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Microbial Quorum Quenching by Natural Products: Mechanisms and its Applications

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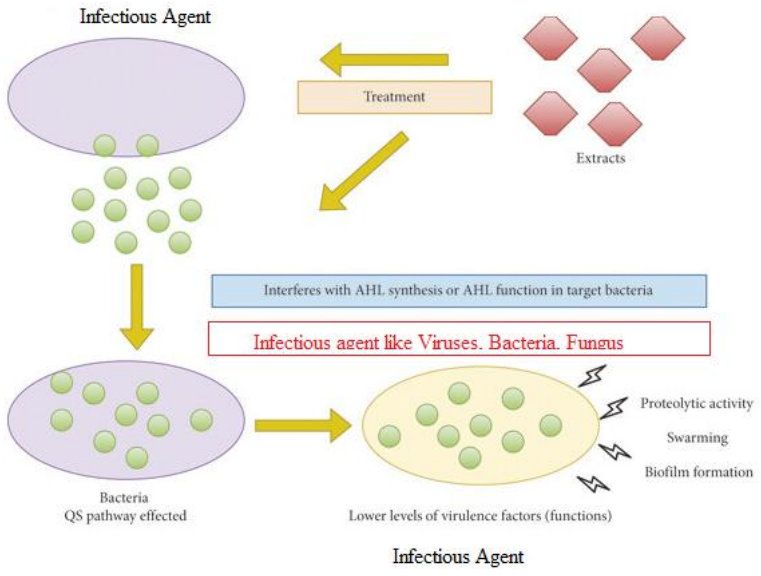
Abstracts: Threats to public health around the world are emerging at an alarming rate, as microbial species (infectious agents) are becoming increasingly resistant to various antimicrobial treatments. Nearly every agent that can spread infection (such as bacteria, fungi, or viruses) at high levels has developed multidrug resistance (MDR) with increased morbidity and mortality and has been called "superbugs". Quorum sensing (QS) enables bacteria to exchange messages, thereby enhancing their ability to cause harm. Attacking the quorum-sensing process may prevent bacteria from being virulent, but it will not make the bacteria resistant. The process of Quorum Quenching (QQ) uses chemicals or enzymes to stop QS from regulating certain behaviors. They are also known as QQ molecules because they are chemical reproductions made in the lab or extracted from plants. Because of this, rather than using cellular and biochemical methods, plants may rely on making anti-QS compounds to protect themselves from QS pathogens. The positive effects of medicinal plants on quorum sensing have been noted, so efforts have been made to thoroughly review them.



Graphical Abstract

Keywords: Quorum sensing, Quorum quenching, secondary metabolites, Multi-drug resistant.

1) Introduction:

The process of QS involves bacteria sending and receiving signals about their density and adjusting the activity of their genes (Abisado *et al.,* 2018). It depends on the making and receiving of outside signals. The first case where this kind of phenomenon was discovered was when the marine bacteria *Vibrio fischeri* started to glow

(Nealson *et al.,* 1979). *Vibrio fischeri* lives in symbiotic harmony with marine species in their light organs. The transcriptional regulator of the luciferase enzyme, which corresponds to a crucial cell density, is connected to the luminescence of this bacterium (Bassler *et al.,* 1994). The signal synthase protein LuxI produces AI chemicals throughout the QS procedure. The quantity of signal molecules rises as the population does.

The environment's build-up of these signaling chemicals is sensed by the bacterial cells about their increasing density, and the population as a whole changes the expression of genes (Vendeville *et al.,* 2005). Plants are constantly subjected to a variety of stress situations in the environment. Temperature variations, nutritional deficiencies, drought, salt, UV radiation, low oxygen levels, pesticides, pollutants, and anthropogenic activities are some of the stress factors that have an impact on plants (Subramanian *et al.,* 2022). Other than environmental stress, several species, including bacteria, fungi, viruses, nematodes, and insects can be harmful. For over a million years, plants have been battling most of their adversaries. Plants have learned and developed defenses against stress and attacks by coexisting with their natural adversaries in a mutually beneficial evolutionary partnership (War *et al.,* 2012). Most secondary metabolites also have therapeutic effects in addition to enhancing resistance to biotic and abiotic stresses.

The objective of this review is to explain the general ways in which bacteria sense a critical density and then form a biofilm. Also, research will focus on quorum-quenching molecules that come from plants and microbes. The possibility of using them as therapies, teamed with antibiotics, to overcome infections caused by multi-drug resistant (MDR) bacteria. Research on how bacteria in biofilms resist antibiotics and how plant extracts might manage biofilms will be examined.

Quorum sensing and biofilm

Bacteria can grow, divide, perceive, and respond to signals from their surroundings on their own. Numerous marine animal hosts are symbiotic partners of *V. fischeri* (Kolibachuk *et al.,* 1993) and the host in these relationships uses the light that *V. fischeri* produces for specialized functions, like enticing prey, evading predators, or locating a mate (Li *et al.,* 2012). It gives *V. fischeri* light in return for an environment rich in nutrients, which is where it resides. It is discovered that *V. fischeri* produces light due to a luciferase enzyme complex. Only at high *V. fischeri* cell densities which are managed by quorum sensing, does bioluminescence occur. To be more precise, *V. fischeri* produces light in response to a minimum threshold concentration and can generate bioluminescent light because of the creation, accumulation, and response of an autoinducer (Zhou *et al.,* 2014).

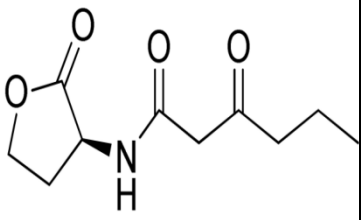
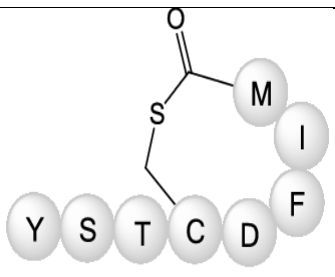
The process of quorum sensing starts with (1) a bacterial cell producing tiny signal molecules and these molecules (2) are released into the environment, sometimes through active methods and sometimes through passive ones.; and (3) Certain receptors recognize the signal molecules once they surpass threshold concentration, resulting in (4) modifications to the regulation of genes. The extracellular environment must accumulate enough signal to trigger the response only at large population densities. This makes sense since it makes the signaling procedure simpler. Bacteria typically exist in nature in a sessile, slime-encased population of cells called biofilms (Jamal *et al.,* 2018). Among these proteins, polysaccharides account for 75% to 89% of the EPS composition. Bacteria develop within the biofilm, shielded from external stimuli like desiccation, immunological response, protozoa intake, and antibiotic use. After the initial phase of attachment, bacteria that have adhered will create a matrix of exopolysaccharides and become more firmly attached. The biofilm will subsequently mature, forming a sophisticated three-dimensional structure of water channels, matrix, and biofilm cells (Zheng *et al.,* 2021). On a global scale, biofilm-related losses deserve billions of dollars to the field of medicine, industry, and environmental sectors.

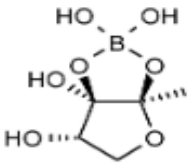
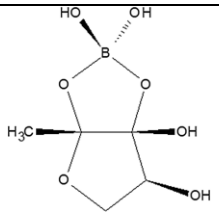
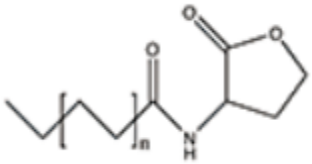
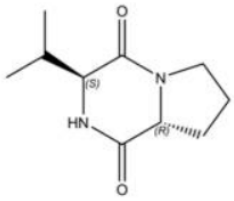
Molecules responsible for Quorum sensing

As the bacterial population expands, auto-inducers are produced at a higher rate. The resulting auto-inducers dramatically activate the transitional regulator protein (Fuqua *et al.,* 1994). The chemicals that are secreted are recognized by protein activators. The molecules majorly responsible for anti-quorum sensing are as follows:

- **Autoinducing Peptides (AIPs):** The majority of gram-positive bacteria rely on a two-component membrane-bound mechanism to recognize signaling molecules called autoinducer peptides (Hense *et al.,* 2015). These are tiny peptides that differ greatly between species and are typically made up of a few amino acids, therefore their inward and outward conveyance requires specific transport proteins (Bouillaut *et al.,* 2008). Sensor kinases anchored to cell membranes are typically responsible for this AIP transfer (Lyon *et al.,* 2002).
- **Autoinducing Oligopeptides (AOPs):** AOPs, which are longer peptides compared to AIPs, are used by some Gram-positive bacteria. For quorum sensing, for instance, *Bacillus subtilis* uses AOPs.
- **Autoinducer-2 (AI-2):** AI-2 is made from (DPD) that, on its own, begins to cycle and makes a collection of similar derivatives that remain in balance with each other. AI-2 is formed through LuxS, which transfers methyl groups during the main metabolic activities of bacteria, particularly methylated cycles. AI-2 has been suggested as a way for bacteria in different species to communicate, which can impact the structure and actions of bacterial groups. AI-2 has been suggested as a way for bacteria in different species to communicate which can impact the structure and actions of bacterial groups.
- **Furanosyl Borate Diester (AI-3):** Some enteric bacteria, such as *Escherichia coli*, use furanosyl borate diester (AI-3) (Walters and Vanessa, 2006), a different kind of signaling molecule, to sense the presence of a quorum.
- **Autoinducer-1 (AI-1):** It is a protein that is produced by several bacteria, including *Vibrio harveyi*(Liu *et al.,* 2013). In these bacteria, AI-1 participates in the regulation of bioluminescence and shares structural similarities with AHLs. The chemical structures with basis description is mentioned in table no.1

Table no.1

S.No	Molecules of Quorum sensing	Description	Chemical Structure	Reference
1)	N-acyl homoserine lactone (*Vibrio fisheri*)	The transcription of certain genes causes the appearance of phenotypes such as the development of a biofilm, increased virulence, growth and the ability to produce light.		Zhang *et al.,* 2020
2)	Autoinducing Peptides (AIPs)	Instead of a smaller molecule, the polypeptide signal is used by the Gram-positive system rather than the ones previously discussed.		Parker and Vannesa, 2008

3)	Autoinducer-2 (AI-2)	Many types of bacteria including Gram-negative and Gram-positive commonly detect a signal known as autoinducer-2 (AI-2).		Parker and Vannesa, 2008
4)	Furanosyl Borate Diester (AI-3)	Discoverers stated that unlike AI-2 which activates genes involved in EHEC's attachment		Kagle *et al.,* 2020
5)	AI-3/QseC system	In the beginning, scientists called AI-3 a compound discovered in spent media that was distinct from AI-2 because it led to changes in genes related to the binding and action of EHEC in the cells of eukaryotes	**Structure unknown**	Sperandio *et al.,* 2003
6)	Autoinducer-1 (AI-1)	LuxI creates AI-1 and makes it available in the surroundings.		Parker and Vannesa, 2008
7)	Cyclic dipeptides	It was found that *Serratia odorifera* which live together with Hypsizygusmarmoreus, use novel QS in their interactions.	 cyclo(Pro-Val)	Sun *et al.,* 2020

Mechanism of quorum sensing

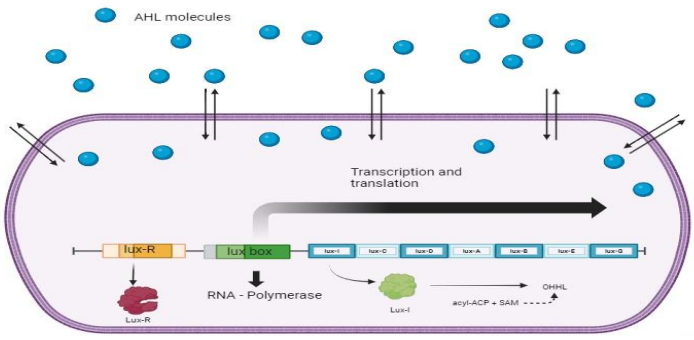


Fig.1. Mechanism of quorum sensing in Gram-negative bacteria: .

QS pathway is relatively easy to understand in Gram negative bacteria as auto inducer easily diffuse to outside of the cell without the help of transporter system as shown in (fig.1). As the density of the auto inducers exceeds relative to inside of cell, the molecules diffuses to inside thereby initiating transcription of all the QS sensing genes.

AHLs can leave cells through membranes, they can diffuse sometimes on the outer surface of the cell. Diffused AHLs adhered to the amino ends of LuxR receptors inside the cell, allowing the LuxI/LuxR complex to control certain genes which happens after AHLs build up to a certain concentration in the surroundings (fig.2). Because of QS, *V. fischeri* releases small amounts of light to guide its host and find suitable places (Nealson et al., 1979).

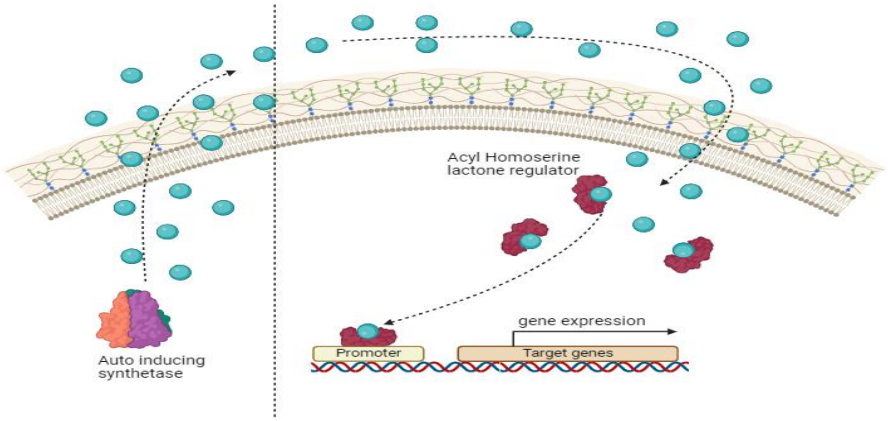


Fig. 2 Binding of nAHL to the promoter thereby initiating QS.

In Gram positive bacteria a particular transport mechanism allows the immature AIP molecules to enter and exit cells (fig.3). The AIP undergoes certain modifications during this process, the immature AIP molecules undergo modification to become mature AIP molecules. ATP binding cassette transporter helps in transport of AIP's and two component systems allows in the entry of oligopeptides (fig.4). In *S. aureus* the QS system controlled by AIPs controls the release of *S. aureus* virulence factors. AIPs may activate AgrC to prevent *S. aureus* from expressing agr-regulated virulence factors. Furthermore, AgrC was discovered in several *Staphylococcus* species, including *Staphylococcus epidermidis* (Singh and Ray, 2014).

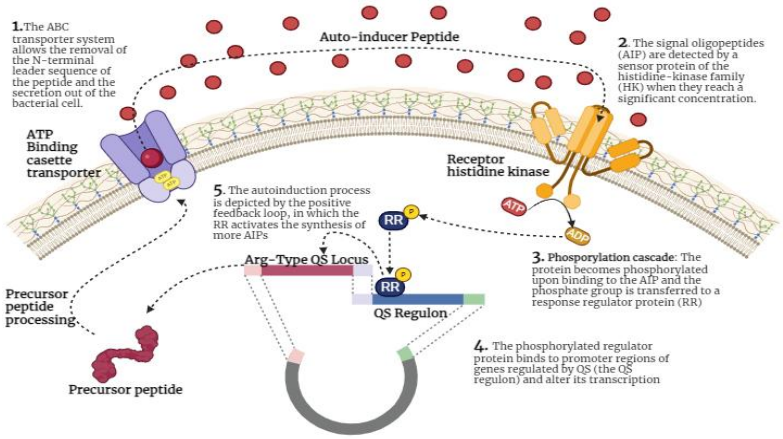


Fig.3 Process of QS in Gram-positive bacteria: the peptide's N-terminal part is removed and secreted with the ABC transporter system and when there is a high number of signal peptides (AIP), the sensor protein HK

detects their presence. 3) After binding to the AIP, the protein is phosphorylated and the phosphate group is moved to a response regulator (RR) protein. 4) When QS signals, phosphorylated regulators protein grabs hold of the promoters of influenced genes and modifies their transcription activity. 5) When it comes to auto induction, the response regulator triggers more AIP synthesis by activating a positive feed back loop.

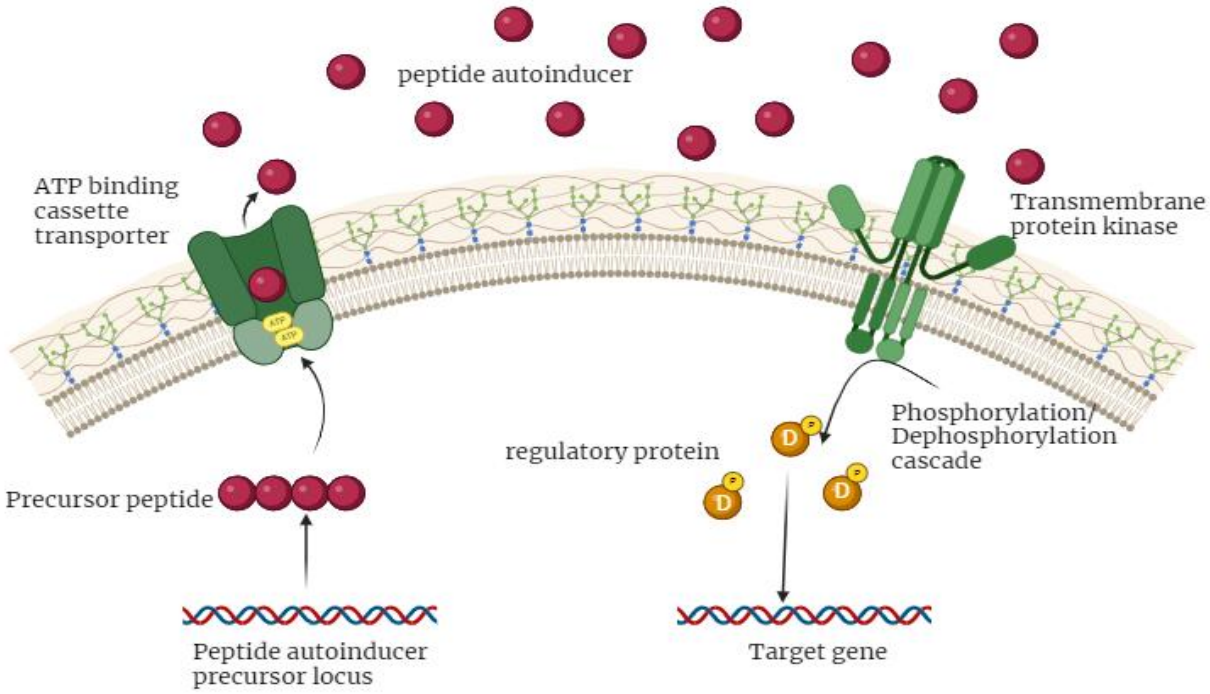


Fig.4 A simplified diagram showing mechanism of QS in Gram-positive bacteria

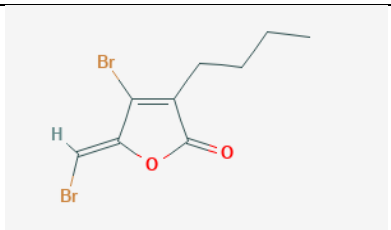
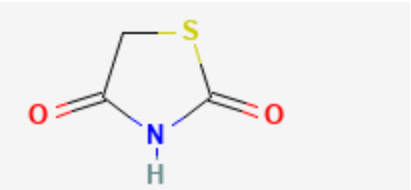
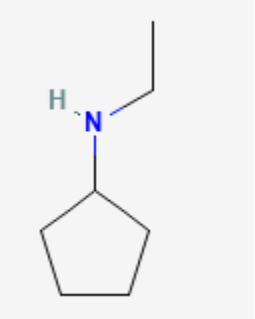
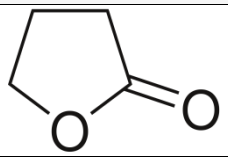
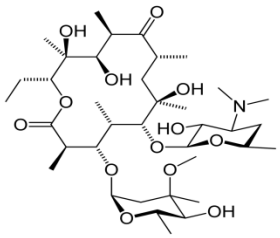
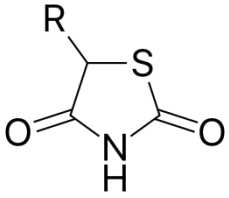
Quorum quenching molecules

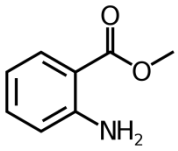
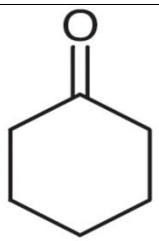
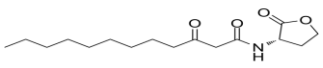
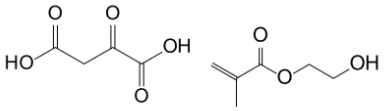
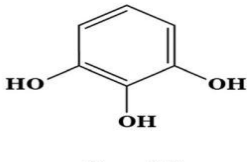
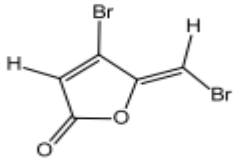
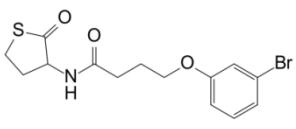
The AHL molecules can be degraded by degradative enzymes, including lactonases that probably act by hydrolyzing the lactone ring, resulting in the production of acylhomoserine or acylases, which break the amide linkages of AHL molecules with the release of fatty acids along with homoserine lactone (Dong and Zhang, 2005). In the second possible mechanism, signal antagonistic molecules have also been employed to target QS by competing with QS signals to bind with signal receptors (Rasmussen and Givskov, 2006). In the third strategy, modification of receptor proteins can be done either by natural or synthetic chemical compounds.

4.1) Synthetic

Natural QSIs are produced in extremely low concentrations, which poses a fundamental limitation to their utilization and the associated toxicity (Kalia *et al.,* 2013). Though these restrictions can theoretically be addressed by chemical synthesis, QS antagonists are still not manufactured on a commercial basis. Targeting the biosynthetic process that results in signal generation, signal substitutions, chain length modifications, etc., has been the focus of efforts to synthesize QSI. It was discovered that an alteration to the 3OC8-HSL acyl chain that substituted methylene for carbonyl at the 3-position acted as an antagonist of QS in *Agrobacterium tumefaciens*. Table no.2 shows various synthetic derived molecules which are effective in QQ.

Table no.2

S.No.	Synthetic derivative	Structure		References
1	(5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone		Antagonist of AHL and AI-2	(Ren *et al.*, 2004).
2	Thiazolidinediones	NA 	Affects AI-2 QS in *V. harveyi*	(Peppoloni *et al.*, 2020
3	N-acyl cyclopentyl amines		N-acyl cyclopentyl amines had a strong effect on killing *P. aeruginosa*	(Wang *et al.*, 2008).
4	γ-butyrolactone		The inhibitors are claimed to be stronger than the natural honaucins	(Choi *et al.*, 2012).
5	Macrolides		Macrolides were found to be effective against *Pseudomonas aeruginosa*	(Tateda *et al.*, 2004)
6	Thiazolidinedione		Biofilm formation is restrained by *Candida albicans.*	(Lidor *et al.*, 2015).

7	Methyl anthranilate		Phenazines are involved in the regulation of virulence which methyl anthranilate was found to decrease	(Calfee *et al.,* 2001; Lesic *et al.,* 2007)
8	Cyclohexanone		Effective against *Pseudomonas* Pao1, it restricts the biofilm formation.	(Smith *et al.,* 2002)
9	3-oxo-C12-D10		Inhibits QS-dependent activities in *P. aeruginosa* such as forming biofilm.	(Smith *et al.,* 2002)
10	Thiophenones		Thiophenones are found to be less toxic than furanones	(Ibrahim *et al.,* 2022)
11	Boronic acid derivate SM23	NA	Less 3-oxo-C12-HSL, C4-HSL and biofilm were produced by the bacteria.	(Peppoloni *et al.,* 2020)
12	Molecularly imprinted polymers (MIPs)		As OdDHL is captured, this blocks QS, halting biofilm formation.	(Ma *et al.,* 2018)
13	Pyrogallol	 Pyrogallol	Functions to counteract the role of AI-2 in quorum sensing in *V. harveyi*	(Ni *et al.,* 2008).
14	Furanones		Took the place of the native autoinducers, lowered virulence factor manufacture and made the bacteria less able to form biofilms	(Proctor*et al.,* 2020)
15	Meta-bromothiolactone		With LasR and RhlR turned off, virulence factors were no longer made and biofilm could not grow	(Loughlin *et al.,* 2013)

QS in microbes

Short and long acyl side chains in AHLs change how the bacteria respond. Still, AHLs that are just a little longer or shorter often cannot work properly and may damage the functions of the bacteria. Short-chain AHLs are the main way *Aeromonas* species regulate quorum sensing. On the other side, *A. salmonicida* and *Aeromonas hydrophila* are affected negatively by long-chain AHLs, which can lower their virulence factors. It is interesting that HSL, a long-chain AHL, can help larvae of the burbot (Lota lota) avoid death resulting from possible organisms. Researchers studying how AHL signals degrade and stop QS-related diseases have mainly focused on AHL lactonases and AHL acylases (Kalia and Purohit, 2011; Kalia, 2013).

Mechanism of quorum inhibition

Quorum quenching means to stop quorum sensing from occurring. Later, as the system was improved, the phrase "quorum quenching" was used for any quorum-sensing blockade due to enzymes or non-enzyme molecules (Vadakkan *et al.,* 2018). Messing with the quorum sensing mechanism used by different bacteria in plaque biofilm can interrupt the process of plaque formation (Bouayed *et al.,* 2016). It first required enzymes to hydrolyze autoinducer AHL or to generate alternate acyl carrier proteins or S-adenosyl methionine, which blocked the production of AHL. Some molecules, for example, Sinefungin, S-adenosylcysteine and L/D-S-adenosylhomocysteine, can restrict AHL synthesis.There are certain ways to inhibit the quorum sensing:

(a) Target the signal molecule

(b) Target the receptor

(c) Blocking the signalling cascade

Enzymatic Quorum Quenching:

- **Lactonases:**Two groups of lactonases have been discovered among prokaryotes, based on similarities as well as on the organisms where they are found. Being part of a highlighted and researched family, the AiiA lactonase metallohydrolase functions with proper support from two Zn^{2+} ions. Even though QsdA lactonase and AiiA both depend on Zn^{2+}, QsdA is the second type of AHL-lactonase to be discovered. It comes from a different group of proteins from the AiiA lactonase family. Lactonases can prefer some kinds of AHLs and other lactones such as δ-, ε- and γ-lactoness and some extremophile examples stay active at high temperatures. A range of lactonases are found classified in various protein superfamilies and folds. Phosphotriesterase-like lactonases (PLLs) are common in bacteria and archaea, while Metallo-β-lactamase-like lactonases (MLLs) have mainly been spotted in bacteria, archaea, and eukaryotes.
- **Amidases/ Acylases:**It takes AHL-acylase to irreversibly hydrolyze the amide bond in AHL molecules, which cuts them apart into homoserine lactone and their acylating fatty acid, both of which lose the ability to signal (Lin et al., 2003). First, AHL-acylase was discovered in VAI-C, the paradoxus strain, which degraded many different AHLs. This unique shape of the first two domains (αβ/βα) places them in the group known as N-terminal nucleophile hydrolases or Ntn-hydrolases. Because of their wide hydrophobic area, the active sites can bind long chains from AHLs. Well-characterized QQ acylases include PvdQ from P. aeruginosa. PvdQ mainly acts on AHLs with more than 10 carbon atoms and it is an important factor in how pyoverdine is formed in bacteria.

2) **Oxidoreductases:**Oxidoreductase changes the way the signal is structured, without breaking it down, since theyact on the acyl tail by oxidizing or reducing it. Changes in the AHL signal might influence how it is picked up and might disrupt the response to any genes regulated only by that particular AHL.

3) Applications of quorum sensing molecules

The molecules that are involved in QQ are known as QQ molecules.In addition to its ability to prevent infections and biofouling, QQ is used in the water treatment industry, the aquaculture industry, and medical fields.

Serial no.	Molecules of QQ	Function	References
1	Quercetin	Shield tissue against damage brought on by a range of medication toxicity, inhibits *Pseudomonas aeruginosa* virulence factors and biofilm formation.	Ouyang *et al.,* 2016
2	Curcumin	Curcumin reduces swimming, biofilm formation, and swarming abilities of bacteria as well as their proteolytic activity	Mangoudehi*et al.,* 2020
3	Resveratrol	May thus help accelerate the treatment of *P. aeruginosa* biofilms, and aminoglycoside antibiotics action restored or improved	Zhou *et al.,* 2018
4	Carvacrol	Has strong inhibitory action against QS in *Chromobacteriumviolaceum,* which is blocks the QS system of *A. hydrophila* NJ-35	Lu *et al.,* 2023
5	Allicin	Stops *P. aeruginosa*from making harmful things and from making biofilms	Xu *et al.,* 2019
6	6-gingerol	Stops biofilm growth and the disease-causing ability of *P. aeruginosa*	Kim *et al.,* 2015
7	acylase PvdQ	Cuts up long N-acylhomoserine lactones (AHLs), like 3-oxo-C12-HSL	Jimenez *et al.,* 2009
8	QuiP	Helps with the cutting up of long AHLs	Chen *et al.,* 2013
9	AaC	Works against AHL,which has acyl side chains longer than C6, for which it has anti-AHL activity	Hong *et al.,* 2012
10	AhlM	Takes off acyl groups	Park *et al.,* 2005
11	AiiC	Cuts up short AHLs only	Romero *et al.,* 2008

Phytochemicals

Curcumin effectively reduced the ability of bacteria to swim, form biofilms, and swarm. Additionally, hemolytic activity was not much impacted, while bacterial proteolytic activity was modestly decreased (Mangoudehi*et al.,* 2020).

Allicin, which is derived from garlic, has been demonstrated to prevent *P. aeruginosa* from producing virulence factors and from forming biofilms. Cinnamaldehyde inhibits AgrA competitively during AgrA-P2 binding, which suppresses Agr system transcription and decreases *L. monocytogenes* biofilm development (Jiang*et al.,* 2019).

Fresh ginger's strong oil, 6-gingerol, binds to *P. aeruginosa* QS receptors antagonistically to inhibit biofilm development and pathogenicity. Six-gingerol was shown in an experiment to decrease mouse mortality, biofilm development, and a number of virulence factors, including exoprotease (Kim*et al.,* 2015).

In a species of *Bacillus*, there's a gene (aiiA) that encodes AI inactivation enzymes, which inactivate AI. This gene has been cloned in many organisms, and this protein was identified as first protein which is capable of inactivation of *N*-acylhomoserine lactones (Dong *et al.,* 2000). Inducer inhibitor from *Cyanobacteria* (AiiC)can break down short-chain AHLs and it may also interfere with signaling in intricate bacterial systems such as cyanobacterial blooms and microbial mats. AiiC may play a role in the diazotrophic filaments' ability to self-regulate their AHL levels. The cyanobacterium may also employ the enzyme as a defense mechanism to prevent outside signals from interfering with its signaling system (Romero*et al.,* 2008). Only long-chain AHLs (C > 8) are degraded by the secreted AHL-acylase HacA, whereas the majority of AHLs are degraded by the unsecreted AHL-acylase HacB.

Future aspect of quorum sensing

QS inhibitory substances are currently routinely applied in medical applications. One of the main causes of nosocomial infections is *P. aeruginosa*, particularly when it comes to pulmonary infections linked to cystic fibrosis. This bacterium demonstrates an amazing resistance to antibiotics. Other medications have shown promise in combating this multi-resistant strain. It can hydrolyze AHL signalling molecules irreversibly (Vuong *et al.,* 2004). QS inhibitory agents have excellent application potential not only in the health-related domains but also in the food business (Shi *et al.,* 2009).

Furthermore, the primary obstacle to improving the medicines currently accessible for several human diseases is still the efficient delivery and release of medications to the target. One approach that shows promise for improving drug delivery, targeting, and protection is the use of nanoparticles (NPs) as "transporters" (Zhang *et al.,* 2020) The management and treatment of bacterial infections, particularly those brought on by multidrug-resistant strains and bacterial biofilms, hold considerable promise for advancements in nanotechnology research. Novel therapeutic approaches that target microbial QS signalling (QQ) may help prevent diseases associated with biofilms since pathogenic bacteria depend on the QS mechanism to form biofilms (Grandclémen *et al.,* 2016).

This would pave the way for soon-to-be implemented combinational therapies. It would be ideal to conduct more research to determine how these tactics affect both individual bacterial species and bacterial populations. (Lee *et al.,* 2017).

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References

[1] Abisado, R. G., Benomar, S., Klaus, J. R., Dandekar, A. A., & Chandler, J. R. (2018). Bacterial Quorum Sensing and Microbial Community Interactions. *mBio, 9*(3). https://doi.org/10.1128/mbio.02331-17

[2] Bassler, B. L., Wright, M., & Silverman, M. R. (1994). Multiple signalling systems controlling expression of luminescence in *Vibrio harveyi*: sequence and function of genes encoding a second sensory pathway. *Molecular Microbiology, 13*(2), 273–286. https://doi.org/10.1111/j.1365-2958.1994.tb00422.x

[3] Bouayed, N., Dietrich, N., Lafforgue, C., Lee, C., & Guigui, C. (2016). Process-Oriented Review of Bacterial Quorum Quenching for Membrane Biofouling Mitigation in Membrane Bioreactors (MBRs). *Membranes, 6*(4), 52. https://doi.org/10.3390/membranes6040052

[4] Bouillaut, L., Perchat, S., Arold, S., Zorrilla, S., Slamti, L., Henry, C., Gohar, M., Declerck, N., &Lereclus, D. (2008). Molecular basis for group-specific activation of the virulence regulator PlcR by PapR heptapeptides. *Nucleic Acids Research, 36*(11), 3791–3801. https://doi.org/10.1093/nar/gkn149

[5] Chadha, N. J., Gupta, N. M., Nagpal, N. N., Sharma, N. M., Adarsh, N. T., Joshi, N. V., Tiku, N. V., Mittal, N. T., Nain, N. V. K., Singh, N. A., Snigdha, N. S., Chandra, N. N. S., John, N. S., &Diwan, N. P. (2021). Antibacterial potential of indigenous plant extracts against multidrug-resistant bacterial strains isolated from New Delhi region. *GSC Biological and Pharmaceutical Sciences, 14*(2), 185–196. https://doi.org/10.30574/gscbps.2021.14.2.0053

[6] Chen, F., Gao, Y., Chen, X., Yu, Z., & Li, X. (2013a). Quorum quenching enzymes and their application in degrading signal molecules to block quorum Sensing-Dependent infection. *International Journal of Molecular Sciences, 14*(9), 17477–17500. https://doi.org/10.3390/ijms140917477

[7] Choi, S., Kim, H. U., Kim, T. Y., Kim, W. J., Lee, M. H., & Lee, S. Y. (2013). Production of 4-hydroxybutyric acid by metabolically engineered *Mannheimiasucciniciproducens* and its conversion to γ-butyrolactone by acid treatment. *Metabolic Engineering, 20*, 73–83. https://doi.org/10.1016/j.ymben.2013.09.001

[8] Churchill, M. E. A., Sibhatu, H. M., &Uhlson, C. L. (2010a). Defining the Structure and Function of Acyl-Homoserine Lactone Autoinducers. *Methods in Molecular Biology*, 159–171. https://doi.org/10.1007/978-1-60761-971-0_12

[9] Diggle, S. P., Cornelis, P., Williams, P., & Cámara, M. (2006). 4-Quinolone signalling in *Pseudomonas aeruginosa*: Old molecules, new perspectives. *International Journal of Medical Microbiology, 296*(2–3), 83–91. https://doi.org/10.1016/j.ijmm.2006.01.038

[10] Doane, T. L., & Burda, C. (2012). The unique role of nanoparticles in nanomedicine: imaging, drug delivery and therapy. *Chemical Society Reviews, 41*(7), 2885. https://doi.org/10.1039/c2cs15260f

[11] Dong, Y., Wang, L., Xu, J., Zhang, H., Zhang, X., & Zhang, L. (2001). Quenching quorum-sensing-dependent bacterial infection by an N-acyl homoserine lactonase. *Nature, 411*(6839), 813–817. https://doi.org/10.1038/35081101

[12] Dong, Y., & Zhang, L. (2005). Quorum sensing and quorum-quenching enzymes. *PubMed, 43* Spec No, 101–109. https://pubmed.ncbi.nlm.nih.gov/15765063

[13] Fuqua, W. C., Winans, S. C., & Greenberg, E. P. (1994). Quorum sensing in bacteria: the LuxRLuxI family of cell density-responsive transcriptional regulators. *Journal of Bacteriology, 176*(2), 269–275. https://doi.org/10.1128/jb.176.2.269-275.1994

[14] He, Z., Huang, Z., Zhou, W., Tang, Z., Ma, R., & Liang, J. (2016). Anti-biofilm Activities from Resveratrol against *Fusobacterium nucleatum*. *Frontiers in Microbiology, 7*. https://doi.org/10.3389/fmicb.2016.01065

[15] Hense, B. A., & Schuster, M. (2015a). Core Principles of Bacterial Autoinducer Systems. *Microbiology and Molecular Biology Reviews, 79*(1), 153–169. https://doi.org/10.1128/mmbr.00024-14

[16] Hong, K., Koh, C., Sam, C., Yin, W., & Chan, K. (2012). Quorum quenching Revisited—From signal decays to signalling confusion. *Sensors, 12*(4), 4661–4696. https://doi.org/10.3390/s120404661

[17] Ibrahim, S. R. M., Omar, A. M., Bagalagel, A. A., Diri, R. M., Noor, A. O., Almasri, D. M., Mohamed, S. G. A., & Mohamed, G. A. (2022). Thiophenes—Naturally occurring plant metabolites: Biological activities and in silico evaluation of their potential as cathepsin D inhibitors. *Plants, 11*(4), 539. https://doi.org/10.3390/plants11040539

[18] Jamal, M., Ahmad, W., Andleeb, S., Jalil, F., Imran, M., Nawaz, M. A., Hussain, T., Ali, M., Rafiq, M., & Kamil, M. A. (2017). Bacterial biofilm and associated infections. *Journal of the Chinese Medical Association, 81*(1), 7–11. https://doi.org/10.1016/j.jcma.2017.07.012

[19] Jiang, Q.,Chen, J., Yang, C., Yin, Y., & Yao, K. (2019). Quorum sensing: A prospective therapeutic target for bacterial diseases. *BioMed Research International, 2019*, 1–15. https://doi.org/10.1155/2019/2015978

[20] Jimenez, P. N**.,** Koch, G., Papaioannou, E., Wahjudi, M., Krzeslak, J., Coenye, T., Cool, R. H., & Quax, W. J. (2009). Role of PvdQ in *Pseudomonas aeruginosa* virulence under iron-limiting conditions. *Microbiology, 156*(1), 49–59. https://doi.org/10.1099/mic.0.030973-0

[21] Kalia, V. C.,& Purohit, H. J. (2011). Quenching the quorum sensing system: Potential antibacterial drug targets. *Critical Reviews in Microbiology, 37*(2), 121–140. https://doi.org/10.3109/1040841x.2010.532479

[22] Kalia, V. C., Wood, T. K., & Kumar, P. (2013a). Evolution of resistance to quorum-sensing inhibitors. *Microbial Ecology, 68*(1), 13–23. https://doi.org/10.1007/s00248-013-0316-y

[23] Kaper, J. B.,& Sperandio, V. (2005a). Bacterial cell-to-cell signaling in the gastrointestinal tract. *Infection and Immunity, 73*(6), 3197–3209. https://doi.org/10.1128/iai.73.6.3197-3209.2005.

[24] Kagle, J. (2020). Small talk: chemical conversations with bacteria. *ChemTexts*, *6*(1). https://doi.org/10.1007/s40828-020-0102-7

[25] Kim, H., Lee, S., Byun, Y., & Park, H. (2015). 6-Gingerol reduces *Pseudomonas aeruginosa* biofilm formation and virulence via quorum sensing inhibition. *Scientific Reports, 5*(1). https://doi.org/10.1038/srep08656

[26] Kolibachuk, D., & Greenberg, E. P. (1993). The Vibrio fischeri luminescence gene activator LuxR is a membrane-associated protein. *Journal of Bacteriology, 175*(22), 7307–7312. https://doi.org/10.1128/jb.175.22.7307-7312.1993

[27] Lee, J., Lee, I., Nam, J., Hwang, D. S., Yeon, K., & Kim, J. (2017). Immobilization and Stabilization of Acylase on Carboxylated Polyaniline Nanofibers for Highly Effective Antifouling Application via Quorum Quenching. *ACS Applied Materials & Interfaces, 9*(18), 15424–15432. https://doi.org/10.1021/acsami.7b01528

[28] Lesic, B., Lépine, F., Déziel, E., Zhang, J., Zhang, Q., Padfield, K., Castonguay, M., Milot, S., Stachel, S., Tzika, A. A., Tompkins, R. G., & Rahme, L. G. (2007). Inhibitors of pathogen intercellular signals as selective Anti-Infective compounds. *PLoS Pathogens, 3*(9), e126. https://doi.org/10.1371/journal.ppat.0030126

[29] Li, Y., & Tian, X. (2012). Quorum Sensing and Bacterial Social Interactions in Biofilms. *Sensors, 12*(3), 2519–2538. https://doi.org/10.3390/s120302519

[30] Lin, J., Zhou, D., Steitz, T. A., Polikanov, Y. S., & Gagnon, M. G. (2018). Ribosome-Targeting Antibiotics: Modes of Action, Mechanisms of Resistance, and Implications for Drug Design. *Annual Review of Biochemistry, 87*(1), 451–478. https://doi.org/10.1146/annurev-biochem-062917-011942

[31] Lin, Y., Xu, J., Hu, J., Wang, L., Ong, S. L., Leadbetter, J. R., & Zhang, L. (2003). Acyl-homoserine lactone acylase from Ralstonia strain XJ12B represents a novel and potent class of quorum-quenching enzymes. *Molecular Microbiology, 47*(3), 849–860. https://doi.org/10.1046/j.1365-2958.2003.03351.x

[32] Lopez, D., Vlamakis, H., & Kolter, R. (2010). Biofilms. *Cold Spring Harbor Perspectives in Biology, 2*(7), a000398. https://doi.org/10.1101/cshperspect.a000398

[33] Lu, L., Wang, J., Qin, T., Chen, K., Xie, J., & Xi, B. (2023). Carvacrol Inhibits Quorum Sensing in Opportunistic Bacterium Aeromonas hydrophila. *Microorganisms, 11*(8), 2027. https://doi.org/10.3390/microorganisms11082027

[34] Lyon, G. J., Wright, J. S., Muir, T. W., & Novick, R. P. (2002a). Key Determinants of Receptor Activation in the agr Autoinducing Peptides of Staphylococcus aureus. *Biochemistry, 41*(31), 10095–10104. https://doi.org/10.1021/bi026049u

[35] Miller, M. B., & Bassler, B. L. (2001). Quorum Sensing in Bacteria. *Annual Review of Microbiology, 55*(1), 165–199. https://doi.org/10.1146/annurev.micro.55.1.165

[36] Ni, N., Choudhary, G., Li, M., & Wang, B. (2008). Pyrogallol and its analogs can antagonize bacterial quorum sensing in Vibrio harveyi. *Bioorganic & Medicinal Chemistry Letters, 18*(5), 1567–1572. https://doi.org/10.1016/j.bmcl.2008.01.081

[37] O'Loughlin, C. T., Miller, L. C., Siryaporn, A., Drescher, K., Semmelhack, M. F., & Bassler, B. L. (2013). A quorum-sensing inhibitor blocks Pseudomonas aeruginosa virulence and biofilm formation. *Proceedings of the National Academy of Sciences, 110*(44), 17981–17986. https://doi.org/10.1073/pnas.1316981110

[38] Ouyang, J., Sun, F., Feng, W., Sun, Y., Qiu, X., Xiong, L., Liu, Y., & Chen, Y. (2016). Quercetin is an effective inhibitor of quorum sensing, biofilm formation and virulence factors in *Pseudomonas aeruginosa*. *Journal of Applied Microbiology, 120*(4), 966–974. https://doi.org/10.1111/jam.13073

[39] Park, S., Kang, H., Jang, H., Lee, J., Koo, B., & Yum, D. (2005). Identification of extracellular N-acylhomoserine lactone acylase from a *Streptomyces* sp. and its application to quorum quenching. *Applied and Environmental Microbiology, 71*(5), 2632–2641. https://doi.org/10.1128/aem.71.5.2632-2641.2005

[40] Parker, C. T., & Sperandio, V. (2008). Cell-to-cell signalling during pathogenesis. *Cellular Microbiology, 11*(3), 363–369. https://doi.org/10.1111/j.1462-5822.2008.01272.x

[41] Pearson, J. P., Passador, L., Iglewski, B. H., & Greenberg, E. P. (1995). A second N-acylhomoserine lactone signal produced by *Pseudomonas aeruginosa*. *Proceedings of the National Academy of Sciences, 92*(5), 1490–1494

[42] Romero, M., Diggle, S. P., Heeb, S., Cámara, M., & Otero, A. (2008). Quorum quenching activity in *Anabaena* sp. PCC 7120: identification of AiiC, a novel AHL-acylase. *FEMS Microbiology Letters, 280*(1), 73–80. https://doi.org/10.1111/j.1574-6968.2007.01046.x

[43] Roy, R., Tiwari, M., Donelli, G., & Tiwari, V. (2017). Strategies for combating bacterial biofilms: A focus on anti-biofilm agents and their mechanisms of action. *Virulence, 9*(1), 522–554. https://doi.org/10.1080/21505594.2017.1313372

[44] Shi, X.,& Zhu, X. (2009). Biofilm formation and food safety in food industries. *Trends in Food Science & Technology, 20*(9), 407–413. https://doi.org/10.1016/j.tifs.2009.01.054

[45] Singh, R.,& Ray, P. (2014). Quorum sensing-mediated regulation of *Staphylococcal* virulence and antibiotic resistance. *Future Microbiology, 9*(5), 669–681. https://doi.org/10.2217/fmb.14.31

[46] Smith, R. S., Harris, S. G., Phipps, R., &Iglewski, B. (2002). The *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-Oxododecanoyl)Homoserine lactone contributes to virulence and induces inflammation in vivo. *Journal of Bacteriology, 184*(4), 1132–1139. https://doi.org/10.1128/jb.184.4.1132-1139.2002

[47] Sperandio, V., Torres, A. G., Jarvis, B., Nataro, J. P., & Kaper, J. B. (2003). Bacteria–host communication: The language of hormones. *Proceedings of the National Academy of Sciences, 100*(15), 8951–8956. https://doi.org/10.1073/pnas.1537100100

[48] Subramanian, K., Selvaraj, H., K, B., Renuga, P. S., S, V., & Aruni, W. (2022). Anti-quorum sensing in pathogenic microbes using plant-based bioactive phytochemicals. *Advances in Materials Science and Engineering, 2022*, 1–7. https://doi.org/10.1155/2022/7532086

[49] Sun, S., Liu, Y., Weng, C., Sun, S., Li, F., Li, H., & Zhu, H. (2020a). Cyclic Dipeptides Mediating Quorum Sensing and Their Biological Effects in *HypsizygusMarmoreus*. *Biomolecules, 10*(2), 298. https://doi.org/10.3390/biom10020298
(*Note: 2020b is a duplicate of 2020a; retain only one unless referenced separately in your text.*)

[50] TanhayMangoudehi, H., Zamani, H., Shahangian, S. S., &Mirzanejad, L. (2020). Effect of curcumin on the expression of ahyI/R quorum sensing genes and some associated phenotypes in pathogenic Aeromonas hydrophila fish isolates. *World Journal of Microbiology and Biotechnology*, *36*, 1-9.

[51] Tateda, K., Standiford, T., Pechere, J., & Yamaguchi, K. (2004). Regulatory effects of macrolides on bacterial virulence: Potential role as Quorum-Sensing Inhibitors. *Current Pharmaceutical Design, 10*(25), 3055–3065. https://doi.org/10.2174/1381612043383377

[52] Tian, Z., Wang, Z., Xu, Y., Tran, C. Q., Myles, D. C., Zhong, Z., Simmons, J., Vetcher, L., Katz, L., Li, Y., & Shaw, S. J. (2008). Investigating amine derivatives of ambruticin VS-5 and VS-4. *ChemMedChem, 3*(6), 963–969. https://doi.org/10.1002/cmdc.200800008

[53] Vadakkan, K., Choudhury, A. A., Gunasekaran, R., Hemapriya, J., & Vijayanand, S. (2018). Quorum sensing intervened bacterial signaling: Pursuit of its cognizance and repression. *Journal of Genetic Engineering and Biotechnology, 16*(2), 239–252. https://doi.org/10.1016/j.jgeb.2018.07.001

[54] Vendeville, A., Winzer, K., Heurlier, K., Tang, C. M., & Hardie, K. R. (2005). Making “sense” of metabolism: autoinducer-2, LUXS and pathogenic bacteria. *Nature Reviews Microbiology, 3*(5), 383–396. https://doi.org/10.1038/nrmicro1146

[55] Vuong, C., Dürr, M., Carmody, A. B., Peschel, A., Klebanoff, S. J., & Otto, M. (2004). Regulated expression of pathogen-associated molecular pattern molecules in *Staphylococcus epidermidis*: quorum-sensing determines pro-inflammatory capacity and production of phenol-soluble modulins. *Cellular Microbiology, 6*(8), 753–759. https://doi.org/10.1111/j.1462-5822.2004.00401.x

[56] Walters, M.,Sircili, M. P., & Sperandio, V. (2006a). AI-3 Synthesis Is Not Dependent on *luxS* in *Escherichia coli*. *Journal of Bacteriology, 188*(16), 5668–5681. https://doi.org/10.1128/jb.00648-06

[57] War, A. R., Paulraj, M. G., Ahmad, T., Buhroo, A. A., Hussain, B., Ignacimuthu, S., & Sharma, H. C. (2012). Mechanisms of plant defense against insect herbivores. *Plant Signaling & Behavior, 7*(10), 1306–1320. https://doi.org/10.4161/psb.21663

[58] Waters, C. M.,& Bassler, B. L. (2005). Quorum Sensing: Cell-to-Cell Communication in Bacteria. *Annual Review of Cell and Developmental Biology, 21*(1), 319–346. https://doi.org/10.1146/annurev.cellbio.21.012704.131001

[59] Williams, P. (2007a). Quorum sensing, communication and cross-kingdom signalling in the bacterial world. *Microbiology, 153*(12), 3923–3938. https://doi.org/10.1099/mic.0.2007/012856-0

[60] Xie, J., Zhang, A., Sun, H., Yan, G., & Wang, X. (2018). Recent advances and effective strategies in the discovery and applications of natural products. *RSC Advances, 8*(2), 812–824. https://doi.org/10.1039/c7ra09475b

[61] Xu, Z., Zhang, H., Yu, H., Dai, Q., Xiong, J., Sheng, H., Qiu, J., Jiang, L., Peng, J., He, X., Xin, R., Li, D., & Zhang, K. (2019). Allicin inhibits *Pseudomonas aeruginosa* virulence by suppressing the *rhl* and *pqs* quorum-sensing systems. *Canadian Journal of Microbiology, 65*(8), 563–574. https://doi.org/10.1139/cjm-2019-0055

[62] Zhang, C., Yan, L., Wang, X., Zhu, S., Chen, C., Gu, Z., & Zhao, Y. (2020). Progress, challenges, and future of nanomedicine. *Nano Today, 35*, 101008. https://doi.org/10.1016/j.nantod.2020.101008

[63] Zhao, X., Yu, Z., & Ding, T. (2020). Quorum-Sensing Regulation of Antimicrobial Resistance in Bacteria. *Microorganisms, 8*(3), 425. https://doi.org/10.3390/microorganisms8030425

[64] Zheng, S., Bawazir, M., Dhall, A., Kim, H., He, L., Heo, J., & Hwang, G. (2021). Implication of Surface Properties, Bacterial Motility, and Hydrodynamic Conditions on Bacterial Surface Sensing and Their Initial Adhesion. *Frontiers in Bioengineering and Biotechnology, 9*. https://doi.org/10.3389/fbioe.2021.643722

[65] Zhou, J., Chen, T., Tan, X., Sheng, J., & Jia, A. (2018). Can the quorum sensing inhibitor resveratrol function as an aminoglycoside antibiotic accelerant against *Pseudomonas aeruginosa*? *International Journal of Antimicrobial Agents, 52*(1), 35–41. https://doi.org/10.1016/j.ijantimicag.2018.03.002

[66] Zhou, L., Slamti, L., Nielsen-LeRoux, C., Lereclus, D., & Raymond, B. (2014). The Social Biology of Quorum Sensing in a Naturalistic Host Pathogen System. *Current Biology, 24*(20), 2417–2422. https://doi.org/10.1016/j.cub.2014.08.049