International Journal of Secondary Metabolite
2023, Vol. 10, No. 4, 590–604
https://doi.org/10.21448/ijsm.1248987
Published at https://dergipark.org.tr/en/pub/ijsm
Review Article

Bacteria-to-bacteria communication, Signaling Molecules: AHLs, AIPs and AI-2, I can't talk now matey, gone to pathogenesis!

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Abstract: How do these primitive tiny organisms' hierarchy operate? The answer is simple: by communicating. Yes, bacteria talk, and it's called: Quorum Sensing System (QS). QS is a phenomenon where bacteria tinychat and arrange their moves via the accumulation of signaling molecules. The cells respond to this stimulus when the cut-off value concentration of molecules is achieved. This phenomenon is widespreadly visible in the bacteria world. Bacteria never move solo and would need to gather up in critical mass because of secrete efficient toxins to be lethal. *N*-Acyl Homoserine Lactones (AHLs): Intercellular signaling molecules used by Gram-negative bacteria ($Gram^-$) to monitor their critical mass density in QS controlling of critic gene expression. AHL signals are synthesized by LuxI proteins. AHLs are vital interbacterial signaling molecules used by bacteria to check their dependent bacteria density. Auto-inducing peptides (AIPs): signaling molecules involved in intercellular communication in Gram-positive bacteria ($Gram^+$). Peptides are exported by dedicated systems, post-translationally modified and eventually sensed by other bacteria cells via membrane-located receptors that are part of a two-component system. AI-2 (Autoinducer-2): signaling molecule used by interspecies bacteria communication. This molecule chemically identified furanosylborate diester synthesized by LuxS proteins. Also, it's a universal signal because it carries out interspecies communication. The aim of this review is to summarize the AHL, AIPs, AI-2 bacterial signal molecules, QS systems target genes, effective in the procaryotic world, and the micro-social lifestyle of bacteria.

ARTICLE HISTORY

Received: Feb. 23, 2023
Revised: Aug. 29, 2023
Accepted: Sep. 13, 2023

KEYWORDS

Signal Molecules: AHLs, AIPs AI-2, Quorum Sensing System, Bacterially Speaking, Bacteria-to-bacteria Communication, Interbacterial Communication.

1. INTRODUCTION

Tinychat comes true via *N*-Acyl Homoserine Lactones (AHL, *N*-AHLs or AHLs) signal molecules managed by a Quorum Sensing System (QS). QS is the coordination of bacterial group movies based on cell density. Thanks to this attitude, bacterial tinychats are established. As a result of tinychat, serious big consequences such as diseases occur (Parveen & Cornell, 2011; Winsberg, 2022). The properties that a real QS molecule should have, unlike a metabolite, are summarized as follows: I. Production of the QS molecule occurs at different phases of reproduction, under special conditions changes. II. The QS molecule agglomerates extracellularly and is detected whereby specific receptors. III. Accumulation of the QS molecule elicits a planned response when it reaches a critical threshold. IV. The cellular

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response elicited by the QS molecule is much broader than metabolizing or detoxifying the QS molecule. While many metabolites show the first three of these four features, the fourth feature is a feature that a QS molecule must have (Winzer *et al*., 2002).

Gram-negative bacteria ($Gram^-$) use AHL as their command language to coordinate population behavior during invasion and colonization of higher organisms. AHL is synthesized from precursors by a synthase protein, "LuxI" and once they have reached a certain cut-off value concentration, they interact with a transcriptional activating "LuxR" protein to induce target gene expression (Fuqua *et al*., 1996). So, QS operates that lets bacteria sense and answer target genes depending on their bacteria density. (Eberl *et al*., 1996; Pütz *et al*., 2022). In Gram-positive bacteria ($Gram^+$), the instrument of the communication system functions via Autoinducing Peptide (AIPs) (Sahreen *et al*., 2022). In interspecies, the instrument of communication is via Autoinducer-2 (AI-2) (Liu *et al*., 2022). Bacteria become more prepotent by communicating. They act simultaneously, perform critical gene expressions such as virulence, and perform gene transfer. They coordinate such multiple social behaviors through signaling molecules. In fact, different types of bacteria can communicate with each other thanks to signal molecules in crosstalk.

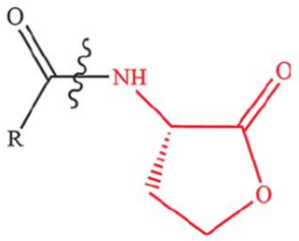
The aim of this review is to summarize the various AHL, AIPs, and AI-2 bacterial signal molecules currently available, QS system management prokaryotic world, and micro-social lifestyle of bacteria.

2. SIGNALING MOLECULES

2.1. AHL Molecules Structure

The main structural components of AHL (Figure 1) are hydrophilic sections of homoserine lactone ring (S-adenosylmethionine) and central amide group, as well as hydrophobic section strain-specific side hydrocarbon chain with varieties in length and level of oxygenation with a 3-oxo group. Acyl chain generally ranges from 4 to 18 carbons (Marin *et al*., 2007). In bacterial signaling, AHL is produced and released by bacteria cells. AHLs produced by different bacteria differ in the length of the R-group sidechain (Kumari, 2006). In QS, LuxI protein is synthesized by AHL. AHL can pass through the cell membrane down a gradient to environmental space. When molecule concentration reaches the threshold value, cognate LuxR protein binds to AHL. So, AHL directs target gene transcription (von Rad *et al*., 2008).

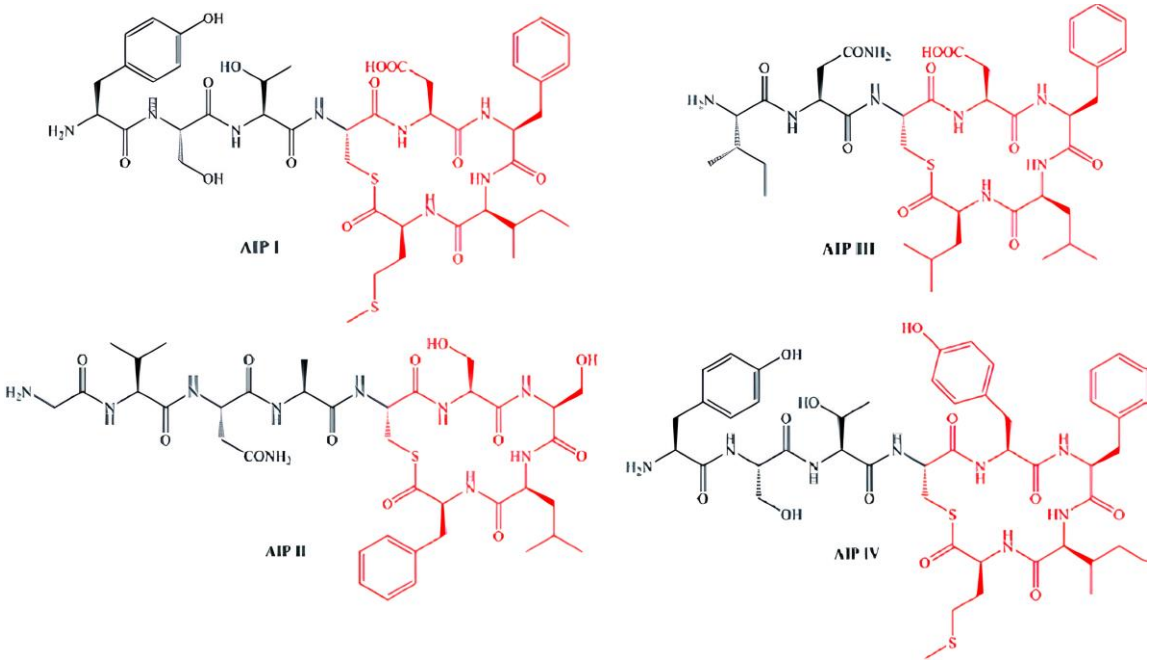
Figure 1. AHLs structure used by $Gram^-$ (Konai *et al*., 2018).



2.2. AIPs Peptide Signaling Molecules Structure

AIPs are characterized as AIP I-II-III-IV (Figure 2). Peptides may have differences in amino acid sequence; however, all of them possess an increased hydrophobicity from their N- to C-terminal end in peptide structure. At the end of the sequence to the C-terminal positions, AIPs are found to have amino acids with hydrophobic side chains (Mayville *et al*. 1999; MDowell *et al*. 2001; Yang *et al*. 2016). AIP linear peptide analogs or hydrolysis of the thioester moiety inactivates its functions molecule. Thioester macrocyclic ring is an ester moiety that was found to inactivate the signaling. Upon removal of N-terminal exocyclic structures, AIP loses signaling (Konai *et al*., 2018).

Figure 2. AIPs structure used by Gram^{+} (Konai *et al*., 2018).

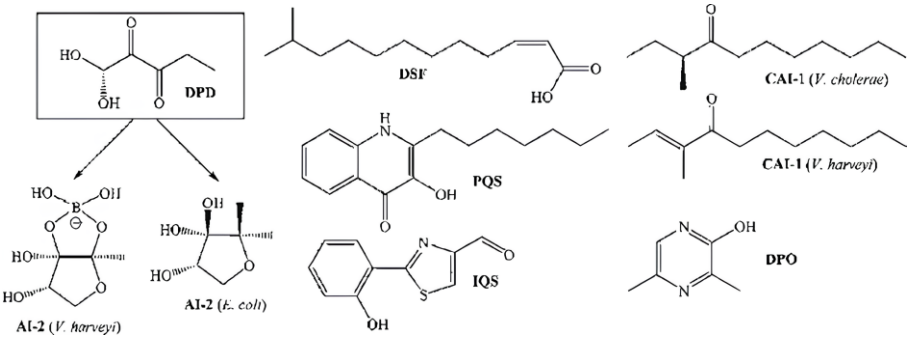


2.3. AI-2 Molecules Structure

AI-2 is a set of interconverting molecules derived from 4,5-dihydroxy 2,3- pentanedione (DPD) (Figure 3) (Qiao *et al*., 2022). LuxS is a synthase enzyme of DPD (Pereira *et al*. 2013). AI-2 synthesis is start with SAM (Federle & Bassler 2003). Different forms of DPD act as AI-2 for interbacteria. AI-2's chemical nature structure is the same for many bacteria species. This suggests that AI-2 is used for inter-species communication (crosstalk) to detect other bacteria (Miller *et al*. 2004). In AI-2-based QS, signal receive, and transduction are conducted by a two-component pathway. The first component consists of LuxP and LuxQ while the second component constitutes phosphotransferase LuxU and cytoplasmic response LuxO. There exist LuxPQ complexes with symmetric heterotetramer in AI-2. Upon binding with AI-2, the tetramer undergoes a change. This change prevents the phosphorylation of the cytoplasmic proteins, LuxU and LuxO, which terminates the expression of genes. Finally, LuxR is produced (Konai *et al*., 2018).

Significant works on the three-dimensional structures of proteins involved in QS first came into light in 2001 by determining the crystal structures of three LuxS orthologs with the help of X-ray crystallography. This was closely followed by determination of the crystal structure of the receptor LuxP of *Vibrio harveyi* with its inducer AI-2 (which is one of the few biomolecules containing boron) bound to it. AI-2 signalling is conserved among many bacterial species, including *Escherichia coli*, the model organism (Lewis *et al*., 2001; Chen *et al*., 2002). A database of QS peptides is existing "Quorumpeps" (Wynendaele *et al*., 2013; Wynendaele *et al*., 2015).

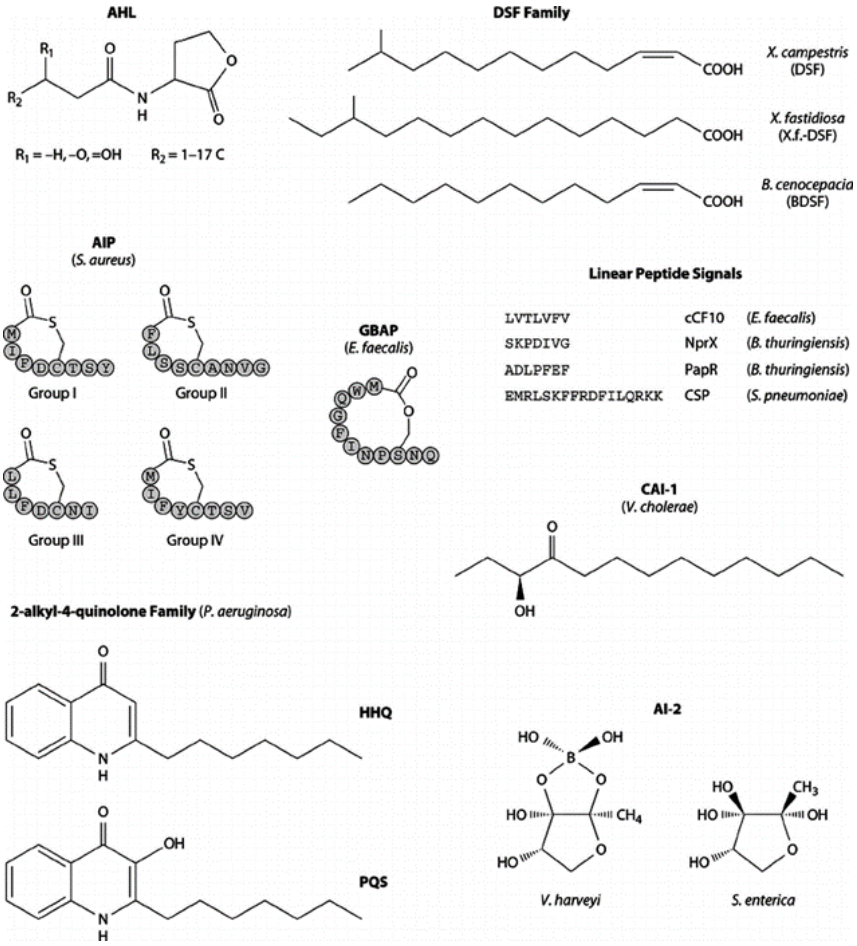
Figure 3. AI-2 and other signal molecules used by bacteria (Qiao *et al*., 2022).



3. COMMUNICATION INSTRUMENTS IN BACTERIA

Briefly, AHL is produced by LuxI-type and by LuxR-type in Gram. The second mechanism involves AIPs in Gram$^+$ which are sensed by two-component systems. The final system is the AI-2 system which is common in both Gram$^-$ and Gram$^+$ (Figure 4) (Brackman & Coeny, 2015). AIPs are often integral elements of a histidine kinase two-component signal transduction system. In this system, extracellular proteases process the secreted precursor-AIP into mature AIP. Kinase phosphorylates regulate gene transcription. This is called a two-component system (Rutherford & Bassler, 2012). AHLs are important "messenger" molecules involved in cellular communication of Gram$^-$ (Rutherford & Bassler, 2012). Usually, AHL does not need additional processing and binds directly to transcription factors to regulate gene expression (Bassler, 1999). Communication instruments in bacteria are shown in Table 1.

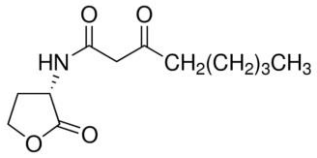
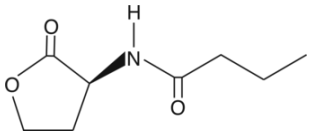
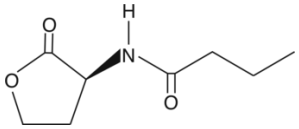
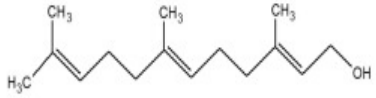
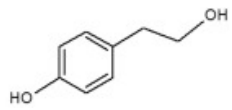
Figure 4. General structures of the selected QS signal molecules (LaSarre & Federle, 2013).

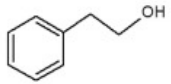
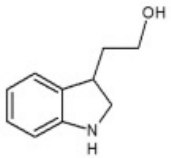
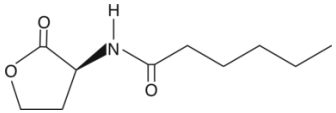
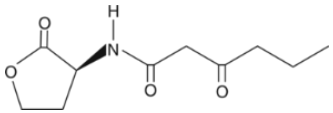
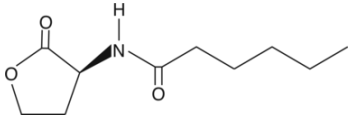
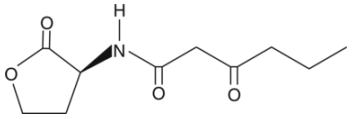


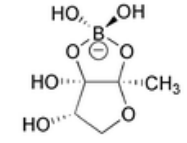
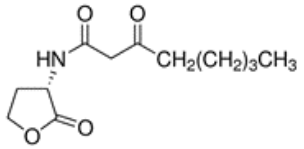
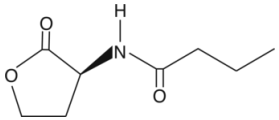
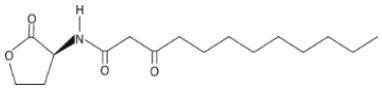
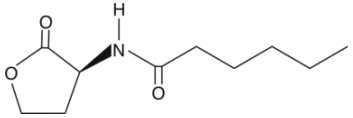
4. DISCOVERY of AHL, AIPs, AI-2

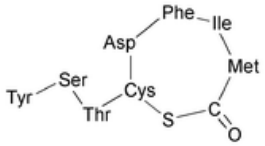
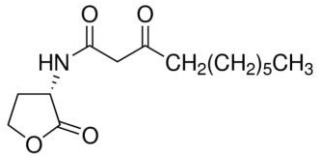
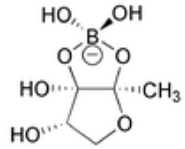
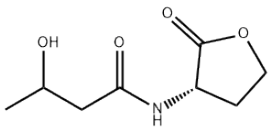
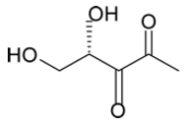
Previously pathogenic bacteria were tested against 2 AHL monitor bacteria (*Agrobacterium tumefaciens* NT1 and *Chromobacterium violaceum* CV026) in a well-diffusion assay (Bruhn *et al*., 2005). However, currently for AHL extraction problem is components present in bacterial culture supernatants. Components are cell growth media and extracellular products produced by bacteria. To reduce extracellular products, a stationary bacteria growth phase is recommended at extraction. Liquid–liquid extraction (LLE) and solid-phase extraction (SPE) are commonly used methods to isolate AHL (Huang et al., 2020). Several methods have been developed for purification, detection and quantification of the AHLs. Methods have been developed for the detection of tinychat molecules. These methods are biosensors of HSLs, Thin-layer chromatography (TLC) (Laj *et al*., 2022), Radiolabeled assay (Schaefer *et al*., 2018), High-performance liquid chromatography (HPLC) (Bao *et al*., 2022), Colorimetry (Jin *et al*., 2020). For identification of AHL spectroscopic properties have been widely used to the characterization of QS molecule structures. Spectroscopic include Mass Spectrometry (MS) (Rosario *et al*., 2022), MS/MS, nuclear magnetic resonance spectroscopy (NMR) (Sundar *et al*., 2022), and infrared spectroscopy (IR) (Deepa *et al*., 2022). These methods are HPLC-MS (High-performance liquid chromatography-Mass spectrometry) and GC-MS (Gas chromatography-Mass spectrometry), Nano-LC-MS/MS (Frommberger *et al*., 2004), At-line coupling of UPLC (Ultra-high-pressure liquid chromatography) to chip-elctrospray-FTICR-MS (Fourier-transform ion-cyclotron resonance mass spectrometry) (Li *et al*., 2007a), Capillary zone electrophoresis mass spectrometry (CZE–MS), Nuclear magnetic resonance (NMR) (Bainton *et al*., 1992), IR spectrometry (IR) (Wang *et al*., 2011).

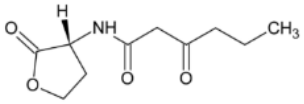
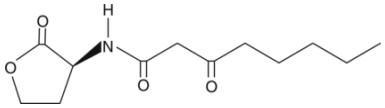
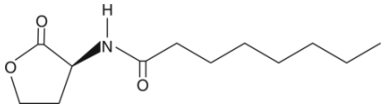
Table 1. Bacteria possessing QS system target genes, signal molecules, structure, and function in talking via chemical languages.

Strain	Gram* staining	Signal molecules	Structure	QS system target genes	Function	Reference
Agrobacterium tumefaciens	Gram$^-$	*N*-(3-oxooctanoyl)-L-homoserine lactone (OOHL)		*traR-traI*	Factors for conjugal Ti plasmids transfer	Zavilgelsky & Manukhov, (2001)
Aeromonas hydrophila	Gram$^-$	*N*-butanoyl-L-homoserine lactone (C_4-HSL, BHL)		*luxI-luxR* *AhyI-AhyR*	Virulence, biofilm, hemolysis	Filik, 2020
Aeromonas salmonicidae	Gram$^-$	C_4-HSL, BHL		*luxI-luxR* *AsaI-AsaR*	Exoprotease production	Miller & Bassler, (2001)
Bacillus subtilis	Gram$^+$	Competence and Sporulation Stimulating Factor (CSF)	Glu-Arg-Gly-Met-Thr		CSF adsorption, serious membrane damage, gene expression	Huang *et al*. (2021)
Candida albicans	Yeast**	Farnesol Tyrosol	 	*LuxS*	Dimorphism, biofilm	Kim & Yeon, (2018)

		Phenylethanol Tryptophol	 			
Chromobacterium violaceum	Gram$^-$	*N*-hexanoyl-L-homoserine lactone (C_6-HSL, HHL)		*luxI-luxR* *CviI/CviR*	Violacein pigment production	McClean *et al*., (1997)
Enterobacter agglomerans	Gram$^-$	3-oxo-C_6-HSL		*luxI-luxR* *EagI/EagR*	Pheromone production	Swift *et al*,. 1993
Erwinia carotovora	Gram$^-$	C_6-HSL, HHL *N*-(β-ketocaproyl)-L-Homoserine lactone (3-Oxo-C_6-HSL)	 	*luxI-luxR*	Carbapenem antibiotic production Virulence	Zavilgelsky & Manukhov, 2001 Burr *et al*., 2006

E. coli	Gram$^-$	AI-2		*LuxS*	Cell division, chromosome replication, cell signaling, translational modification, pathogenesis mechanismsprotein	Soni *et al*., 2007
		3OC$_8$HSL		NA (Not applicable) - SdiA	Motility, acid resistance	Soares & Ahmer 2011
Pseudomonas aeruginosa	Gram$^-$	C$_4$-HSL, BHL		*rhlI-rhlR*	Virulence, secondary metabolites (rhamnolipids)	Zavilgelsky & Manukhov, 2001
		N-(3-oxododecanoyl)-L-homoserine lactone (OdDHL, 3OC$_{12}$-HSL)		*lasI-lasR*	Virulence (toxin A, elastase)	
Pseudomonas aureofaciens	Gram$^-$	C$_6$-HSL, HHL		*LuxI-LuxR PhzI-PhzR*	Produces of exoproducts, including protease, phenazines, phenazine antibiotic biosynthesis	Zhang & Pierson, 2001

Staphylococcus aureus	Gram^{+}	Oligopeptide Autoinducers Peptides (AIPs)		*Agr*	Virulence	Malone *et al*., 2007
Vibrio anguillarum	Gram^{-}	3-oxo-C_{10}-HSL (ODHL)		*LuxI-LuxR* *VanI/VanR*	Bioluminescence Violacein pigment production	Milton *et al*. 1997
Vibrio harveyi	Gram^{-}	*N*-octanoyl-L-homoserine lactone (OHL), Autoinducer-2 (AI-2) *N*-(3-hydroxybutanoyl)-L-homoserine lactone (HBHL), AI-1 4,5-dihydroxypentane-2,3-dione (DPD)	  	*ainS-ainR* *luxL-luxM* *luxR-luxN* *luxS-luxQ*	Bioluminescence	Geske, 2008

Vibrio fischeri	Gram$^-$	*N*-(3-oxohexanoyl)-L-homoserine lactone (OHHL), AI-1		*luxI-luxR*	Bioluminescence	Zavilgelsky & Manukhov, 2001
Yersinia ruckeri	Gram$^-$	OOHL OHL	 	*luxI-luxR*	Virulence	Bruhn *et al*., 2005

*Gram staining is an assay applied only to bacteria.
***C. albicans* is yeast and has nothing to do with gram stain.

5. DISCUSSION and CONCLUSION

Interbacterial communication systems based on signaling molecules have been determined in pathogenic $Gram^-$ and $Gram^+$ causing tough problems. The ability to mark bacterial communication at single-cell level in situ enables exploration of interbacterial communication, intercellular signal transduction, and QS, and it gives us a tremendous potential for studying the efficiency of communication systems in complex virulence systems scenarios (Andersen *et al*., 2001). Many species of microorganisms exhibit a social behavior.

QS in prokaryotic biology refers to the ability of bacteria to sense information from other cells in the population when they reach a critical concentration. They communicate with each other through signal molecules they have produced, monitor whether they have reached a certain majority, and trigger critical gene expressions such as synthesis of virulence as soon as they reach a sufficient majority. Thus, by not stimulating the host's immune system prematurely, it creates a successful infection process (Thirunavukkarasu *et al*., 2023).

Researchers have established “SigMol” (http://bioinfo.imtech.res.in/manojk/sigmol), a specialized repository of molecules in procaryotes. SigMol harbors information on QSSMs pertaining to different signaling systems namely AHL, AIPs, AI-2, and others. The database consists of 1382 entries of 182 peerless signal molecules from 215 microorganisms. SigMol encompasses biological (genes etc.) and chemical (IUPAC name, SMILES and structure etc.) properties of molecules (Rajput *et al*., 2016).

By secreting chemical toxins, all bacteria by themselves would receive the signals and answer them by activating the transcription of virulent genes and changing their social behavior to become highly pathogenic. Bacteria possess an extraordinary repertoire for interbacterial communication and social movements.

The discovery of communication molecules in the bacterial world attracts attention to fish disease control. Destroying AHL signal molecules, which are communication instruments, before they can occur the disease, brings up the concept of early diagnosis and in this case, it is aimed to era in prophylaxis. So, explaining to molecules in all detail will be an important step in diagnosis.

The similarities between the signals used by bacteria and artificial neural networks are striking. Based on the finding that bacteria have many of the properties of a neural network, bacteria may have a low level of intelligence. Researchers have stated that billions of bacteria collectively carry out the same command in their experiment by putting bacteria into communication with each other with the program loaded in their DNA. Scientists state that billions of bacteria that can communicate with each other can be managed at the same time and directed to certain tasks. They point out that in the future, smart biological devices will also be reflected in daily life.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Nurdan Filik: Investigation, conceptualized the review articles. Also, a literature review. **Fethi Filik**: The draft preparation and involved in the drafting and edition. Also, a literature review. The drafts were critically discussed and revised by all authors.

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