

Acinetobacter baumannii Quorum sensing: A way to communicate and a target to eradicate

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Abstract

Quorum sensing is a communication system based on the actions of chemical signal molecules depending on the density of the cell population. These molecules are widely considered as effectors of the gene expression of several virulence factors. As a result, it has attracted a lot of attention because of its possible applicability as a target for treating infections. This review attempts to give a description of this system on gram negative bacteria specifically on *Acinetobacter baumannii* as an important nosocomial pathogen. Additionally, quorum sensing in biofilm will be also treated because it is considered as the origin of several chronic infections. Numerous studies have been carried out to prove the role of inhibitors in the disruption of quorum sensing, known as quorum quenching. Quorum quenching is a new strategy to eradicate bacterial infections due to the crucial intervention of quorum sensing in different virulence factors and particularly in the biofilm formation.

Keywords: Quorum sensing; Acylated homoserine lactone; Biofilm; *Acinetobacter baumannii*; Anti-infection

1. Introduction

In recent decades, it has become clear that bacteria coordinate interactions with each other and with higher organisms through intercellular communication systems, called quorum sensing (QS). These latter are often based on the expression of new genes [1, 2]. The first works highlighting the mechanism of bacterial communication appeared in 1965 and 1970 [3, 4]. The researchers established a link between the control of the genetic competence of *Streptococcus pneumonia* [4] and the control of the activity of luminescent bacteria [3] and the production of extracellular molecules. In 1980, other important studies were published on the luminescent genes of *Vibrio fischeri* [5] and the autoinducer was the N-3-oxohexanoyl-L-homoserine lactone-3OC6-HSL [6]. The term quorum sensing was first used by Fuqua et al (1994) in a review article. These authors defined quorum sensing as an environmental sensing self-induction system that allows bacteria to monitor their own population density, producing a diffusible compound called an autoinducer [7].

The importance of this system is reflected by its involvement in various bacterial processes and behaviors such as bioluminescence, sporulation, biofilm formation, secretion of virulence factors, symbiosis, and conjugation [8–12]. Thus, QS represents an interesting target for developing a new strategy to combat infections caused by bacterial pathogens.

Herein, we aim to provide an overview of simple and summarized information about QS system, focusing on gram-negative bacteria. It will also cover the close relationship between pathogenicity and QS, giving the example of *Acinetobacter baumannii* and its biofilm formation as one of the most frequent nosocomial pathogens. At the end of this review, the possible application of QS as one of the probable anti-infectious strategies will be discussed.

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2. Definition of Quorum sensing

QS is a bacterial communication based on ligand-receptor signal molecules; these are so-called self-inducing bacterial pheromones secreted by bacteria to regulate certain functions [13]. Gene expression of these pheromones will only take place when a bacterial population reaches a significant cell density threshold, thus leading to the activation or repression of the genes. Therefore, any bacterial population capable of expressing these autoinducers is called a quorum [13, 14].

The QS mechanism is based on an enzyme that catalyzes the synthesis of chemical signals and a receptor that binds with these signals to induce the expression of genes responsible for various bacterial functions (sporulation, biofilm formation, conjugation, motility) and virulence factors (proteases, toxins, and adhesins) [15, 16]. QS is a very common molecular mechanism in bacteria, which gives them an important advantage in terms of evolution, allowing them to adapt to changes in the environment [17]. Moreover, it permits the bacteria to coexist in a community and express phenotypes that are beneficial and ensure bacterial survival [18]. The expression of autoinducers depends on the nature of the bacteria (QS used by both Gram positive and Gram negative) and its physiological state (cell density), but also requires the presence of other elements: synthase signals, receptor signals, genes and regulatory signals [19].

3. Quorum sensing system in gram negative bacteria

Gram negative bacteria produce autoinducers from an initial precursor called Acylated Homoserine Lactone (AHL or N-acyl homoserine lactones). AHL synthesis is catalyzed by enzymes of the signal synthase family (LuxI; enzymes encoded by the Lux operon). The transcription of the Lux operon depends on cell density; its activation requires significant cell density [19]. The system of QS is well known for several gram-negative bacterial species such as *Pseudomonas aeruginosa* and *Agrobacterium tumefaciens*. These two species are able to couple their gene expression according to fluctuations in cell density [20].

AHL is also known as AI-1 and it consists of homoserine lactone rings with an additional fatty acid side chain, which differ in length, and their residue depending on the bacterial species [18]. Even AHL signaling has traditionally been considered as intraspecific communication, V. C. Kalia (2013) suggests that AHL can also be used to detect potential environmental competitors.

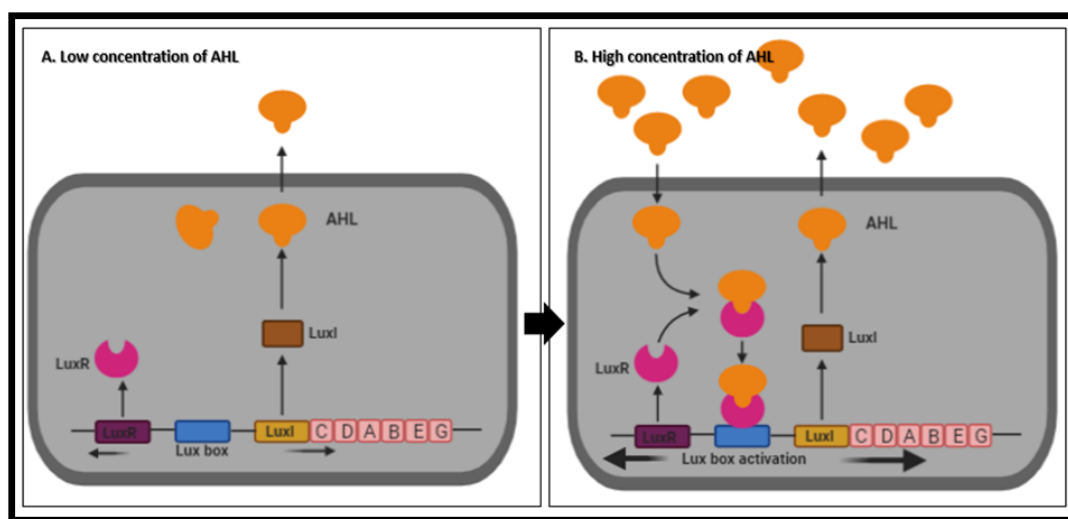


Figure 1 LuxI/LuxR QS system of *Vibrio fischeri* with bioluminescence regulation A: at low population density and B: high population density

In the 1980, the first LuxI/LuxR quorum detection mechanism was discovered in *Vibrio fischeri* (fig. 1), whose bioluminescence is controlled by the regulation of a transcriptional regulatory protein (LuxR) and a signal synthase molecule (LuxI) [5, 22]. The LuxI enzyme catalyzes the amide bond formation between the substrates S-adenosylmethionine (SAM) and the acyl-acyl carrier protein (acylACP) to form AHL signal molecule. Cells express LuxI even when the population density is low (fig. 1A), but the concentration of AHL is maintained at a low level [23, 24]. When the population density increases, the concentration of AHL in the medium gradually rises and reaches a threshold

level (corresponding to the detection of quorum). Then, the AHL enters the cell and binds to the LuxR protein (fig. 1B). The LuxR complex that is activated by AHL binds to a lux box located at the LuxI transcription start site. The LuxICDABEG transcription is subsequently activated (fig. 1B), resulting in an increase in light output and AHL [23, 24]. The newly generated signal molecules are capable of activating more LuxR proteins, leading to self-induction, and then the exponential production of bioluminescent molecules and signals [23, 24]. Since the discovery of the LuxI/LuxR quorum, many Gram-negative bacteria have been found to regulate the quorum detection system using LuxI/LuxR homologues (Table 1).

Table 1 Quorum sensing systems of Gram-negative bacteria with their regulated functions

Microorganism	QS system	Regulated functions	Reference
<i>Acinetobacter baumannii</i>	Lux (Aba)	Motility and biofilm formation	[25]
<i>Vibrio fischeri</i>	LuxI, Ain, LuxS	Expression of bioluminescence, colonization in the host, and motility	[16]
<i>Pseudomonas aeruginosa</i>	Las, Rhl, PQS, IQS	Virulence factors: pyocyanin, pyoverdine, elastase, alkaline protease, motility, rhamnolipids, and biofilm formation	[2]
<i>Escherichia coli</i>	SdiA	Motility and biofilm formation	[26]
<i>Serratia liquefaciens</i>	Swr	Motility, biofilm formation	[27]

4. Others Quorum sensing systems

The third class of signaling molecules is the autoinducer 2 (AI-2), which can be found in Gram-positive and Gram-negative bacteria. The AI-2 system was first described in *Vibrio harveyi* and its extracellular signaling molecule is a furanosyl borate diester [28]. This class is widely involved in interspecies communication (cross talk), and is therefore considered a universal communication signal between different bacterial species [29].

Quinolone, the PQS (*Pseudomonas* Quinolone Signal) autoinducer, also known as quinolone, identified in *Pseudomonas aeruginosa* (table1), is produced by proteins encoded by the pqsABCDH genes. Together with other AHL autoinducers, PQS controls biofilm formation and the production of virulence factors such as elastase, pyocyanin and leticin [30, 31].

Recently, the autoinducer IQS (2-(2-hydroxyphenyl)-thiazole-4-carbaldehyde) was found in *Pseudomonas aeruginosa* (table1), it is produced by proteins encoded by AmbBCDE. This molecule controls the expression of several genes associated with the production of pyocyanin, rhamnolipids and elastase in response to phosphate-stress [2].

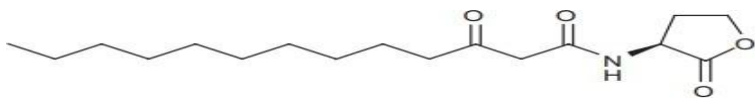
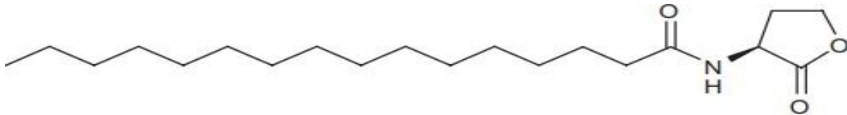
5. Quorum sensing and pathogenicity

Several studies have shown that cell-to-cell communication and regulation of numerous virulence factors in bacteria are managed by QS systems [32–36]. In *Staphylococcus aureus*, the Agr system controls the production and dissemination of biofilm, consequently, inducing both acute and chronic biofilm-associated infections [36]. Moreover, Arg is involved in the production of many toxins and degradable exoenzymes in *Staphylococcus aureus* [34]. For *Pseudomonas aeruginosa*, AHL controls approximately 300 genes responsible for various cellular functions, including its pathogenesis in response to the surrounding environment [37]. The LasI is one of the major mechanisms of pathogenicity and resistance of *Pseudomonas aeruginosa*. It regulates the biofilm formation, and virulence factors such as exotoxin A, elastase, pyocyanin, alkaline phosphatase, and rhamnolipid [35]. Similarly, *Bacillus cereus* virulence factors, such as phospholipases C, proteases and hemolysins, are controlled by the expression of QS system [38]. QS also contributes to the expression of several genes of virulence and survival within the host cell in *Brucella melitensis* [39]. It is becoming a fact that the biofilm is a protective barrier against the external environments. It gives to the bacteria the ability to maintain communities efficiently by secreting extracellular molecules (QS molecules) to communicate [40–42]. Moreover, biofilm allows microorganisms to be more resistant to the antimicrobial treatments by preventing the spread of antimicrobial agents and expression of gene involved in resistance [43]. Interestingly, when bacterial population densities are low, the expression of virulence genes is deactivated to avoid detection of the pathogen and immune stimulation against pathogenicity factors. This gives the bacteria sufficient time to colonize and establish themselves in the host. Once established and having reached a sufficient number, the pathogen begins its virulence activities and causes a total infection [11].

6. *Acinetobacter baumannii* quorum sensing

The genus *Acinetobacter* comprises a group of non-motile bacteria, Gram-negative coccobacilli, with strict aerobic metabolism [44]. They are catalase-positive, oxidase-negative and grow well at an incubation temperature of 37 °C [45]. *A. baumannii* is an important nosocomial opportunistic human pathogen that is gradually gaining more attention as a major health threat worldwide. Over the last 6 years, the number of deaths caused by drug resistant *A. baumannii* has increased by approximately 60% [46]. This bacterium has a remarkable ability to upregulate and acquire the determinants of antibiotic resistance and to form biofilm [47–50].

Table 2 Examples of *A. baumannii* Acylated homoserine lactones [51].

Acyl Homoserine Lactones	Molecular Formula	Structure
N-(3-hydroxydodecanoyl)-L-homoserine lactone (3-OH-C12-HSL)	C ₁₆ H ₂₉ NO ₄	
N-Dodecanoyl-L-homoserine lactone (Unsubstituted C-12-HSL)	C ₁₆ H ₂₉ NO ₃	
N-Dodecanoyl-L-homoserine lactone (Unsubstituted C-10-HSL)	C ₁₄ H ₂₅ NO ₃	
N-Tetradecanoyl-L-homoserine lactone (Unsaturated C-14-HSL)	C ₁₈ H ₃₃ NO ₃	
N-(3-Oxotridecanoyl)-L-homoserine lactone (Unsaturated 3-oxo-C13-HSL)	C ₁₇ H ₂₉ NO ₄	
N-Hexanoyldecenoyl-L-homoserine lactone (Unsaturated C-16-HSL)	C ₂₀ H ₃₅ NO ₃	

A. baumannii QS machinery is mediated by a two-component system which is homologous to the typical LuxI/LuxR system found in Gram-negative bacteria, AbaI/AbaR genes. These genes were acquired horizontally from *Halothiobacillus neapolitanus* [51]. The AbaI belongs to LuxI family of autoinducer synthases that produced more than one AHL (table 2) for 63% of *Acinetobacter* strains [51]. For example, AbaI gene of *A. baumannii* strain M2 has been cloned in *Escherichia coli* which catalyzed the synthesis of N-(3-hydroxydodecanoyl)-L-HSL (3-hydroxy-C12-HSL) [51]. The 3-hydroxy-C12-HSL was the primary AHL of *A. baumannii* and minor amounts of additional AHLs were also identified [52]. Subsequently, the autoinducer receptor protein AbaR interacts with AHL to control the gene expression

of *A. baumannii* [51]. Another study demonstrated that QS signaling molecules enhance expression of the chaperone-usher secretion system (which is necessary for the motility of contractions), allowing *A. baumannii* to easily attach to abiotic surfaces and to form biofilms [53]. According to antibiotic resistance, an AHL-deficient *A. baumannii* strain S mutant (AbS-M) was more sensitive to meropenem and piperacillin than wild-type AbS [25]. When AHL N-3-hydroxy-dodecanoyl-homoserine lactone (N-3-OH-C12-HSL) was supplemented, the resistance was restored [25]. Furthermore, the drug-resistance genes were expressed by lower levels in meropenem-treated AbS-M, while the treatment with N-3-OH-C12-HSL restored the expression of these genes [25].

7. *Acinetobacter baumannii* biofilm and quorum sensing

A. baumannii is widely distributed in nature and able to adhere to and colonize biotic and abiotic surfaces [47, 54, 55]. These characteristics lead the bacteria to persist and form biofilms in various hospital settings, causing widespread infections. The infection with *A. baumannii* is a cause of clinical illnesses such as pneumonia, sepsis, secondary meningitis, urinary tract infections and surgical wounds, especially in immunocompromised patients in intensive care units [56–59]. It is relevant to point out that most of infectious diseases, at least 65% are linked to bacterial communities that proliferate by forming biofilms [60]. Biofilm is a sessile community of microbial origin characterized by cells that are irreversibly attached to a substrate or an interface or to each other. These attached cells are ensconced in a matrix of extracellular polymeric substances produced by them, and exhibit an altered phenotype with regard to growth rate and gene transcription [61]. It is estimated that 60 to 80% of bacterial infections are caused by biofilms [62]. Efforts to disrupt biofilms have enabled to target QS as one of the implicated factors on biofilm formation. Recent studies have linked biofilm development to QS [63–65]. In this regard, maturation of *A. baumannii* biofilm needs communication among bacteria with respect to cell density [52, 66]. Moreover, the mutation in *Abal* resulted in 30–40% reduction in biofilm when compared to no mutant strain [67]. Suppression of *Abal* reduces biofilm formation in *A. baumannii* and exogenous addition of purified AHL restored it [52]. In addition, the loss of *Abal* activity results in reduced survival and growth of soft tissue infections [68]. In addition, an AHL synthase-deficient *A. baumannii* displayed a reduced capacity to form biofilm compared to its wild one [69].

Aba QS system plays an essential role in *A. baumannii* by regulating virulence factors, biofilm formation, surface motility and bacterial competence [70]. To evaluate the effects of *abaR* on *abal* expression, motility, biofilm and pellicle formation by *A. baumannii*, Oh and Han (2020) have constructed an isogenic mutant of *abaR*. The mutant resulted in a decreased *abal* expression, substantial defects in motility and biofilm and pellicle formation by this pathogen [71]. In addition, a study based on RNAseq showed that 264 genes were upregulated in *A. baumannii* biofilms [72]. Alcohol dehydrogenase encoding gene, a QS molecule that plays a key role in *A. baumannii* biofilm formation, was one of the most upregulated genes [72].

8. Quorum quenching

The increasing bacterial resistance and biofilm formation ability make the fight of bacterial infections more complicated, thus the development of new antimicrobial alternatives is needed. As mentioned before, QS plays a crucial role in various bacterial functions such as pathogenicity, biofilm formation, expression of virulence factors, and antibiotic resistance. Consequently, QS can be one of the effective therapeutic targets, technically referred to as "Quorum Quenching QQ" or quorum sensing inhibitors (QSI) [15, 16, 73, 74]. The properties of QQ (chemical compounds, enzymes), the mechanisms of action (inhibition, competition, prohibition of QS signal, etc.) and the targets are different. Consequently, the dysfunction of the QS system can be achieved by different methods: 1 reducing the activity of the AHL-related receptor protein or AHL synthase, 2 inhibiting the production of QS signaling molecules, 3 degrading AHL, and 4 mimicking signaling molecules using mainly synthetic compounds as analogues of signaling molecules [21]. The first halogenated furanone QQ compound that interferes with bacterial QS was identified from the Australian marine red alga *Delisea pulchra* [75].

Since antiquity, plants and their derivatives have been used in the treatment of diseases [76, 77]. This is due to their extremely complex composition, containing several compounds such as terpenoids, acids, alcohols, aldehydes, aliphatic hydrocarbons and acyclic esters [77]. Therefore, numerous studies have been carried out in this framework, to identify new herbal agents that could have a QQ effect. The QQ activity of *Cinnamon* oil against *P. aeruginosa* was investigated by testing the inhibition of biofilm formation and other virulence factors such as pyocyanin, rhamnolipid, protease, alginate production, and swarming activity [78]. The results have showed that *Cinnamon* oil can influence QS-based mechanisms in *P. aeruginosa* PAO1 [78]. The phenolic extract of wild strawberry (*Rubus rosaefolius*) was tested for its QQ activity against *Chromobacterium violaceum* ATCC6357, *Aeromona hydrophila* IOC/FDA110-36 and *Serratia marcescens* UFOP-001 [79]. It has been proven that the extract was able to inhibit all the phenotypes typically regulated

by quorum sensing in bacteria, including violacein production, swarming motility and biofilm formation [79]. Another work on the anti-QS and antibiofilm effects of *Thymus daenensis* and *Satureja hortensis* essential oils against *Staphylococcus aureus* showed that these oils have an anti-QS effect by inhibiting the formation of *Staphylococcus aureus* biofilm [80]. By the same token, *Syzygium aromaticum*, *Dionysia revolute* and *Eucalyptus camaldulensis* showed anti-QS activities through reducing the violacein formation depletion of QS signals produced by *Aeromonas veronii* and *Pseudomonas aeruginosa* [81]. In addition, Aqueous extracts of edible plants and fruits such as *Ananas comosus*, *Musa paradisiaca*, *Manilkara zapota* and *Ocimum sanctum* have been shown to significantly reduce AHL-mediated violacein production in *Chromobacterium violaceum* as well as pyocyanin pigment, staphylolytic protease, elastase production and biofilm formation in *Pseudomonas aeruginosa* PAO1 [82].

Naturally occurring QQ activities have been reported for a large number of organisms. But in some cases, the main limitation of these QS inhibitors is the low concentration in which they are produced and the associated toxicity [21]. We can circumvent these limitations by chemically synthesizing them [21]. In the same context, the condensation of anthranilate and β -keto fatty acids such as (β -ketodecanoic acid) results in the production of secondary metabolites such as 2-heptyl-3-hydroxy-4-quinolone (the *Pseudomonas* quinolone signal) [21]. A methyl anthranilate (an anthranilate analogue) suppressed the production of *Pseudomonas* quinolone signal and reduced elastase production without affecting the growth of *Pseudomonas aeruginosa* PAO1 [21]. Similarly, the bioluminescence in *Vibrio fischeri* was inhibited by AHLs carrying various substitutions at the C4 position of the acyl chain of 3OC6HSL or C6HSL [83].

QQ molecules have several advantages compared to others antimicrobial molecules: lesser selective pressure than antibiotics, minimal impact on host commensal flora, inactivate the target rapidly, supplementation of antibiotics to increase efficacy, protection for immunocompromised and unvaccinated individuals, and block the secretion of multiple virulence factors [84]. Furthermore, comparing QQ method to antibiotics which mainly aim at inhibiting and killing microorganisms, targeting QS is widely accepted as an antivirulence (attenuate bacterial virulence) strategy as it is non-bactericidal. Therefore, it doesn't increase the antibiotic resistance of strains [85].

9. Anti-Acinetobacter baumannii quorum sensing

In 2017, the World Health Organization published a catalog of 12 bacteria (grouped into three levels; critical, high and medium) that urgently require the development of new antimicrobial agents. Among these species, carbapenem-resistant *A. baumannii* is considered as one of the most redoubtable species (critical level) [86]. Previous research demonstrated that *A. baumannii* possessed a strong ability to form biofilms and rapidly develop antibiotic resistance [87–89]. This made it difficult for clinicians and healthcare providers to treat and control its spread leading to death.

QS signaling and biofilm formation have been positively associated with the development of microbial resistance, virulence, and the spread of resistance [33, 90]. Moreover, Biofilm formation depends on the cell density at which cells coordinate via QS molecules, resulting in biofilm formation [91]. The formation of biofilm by this bacterium depends on AHLs of which 3-hydroxy-C12-homoserine lactone is the most predominant [65]. Hence, targeting the QS system could accelerate the development of effective intervention strategies [65]. Meanwhile, several attempts have been performed to interfere with QS as an effective target against *A. baumannii* (table 3) [69, 92–99].

Luís et al (2016) carried out a study based on the analysis of the antioxidant, antibacterial and anti-quorum sensing activities of the essential oils of *Eucalyptus globulus* and *Eucalyptus radiata*. They have found that both oils have an ability to inhibit QS, by inhibiting the production of violet pigments regulated by QS in *A. baumannii* without interfering with their growth [93]. An interesting work has synthesized 22 inhibitors of quorum detection by mimicking the structure of the autoinducer and acinetobactin of *A. baumannii* [100]. The partially purified fraction of *Glycyrrhiza glabra* down-regulated the expression of the autoinducing synthase gene *ahbA* of *A. baumannii*. It has therefore reduced (92%) the production of 3-OH-C12-HSL (*A. baumannii* AHL) and then regulated virulence factors (motility, biofilm formation and antioxidant enzymes production) [94]. Essential oils of *Cinnamomum verum*, *Thymus vulgaris* and *Eugenia caryophyllata* have a remarkable anti-biofilm and anti-QS activities against all tested species which *A. baumannii* is among them [95]. Additionally, Linalool, the main compound of *Coriandrum sativum*, have the capacity to interfere with the QS, to alter the adhesion to surfaces, to inhibit the biofilm formation and to disperse the established biofilms of *A. baumannii* [92]. Besides, a modified AHLase, as a QQ enzyme, could disrupt biofilm formation in a clinical isolate of *A. baumannii* S1 [69]. Pentacyclic triterpenoids could disrupt *A. baumannii* AHL-based signaling, thus leading to inhibition of biofilm formation and destabilization of the overall structure of biofilms [96]. Results from Mayer et al (2020) demonstrated that the combination of QQ strategies and other enzyme treatments such as DNase could represent a fairly effective approach to prevent the colonization of *A. baumannii* on surfaces and therefore also prevent infections caused by this pathogen. A recent study found that a marine steroid, Siphonocholine (Syph-1), isolated from *Siphonochalina siphonella*, can inhibit biofilm formation in *A. baumannii* and has anti-QS properties [98].

Regarding antibiotics, Saroj and Rather (2013) have found that Streptomycin at the subinhibitory concentration had a potential QQ activity against *A. baumannii*. they suggested that the subminimal inhibitory concentration of Streptomycin may act as an antagonist of 3-OH-C12-HSL, interfering with the binding of the signal to the AbaR protein [99].

Interestingly, *Acinetobacter* has been cited among few bacteria known to possess both AHL-producing and -degrading activities (producing QQ molecules) [21, 101].

Table 3 Examples of quorum quenching strategies against *A. baumannii*

Inhibitor	Source	Activity	Reference
Essential oils	<i>Eucalyptus globulus</i> <i>Eucalyptus radiata</i>	Inhibition of the production of violet pigments regulated by QS in <i>A. baumannii</i>	[93]
Partially purified fraction	<i>Glycyrrhiza glabra</i>	Down-regulation of the expression of the autoinducing synthase gene <i>abaI</i>	[94]
Essential oils	<i>Cinnamomum verum</i> <i>Thymus vulgaris</i> <i>Eugenia caryophyllata</i>	Anti-biofilm and anti-QS activities	[95]
Linalool	<i>Coriandrum sativum</i>	Interfering with the QS, to alter the adhesion to surfaces, to inhibit the biofilm formation and to disperse the established biofilms of <i>A. baumannii</i>	[92]
Modified AHLase	QQ lactonase obtained by directed evolution	QQ and disruption of biofilm formation	[69]
Pentacyclic triterpenoids	–	Disruption <i>A. baumannii</i> AHL-based signaling	[96]
QQ enzyme Aii20J	–	QQ activity Interfering with motility Prevention of the colonization on surfaces	[97]
Siphonocholine	<i>Siphonochalina siphonella</i>	Anti-QS properties Inhibition of biofilm formation	[98]
Streptomycin	Antibiotic	Antagonist of 3-OH-C12-HSL	[99]

10. Conclusion

Bacteria do not live in solitary and secluded places, but rather communicate using a variety of chemical languages; QS system or bacterial talking. This review describes communication in gram-negative bacteria and *A. baumannii* in particular as one of the most troublesome pathogens. Since cell-cell communication controls the virulence factors of this bacteria, anti-quorum sensing tactics can be an effective target for preventing and treating infections. Biofilm and quorum detection are two sides of the same coin in the fight against bacterial infections. They are considered the hot factors that the bacteria dynamically establish during host infection or abiotic surface contamination. As a result, the implementation of antimicrobial strategies that target QS is of increasing interest, so further work to better understand these chemical languages could have enormous practical applications.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest was declared by the authors.

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