastase, pyocyanin, pyoverdine, pyochelin and rhamnolipid of *P. aeruginosa*	*C. violaceum* and *P. aeruginosa*	Singh et al. (2015)
3.	Silver nanowires	Inhibition of violacein of *C. violaceum*, inhibition of biofilm of *P. aeruginosa*	*C. violaceum* and *P. aeruginosa*	Wagh et al. (2013)
4.	Silver nanoparticle	Inhibition of violacein of *C. violaceum*	*C. violaceum*	Arunkumar et al. (2013)
5.	Silver nanoparticle	Inhibition of violacein of *C. violaceum*	*C. violaceum*	Anju and Sarada (2016)
6.	Silver nanoparticle	Inhibition of violacein of *C. violaceum*, inhibition of production of pyocyanin, protease, hemolysin and biofilm of *P. aeruginosa*	*C. violaceum* and *P. aeruginosa*	Ali et al. (2017)
7.	Honey polyphenol carrying silver nanoparticle	Inhibition of violacein of *C. violaceum*, inhibition of elastin-degrading elastase, exoprotease, pyocyanin, biofilm, swarming motility and rhamnolipid of *P. aeruginosa* in mice model	*C. violaceum* and *P. aeruginosa*	Prateeksha et al. (2017)
8.	Zinc oxide nanoparticles	Inhibition of violacein of *C. violaceum*, inhibition of elastase, total protease, pyocyanin production, exopolysaccharide production and swarming motility of *L. monocytogenes*, *P. aeruginosa*, *E. coli* and *C. violaceum*, disruption of mature biofilm, down regulation in *pqsA*	*L. monocytogenes*, *P. aeruginosa*, *E. coli* and *C. violaceum*	Al-Shabib et al. (2016)
9.	β-cyclodextrin functionalized silicon dioxide nanoparticles	Inhibition of bioluminescence of *Vibrio fischeri*, down-regulation of *luxA* and *luxR* gene of *V. fischeri*	*Vibrio fischeri*	Miller et al. (2015)
10.	Silver coated carbon nanotubes	Down-regulation of *sdiA* (a quorum sensing gene) and many virulence genes (*safC*, *ychP*, *sseA* and *sseG*) of *S. aureus*	*S. aureus*	Chaudhari et al. (2015)
11.	Silver-titanium nanocomposite	Inhibition of violacein of *C. violaceum*, inhibition of biofilm formation and degradation of homoserine lactone	*C. violaceum*	Naik and Kowshik (2014)
12.	Silver and curcumin nanoparticles	Inhibition of biofilm formation of *P. aeruginosa* and *S. aureus*	*P. aeruginosa* and *S. aureus*	Loo et al. (2015)

expression of QS regulated virulence genes was also significantly reduced. It was revealed by RT-qPCR in planktonic cells of PAO1 that the expression of *lasA*, *lasB*, *phzA1* and *rhlA* were repressed by 79, 84, 68 and 72%, respectively at 25 mg/l of AgNPs. There was also remarkable inhibition (71%) of LasI transcriptional activity and 50% down-regulation of LasR. The level of RhlI and RhlR was also decreased by 64 and 55%, respectively. Many other QS-regulated genes such as *lasI*, *lasR*, *rhlI*, *rhlR*, and *fabH2* were also down-regulated by 71, 51, 63, 36, and 81%, respectively while expression of the *proC* housekeeping gene was not affected. The synthesis of C12-AHL and C4-AHL was also inhibited dose-dependently at tested concentration. Similarly, AgNPs exhibited reduction in biofilm formation at 5–25 mg/l which was evident from confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM) data (Singh et al. 2015).

Similarly, silver nanowires (SNWs) synthesized by polyol process was found to inhibit quorum sensing. It was found the nanowires were able to inhibit synthesis of violacein by 60 and 80% at 0.5 and 4 mg/ml respectively, in *C. violaceum* CV026. The concentration above 4 mg/ml was inhibitory to the growth of the tested bacteria. Biofilm of *P. aeruginosa* NCIM 2948 was maximally inhibited by SNWs at 4 mg/ml without interfering its growth (Wagh et al. 2013). The QS-mediated inhibition of biofilm is considered important as at sub-inhibitory growth concentration, there is no selective pressure for the development of resistance against test compound or nanoparticle. Recently, there is growing interest for the development of biomaterials that has shifted from drug molecules to nanomaterials (Knetsch and Koole 2011; Bazaka et al. 2012). Many medical devices have been made using nanomaterials as antibiofilm agents which is aimed to minimize the biofilm formation on their surface (Monteiro et al. 2009).

A preliminary investigation of AgNPs synthesised from double mutant strain *Klebsiella pneumoniae* found the inhibitory effect on formation of purple pigment in CV026. A clear zones of pigment inhibition around wells at varying concentrations (15, 10, 5 µl) of AgNPs were indicative of quorum sensing inhibition. Additionally, antibacterial activity of green synthesized AgNPs and its synergy in combination with antibiotics were also found (Arunkumar et al. 2013). A recent study on anti-QS activity of AgNPs also supported earlier finding and exhibited clear zone of violacein inhibition around the sample followed by a turbid halo zone where indicator organism was not inhibited but depigmented highlighting the anti-QS potential. Not only QS, but bacterial growth was also significantly inhibited of multi-drug resistant pathogens such as *S. aureus* and *P. aeruginosa* (Anju and Sarada 2016). In another investigation, anti-quorum sensing activity was reported by silver nanoparticles at sub-MIC (15 µg/ml) against *C. violaceum*. Similarly, many QS-mediated virulence factors of *P. aeruginosa* were successfully inhibited. The production of pyocyanin was inhibited up to 74.64%, protease production was decreased up to 47.3%, hemolysin activity was decreased to 47.7% in all tested drug resistant clinical isolates of *P. aeruginosa*. The formation of biofilm was also remarkably reduced by 70.9–79.7% as also evident from confocal laser scanning microscopy (Ali et al. 2017).

The inhibition of quorum sensing regulated traits by silver nanoparticle is also attributed to silver. It was found that silver dose dependently attenuated the attachment of *P. aeruginosa* to the cover slip significantly compared to the control group. The biofilm inhibition data at sub-MIC levels was further evaluated by crystal violet assay and total protein assay. The growth cycle of test organism was evaluated at sub-MIC dose of silver to further validate and it was found that after identical period of incubation, silver treated and untreated microorganisms exactly followed the same trend in their growth kinetics (Sharma et al. 2015).

11.3.2 Other Nanoparticles

Prateeksha and colleagues demonstrated that selenium nano-scaffold exhibited enhanced anti-QS activity, anti-virulence potential and anti-biofilm efficacy under *in vitro* and *in vivo* compared to both selenium nanoparticles and honey polyphenols. Preliminary investigation demonstrated that surface conjugated selenium nanoparticles (SeNPs@HP) interfere QS by interacting with AHLs and their receptors. At 4.5 μg/ml of SeNPs@HP, there was decrease in virulence factors elastin-degrading elastase (52.7%), exoprotease (60.2%), pyocyanin (49.6%) and rhamnolipid (59.6%) of *P. aeruginosa* PAO1. A significant reduction in swarming motility was also observed at same tested concentration. As evident from calorimetric and microscopic data, SeNPs@HP reduced the formation of biofilm by more than 90% at sub-MIC concentration. To further validate under *in vivo* condition, the infected mice (with 10^7 cfu/ml of *P. aeruginosa* PAO1) were treated with SeNPs@HP. At early stage of infection (on first day), there was insignificant difference in treated and untreated groups. However, treatment with 4.5 μg/ml of SeNPs@HP, on day 5, 10, 15 and 20 post-infection, there was 31.7, 69.6, 81.6 and 97.3% wound healing respectively. The molecular docking results revealed that interaction of honey polyphenols with *N*-(3-oxododecanoyl)-l-homoserine lactone binding site of LasR might be the reason for successful inhibition of virulence of *P. aeruginosa* PAO1 (Prateeksha et al. 2017).

Zinc oxide nanoparticles (ZnO-NPs) also possess anti-QS potential. Preliminary investigation by disc diffusion assay suggested the QS inhibition in bio-indicator strain *C. violaceum* 12472. It was found that maximum inhibition of violacein was observed at 400 μg/ml (91%) followed by lower concentrations (200–50 μg/ml) in a dose dependent manner. ZnO-NPs inhibited many virulence factors including elastase (35–82%), total protease (20–77%) and pyocyanin production (48–93%). At 10, 20, 40 and 80 μg/ml, there was 35, 55, 78 and 85% inhibition of *lasB* transcriptional activity. Similarly, 41–84% down regulation in *pqsA* was also recorded at varying (10–80 μg/ml) levels of ZnO-NPs. A significant decrease in exopolysaccharide (EPS) production (25–90%) and swarming motility (7–78%) was recorded.

The biofilm formation by *Listeria monocytogenes*, *P. aeruginosa*, *Escherichia coli* and *C. violaceum* was inhibited up to 91, 93, 82 and 83% respectively. Disruption of mature biofilm of different bacterial strains was also achieved at sub-MIC levels (Al-Shabib et al. 2016).

Similarly, β-cyclodextrin functionalized silicon dioxide nanoparticles with 2 μM 3OC6-HSL demonstrated that the β-cyclodextrin moiety was significantly more effective at dimming bioluminescence of *V. fischeri* when functionalized to silicon dioxide nanoparticles than it was as a free-compound. At environmentally-relevant levels of HSLs, bioluminescence of *V. fischeri* was significantly diminished by β-cyclodextrin ($P = 0.05$). The functionalization of β-cyclodextrin to 50 nm NPs, 133 nM β-cyclodextrin produced similar result as that of 2X concentration of free 250 nM β-cyclodextrin. Quantitative PCR and transcript analysis found that the quantity of transcripts produced by untreated cultures and treated cultures (with 250 nM β-cyclodextrin) were not significantly different. The result confirmed that lower concentrations of free β-cyclodextrin were ineffective in down-regulating *luxA* and *luxR* at environmental levels of *N*-acyl-L-homoserine lactones, however, higher concentration (*i.e.* 2 mM) β-cyclodextrin was able to significantly reduce their expression. The 133 nM -cyclodextrin, in presence of functionalized 50 nm NPs, produced most down-regulation of luxA and luxR transcripts in all treatment groups (Miller et al. 2015).

Chaudhari and co-workers found the anti-QS activity of pegylated silver coated carbon nanotubes (pSWCNTs-Ag). Treatment of pSWCNTs-Ag to *S. aureus* exclusively down regulated the expression of *sdiA* (a quorum sensing gene) and many virulence genes (*safC*, *ychP*, *sseA* and *sseG*) by several folds. It was of noteworthy that pSWCNTs-Ag at bactericidal concentration was found non-toxic to human cells (Chaudhari et al. 2015).

Composite nanoparticles are reported to exhibit anti-QS activity. A qualitative estimation of silver-titanium nanocomposite (AgCl-TiO_2NPs) resulted in concentration dependent violacein pigment inhibition of *C. violaceum*. Violacein production was inhibited by 82% at 100 μg/ml and at 300 μg/ml, there was complete (100%) inhibition in nutrient broth. In modified Tris minimal medium, treatment with 50 and 75 μg/ml of AgCl-TiO_2NPs inhibited violacein production by 87 and 99% respectively. At 20 μg/ml, there was remarkable decrease in biofilm production and complete inhibition was obtained at 100 μg/ml. One of underlying mechanism of QS-inhibition was found to be degradation of homoserine lactone (HSL) by AgCl-TiO_2NPs. HPLC chromatogram exhibited single sharp peak with retention time of 21 min due to HSL. The peak was corresponding to HSL was absent in AgCl-TiO_2NPs treated samples and presence of two smaller peaks were attributed to the degradation products/precursors of the signalling molecule (Naik and Kowshik 2014).

Combination of silver and curcumin nanoparticles was also effective in eradication of established mature biofilm as well as inhibition of biofilm formation.

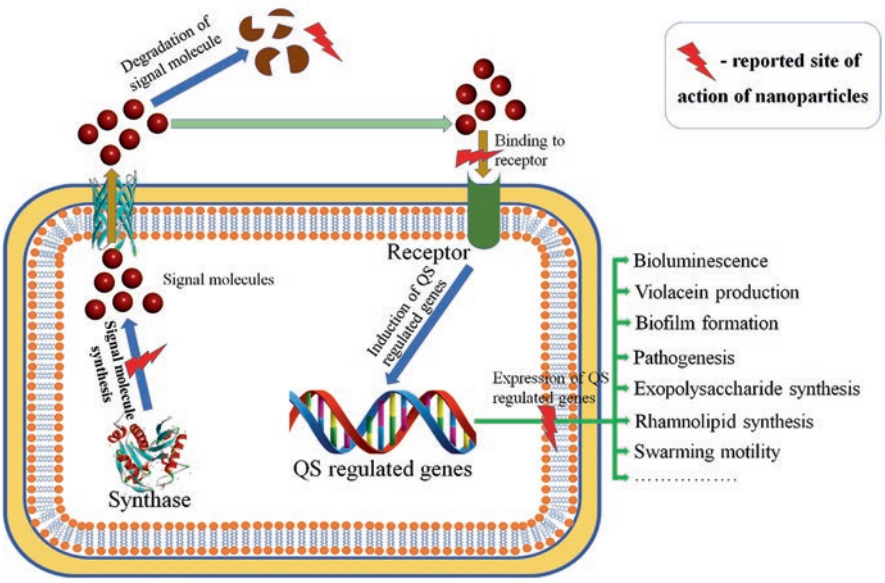

Fig. 11.1 Schematic representation of anti-QS mechanisms of nanoparticles

Treatment of 400 μg/ml of curcumin nanoparticles successfully reduced biofilm biomass of both *P. aeruginosa* and *S. aureus* (Loo et al. 2015). The anti-biofilm activity of curcumin is by attenuation of QS virulence factors and by interfering with the signal molecules (Rudrappa and Bais 2008).

In the beginning of twentieth century, discovery of antibiotics revolutionized the field of medicine by combating a large number of life threatening diseases. The indiscriminate and excessive usage of antibiotics caused the emergence of drug resistance in bacteria (Ciofu et al. 1994). It is important to mention that at least 65% of all infectious diseases are associated with bacterial communities which become virulent by forming biofilms (Lewis 2007). Once in biofilm mode, bacteria become up to 1000 times more resistant to antibiotics compared to their planktonic counterparts (Olson et al. 2002). The behaviour and virulence with in the biofilm is in QS control in which bacteria synthesize chemical signals and express their virulence genes in a cell density dependent manner (Romero et al. 2012). The efforts are being made for the search and synthesis of molecules having tendency to disrupt biofilm formation by quenching the QS system, this phenomenon is called quorum quenching (Huma et al. 2011; Kalia et al. 2011). The quorum sensing inhibitors (QSIs) may target at various sites of QS circuit that can provide an opportunity for the development of new therapeutic agents against pathogens to combat infections (Kalia 2013). Based on the above literature and many other reports, the mode of action nanoparticles in inhibition of QS is summarized in Fig. 11.1.

11.4 Nanoparticles in Delivery of Quorum Sensing Inhibitors (QSI)

The activity of quorum sensing inhibitors (QSI) can also be enhanced by their application and delivery in the form of nano-formulations. Various systems have been developed for the delivery of antibiofilm and anti-QS agents including liposome, noisome, PGLA, dendrimers, chitosan etc. (Sajid et al. 2014). The biodegradable and biocompatible nanoparticles used for controlled delivery of drugs is an effective therapeutic strategy (Daum et al. 2012). In last few years, several nano-based delivery systems like poly(lactic-co-glycolic acid) nanoparticle (PLGA), fusogenic liposomes, solid lipid nanoparticles (SLNs) and lipid-polymer hybrid nano-formulation have proven to be promising vehicles for targeted delivery of drugs (Forier et al. 2014). Many such formulations like protein–polymer conjugates (*e.g.* Intron® A) and liposomes (e.g. AmBisome®) have already reached to market authorization stage. There are many other formulations under preclinical or clinical investigation such as polymeric nanoparticles, dendrimers, lipid nanoparticle, nanosomes, drug–polymer conjugates and complexes (Mohamed-Ahmed et al. 2013). Solid lipid nanoparticles (SLNs) are physiological lipids dispersed in aqueous surfactant solution are one of the attractive class of nanocarriers (Bondì and Craparo 2010). SLNs have advantage of improved drug stability, tendency of readily incorporation of lipophilic drugs, controlled release and a higher safety threshold values due to the evasion of organic solvents (MuÈller et al. 2000; Mehnert and Mäder 2012). There are certain limitations associated with SLNs including risk of drug leakage gelation during storage, low drug loading owing to lipid polymorphism (Müller et al. 2002).

Nafee and co-workers investigated the effect of SLNs incorporated with QSI on pyocyanin production in *P. aeruginosa* PA14. It is interesting to note that not only the biological activity of QSI was maintained but exhibited superior action in its nano-formulation. Further, inhibition of pyocyanin production by QSI encapsulated SLNs was most pronounced at lower concentrations and weaker dependence on dose, while free compound resulted in a clear dose-dependent inhibition. It was also found that free SLNs also inhibited pyocyanin production that strongly suggests an additive inhibitory effect by the QSI and the SLNs. The growth curve data of *P. aeruginosa* confirmed the inhibitory potential of plain SLNs was not due to bacteriostatic or bactericidal effect (Nafee et al. 2014). The result rules out the possibly of QS inhibition by inhibiting microbial growth which is often associated with nanoparticles (Bae et al. 2011).

11.5 Prospects and Limitations

Recent development on efficacy of nanoparticles as antimicrobial and anti-pathogenic agents (anti-biofilm and anti-QS) have indicated the promising prospect in the treatment and prevention of bacterial infections. Due to unique physical and

chemical characteristics of nanoparticles, it has also been evaluated and found effective as carrier for a number of therapeutic drugs such as antibiotics, anticancer drugs. Therefore, it is expected that with the increase in discovery of anti-QS agents from natural and synthetic sources, nanoparticles could also be effectively useful in delivery of such anti-QS agents for combating bacterial infection. Different combination or formulations of nanoparticles may be developed to enhance efficacy, safety and availability *in vivo* system.

The *in vitro* reports on efficacy of nanoparticles in interfering QS and its regulated functions are increasing. However, the *in vitro* conditions are different from *in vivo* conditions. Therefore, suitable animal model studies should be conducted to assess the therapeutic efficacy of nanoparticles as anti-QS agents. Anti -QS nanoparticle should not exert toxicity to host cell as well as should not create selection pressure on microbial pathogens especially on MDR bacteria to develop resistance to nanoparticle. Further understanding the role of nanoparticles as anti-QS needs to be evaluated through systemic investigation in suitable animal models.

11.6 Conclusion

Interference of QS is an effective alternate strategy to combat microbial infections. In the present scenario when the efficacy of antibiotics cannot be ensured for longer time, nanoparticles with anti-QS activity may become promising therapeutic agents against bacterial pathogens. Various reports indicated that nanomaterials can also be used as vehicles for the targeted delivery of natural and synthetic compounds which are known for their promising anti-QS activity and reduces the toxicity to non-target tissues. Studies have shown the quorum sensing inhibitory activity of many nanoparticles in biosensor strains and such nanoparticles should be evaluated against clinically relevant pathogens both *in vitro* and in experimental animals to uncover the therapeutic efficacy.

11.7 Opinion

Current antibiotic therapy to combat MDR problem requires immediate attention to develop new anti-infective drugs. QS inhibition is considered a promising drug target to attenuate bacterial pathogenicity and reduce the risk of antibiotic resistance. Recent research indicated that nanoparticles may prove to be better antimicrobial agents compared to conventional antibiotics against MDR bacteria as nanoparticles have multiple targets resulting in broad-spectrum action against pathogenic bacteria. On the other hand, nanoparticle have greater scope for manipulation and can be modified according to specific needs. Although research in the area of medicine is at the early stage and still restricted to the laboratory but the results so far reported is promising. Further research on nanoparticles as QSIs must be continued with

special reference to its toxicological impact on host system and *in vivo* efficacy. It is expected that time is not far when inhibition of cellular communication (quorum sensing) by nanoparticles may become a better alternative for treatment of microbial disease in man and animals specially against drug resistant strains.

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