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A Review

Current trends and advances of Quorum sensing inhibitors and their biotechnological applications

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Serious setbacks were witnessed in shrimp farming, the food industry, and the ship industry during the past three decades primarily due to bacterial pathogens that coordinate by quorum sensing (QS). The influence of bacterial pathogens utilizing QS. The impact of QS cell communication on public health is extremely disastrous in terms of spread, spectrum, apart from their economic impact. The overuse of antibiotics has increased drastically to battle bacterial infections, including tons of antibiotics are distributed in the biosphere. Due to the indiscriminate use of antibiotics, multiple antibiotic-resistant strains have emerged, as the antibiotic resistance genes are being transferred to bacteria of terrestrial animals, humans, and pathogens. The increased public awareness of the negative drawbacks caused by over-exposure to antibiotics, also the emergence of multiple antibiotic resistant pathogenic stains led to the search for alternatives and unique solutions. One such unconventional, promising method is the interruption of bacterial cell to cell communication, which is currently termed QS inhibition. Now-a-days, QS inhibition is the potential objective for antimicrobial chemotherapy. This review summarizes the regulatory factors that attenuate the QS activities of deadly pathogens and discusses their distinctive characteristics. Improving awareness of the natural roles of regulatory elements might be useful in unveiling inhibitor applications to understand how QS is inhibited in pathogenic bacteria by different QS inhibitors.

Keywords: Applications, Cell communication, Pathogen, QS inhibitors, QS

Introduction

Multiple drug resistance bacterial strains have emerged due to the extreme versatility and discriminate application of antibiotics, such as to eradicate life-threatening and debilitating diseases in humans and to enhance the disease resistance of plants, to improve production and increase the shelf lives of plant-derived products[1]. Some of the drugs that have been developed to combat antibiotic resistance to linezolid, vancomycin, and the most recent beta-lactams have lost efficacy against a few microbial strains[2]. In the last decade, drug development has drastically slow down, and the development of novel drugs is limited to serious chronic diseases and infections, so as to avoid indiscriminate usage. There is a large extent need to develop alternative approaches and novel strategies that can combat multiple drug resistance bacterial strains and provide long-term effectiveness against disease causing microbes[3]. One of the effective and promising strategies is quorum sensing (QS) inhibition, which eradicates bacterial infection by inhibiting microbial cell-to-cell communication, also known as signal interference or quorum-quenching. It is significant to emphasize that among the infectious diseases, more than 65% of them are related to the bacterial species that proliferate by synthesizing biofilms[4]. QS-based bacterial behaviours cause severe economic loss to other sectors such as aquaculture, food spoilage, the ship industry, water purification, *etc*[5]. As QS inhibition is having a hopeful effect as a substitute for antibiotics, it is an intensively researched area, and there are several reports demonstrating the inhibitory capability of many natural and synthetic compounds[6-13].

Cell to cell communication system

In QS, or cell-to-cell communication, bacteria generally utilize auto-inducers, which are tiny diffusible signalling particles, to communicate and evaluate their population densities. The QS mechanism is dependent on the production, delivery, and intake of auto-inducers from the surrounding area, whose concentration is parallel to the density of secreting bacteria in the surrounding environment. In QS, the crucial process is the connection of the auto-inducer to the transcriptional regulator, either by activation of

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sensor kinase or directly. In bacteria, a different type of signalling molecule acts as a local sensor for QS to communicate population densities. Usually, Gram-negative and Gram-positive bacteria involve auto-inducers that are specific to their species to activate the QS process. There are different types of QS signalling molecules that can act as sensors to communicate among bacteria. These QS signalling molecules and their specific receptors are roughly divided into three major categories: auto-inducer-2 (AI-2), auto-inducing peptides or oligopeptides (AIP), and *N*-acyl homo-serine lactones (AHLs)[11-13]. An overview of how QS works in bacteria is represented in (Fig. 1).

Quorum sensing can help facilitating disease progression

Antibiotics are still the first-line treatment for bacterial illnesses. Nevertheless, biofilms, which create a barrier surrounding bacterial cells, reduce medication resistance and induce persistent infections. It has been established that bacteria in a biofilm increase their antibiotic resistance by a factor of 1000. Traditional antibiotics are ineffective in controlling bacterial infections due to the formation of biofilms. As a result, developing a way to limit the creation of biofilms is crucial in order to control these increasingly deadly infections[14]. The hydro-dynamical condition of QS in biofilm formation is investigated using the Langevin equation to investigate how hydrodynamics and structural heterogeneities impact mass transfer while taking environmental factors into consideration[15].

AI-2-based Quorum sensing

It was first recognized as anAI-2 QS signal in *Vibrio harveyi*. Later, in several gram- negative bacteria, such

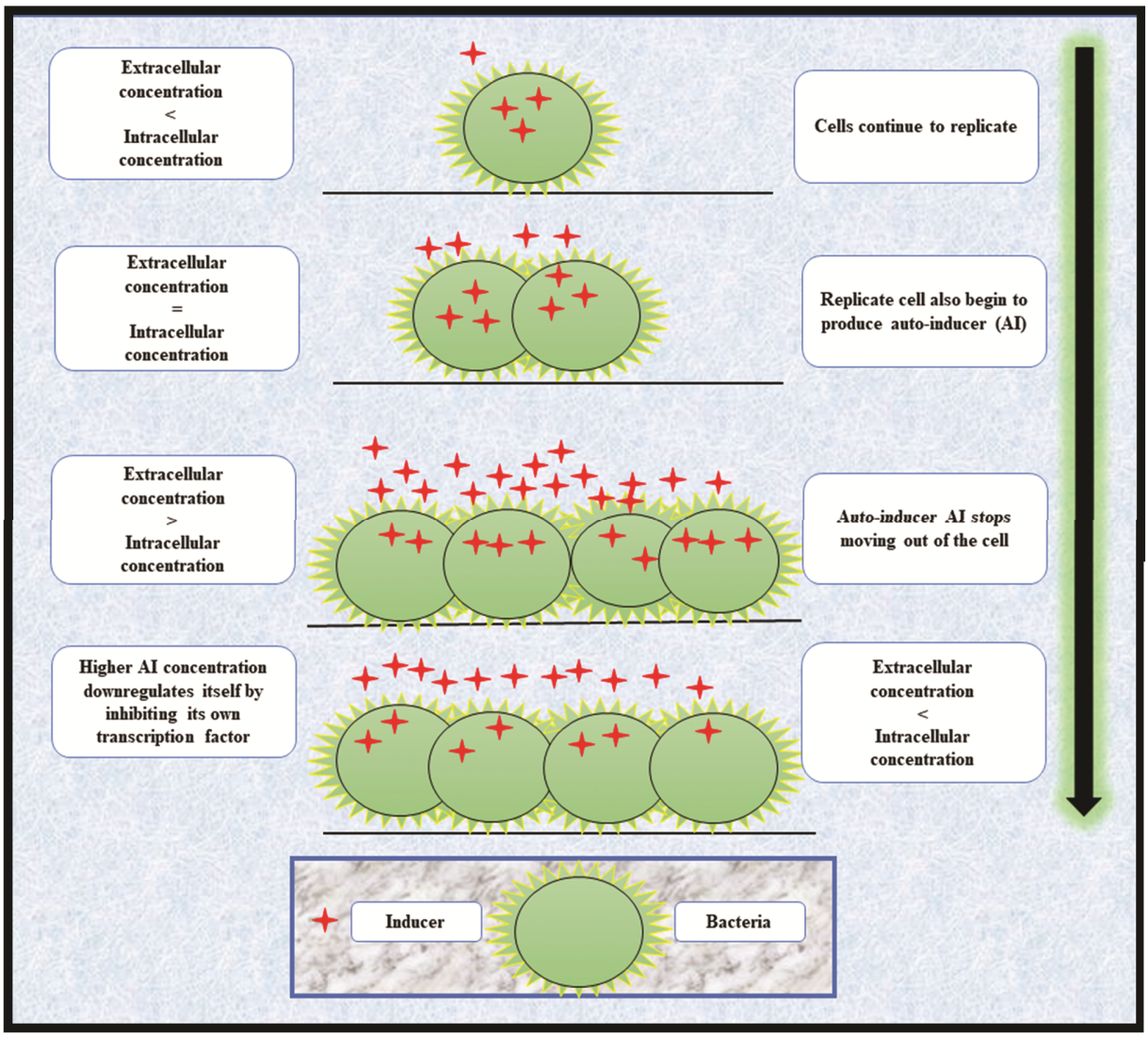

Fig. 1 — Overview of how quorum sensing works in bacteria

as *Escherichia* spp., *Erwinia* spp., and *Salmonella* spp., the AI-2 type of quorum-sensing signalling was found. AI-2 type signalling can be seen in both gram positive and gram negative bacteria.AI-2 type signalling is used for interspecies communication, so it is generally referred to as a global signal molecule.

The precursor S-adenosylhomocysteine (SAH) gives rise to AI-2 with the help of the chronological enzymatic activities of the metalloenzyme LuxS and 5′ methylthioadenosine/S-adenosylhomocysteine nucleoside (MTAN). Because of the enzymatic activities of metalloenzyme LuxS and 5′ methylthioadenosine/S-adenosylhomocysteine nucleoside (MTAN), a molecule named 4, 5-dihydroxy-2, 3-pentanedione (DPD), which is very unstable in aqueous solution, is generated. DPD goes through random and irregular reorganization into several interconvertible cyclic furanone compounds, which as a group are known as AI-2. Both from gram-positive and gram-negative bacteria, AI-2 can be easily diffused out and accumulates in the extracellular environment, where it plays the major role for all other QS signals. It was reported that many species produce and react to AI-2 and in microorganisms like *Salmonella enterica* serovar *Typhimurium* and *V. harveyi,* AI-2 receptors have been identified. The boric acid-complexed form of AI-2 can be identified by *V. harveyi* through the LuxP/LuxQ receptor/sensor kinase complex. However, it is quite different in the case of *S. typhimurium,* where its transporter LsrB comes in contact with the non-borated form of AI-2 which leads to its phosphorylation, internalization, and linking with the transcriptional regulator LsrR. Therefore, diverse bacterial species can recognize several and unlike forms of AI-2 and their recognition can be done intracellularly or extracellularly depending on the type of bacteria.

In the year 2020, Jon Windsor group has discovered a strong link between auto-inducer-2 (AI-2)-mediated QS and the performance of a submerged anaerobic membrane bioreactor during its recovery from pentachlorophenol (PCP) shock. The lower AI-2 levels were associated with lower volatile fatty acid concentrations, and were significantly linked to a decrease in firmicutes relative abundance and an increase in *Bacteroidetes* and symbiotic bacteria. When an AI-2-regulating *Escherichia coli* mutant culture was added to the batch experiments, it was discovered that reducing AI-2 levels resulted in the highest methane production rate during a PCP shock. A spike in AI-2 levels generated by the introduction of the *E. coli* wild-type strain or an AI-2 precursor, on the other hand, had no detectable effect on biogas production. Our findings suggest that firmicutes are the principal regulators of AI-2 in anaerobic sludge and that AI-2-mediated QS modifies anaerobic sludge's toxic shock response *via* controlling the activities of firmicutes and synergistetes. Decreased AI-2 levels may favor hydrogen trophic methanogens, leading to reduce VFA accumulation and more methane synthesis during the PCP shock. This is the first research of its sort to look at the role of QS in anaerobic sludge's toxic shock response; it provides a unique way for lowering anaerobic process recovery time by modifying the AI-2-mediated QS[16].

AHL-based Quorum sensing

Generally, Gram-negative bacteria use N-acylhomoserine lactones (AHLs) as QS auto-inducers. N-Acylhomoserine Lactones contain an unchanging homoserine lactone (HSL) ring coupled to an acyl chain that can change in length between four and eighteen carbon atoms. Apart from acyl chain length, AHLs sometimes may vary in the oxidation state at the 3rd position and the saturation state of the acyl chain. Acylated acyl carrier protein (acyl-ACP) and S-adenosylmethionine are used as substrates by members of the LuxI family of AHL synthases to biosynthesize AHLs. AinS and LuxM of *Vibrio fischeri* and *Vibrio harveyi* are very different; they catalyse the same reaction but do not have the same homology of LuxI-type proteins. Generally, each AHL synthase mostly synthesizes a single type of AHL, while a few synthases can synthesize additional AHLs in small quantities. After synthesis, AHLs usually diffuse freely across the cell envelope and gather in the local surroundings. On the other hand, there are reports that many AHLs are vigorously transported across the cell membrane by a particular type of bacterial species. Once a vital concentration threshold is obtained, coupling of the LuxR-type receptor protein with AHL in the cytoplasm of the cell becomes very easy. The DNA-binding behavior of LuxR family members varies upon ligand interaction, which leads to modulation of target gene regulation in response to AHL accumulation. Hence, members of the LuxR family are known as transcriptional regulators. The perfect instance of Lux/R signalling can be seen in *Chromobacterium violaceum,* which uses AHLC6HSL, CviR, and CviI to regulate violacein production. The LuxN of *V. Harveyi* is a membrane bound sensor kinase that detects some types of AHLs and begins phosphorylation signalling cascades following ligand

binding. Moreover, every AHL receptor protein exhibits some degree of AHL binding specificity depending on the saturation, length, and oxidation of the AHL acyl chain. Therefore, several bacterial species possess a cognate synthase/receptor pair that synthesizes and reacts to a particular AHL molecule. There are some bacterial species, like *P. aeruginosa,* that use several synthase/receptor pairs that synthesize and react to specific AHL molecules. Some bacterial species possess "solo" LuxR-type receptors that have no cognate LuxI-type synthase, such as SidA of *Escherichia coli* andQscR of *P. aeruginosa.* The general steps and key components of AHL-type quorum-sensing systems the key component of the quorum-sensing process is well tabulated in (Table 1).

N-acyl homo-serine lactones (AHLs) are one type of signaling molecule employed in QS, a type of chemical communication that allows bacteria in natural biofilm communities to perceive and coordinate activity. For AHL-based communication to operate, bacteria must make and recognize the same signals that activate identical genes in different species. According to our present knowledge of AHL-QS, communication across species occurs at random, which is implausible. We believe AHL-QS signalling is a dynamic and adaptable system within specific bounds. Although AHLs are highly conserved signals, the receptor proteins linked with them (LuxR) are not. We argue that receptor proteins are adaptable and flexible, allowing complex signalling networks to form in biofilms over time.

Bio-augmentation is an efficient treatment technique for wastewater containing resistant organic pollutants. Unfortunately, it is hampered by a number of technical challenges, including the difficult colonization and survival of the injection bacteria, as well as the lengthy start-up procedure. Because of the relevance of QS (QS) in modulating microbial behaviours, the effects of N-acyl-homo-serine lactones (AHLs)-based manipulation on the start-up of biofilm reactors augmented with a pyridine-degrading strain, *Paracoccus* sp. BW001, was investigated. The results showed that in the presence of two unique exogenous AHLs (C6-HSL and 3OC6-HSL), the biofilm development process on carriers was considerably accelerated, producing thick and structured biofilms. Protein and polysaccharide levels in sludge were also greater, probably due to an increase in the number of several EPS-producing bacterial taxa. Protein structural stability and complexity were especially enhanced. AHL change, rather than reactor operating duration, was discovered to be the primary cause of the shift in bacterial community structures in the reactors. Exogenous AHLs accelerated bacterial community succession while reducing bacterial alpha diversity. Most notably, the AHL change raised the final proportions of the inoculated strain BW001 in both the sludge and biofilm communities by roughly 100%. Our findings showed that AHL-based QS was critical for biofilm development, sludge characteristics, and the creation of microbial communities in bio-augmented reactors, indicating a potential bio-augmentation technology start-up technique.

Many gram-negative bacteria regulate their pathogenicity by an AHL-mediated QS mechanism. Disrupting this signalling system may be a novel method of reducing bacterial pathogenicity. Using the biosensor strain *Chromobacterium violaceum* CV026, foodborne bacterial isolates were tested for QS-inhibitory properties against pathogenic bacteria, and the extracted putative active components were tested for anti-QS and anti-biofilm activity against pathogenic bacteria. *Enterobacter xiangfangensis* PUFSTI26 cell-free supernatant reduced violacein synthesis in the reporter strain as well as extracellular virulence factors such as biofilm development, pyocyanin production, and *Pseudomonas aeruginosa* motility. The extracted active component was compared to hydrocinnamic acid using gas chromatography-mass spectrometry (GC-MS) (HCA). HCA usage resulted in a substantial decrease in virulence factors. Additionally, confocal laser microscopy was used to demonstrate biofilm inhibitory activity, which revealed that biofilm biomass

Table 1 — General steps and key components of AHL-type quorum-sensing systems quorum-sensing process key component

High-population density	Signal reception	LuxR-type (R) transcription factor; putative influx system for long-chain AHL signal
	Auto-induction and activation of quorum-sensing regulon	R and I proteins involved in boosted AHL signal production; quorum-sensing dependent transcription factors
	signal decay	AHL degradation enzyme and its regulatory mechanisms
Low-population density	basal signal generation	proteins and enzymes involved in biosynthesis of acyl chain and S-adenosylmethionine (SAM); LuxI-type (I) protein
	signal accumulation	proteins involved in long-chain signal active efflux

was decreased. According to *in silico* studies using gene quantification analysis, HCA also decreased the expression of essential QS-regulated genes. HCA interacts with the LasR receptor protein in a competitive way which clearly demonstrate that HCA extracted from food-borne *E. xiangfangensis* has anti-virulence properties. This is also the first report of HCA's QS inhibitory activity.

Auto-inducing peptides based Quorum sensing

LuxI or LuxR homologues are not present in the gram positive bacteria, so they use customized oligopeptides as auto-inducer molecules. These customized oligopeptides are genetically encoded and synthesized inside the cell. The active transport of these peptides out of the cell is done by specialized transporters because of their inability to permeate the cell membrane. Peptides undergo several alteration processes, such as cyclization and processing. During the export, translation, and detection processes. Generally, the recognition of these peptide signals can take place intracellularly or at the surface of the cell. Different types of peptide auto-inducers are recognized by a membrane-bound sensor kinase. The membrane bound sensor kinase initiates its phosphatase/kinase activity in response to an interaction with a peptide. This modifies the phosphorylation state of the cognate response regulator and finally leads to the suppression or activation of QS target genes. The *fsr* system of *Enterococcus faecalis* and the *agr* system of *Staphylococcus aureus* control virulence factor synthesis and use extracellular identification. The *agr* system of *S. aureus* contains cyclic auto-inducing peptides of four different and specific groups that link with the cognate AgrC sensor kinases of the same group to control biofilm spreading and exotoxin production. One of the different cyclic peptides, gelatinase biosynthesis-activating pheromone (GBAP), which is identified by the sensor kinase FsrC, is used by *the FSR* system for the synthesis of gelatinase. The competence inducing QS system of *Streptococcus pneumonia,* which is detected extracellularly, is catalysed by the competence stimulating peptide (CSP). Several other bacteria also use linear peptide auto-inducers that are detected extracellularly. There are few linear peptide-based QS systems, such as the PlcR and NprR systems of *Bacillus thuringiensi*s and the PrgX system of *E. faecalis,* which vigorously transport the auto-inducers back into the cell, so that the peptide signal can interact directly with a cognate regulator to alter target gene expression, as illustrated in (Table 2).

Current Advancements on Quorum sensing inhibitors obtained from different origin

Designing and identifying QS inhibitors to combat antimicrobial resistance is becoming a strategic approach that could help give old antibiotics a new lease on life. QS Inhibitors can also be classified by their source, such as microbe-produced compounds, natural product-based inhibitors (mainly of plant origin), or chemically generated inhibitors. On the

Table 2 — Basic elements of the quorum sensing systems in bacteria

Type	Sensing molecules	Unique features	Receptor(s)
Autoinducer type 1, LuxR-I type	*N*-acyl-homoserine lactones	Found in Gram-negative bacteria (*Burkholderia*, *Vibrio*, *Pseudomonas* spp.); might affect human genes	Intracellular Lux-R homologues as transcriptional coactivator
Auto-inducer type 2, LuxS type	Heterocyclic furanosyl-borate	Widespread in Gram-negative and Gram-positive bacteria; might be a primary metabolic system rather than a communication system	Two-component membrane receptor-cytoplasmic kinase complex
Auto-inducer type 3, epinephrine/norepinephrine epinephrine/norepinephrine	Catecholamine-like molecules	Found in Gram-negative, enteric bacteria *enterohemorrhagic* *Esch richia coli*, enter pathogenic *E. coli*, *Shigella Salmonella* spp.; functional role unclear at present	Two-component membrane sensor kinase/response regulator (QseBC)
Cyclic short-peptide systems (AgrC/AgrA, staphylococci; competence stimulating peptide, pneumococci; *Enterococcus faecalis* regulator, *Enterococcus faecalis* regulator,	Small cyclic peptides with thiolactone ring	Gram-positive bacteria *Staphylococcus*, *Bacillus Enterococcus*, *Streptococcus* spp.	Two-component sensor kinase (AgrC)-response regulator (AgrA)

Agr, accessory gene regulator; QseBC, auto inducer type 3 system in enteric bacteria

basis of their original sources, we have attempted to summarize the most recently discovered lead compounds linked with QS inhibitory activity in this section.

Quorum sensing inhibitors identified through Drug repurposing

According to current data obtained from literature published in 2018–20, the results of research undertaken on FDA-approved pharmaceuticals for drug repurposing purposes have proven the potential of various known treatments as QS inhibitors. Most of the evaluated drugs were shown to interfere with *P. aeruginosa* QS signaling with its multiple QS targets, as indicated by the activity of the tested molecule *in vitro* studies. Several of the "tried and true" methods of genetic analysis and modification along with chemical peptide synthesis are still used to study QS in gram-positive bacteria. The overall workflow has not changed, though improvements have been made in several places to speed up the process, which begins with the identification of the peptide and related machinery, progresses through SAR and lead design, and concludes with the assessment of triggered regulatory responses and therapeutic evaluation. The confirmation of mature peptides from cell cultures, which is one of the most challenging steps, is being accelerated using mass spectrometry-based approaches. Additionally, as the corpus of QS data expands, *in silico* approaches have become more practical, possibly accelerating research efforts as predictions are tested and models are modified. Peptide analogue modulators that can reduce Streptococcus pneumonia infections have been found to be therapeutically promising peptide analogue modulators. A growing number of studies are being conducted to better understand the complexities of microbiomes and to allow the creation of increasingly sophisticated peptide modulators of bacterial group behaviors[17].

Quorum-sensing systems utilizing other auto-inducers

Apart from the three chief classes of auto-inducers, there exist other types of auto-inducer molecules that are totally different from the three chief classes of auto-inducers. 2-Heptyl-3-hydroxy-4(1H)-quinolone [PQS *Pseudomonas* quinolone signal] and its precursor, 2-heptyl-4(1H)-hydroxyquinoline (HHQ), are produced during the synthesis of the *pqsABCDE* operon. This operon catalyzes the condensation of keto-fatty acid and anthranilate. The molecules HHQ and PQS play an active role as QS auto-inducers through their interaction with the PqsR transcriptional regulator, which leads to an alteration in the expression of the target gene. There is only one structural difference between the PQS and HHQ, the PQS has an extra hydroxyl group at the 3′ carbon atom of HHQ, which is added by the PqsH enzyme. This extra hydroxyl group makes the PQS able to function in iron acquisition along with its QS ability. Among the *Pseudomonas* species, only *P. aeruginosa synthesizes PQS, while other species of Pseudomonas and Burkholderia* species produce QS signals using HHQ.

In *Xanthomonas campestris* PV. Campestris, *cis*-11-methyl-2-dodecenoic acid, which is known as a diffusible signal factor [DSF] and signaling molecule, was first detected. Later, *cis*-11-methyl-2-dodecenoic acid was determined to belong to a family of QS signals, and it is utilized by several bacterial species, like *Xylella fastidiosa* and *Burkholderia cenocepacia.* The synthesis of diffusible signal factor, or *B. cenocepacia* diffusible signal factor needs RpfB belonging to *X. campestris* or RpfB homologue Bcam0581 belonging to *B. cenocepacia.* Moreover, in recent times, it was shown that*B. cenocepacia* diffusible signal factor is synthesized from the acyl carrier protein (ACP) thioester of 3-hydroxydecanoic acid by chronological Bcam0581 mediated thioester cleavage reactions and dehydration. The identification of the DSF family signal is very different between the species, even though both presently known mechanisms carry the familiar characteristic of varying intracellular levels of cyclic di-GMP (c-di-GMP). If diffusible signal factor (DSF) is accumulated in the extracellular environment of *X. campestris.* It reacts with the RpfC sensor kinase to induce a phosphor-relay cascade that stimulates the RpfG response regulator. The activation of RpfG degrades c-di-GMP and thereafter, the reduction in the c-di-GMP intracellular concentration leads to the launch of Clp regulators, which indirectly or directly regulate the expression of target genes. The diffusible signal factor in *X. fastidiosa* is very similarand needs similar genetic machinery, but the specific system design seems to be different from that of *X. campestris* and requires additional characterization. An EAL domain, a GGDEF domain, and a PAS domain containing the RpfR receptor protein are used to detect the BDSF in *B. cenocepacia.* The function of the EAL domain is to present phosphodiesterase activity to RpfR when it comes in contact with cis-2-decenoic acid (BDSF).

A-hydroxyketones (AHKs) are used as signal molecules in *Legionella pneumophila* and different

*Vibrio species.*The genomes of *Vibrio harveyi* and *Vibrio cholerae* possess the *cqs* gene cluster, which is very much responsible for the synthesis and recognition of the AHK signal, 3-hydroxytridecan-4-one (cholera auto-inducer-1 [CAI-1]). The enzyme CqsA is responsible for the synthesis of CAI-1.The substrates decanoyl coenzyme A (decanoylCoA) and (*S*)-2-aminobutyrate are utilized by the enzyme CqsA to synthesize amino-CAI-1 which is later transformed into CAI-1 by a CqsA-independent reaction. In species, *Vibrio harveyi* and *Vibrio cholera*, AI-2 signaling is generated by two proteins known as LuxO and LuxU. These two proteins are involved in phosphorylation cascade reactions, which are activated by the linking of CAI-1 with the sensor kinase CqsS. Moreover, LuxO and LuxU are involved in the AHL signaling in *Vibrio harveyi. V. haryevi* and *V. cholera* join together AI-2, AHL, and CAI-1 signalling to control virulence associated processes through the utilization of general downstream regulatory proteins.

Some of the enteric pathogens and bacteria in the human intestinal microflora synthesize an aromatic signalling molecule known as auto-inducer AI-3. The gene responsible for AI-3 synthesis and the molecular structure of AI-3 are not known. *Salmonella Typhimurium and Escherichia coli* identify theAI-3 by using the sensor kinase QseC, which phosphorylates the QseB response regulator to stimulate the transcription of target genes. It has been reported that the two-component system QseC/B is utilized for the bacterial identification of norepinephrine and epinephrine synthesized by the host. Moreover, it is also assumed that the structure of AI-3 is very similar to the two hormones norepinephrine and epinephrine.

Quorum sensing induced worries

In recent times, the QS based biofilm synthesized by infectious bacteria has been one of the most worrying problems for health departments throughout the globe. The pathogenic bacteria of fish, such as *Yersinia ruckeri, Vibrio anguillarum, A. salmonicida, Aeromonas hydrophila,* and *V. harveyi,* which cause their pathogenicity by QS systems, cause major damage to the fishery departments. The microorganisms such as Pseudomonas and *Burkholderia* species cause very serious health damage to the patients with cystic fibrosis. During the production of drinking water, desalination of sea and brackish water, and wastewater reclamation, reverse osmosis membranes are used for purification, the biofilms formed on these membranes cause heavy economic losses. In the above mentioned cases, biofilms are synthesized by the interaction of *Rhizobium*, *Pseudomonas,* and *Escherichia* with *Legionella.* One of the other problems that are of great concern is the fast corrosion of monuments and constructions of high archaeological value due to the formation of biofilms, which indirectly support other microorganisms and Gloethece.

There are several reports that biofilm synthesis in food related bacteria occurs through QS. The most common type of food contaminant in fish, dairy, and meat products is the *Hafnia alvei* bacterium, which has the ability to form biofilms. The food processing machinery in the food industry is made of stainless steel, and on these stainless steel surfaces, biofilms are formed. These biofilms play a very vital role as good sources of microbial contamination, resulting in the transmission of diseases and spoilage of food. There is lots of increasing evidence that states that, in several different types of bacterial species, biofilm formation is achieved by QS. *Salmonella* Thompson forms the biofilm on stainless steel in growing conditions like 25°C and 72 h, just as in the cases of AI-2 negative and positive strains. The research on QS in food microbial ecology is in its infancy, and the reports and studies in this area are very limited. Some of the investigators reported that QS signaling compounds such as AI-2 and AI-1 are present in the stored meat, vegetables, milk, and other different stored food systems. Research reported that of all the infectious diseases, about 65% are related to the bacterial group, which proliferates by synthesizing biofilms.

Strategies for inhibition of Quorum sensing

The following processes involved in QS, such as production of the signal molecule, function of the signal, recognition of the signal molecule by its specific receptor, and stimulation of the QS regulon by aiming at gene expression, are also targeted for inhibition of QS is also shown in the (Table 3).

Suppression of AI-1 pathway

Interfering with the signal generation

AHL molecules are produced by the AHL synthase protein, which utilizes related acyl chains synthesized from S-adenosylmethionine (SAM) and the fatty acid biosynthesis pathway. AHLs with long chains need MexAB OprM efflux pumps for their transport across the bacterial membrane, while AHLs with small chains are readily and freely diffusible. It was reported that a null mutation in the BpeAB-OprB pump in

Table 3 — Biotechnological aspects of quorum sensing inhibitors

Quorum sensing inhibitors and origin	Biotechnological Application
AHL homologs Genetically engineered in *Escherichia coli*	Anti-cancer toxicity property
A nano-filtration membrane immobilized with Porcine kidney acylase I	Suppress exopolysaccharides and inhibits biofilm formation, antibiofouling agent
Epiphytic bacterial strains members of Pseudomonas, Erwinia and Pantoea spp.	Premature induction of QS leading to reduction of disease symptoms caused by Pseudomonas syringe on tobacco plant
Heterologous expression of Aiia enzyme in Erwinia carotovora	Reduced pathogenicity towards Chinese cabbage, cauliflower and tobacco plants
Kojic acid (Pyranone) from *Aspergillus* spp. incorporated into a non-toxic paint matrix at a concentration of 0.5%	Significantly inhibited formation of microbial communities, decreasing the densities of bacteria and diatoms
Micro-bacteriumtestaceum StLB037 associated with potato leaf	AHL degrader — effective against Pectobacterium carotovorum subsp. carotovorum, which causes soft rot diseases in many plants
Microbes isolated from the guts of marine organisms such as *Penaeus vannamei* shrimp	Degrade *Vibrio harveyi* HAI-I *in vitro* and improve growth rates of rotifers
Microbes isolated from the guts of marine organisms such as European seabass, Dicentrarchus labrax L, and Asian seabass, Lates calcarifer	Cultures enhanced the survival of turbot larvae Helped to improve the survival of larvae of Macro-brachiumrosenbergii, which could also tolerate higher concentration of ammonia
Metabolites from red algal family Bonnesmaisoniae for *Asparagopsis armata, Bonnesmaisonoa hamifera, B. asparagoides* and *Delisea pulchra*	Antifouling activities against various fouling propagules and the settlement and growth of both micro and macro-fouling bacteria
Microflora (*Shewanella* sp. strain MIB010) from the intestine of Ayu fish, *Plecoglossus altivelis*	Effective against QS regulated biofilm produced by fish pathogen, *Vibrio anguillarum*
QQ enzyme (porcine kidney acylase 1) based membranes	Waste water treatment — biofouling
Natural and synthetic brominated furanones	Protect brine shrimp — *Artemia franciscana* from pathogenic *Vibrio* spp.
	Protect rotifer — *Brachionus plicatilis* from *V. harveyi* Decreased death in rainbow trout infected with *V. anguillarum*
Transgenic expression of human paraoxonase 1 in Drosophila	Reduced lethality caused by pathogenic bacteria — *Psedomonas aeruginosa* and *Serratia marcescens*

Burkholderia pseudomallei reduced the accumulation of AHL in the medium. This makes it evident that any compound that suppresses SAM production, fatty acid production, efflux pumps, or I protein biosynthesis could be a good and potential QS inhibitor. Some of the compounds, such as sinefungin, holo-acyl carrier protein, L/D-S-adenosylhomocysteine, and butyryl-S-adenosylmethionine act as substrate analogues and can obstruct AHL production *in vitro*. The *in vivo* screening of the above discussed substrate analogues has not been studied because they are likely to influence the central pathways of fatty acid and amino acid metabolism. Therefore, this approach is not well liked and is not practiced for quorum signal inhibition.

Quorum sensing signal inhibition/interfering with signal reception

In this strategy, QS inhibition is achieved by non-enzymatic inhibition. The main objective of this approach is that analogues of AHL signal molecules are designed to obstruct the receptor. These analogues are synthesized by altering the AHL molecule's lactone ring, acyl side chain, or both of them. Halogenated furanones with structures very similar to AHLs are produced by the alga *Delisea pulchra*. These halogenated furanones act as antagonists for quorum signaling and suppress biofilm formation, swarming, and colonization in gram negative bacteria. Halogenated furanones remove the AHLs from their specific receptors. Three such AHL antagonists are present in the garlic extract and interfere with the LasR of *P. aeruginosa,* making the biofilms more susceptible to detergents and antibiotics. By altering the structures of natural halogenated furanones and AHLs, different types of molecules have been synthesized that are very similar to natural AHL antagonists. They are very effective against *V. anguillarum* infections in trout and *P. aeruginosa* lung infections in mice. The fungal quorum signal inhibitors such as penicillic acid and patulin were reported to speed up the turnover of LuxR receptors, thus inhibiting the quorum signal in *P. aeruginosa*.

Any of the methods, such as metabolism of the AHL molecules, chemical degradation, or enzymatic destruction of AHL molecules, can be used for the degradation or inactivation of the AHL signal molecules. Many enzymes have been recognized in nature that can degrade AHL in pathogenic bacteria such as *P. aeruginosa* and *A. tumefaciens* that

synthesize AHL. The disruption of QS is technically termed "quorum quenching." Some of the enzymes, such as paraoxonase, and AHL-acylase, are very effective in the destruction of AHL. Generally, by lactonolysis, i.e., the opening of the lactone ring, we can achieve the degradation of the AHL molecule. This is attained by enzymatic degradation of the lactone ring or by increasing the pH. *B. thuringiensis, B. mycoides,* and *Bacillus cereus* produce the AiiA enzyme, which is a lactonase; it opens the lactone ring in the AHL molecule and degrades it. This gene has been utilized to stop the pathogenicity of plant pathogens like *A. tumifaciens* and *E. carotovora*. Some of the pathogenic bacteria, such as *A. tumeficians, P. aeruginosa,* and *Klebsiella pneumonia,* synthesize AiiA homologues and use them as defence mechanisms against other invaders. At an acidic pH, the lactonoloysis is reversible, so it is very essential to take necessary precautions while using the QS inhibitors based on this reaction. Few of the AHL signal molecules, such as 3-oxoC12 HSL, react with the oxidized halogen compounds like hypochlorous and hypobromous acids and get inactivated. Same as in the case of lactonolysis, this inactivation occurred by oxidation, another approach implemented by algae-like organisms against bacterial attack. To avoid quorum signal linked processes, some bacteria adopt strategies such as metabolizing the AHL molecules. *Variovorax paradoxus and P. aeruginosa* PAI-A utilize AHLs as their sole sources of carbon, nitrogen, and energy.

Inhibition of AI-2 and AI-3 Pathways

By utilizing inhibitors of intermediary molecules of the methyl activation pathway, such as S-anhydroribosyl-L-homocysteine (SAH) and S-homoribosyl-L-homocysteine (SHR), the researchers were able to block the major enzymes of the AI-2 synthesis route, using methyl transferase and 5′-methylthioadenosine (SRC). Many PFS enzyme inhibitors have been discovered this way. In E. coli, molecular docking is utilized to characterize the interaction between AI-2-P and the LsrR regulator protein, as well as hydrogen-bridge connections between amino acids in the LsrR catalytic region (PDB: 4L51) and the natural ligand. The major interactions between AI-2-P and LsrR occur in the cyclopentane ring of AI-2, which binds with the LsrR amino acids Gly 209, Asp 243, and Leu 245. The LsrR amino acids Lys 288, Ala 127, Thr 220, and Glu 126 may interact with the AI-2-P PO42 group. Using molecular docking techniques and bioinformatics tools, we can explain the interactions of the synthetic inhibitor 2S-2,3,3-trihydroxy-4-isopentyl dihydrogen phosphate (D5P) (PDB: 4L4Z) with the LsrR amino acids Glu 126, Thr 220, Lys 288, Ala 127, and Asp 243. Meanwhile, the amino acids Ala 127, Lys 288, Glu 126, Thr 220, Asp 243, and Phe 124 E and F interact with the LsrR (PDB: 4L50). In this manner, QSIs mimic the ability to signal molecules to attach to receptors. This demonstrates how molecular docking may be utilized *in silico* to find and verify FDA-approved medications as anti-QS agents[20]. In the AI-3 quorum signalling system, the receptor molecule named QseC is present. This QseC receptor molecule is a striking drug target, as we cannot find it in mammals. However, it is present in many plant pathogens and some animals. Quorum signal inhibitors inhibiting the histidine sensor receptor/kinase are most studied and investigated as effective and wide spectrum drugs. The virulence of many pathogens that cause diseases in many animals and plants is inhibited by QSI LED209 as it suppresses the interaction of signals with Qsec receptor[21].

Quorum sensing inhibitors

QS is a main aim for therapeutic interference with pathogenic infections; as a result, QS inhibitors have become a new class of antimicrobial drugs.One of the most serious issues with antibiotic use is bacteria developing resistance to them. However, the QS inhibitors are more successful, as the pathogenic bacteria are unable to gain resistance to them.

QS Inhibitors have emerged as an effective technique for destroying the pathogenicity of the pathogens by disabling them to sense their cell density and by reducing their ability to trigger the virulent expression. This potentiality makes sure that the host has time to prevent the bacteria naturally through their immune system defence, resulting in the overcoming of bacterial infections. Moreover, it is very different from traditional antibiotic therapy, which destroys pathogens by interfering with RNA, DNA, and protein synthesis, which sometimes leads to the evolution of pathogens with antibiotic resistance. QS Inhibition is an effective strategy that will result in the development of potential next generation antibacterial drugs based on interfering with bacterial communication to inhibit QS based bacterial infection (Refer Table 3).

Requisites for ideal Quorum sensing inhibitors

The ideal QS inhibitor could contain the following characteristics:

- QS Inhibitors could be very definite for the QS regulators.

- QS Inhibitors could not be toxic or causing side effects to the hosts where bacteria are targeted or pathogenic infections are treated.
- QS Inhibitors could be of low molecular mass so that they effectively suppress the QS related genes expression.
- QS Inhibitors could be chemically stable compounds, could be capable to exist in the host for prolonged time for its successful action and could be able to withstand host metabolism.
- QS Inhibitors could not involve in the basic metabolic functions of the bacterial cell like DNA metabolism, cell wall synthesis and protein synthesis which are the drug targets for emerging drug resistance.

Quorum sensing inhibitors (QSIs)

Natural QSIs

A large number of organisms exist in nature's ecosystems. And there are many reports that some of the bacterial community in nature's ecosystems communicates heavily to assist among them and compete with other different microorganisms. In this circumstance, certain bacteria try to quench the QS systems of other microbes by producing QS inhibitors. The natural, plant-derived compounds significantly decrease the inhibition of QS systems in *P. aeruginosa*. The effect of naturally isolated plant chemicals on the regulation of the QS (QS) system in *Pseudomonas aeruginosa* is that trans-cinnamaldehyde (CA) and salicylic acid (SA) substantially block expression of QS regulatory and virulence genes in *P. aeruginosa* PAO1 without having any bactericidal effect. CA strongly inhibited both the las and rhl QS systems during the stationary growth phase, with lasI and lasR levels lowered by 13- and 7-fold, respectively, compared to 3- and 2-fold declines with SA treatment. QS Inhibitors(QSI) significantly reduced the production of extracellular virulence factors like CA-reducing protease, elastase, and pyocyanin by 66%, 22%, and 32%, respectively, with CA-lowering protease, elastase, and pyocyanin. Once the QSIs significantly decreased biofilm formation and suppressed rhamnolipid gene expression, just a minimal amount of extracellular rhamnolipids were observed. The QSIs did not completely inhibit virulence factor expression and synthesis, but they did significantly lower virulence features at both the transcriptional and extracellular levels.

Plant based QSIs

Many of the plant extracts are very similar in their chemical structure to those of the QS signals (AHL), and they also have the capability to destroy signal receptors such as LasR and LuxR. The plant extract of *Emblica officinalis,* known as Pyrogallol, and its analogues show antagonistic behaviour against AI-2. The seed exudates from *M. sativa,* known as L-canavanine, inhibited QS expression. γ-aminobutryric acid (GABA) is synthesized by plants as a promoter for the destruction of the AHL signal OHC8HSL produced by lactonase (AttM) of *A. tumefaciens,* thereby destroying the QS based infection process. However, the disadvantage of the GABA defense system is that it antagonizes abiotic stress such as salinity and drought due to the accumulation of proline. The reporter activities of LuxR, CviR, and AhyR in several organisms are altered by seedlings of *Medicago truncatula,* and they can also inhibit the QS in *S. meliloti* and *P. aeruginosa*. Cinnamaldehyde and its derivatives can influence a broad spectrum of QS-regulated activity, like AI-2 mediated QS in several *Vibrio* species and biofilm synthesis in *P. aeruginosa*. The expression of virulence genes in *P. aeruginosa* PA01 was inhibited by curcumin, which is produced by *Curcuma longa*.

In recent times, flavonoids have gained a lot of attention from researchers as they have different characteristics such as being anti-cancer, anti-inflammatory, and antioxidant agents. Some of the flavanoids, such as apigenin, kaempferol, naringenin, and quercetin, have many health benefits, so they are assessed for their QS inhibition activities. The above mentioned flavonoids suppress the AI-2 or HAI-1 based bioluminescence in *V. harveyi* MM32 and BB886. The biofilm synthesis in *E. coli* O157:H7 and *V. harveyi* BB120 is inhibited by naringenin and quercetin. *Combretum albiflorum* produces the flavonoid flavan-3-ol catechin from its bark, and it can inhibit the synthesis of biofilm formation, elastase, pyocyanin, and QS-based virulence factors in *P. aeruginosa* PAO1. Extracts of the fruit, flowers, leaves, and bark of plants such as *Sonchus oleraceus*, *Laurus nobilis,* and *Combretam albiflorum* were found to exhibit several anti-QS activities. The fruits and edible plants of *Ocimum sanctum*, *Manilkara zapota*, *Musa paradiciaca*, and *Ananas comosus* inhibited the QS against violacein synthesis by *C. violaceum* and biofilm synthesis, pyocyanin pigment, elastase synthesis, and staphylolytic protease in *P. Aeruginosa* PAO1. The biofilm production of *Lactobacillus* species, *Listeria, Pseudomonas, Salmonella,* and *Staphylococcus* species is effectively inhibited by hydrosol, poly-toxinol, and the essential oil of *Satureja thymbra*.

The furocoumarins naturally available in grapefruit can suppress biofilm synthesis by pathogenic bacteria such as *P. aeruginosa*, *E. coli O157:H7,* and *Salmonella Typhimurium*, and they can also inhibit the AI-2 and AI-1 activities of *V. harveyi* reporter strains BB170 and BB886. The pure forms of berggamottin and dihydroxybergamottin can inhibit the AI signal in the range of 94.6–97.7%. Grapefruit juices had shown 16.8–27.5% inhibition in the case of AI-2 and 47–62% inhibition in the case of AI-1. This type of low inhibitory effect can be achieved by the low concentration of furocoumarins in grape juice. The phytochemicals in medicinal plant extracts can effectively inhibit bacterial cell signaling molecular mechanisms, which can prevent the production of various virulence factors and could be used to create effective, safe drugs[18-19]. The natural compounds that act as QS inhibitors are tabulated in (Table 4).

Table 4 — Natural compounds as quorum sensing inhibitors

Source	Natural compound(s)	QS activity
Macroalga (*Deliseapulchra*)	Furanone/ 2(5H)-Furanone/	Mimics AHL signal by occupying the binding site on putative regulatory protein which results in the disruption of QS-mediated gene regulation. Inhibit biofilm formation in *Aer. Hydrophila*
		Repress LuxR protein dependent expression of P (luxI)-gfp (ASV) reporter fusion. Inhibit virulence factor in *E. coli* XL-1
Macro alga (*Deliseapulchra*)	(5Z)-4-bromo-5-(bromomethylene)-3 -butyl-2(5H)-furanone.	Disrupts QS-regulated bioluminescence in *V. harveyi*by interacting with Hfq protein. Inhibit swarming motility and biofilm formation in *E. coli*
Garlic extract (*Allium sativum*)	Ajoene (1-Allyldisulfanyl-3-(prop-2-ene-1-sulfinyl)-pro pene)	Blocks the QS-regulated productions of rhamnolipid resulting in phagocytosis of biofilm. Targets Gac/RSM part of QS and lowers the expression of regulatory RNAs in *P. aeruginosa* PAO1
Horseradish extract (*Armoracia rusticana*)	Iberin (1-Isothiocyanato-3-(methylsulfinyl)propane)	Inhibit expression of QS-regulated *lasB-gfp*and *rhlA-gfp*genes responsible for virulence factor in *P. aeruginosa*
Boroccoli	Sulforaphane(1-Isothiocyanato-4-(methylsulfinylbutane)	Reduce the expression of lasI-luxCDABE reporter in *P. aeruginosa*
Boroccoli	Erucin (4-methylthiobutyl iso-thiocyanate)	Reduce the expression of lasI-luxCDABE reporter in *P. aeruginosa*
Citrus extract	Naringin (4'5-diOH-Flavone-7-rhgluc)	Decrease the QS mediated biofilm formation and swimming motility in *Y. enterocolitica*
Malagasy bark extract (*Combretumalbiflorum*)	Naringenin (4',5,7-Trihydroxyflavanone)	Reduces production of pyocyanin and elastase in *P. Aeruginosa* PAO1. Also inhibit 3-oxo-C12-HSL and C4-HSL synthesis driven by*las*l and*rhll*genes
Malagasy plant extract (*Combretumalbiflorum*)	Taxifolin/ Distylin (dihydroquercetin)	Reduces production of pyocyanin and elastase in *P. Aeruginosa* PAO1
Grapefruit (*Artocarpusheterophyllus*)	Morin (2',3,4',5,7-Pentahydroxyflavone)	Inhibit LasR and RhlR dependent protease, elastase and hemolysin in *P. aeruginosa* PAO1
Penicillium sp.	Penicillic acid (3-Methoxy-5-methyl-4-oxo-2,5-hexadienoicacid)	Down-regulates QS genes for biofilm formation in *P. aeruginosa*
Penicillium sp.	Patulin/ Clavacin (4-Hydroxy-4*H*-furo [3,2-*c*]pyran-2(6*H*)-one)	Targets the RhlR and LasR proteins. Down-regulates QS genes for biofilm formation and virulence in *P. aeruginosa*
Vanillin (4-Hydroxy-3-methoxybenzaldehyde)	Vanilla beans extract (*Vanilla planifolia Andrews*)	Interfere with AHL receptors. Inhibit C4-HSL, C6-HSL, C8-HSL, 3-oxo-C8-HSL. Inhibit biofilm formation in *Aer. hydrophila*
Crown gall cells	Agrocinopine B ([(3S,4R,5R)-3,4,5,6-tetrahydroxy-2-oxohexyl][(2R,3S,4S)-3, 4,5-trihydroxy-1-oxopentan-2-yl]hydrogen phosphate)	Control conjugation of pTiC58 by regulating expression of the arc operon in *A. tumefaciens*
Seed exudates (*Medicao sativa*)	L-canavanine (L-α-Amino-γ-(guanidinooxy)-n-butyric acid)	Inhibit the expression of QS-regulated phenotype exopolysaccharide II production in *Si. meliloti*

(*Contd*.)

Table 4 — Natural compounds as quorum sensing inhibitors — (*Contd*.)

Source	Natural compound(s)	QS activity
Plants (*Arabidopsis sp.*)	L-canavanine (L-α-Amino-γ-(guanidinooxy)-n-butyric acid)	Induce the expression of attKLM operon to stimulate inactivate 3-oxo-C8-HSL by *A. tumefaciens*lactonase AttM
Sweet basil (*Ocimumbasilicum*)	Rosmarinic acid (R-O-(3,4-Dihydroxycinnamoyl)-3-(3,4-dihydroxyphenyl lactic acid)	Inhibit protease, elastase, hemolysin production, biofilm formation and virulence factor in *P. aeruginosa*
Plant phenolic secondary metabolite	Salycilic acid (2-Methyl-5-tert-butylsalicylic acid)	Inhibit the expression of vir regulon in *A. tumefaciens*. Also stimulates AHL-lactonase expression which degrades AHLs.
Plant extract (*Moringaoleifera*)	Chlorogenic acid (3-Caffeoylquinic acid)	Inhibit QS-regulated violacein production in *C. violaceum*12472
Garlic extract (*Allium sativum*)	Allin (2-Amino-3-[prop-2-ene-1-sulfinyl]-propionicacid)	Inhibit QS-regulated gene expression by interacting with receptors in *P. aeruginosa* and make biofilm sensitive to antibiotics
Plant extract (*Sambucus chinesis)*	Ursolic acid (3beta-Hydroxyurs-12-en-28-oic acid)	Inhibit biofilm formation by suppressing cystenine synthesis in *E. coli*
Fruit extract of *Terminalia chebula Retz.*	Ellagic acid (Benzoaric acid)	Down-regulate the expression of virulence gene in *P. aeruginosa* PAO1. Reduces biofilm formation and swarming motility in *B. cepacia*
Arabidopsis exudates	α-Hydroxybutyric acid (2-hydroxy-butanoicacid)	Induce the expression of attKLM-lacZ fusion in *A. tumefaciens*
Green tea (*Camellia sinensis*L.)	Epigallocatechin gallate (Epigallocatechol)	This compound has gallic acid moiety and specifically block AHL-mediated biofilm formation in *Sta. aureus* and *B. cepacia.* Inhibit transfer of conjugative R plasmid in *E. coli*
Plant extract (*Punicagranatum*)	Pyrogallol (1,2,3-Trihydroxybenzene)	Inhibit AI-2 mediated bioluminescence in *V. harveyi*
Cinnamomumzeylanicum	Cinnamon oil/ Cynnamaldheyde (trans-Cinnamaldehyde)	Interfere with AI-2 based QS and decreases the DNA-binding ability of LuxR protein to reduce virulence in *V. spp.* Reduces LuxR-mediated transcription from the PluxI promoter which influences biofilm formation in *P. aeruginosa*
Grapefruit juice and extract (*Psoraleacorylifolia*L.)	Furocoumarin/ Psoralen (7H-Furo[3,2-g][1]benzopyran-7-one)	The structural resemblance of furan moiety results in QS-mediated inhibition of biofilm formation in *E. coli*. Inhibit QS-mediated swarming motility in *P. Aerugionsa* PAO1
Ellagitannin-rich extract from Pomegranate	Urolithin (3,8-Dihydroxy-benzo[c]chromen-6-one)	Inhibit C6-HSL and 3-oxo-C6-HSL associated biofilm formation in*Y. enterocolitica*. Inhibit QS-mediated swarming motility in *E. coli* and *P. aeruginosa* PAO1
From *Curcuma longa*	Curcumin (E,E)-1,7-bis(4-Hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	Down-regulates virulence factors and biofilm initiation genes in *P. aerugionsa*PAO1 and inhibit its phenotype expression.
		Attenuate QS-dependent EPS production, swarming motility and biofilm formation in uropathogenic *E. coli*, *P. aerugionsa*, *Pr. Mirabilis* and *S. marcescens*
Red alga (*Ahnfeltiopsisflabelliformis*)	α-D-galactopyranosyl-(1→2)-glycerol (floridoside) (N), Betonicine(O), and Isethionic acid	Inhibit C8-HSL mediated QS in *A. tumefaciens*NTL4
Musaceae extract (*Musa paradiciaca*)	Musaceae	Inhibit QS-mediated elastase production and biofilm formation in *P. aerugionsa*PAO1
Garlic extract	Garlic	Interferes with expression of QS-controlled virulence genes in *P. aeruginosa*
*Piper betle*extract	*Piper betle*	Inhibit QS-mediated biofilm formation in *P. aeruginosa*
*Cuminumcyminum*extract	*Cuminumcyminum*	Reduce LuxR dependent biofilm formation and swarming motility of *P. aerugionsa*

Animal based QSIs

The AI-2 activity of *V. harveyi* BB170 is effectively inhibited up 25-99% by long chain fatty acids in poultry meat. Further investigations discovered that these inhibitors lead to a degree of difference in the expression of virulence related genes, such that 60% of the response was to *in vitro* synthesized AI-2 and an 87.5% decline in bioluminescence occurred in comparison to that caused by cell free supernatant. It was also reported that the compounds present in the ground beef can inhibit more than 90 percent of the bioluminescence, which is mediated by AI-2 in *V. harveyi*.In this case, the extract of ground beef inhibited the AI-2 from upregulating virulence genes like hha and yadK.

Mammalian or animal paraoxonases (PONs) are very effective at executing hydrolytic activities on lactones and esters, which are very much connected to the detoxification of nerve agents and drug metabolism. PON-lactonases are very different from prokaryotic lactonases as they need calcium ions for their activity and are deficient in the "HCDH~H~D" motif. Quorum inhibition/quenching enzymes are found in animals such as rats, zebrafish, and mice. Porcine kidney acylase I was very successful in inhibiting biofilm production by *Pseudomonas putida* and *A. hydrophila.* It is also very effective at inhibiting QS signals such as 3OC12HSL and C6HSL.

Inhibition of Quorum sensingin animal models

Caenorhabditis elegans

The molecular processes behind α-T's anti-virulent was found significantly affected against *P. aeruginosa.* It was demonstrated that sub-inhibitory doses of α-T effectively block QS pathways in *P. aeruginosa* and downregulate QS gene expression, impacting AHL production and QS-regulated bacterial pathogenicity. *In silico* results revealed substantial molecular interactions between α-T and the QS receptors, reducing the synthesis of virulence factors and biofilm development in *P. aeruginosa*[23].

Mice model

The mice were given *P. aeruginosa* embedded in alginate beads and developed a persistent lung infection as a result of the bacteria stuck in the beads, which resembled cystic fibrosis. When the QS impaired *P. aeruginosa* mutant LasR was employed in the burn mouse model, garlic extracts were shown to reduce *P. aeruginosa* pathogenicity in mice[24].

Other models

The significance of accessory gene regulators in the pathogenesis of *S. aureus* has been studied using a variety of models, including the rabbit osteomyelitis model, the rabbit endophthalmitis model, and the mouse septic arthritis model. The Drosophila melanogaster was utilized to investigate QS and inhibitors, as well as the dynamics of *P. aeruginosa* infection and the relationship between pathogenicity and biofilm formation in this bacterial species. Natural products were shown to induce organo-sulfur compounds such as S-phenyl-L-cysteine sulfoxide, a QS inhibitor that suppressed *P. aeruginosa* infection, biofilm development, and QS.

QSIs in clinical trials

The clinical trials implicated previously certified and commercialized QS inhibitors, despite the fact that their basic uses and specialized biological activity show no association with bacterial QS, despite the fact that they were cytotoxic, antimicrobial, and bactericidal. In clinical trials, azithromycin has been widely utilized to treat pulmonary transplanted and cystic fibrosis patients. This antibiotic improved the patients' quality of life, but it did not diminish the bacterial load in sick individuals. Azithromycin's potential to inhibit bacterial signaling at non-bactericidal doses for *P. aeruginosa* strains was also demonstrated *in vitro*. Azithromycin's effect on *P. aeruginosa* quorum-sensing in patients with ventilator-associated pneumonia was also investigated. These investigations explained the anti-virulence effect of azithromycin in high-risk patients, however, the findings were not statistically significant.

Garlic extracts are well known for their quorum quenching properties and have been tested in a clinical experiment for the treatment of cystic fibrosis patients, but the results were inconclusive in proving the therapeutic effects of garlic in these patients. In-vitro tests showed that the anti-cancer medicine 5-fluorouracil, a pyrimidine analogue, inhibited the quorum-sensing regulated virulence factors in *P. aeruginosa,* hence, its usage as a catheter coating was suggested in clinical trials. Eventually, a large number of quorum quenching compounds made it to clinical trials, however, they tended to have some useful QS inhibitor properties. Despite the fact that several pieces of evidence for the idea have been implemented in animal models, more work needs to be done in the clinical stages to validate its therapeutic use.

QSIs in medical devices

The use of various medical devices is associated with the majority of hospital-acquired illnesses. Hospital-acquired infections are primarily caused by biofilm-forming and multidrug-resistant bacteria, which cause major medical issues as well as a high risk of mortality and morbidity. Given quorum quenching's capacity to reduce bacterial pathogenicity, creating novel medical devices that use quorum quenching is a top priority. Dressings, catheters, contact lenses, aerosols, trauma, and orthopaedic or implanted devices are all being developed at the moment. Initially, a quorum-sensing inhibitor was investigated for catheter functionalization. The furan ones have been covalently bonded and have been proven to inhibit biofilm formation by the *Staphylococcus* epidermidis reference strain and to control infection in a sheep model (up to 65 days). In a study involving 960 patients admitted to intensive care units in the United States, 5-fluorouracil was used to coat a central venous catheter and was found to be successful and equivalent to the regularly used chlorhexidine and silver sulfadiazine-coated catheters. Though the link to QS was not fully explored in the studies, 5-fluorouracil-coated catheters showed a lower level of contamination, particularly among gram-negative bacteria, when compared to conventional coatings, suggesting that 5-fluorouracil interferes with AHL-dependent QS. The colonization of *P. aeruginosa* strain MH602 and a *S. aureus* strain was reduced using polyethylene glycol coatings containing the QS inhibitor DHP (5-methylene-1- (prop-2-enoyl)-4-(2-fluorophenyl) dihydropyrol-2-one). The mixtures of DHP derivatives and furanone remained covalently bonded to the glass surface, reducing the adherence of *P. aeruginosa* strain PAO1 and a *S. aureus* strain significantly. The catheters were proven to be effective against *Candida albicans* biofilms using delivery systems based on varnishes that emit the QS inhibitor TZD-8 (thiazolidinedione-8). The polyphenols from honey were included in the scaffold of selenium nano-vectors for the *in vivo* and *in vitro* quenching of *P. aeruginosa* strain PAO1. Inhibiting peptides for different biomaterials were used to suppress agro-based QS in *S. aureus*. The macrocyclic peptides were introduced into non-woven polymer nanofibers, and their biological activity against *S. aureus* was validated for three weeks. Surface coating with click chemistry has been proposed for coating pro- and anti-QS peptides, namely AIP-I and TrAIP-II, which have been proven to be effective in inhibiting *S. aureus* biofilms. Daptomycin was used to test the interaction of antibiotics with the QS inhibitory pepeptide S3 and was found to be extremely effective in combination with the FS3-coated prosthesis against *S. aureus* infections. Similarly, the RNAIII-inhibiting peptide was found to be particularly successful in reducing infections caused by *S. epidermidis* strains inside a Dacron tube graft.

QS Inhibitory materials have been created by immobilizing peptides, or QSIs, and quorum quenching enzymes have also been thoroughly investigated since they work on secreted auto-inducers and do not require direct contact with the microbial surface to disrupt communication. *P. aeruginosa* ATCC 10145 and PAO1 strain biofilm formation was reduced by incorporating *Aspergillus melleus* acylase into silicon catheters and polyurethane coatings. In a rabbit model of infection, the acylase, in conjunction with the amylase produced from *Bacillus amyloliquefaciens,* was reported to delay the biofilm formation of E. coli and *P. aeruginosa* reference strains for nearly 7 days. *P. aeruginosa* PAO1 biofilm growth was reduced by immobilizing acylase from the pig kidney onto carboxylated polyaniline nanofibers (cPANFS) to generate nano biocatalysts. Using the *P. aeruginosa* reference strain PAO1, the topical administration of lactonases derived from Bacillus species was also investigated in a mouse model of burn infection. Lactonase-containing gels halted the spread of germs throughout the body, reduced mortality, and had a synergistic effect with ciprofloxacin in burn infections. The numerous enzymes from extremophiles were also investigated because the stability of the enzymes is the key challenge in manufacturing bio-based materials. The PLL SSoPox enzyme from *Sulfolobus solfataricus*, in particular, has been discovered to have an exceptional manner of quenching bacterial pathogenicity. This extremely stable enzyme was first immobilized on nanoporous alumina membranes with the powerful effect of reducing virulence factors, elastase, and pyocyanin secretion in *P. aeruginosa* PAO1. SsoPox-W2631, a variant enzyme, has been shown to significantly reduce the virulence of 51 clinical isolates from diabetic foot ulcerations by maintaining efficiency against the bacterial strains after immobilization in the polyurethane covering through glutaraldehyde cross-linking. These enzymes have also been used for intra-tracheal administration, which significantly increased the survival rate in rats as observed in a pneumonia infection model for a reference strain of *P. aeruginosa*[25]. Apart from the

studies using the acyl-homo-serine lactones-based QS quenchers, the use of the AI-2 synthesizing kinase LsrK. The enzyme was combined with the biological polymers, such as alginate and chitosan, and ATPase was added, which ultimately decreased the AI-2 mediated QS. Various alkyl gallates used in food preservation, such as octyl gallate (OG), propyl gallate (PG), and hexyl gallate (HG), were tested for their ability to suppress *P. aeruginosa* QS. As per the QS gene expression experiment, HG inhibited RhlR, whereas OG inhibited PqsR. Alkyl gallates have a lot of potential as a QS inhibitor against *P. aeruginosa*[26]. Devices based on quorum quenching have gotten a lot of attention because they have the potential to prevent hospital-acquired illnesses by controlling biofilm formation and bacterial pathogenicity. More work is needed to validate the concepts *in vitro*, as well as in animal or clinical research. The effectiveness of these devices must be determined not only in bacterial strain models but also in clinical strains that are phenotypically and genetically heterogeneous. Regulatory difficulties must be addressed for authenticating the capability of these systems for therapeutic applications, even though medical device development appears to be less complex than medication development.

Limitation

The global rise of antibiotic-resistant forms of *Pseudomonas aeruginosa* poses a significant danger in both hospital and community settings. *Pseudomonas aeruginosa* is an opportunistic human pathogen that infects a variety of model species, including the worm *Caenorhabditis elegans.* QS (QS) promotes cell-to-cell communication in bacteria and is vital in controlling virulence genes, antibiotic resistance, and biofilm formation, all of which are required for infection establishment. The QS system regulates the expression of various virulence factors in *P. aeruginosa*, including pyocyanin and proteases, which are mediated by small molecules such as acyl homoserine lactones. Interfering with the QS system would thus give alternative methods of regulating pathogenicity. *Murraya koenigii* is a popular medicinal herb in India. The current work used *C. elegans* to test the *in vivo* inhibitory action of *M. koenigii* essential oil (EO) on QS-controlled virulence factors of *P. aeruginosa* PAO1. *P. aeruginosa* PAO1 pyocyanin synthesis and staphylolytic LasA activity were dramatically reduced by *M. koenigii* EO. In comparison to the control group, *M.* koenigii EO was able to save an average of 60% of *C. elegans* from mortality owing to the toxic action of *P. aeruginosa*. Hence, the current investigation reveals that *M. koenigii* EO has anti-QS potential and may thus be regarded as a prospective therapeutic agent for the control of *P. aeruginosa*-mediated illnesses[27].

Bacterial enzymes as QSIs

Tiny molecules, such as intermediates produced during the biosynthetic pathway of AHL, dicyclic peptides, and non-cognate AHLs produced by bacteria, have the ability to function as quorum-quenching molecules. AHL-acylase, synthesized by *Streptomyces sp.,* is very specific and important as it degrades AHLs that have six or more carbons. In the same way, *P. aeruginosa* synthesizes AHL-acylase, which degrades 3-oxoC12-HSL but cannot degrade C4-HSL. *Tenacibaculum maritimum,* which is a pathogenic bacterium of fish, can destroy long-acyl AHLs (C10-HSL) through acylase-type activity, and it can also synthesize biofilm with the help of shot-type AHL (C4-HSL) activity. AHL-acylases present in *P. aeruginosa PAO1* and *Ralstonia sp. XJ12B* inhibit the QS signal; the AHL-acylases of these two organisms are different and share only 39% identity at the amino acid level. Two effective acylases, HacC and HacA that can inhibit the quorum signal AHL are produced by *Pseudomonas syringae* B728a.

A. tumefaction's produces AHL-lactonase (AttM) which is very potential in inhibiting the AHL based QS and it shows broad heterogeneity with only 30% to 50% amino acid identity with AHL-lactonase (AttM) produced by *K. pneumonia* and *Arthrobacter sp*.,AHL-oxidase produced by *Bacillus megaterium* can effectively degrade AHL signals such as OC12-HSL and C4HSL 52. Several Bacillus species such as *B. thuringiensis*, *B. subtilis* and *B. cereus* can produce AHL-lactonase which had reported to be highly efficient in breaking the QS signals. The enzyme named Cytochrome P450 monooxygenase from *B. megaterium* has wide range of substrate specificity and it oxidizes the acyl side chain to inhibit AHL based QS.In 2010, it was reported a novel quorum signal quenching bacterium named *Bacillus macrorestinctum* which can decrease potato tubers soft-rotting caused by *Pectobacterium carotovorum*.

Fungus based QSIs

Fungi are famous to produce secondary metabolites like vitamins and antibiotics. Since the turn of the century, Penicillium species have been very successful in controlling pathogenic bacterial infections.

Researchers have reported that Penicillium species have been discovered to synthesize penicillic acid and patulin, which can inhibit QS. By means of the mouse pulmonary infection model, the utilization of patulin can appreciably trim down *P. aeruginosa* infections in mice. *Basidiomycota* and *Ascomycota* fungi present in the plant rhizosphere can degrade 3OC6HSL and C6HSL through lactonase activity. *Auricularia* auricular could produce some natural pigments that have the capability to inhibit the QS, and it could effectively suppress the violacein synthesis in *C. violaceum*.

Farnesol

Farnesol, a secondary metabolite secreted by many dimorphic yeasts (described in detail in the QSMs section above), also functions as a QSI. It possesses antimicrobial potential against a wide range of bacteria, including *Fusarium graminearum*, non-albicans *Candida* species*, Paracoccidioides brasiliensis, Candida neoformans,* and others. When used with antibiotics, it has an additional effect on S. epidermidis by disrupting its biofilm matrix. Several investigations found that a high concentration of farnesol reduced the formation of biofilms or new cells inside biofilms[28].

Others fungal QSIs

Auricularia auricular (fruiting body), which contains various heterocyclic chemicals (cysteinyldopas, leucodopachrome, and dopaquinone), hinders N-acylhomoserine lactone (AHL) formation. Similarly, QSIs can be released by *Ganoderma lucidum, Phellinus igniarius, F. graminearum,* and *Lasiodiplodia* species. The main compound and method of action, however, have yet to be identified. Around 33 Penicillium species produced QSIs; (penicillic acid and patulin), as compared to previous studies, it was found that a methanolic extract of the *Agrocybe aegerita* mushroom suppressed biofilm formation (84.24 percent) more effectively than the conventional antibiotics streptomycin and ampicillin (50.60 and 30.84 percent, respectively). At a concentration of 200 g/mL, hot water *Agaricus blazei* extract had considerable anti-QS activity. *Polyporus squamosus* and *Armillaria mellea* extracts were also found to have anti-QS properties.

The antifungal potential of QSMs/QSIs

Every year, the number of people who die from fungal diseases rises dramatically. Every year, it is estimated that more than one million individuals die as a result of a fungus infection. Candida, Aspergillus, and Cryptococcus are three prevalent fungi that have been linked to invasive fungal infections. To treat fungal infections, a variety of antifungal medications (azoles, polyenes, echinocandins, flucytosine, and allylamines) are available on the market. Unfortunately, all of these medications have some side effects or limits in terms of safety, toxicity, pharmacokinetics, and action spectrum. Furthermore, long-term use of these medications leads to an increase in drug resistance. As a result, alternative antifungal medications with fewer adverse effects are urgently needed to address fungal infections. The published data highlighted some pathways for fungal infection control, including ATP sulfurylase, aspartate kinase, homoserine dehydrogenase, ROS (reactive oxygen species) production, threonine synthase, mitochondrial phosphate carrier, transcription factor protein (MET4), biofilm formation, methionine synthase, homoserine kinase, homoserine transacetylase, It was also discovered that fungal QSMs have a major impact on ROS production and biofilm development and could be employed to treat fungal infections. Farnesol was the subject of investigation due to its broad range of antibacterial capabilities. It exhibited good efficacy against *C. albicans, Aspergillus niger, S. cerevisiae, F. graminearum, P. brasiliensis, A. flavus, A. fumigatus,* and *A. nidulans*[29].

In *Streptococcus* mutants, high doses of farnesol hinder bacterial biofilm formation, whereas intermediate levels (25 M) upregulate microcolony development and biofilm formation. Furthermore, in the presence of S. mutants, farnesol synthesis in *C. albicans* was shown to be reduced. As a result of QS's interaction with both fungal species, mixed biofilm production in oral plaque biofilm may be stimulated. Farnesol also protects against oral candidiasis and works in tandem with antifungal drugs like fluconazole. Farnesol inhibits *S. cerevisiae* growth by lowering the amount of diacylglycerol (DAG) and decreasing the G1 stage of the cell cycle. Farnesol has also been shown to inhibit *A. nidulans* by causing the generation of reactive oxygen species (ROS). In the instance of *A. fumigatus*, farnesol disrupted the cell wall integrity signaling pathway, which led to Rho protein mislocalization, which prevented hyphal morphology from replicating. Due to the upregulation of genes associated with aging, farnesol has been shown to suppress *C. parapsilosis.* Farnesol also has a deleterious impact on sterol metabolism, oxidation-reduction, and biofilm formation genes. In *C. dubliniensis*, it also prevents the development of hypha. At higher

concentrations, farnesol inhibited *P. brasiliensis* growth, whereas at lower quantities, it suppressed yeast to hyphal conversion. When combined with *echinocandins* (caspofungin and micafungin), farnesol greatly reduced biofilm development in *C. parapsilosis*. Farnesol also participates in sterol production and stimulates apoptosis by accumulating reactive oxygen species (ROS) that damage cellular compartments. Farnesol had antagonistic effects when combined with terbinafine and itraconazole, but synergistic effects when combined with fluconazole/5-flurocytosine against biofilm formation in *C. albicans*-resistant strains. This putative antifungal effect against *C. albicans* was recently discovered to be linked to the control of CYR1 and PDE2 gene expression, which suppresses biofilm formation. Apart from farnesol, another QSM (tyrosol) showed antifungal effectiveness whether used alone or in combination with farnesol and conventional medicines. For example, it was postulated that tyrosol inhibited Candida species-induced denture stomatitis. Tyrosol considerably reduced the number of adherent cells to the acrylic surface in a mixed and single culture of *Candida albicans* and *Candida glabrata* (1.74 to 3.64 log 10 CFU/cm^2). Similarly, tyrosol was tested on hydroxyapatite (HA) and acrylic resin against the single and mixed biofilm development of several strains, including *C. glabrata* ATCC 90030 and *C. albicans* ATCC 10231. Tyrosol considerably prevented biofilm formation against oral pathogenic organisms, according to their findings[32]. Tyrosol, in conjunction with chlorhexidine gluconate, demonstrated promising results against *C. albicans* by lowering the amount of hyphae[30]. It also demonstrated *C. albicans'* significant inhibitory effect when combined with farnesol, which could be useful in the development of oral care products[31]. Tyrosol has also been shown to have potent inhibitory activity against dimorphic fungal species (*Coccidioides posadasii and Histoplasma capsulatum*) via intracellular molecular leakage.

Marine organism based QSIs

Delisea pulchra produces halogenated furanones, which are very similar to bacterial AHLs and reduce QS-induced activities by competing with cognate AHL signals for the LuxR receptor site. Some of the compounds produced by *Chlamydomonas reinhardtii* were found to imitate bacterial signals, involve their QS system and inhibit those. The algae named *Laminaria digitata* synthesize the bromoperoxidase enzyme, has the property to suppress the quorum signal by blocking AHL signal -3OC6HSL by oxidation process. Researchers reported that out of 284 extracts of marine organisms procured from 1 to 10 m from different areas in Central Great Barrier Reef, Australia, 64 of them showed QS inhibiting property[75]. The extracts of *Lufariella variabilis* which is marine sponge showed very potential in suppressing QS system of *P. aeruginosa*. The marine quorum quenching in bacteria is categorized in (Table 5).

Recent investigations have proved that marine organisms are excellent sources of QS inhibitors. Experimental studies revealed from his metagenomic studies that marine bacteria are very effective in QS inhibition and have a high frequency of quorum quenching enzymes. Lyngbyoic and Malyngolide acids isolated from *Lyngbya majuscule* were very effective in suppressing pyocyanin and elastase production in *P. aeruginosa* and violacein production in *C. violaceum*. About 12 percent of the 96 epibiotic bacteria associated with brown algae *Colpomenia sinuosa* produces QS inhibitor compounds. *Blenothrix cantharidosmum* produces tumonoic acids which are having moderate QS inhibition property against bioluminescence production in *V. harveyi*. 8-epi-malygamide and malyngamide C isolated from L. majuscule were very potential to suppress QS activities in *P. aeruginosa*[33].

QSIs from marine bacteria

The marine environment, among natural sources, offers a plethora of resources (plants and animals) of pharmaceutical interest that have yet to be investigated. Marine creatures (which include corals, sponges, algae, and bacteria) have little biotechnological promise, and only a few marine-derived products are in clinical use. Cytarabine (Cytosar-U®, 1969; Depocyt®; cancer and leukaemia) and vidarabine (Mar. Drugs 2019, 17, 427 8 of 25) are examples of products. (Vira-A®, 1979; antiviral for herpes simplex virus), ziconotide (Prialt®, 2004; severe chronic pain), omega-3-acid ethyl esters (Lovaza®, 2004; hypertriglyceridemia), eribulin mesylate (Halaven®, 2010; cancer: metastatic breast cancer), are now approved marine-derived medications by the Food and Drug Administration (FDA) except brentuximab vedotin (Adcetris®, 2011; cancer) was later approved by the European Agency.

Antibody based QS inhibition

Some of the organisms have orphan receptors for QS molecules, which can be instrumental in quorum quenching. In eukaryotes, the immune systems of mammals produce antibodies in response to allergens. AHLs and interrelated signal molecules of lower molecular weight and non-proteinaceous in character

Table 5 — Marine quorum quenching bacteria

Strain	AHL-Degrading Ability	Origin	Activity
Alphaproteobacteria			
*Rhodobacter*sp. Th15	C8-C14 and 3OC14	Flounder	ND
Paracoccus sp. PP2-663	C4-C12	Manila clam	ND
Stappia sp. USC5	C4, C6, C10 and 3OC12	*Fucus vesiculosus*	Lactonase
*Marivita*sp. Th30	C6, C12 and C14	Flounder	ND
Hyphomonas sp. USC2	C4, C6, C10 and 3OC12	*Fucus vesiculosus*	Lactonase
Roseovarius aestuarii USC61	C4, C6, C10 and 3OC12	Water tank	Lactonase
Actinobacteria			
Rhodococcus erythropolis strains	C4, C6, C10 and 3OC12	*Fucusvesiculosus*and sedimen	Lactonase
Flavobacteria			
T. maritimum 2154	C10	Fish farm disease	Acylase
Muricaudaolearia Th120	C6-C14 and 3OC6-3OC14	Latonaseand acylase	Latonaseand acylase
*T. soleae*strains	C6-C14 and 3OC6-3OC14	Gill of flounder	Lactonase
Flaviramulusichthyoenteri Th78	C6-C14 and 3OC6-3OC14	Flounder	Lactonase
Maribacter sp. 139	C4, C6, C10 and 3OC12	Ocean water	Lactonase
Firmicutes			
Oceanobacillus spp.	C4, C6, C10 and 3OC12	*Fucus vesiculosus*	Lactonase
Bacillus sp. KT7	C6-C14, 3OC8-3OC12 and 3OHC8-3OHC12	Intertidal rockscolonized by *Ulva*	ND
Gammaproteobacteria			
*Glaciecola*sp. B20	C10-C14, 3OC10-, 3OHC10, 3OC12 and 3OHC12	Intertidal rocks	ND
Alteromonas sp. USC168	C4, C6, C10 and 3OC12	*Fucus vesiculosus*	ND
Halomonas taeanensis USC33	C4, C6, C10 and 3OC12	Sediment	Lactonase
Colwellia aestuarii T171	C8-C14 and 3OC10-3OC14	Gill of flounder	ND

were not predictable to obtain an antibody-based immune response. However, bacterial AHLs have been reported to exert a wide range of expressions, such as apoptosis, modulation of NF-kappa activity[34].

The preliminary research on production of anti-AHL antibody, in opposition to synthetic 3-oxo-AHL analogue RS2 demonstrated to be very successful in quenching 3OC12HSL of *P. aeruginosa,* however, it was not effective against shorter chain length AHLs. In addition, few proofs on the effectiveness of AHL-antibody were achieved by avoiding of cell death in primary bone marrow derived murine macrophages. The most effective antibody is XYD-11G2 among several numbers of antibodies which were screened for their ability to degrade 3OC12HSL of *P. aeruginosa.* It was reported that AHL hydrolysis can be obtained by designing and producing transition state mimics to act as quorum quenching antibodies. 3OC12HSL — BSA (protein) conjugate is used for active immunization of mice to produce particular antibody in serum. In intranasal challenge of mice, compared to controls, thirty six percent of the immunized mice were survived up to day four. In the immunized mice, the pulmonary tumor necrosis factor (TNF-α) was very low when compared to the controls. The potential mechanism of action seems to be through blocking an excessive pro-inflammatory host response[35].

The use of antibodies to block QS have shown that RS2-1G9 antibody is capable of binding to 3-oxo-C12-HSL in the environment outside of the *Pseudomonas aeruginosa* cell, thus causing the attenuation of the response to inflammation by the host. The antibody XYD-11G2 has also been found to mediate the breakdown of the 3-oxo-C12-HSL signaling system, preventing Gram-negative bacteria from producing pyocyanin. Other studies have shown that the antibody AP4-24H11 can block the QS signaling system of *Staphylococcus aureus* and can remarkably reduce the tissue necrosis inside of the infected model.

Synthetic QS inhibitors

The major limitations of naturally occurring QS inhibitors are, they are produced in very little concentration and they are sometimes toxic. We can overcome these drawbacks by synthesizing QS inhibitors using chemicals. Many investigations have shown chemically synthesized synthetic QS inhibitors are very efficient in inhibiting bacterial pathogenesis.

Research is going on to produce QS inhibitors which can target the biosynthetic pathway responsible for signal synthesis, modification in chain length and substitution in signals. Though synthetic QS inhibitors have good commercial value still there is lot of demand and scarcity of synthetic QS inhibitors.

Alterations in the AHL side chain

In many investigations, modification in the acyl chain of QS signal was effective in inhibiting the QS. By modifying at various chains at C4 position of the acyl chain of either C6HSL or 3OC6HSL in *Vibrio fischeri*, it resulted in inhibition of bioluminescence. Replacement in 3 position of 3OC8-HSL of TraR in *A. tumefaciens* with methylene instead of carbonyl transformed it into antagonist of corresponding activity. The length of the acyl side chain is very important for its activity. Increase in acyl chain length by one methylene unit showed 50% decrease in activity while adding up of 2 methylene units reported in 90% activity loss. As the AHL analogues with a side chain length longer than the native AHL demonstrated to be very successful inhibitor, it was concluded from scientific studies that AHL analogues could be longer than the native QS signal.

Intervene in signal synthesis

A novel strategy was followed for developing analogues of intermediates which are very essential for the production of quorum synthesis signals in *P. aeruginosa.* Secondary metabolites such as 2-heptyl-3-hydroxy-4-quinolone — the Pseudomonas quinolone signal (PQS) is synthesized by the condensation of β-keto fatty acids and anthranilate. An analogue of anthranilate known as methyl anthranilate decreased elastase synthesis without effecting the growth of *P. aeruginosa* (PAO1) and inhibited Pseudomonas quinolone signal production.

Substitutions and modifications in the AHL ring moiety

Changes in the γ-butyrolactone ring of the AHLs have disclosed the significance of the heteroatom in the ring with respect to their biological activity. Synthetic QS inhibitors with substitutions at the third and fourth position of the HSL ring of 3OC8HSL led to the formation of similar structure furanones and proved to be very efficient. Lactam analogue of the *P. aeruginosa* AI3OC12HSL had clearly decreased the activity. The 3-hydroxy Trans or cis analogues were functional only at extremely elevated concentrations. Among cis and Trans analogues, cis analogue was very effective and successful than the Trans analogue. In several studies, different analogues were screened, HSL (3-OC12HSL) analogue N-(2-oxocyclohexyl)-3-oxododecanamide was very potential as antagonist of QS activities such as biofilm development and reduction in elastase and pyocyanin, by *P. aeruginosa*[36].

Biotechnological applications of QSIs

Agriculture

The epiphytic bacteria with capability to synthesis 10 fold more yield of 3OC6HSL which is similar signal molecule for *P. syringae* initiated premature induction of QS expression. It resulted in the inhibition of spilling over motility and disease on tobacco plants. This exceptional property of epiphytic bacteria can be utilized for controlling diseases. *M. testaceum* which is a AHL-degrading bacterium generally seen on the surface of potato leaf is very effective to defend the plant from bacterial pathogens such as *P. carotovorm* which causes soft rot disease.

Transgenic plants obtained by insertion of lactonase into potato and tobacco plants and heterologous expression of Aiia in *E. carotovora*enzymeshowed reduced pathogenicity towards tobacoo, Chinese cabbage, cauliflower and potato plant [7]. Plants such as *Pisum sativum* and *M. tranculata* are capable to display QS mimics in response to bacterial infections. These AHL signal mimics defend plants from pathogenic bacteria by controlling their virulence behaviour.

Aquaculture

Aquaculture is a one of the important sector of the food industry and key source of food throughout the globe. One of the drawbacks of this industry is drastically affected by disease outbreaks. The over usage of antibiotics in aquaculture and in advance usage of antibiotics even though there is no threat of bacterial infections has shown the way to evolution of the multiple drug resistant bacteria. The rotifers are very significant in aquaculture industry as they are used as live feed. The opportunistic pathogens such as *Pseudomonas sp., Aeromonas sp.,* and *Vibrio sp.,* are opportunistic pathogens and greatly influence fish larvae and cause harmful effects when used as feed for these rotifers. Since these pathogens operate through QS, interference of QS is a novel anti-infective method and it is proved to be very potential for application in aquaculture.

Brominated furanone which is one of the QS inhibitor was reported to be very effective in reducing the growth retarding effect of *V. Harveyi* strains and enhanced the growth and survival of rotifers. The defense of

gnotobiotic brine shrimp Artemia fransciscana from pathogenic *Vibrio* spp. By synthetic and natural brominated furanones has offered additional support to the successful applications of QS inhibition in aquaculture. It was demonstrated that addition of Bacillus spp, AHL-degrading bacteria along with enrichment cultures increased the survival of different aquaculture species such as *M. rosenbergii*— the giant freshwater prawn, *Sparus aurata* larviculture and *Scophthalmus* maxima which is a larvae of turbot. *Tenacibaculum maritimum* NCIMB2154T which is a fish pathogen produces acylase type quorum quenching enzyme which can degrade long chain AHLs, this report gave a new hope in quorum quenching in bacteria-eukaryote interactions in the marine environments.

Biotransformation

Biofilms are very key platform for chemical transformations in bio-refineries. The main requirement is to disperse the biofilm and reprocesses the platform for a new round of bio-catalysis. Cyclic diguanylate-binding (BdcAE50Q), and Hha13D6 which is global regulator are used for biofilm dispersal. *P. aeruginosa* QS signal 3OC12HSL regulates the biofilm dispersing proteins. The disperser cells had a 14 percent slower growth rate compared to the first colonizers but had a capability to synthesize 14 fold more amount of the similar QS signal molecules 3OC12HSL than planktonic cells. This hopeful approach can be functional to a broad range of industrial applications such as biofouling, bio-corrosion, biosensors and bioremediation.

Animals

As animals get infected by diverse disease causing bacteria, researchers have developed distinctive approaches to identify QS signals and inhibit them through lactonase activity of paraoxonases, which hydrolyze the lactone ring. Human paraoxonases 1 present in the transgenic drosophila decreased the lethality presented by the pathogens such as *P. aeruginosa*. These transgenic drosophila flies had also defended *S. marcescens* lethality. It was also proved that PON1 afford safety to flies from bacteria which used AHLs to control pathogenesis. These disclosures of human-pathogen communication through quorum quenching studies have been predicted to make available beneficial modalities for inflammation or infection and cardiovascular disease.

Waste water treatment

In waste water treatment technology, membrane bioreactor is used for desalination and reclamation of sea and brackish water, but the main drawback of this technology is biofouling of the membrane filters present in membrane bioreactor. The formation of biofouling arises transmembrane pressure which badly affects permeability and outcome in higher treatment costs. *P. putida* and *Aeromonas hydrophila* are the main cause for the formation of biofilms. Immobilized quorum quenching enzymes or engineered marine organisms engineered to secrete QS inhibitors are used in antifouling treatments, sometimes QS inhibitors are added to antifouling coatings.20- 24% of biofilm formation was reduced by acylase 1. Quorum quenching enzyme based membrane was developed to manage biofouling. Batch type of reactor was developed to utilize in recycle method to overcome the loss of enzyme at the time of processing. The effectiveness of the process was more improved by immobilizing the enzymes on magnetic particles.

Human health

The gastro-intestinal tract has several number of bacterial which communicate through signals and influence the host metabolism. At the time of bacteria-host interactions different types of signals operate, noraderenaline, indole and 3OC12HSL support the growth of *P. aeruginosa* and *E. coli*. Moreover, adenosine has been shown to play an important role in down regulation of inflammation, controlling secretion of electrolytes, disruption of epithelial cells to facilitate *Bacillus anthracis* and *S. aureus* to getaway phagocytic action.The effect of adenosine in protecting *C. elegans* from the pathogenicity of *P. aeruginosa* by reducing the expressions of its virulence factors offers an effective method to control bacterial pathogenesis. It was proved that adenosine was effective by suppressing the iron acquirement which is very crucial for bacterial growth. Addition of 10 mM adenosine upregulated eighty-eight genes and repressed 193 genes. Two of the induced genes were responsible for degradation of anthranilate which is a precursor of *P. aeruginosa* QS. The adenosine which is having the QS inhibition characters is very much responsible for reduction in *P. aeruginosa* QS production. QS Signal 3-OC12HSL of *P. aeruginosa* induced apoptosis and suppressed the proliferation of human breast cancer cell lines.This observation gave a new hope in application of QS inhibitor in cancer therapy. There are also few reports stating that synthetic AHL homologs may be used as QS inhibitors and also used in anti-cancer therapy due to their anti-cancer toxicity property. There is urgent need of research studies to genetically engineer

bacterial which can particularly target cancer cells. *E. coli* was genetically engineered where invasion gene of *Yersinia pestis* was under the control of *V. fischeri* QS signal. The attaching of *E. coli* and attack into mammalian cells was directed by the expression of invasions, which was initiated by high AHL concentration. These genetically engineered organisms could go through human cancer derived cell lines.

Prof. Michael Givskov researched on garlic extracts to explore their QS inhibition properties. *P. aeruginosa* which is basically resistant to numerous antibiotics and also trigger chronic infections is inhibited by garlic extracts. The garlic extracts suppress the biofilm formation of *P. aeruginosa*. This treatment made the biofilm vulnerable to antibiotics like tobramycin and the phagocytosis by neutrophils. Cystic fibrosis suffering patients were the first to use QS inhibitors in clinical trial. In this investigation, 656 mg/day of garlic oil macerate, a quantity very low than the toxic dose was given to patients for 2 months on 26 patients. The outcome of the research was not noteworthy but they were encouraging. There was progress in lung function, weight and patients' health.

Biomedical applications of QSIs in model pathogen *P. Aeruginosa*

P. aeruginosa is a big hazard to patients with cystic fibrosis, badly burned victims, with implanted medical equipment since it is the most common source of hospital-acquired infections. It's also been found as a prevalent co-infecting infection in COVID-19 patients, and it increases the severity of the illness by producing an extensive biofilm, which may promote antibiotic resistance. It is the most common pathogen in COVID-19 patients in most hospitals[37]. *P. aeruginosa* QS regulates the synthesis of virulence components and the generation of biofilms. As a result, QS inhibition was viewed as an appealing target for reducing bacterial pathogenicity without eliciting resistance, and anti-QS compounds were viewed as a possible target for preventing *P. aeruginosa* infection[38].

Environmental applications of QSIs as anti-biofouling agents

The biofouling process is characterized as the build-up of microbial cells and extracellular polymeric compounds on submerged surfaces, resulting in surface deterioration. The mechanical stability of the QQ-beads over a long length of time indicates that QQ of MBR microorganisms has good potential in practical applications, and the results validated the usefulness of QQ enzyme as antibiofouling agents. Many investigations focusing on the identification of novel QQ-bacteria and testing their stability are still focusing on membrane biofouling due to bacterial biofilm polymeric material deposition. A new review provides more information on utilizing QQ enzymes to cure biofouling.

Environmental applications of QSIs in bioremediation

Bioremediation is the use of living organisms to remove toxic pollutants from the environment. A biofilm generated by several microorganisms can provide an ideal environment for a successful bioremediation procedure. Engineered QS systems have been demonstrated to be effective in bioremediation of oil and heavy metal contaminated soil, as well as metal ion biosensing[39]. For bioremediation applications, cells are designed to release QS signals to control the behaviour of neighbouring cells in a bacterial consortium. QS Is an important element that affects the structure and composition of bacterial colonies? QS Signals have a lot of potential for increasing wastewater treatment performance[40]. Antibiotic overuse in treatment techniques for infection caused by the opportunistic pathogen *Serratia marcescens* has rendered the bacterium multidrug resistant (MDR). As per an article published in 2017, explores the possibility of a function-driven meta-genomic approach in elucidating the hitherto undiscovered marine sediment of the Palk Bay coastal region as a novel source of anti-QS compounds[41].

Numerous QS bacteria have been discovered in wastewater treatment systems, including several that are essential for sewage function. Another application of QS is the removal of nitrogen from wastewater using an anaerobic ammonium oxidation-based biological process. A new review paper has more information on QS's involvement in wastewater treatment. QS is also important in marine *P. aeruginosa* N6P6's breakdown of polyacrylic aromatic hydrocarbons (PAH) [42]. These findings are significant because PAHs are widely distributed in the environment and, due to their poor water solubility and hazardous, mutagenic, and carcinogenic properties, the majority of them are persistent. QS systems, on the other hand, are diverse and are influenced by a variety of inherent and exogenous factors. As a result, if QS technology is to be used in industrial bioremediation processes, a lot of focus could be placed on QS reactions to various environmental inputs[43].

Industrial applications of QSIs for mitigation of MIC

It is now well known that MIC is the direct cause of catastrophic corrosion failures in many industries, with annual repair expenditures in the billions of dollars. Bacteria in a biofilm have been shown to be

substantially more persistent than planktonic cells in the bulk fluid. Amino acids and peptides have been used in studies to develop long-term strategies for reducing biocide doses. Although these tests revealed an increase in biocide activity, the mechanism behind this is unknown. It is unknown whether adding these components to biocides improves their penetration into biofilms and thus their efficacy. Furthermore, it was obvious that the majority of these studies measured their antimicrobial properties by introducing them to the bacterial culture before the biofilm formed. As a result, their ability to disperse a mature biofilm remains in question because they are rarely tested for their ability to disperse an already existing biofilm. Meanwhile, MIC studies frequently overlook microscopic techniques that assess bacterial viability, such as the live/dead assay, and those that do always demonstrate that their compounds have a biocidal effect on bacteria, potentially increasing resistance. Notably, when biocides reach bacteria in biofilms in low concentrations (sub-MICs), it can result in an increase in bacterial growth rate[44].

Furthermore, unregulated and uncontrolled use of biocides contributes significantly to the development of resistance to the majority of effective antimicrobial classes, a phenomenon known as co-resistance. The impact of antibacterial agents and the usage of biocides on the prevalence of antibiotic resistance is summarized in many published reviews. However, there are still research gaps regarding the impact of corrosion inhibitors used in various industries on antibiotic resistance, corrosion inhibitors' effects on microbiology, the quantity of resistance genes, and antibiotic-resistant bacteria.

Organic molecules have been employed to prevent corrosion since they are thought to be more effective and efficient than other methods. Benzo-triazole and its derivatives, substituted imidazole, triazole, thiadiazole derivatives, and amino acids are examples of these compounds. Although they exhibited good anticorrosive qualities, they are costly, and some of them pose health and environmental risks[45]. As a result, researchers began to concentrate their efforts on determining the efficacy of natural materials as a potential eco-friendly corrosion inhibitor.

Although several natural compounds have shown some QS inhibitory effects, this activity was not connected to their corrosion inhibitory action, and they were nonetheless employed at their biocidal dose. Cinnamaldehyde has been utilized as a green corrosion inhibitor in an abiotic environment, but its effectiveness in the presence of bacteria has yet to be determined. Cinnamaldehyde has QSI action against a variety of microorganisms. As a result, it would be fascinating to see how effective it is at reducing MIC. QSIs such as ajoene, coumarin, and green tea extracts inhibit a wide spectrum of QSs via inhibiting small regulatory RNAs (sRNA) and other methods. Garlic extract was also reported to inhibit metal corrosion in the presence and absence of bacteria, although it was evaluated at its biocidal concentration and its QSI action was not studied in the corrosion investigations. MIC has received several positive evaluations over the years. Despite advances in MIC research, the processes of fundamental interactions between bacteria and metallic substrates that ultimately contribute to fast corrosion remain unknown[46].

MSSA isolates, MSSA, and QS (QS) systems are important for the regulation of Staphylococcus aureus's accessory genes, which are a significant cause of antibiotic resistance. Antibiotics may be used with quorum quenchers to reduce drug resistance. As per the recent article published in the year 2021, the antibacterial and Quorum Quenching (QQ) activities of ethanolic extracts of mango seed kernel, guava leaf, and polylysine using 10 MRSA and 10 MSSA isolatedates. Results showed that -PL, MSKE, and GLE had an impact on the expression and motility of hemolysin activity, indicating that they all interfere with QS activity. The quantification of hld (delta hemolysin) and rnaIII transcripts by qPCR served to validate the QQ effect, providing evidence for adjunct treatment and anti-virulence therapy of MRSA infections. Sub-MIC doses of mango seed kernel, guava leaf extract, and -PL quench the agr QS system, attenuating signal transmission and preventing *S. aureus* from moving around. MRSA isolates were more susceptible to QQ than MSSA isolatedates, with guava leaf extract and mango seed germ extract being more effective inhibitors of delta hemolysin activity. In the future, QQ and anti-virulence treatment is important for managing and preventing infectious illnesses, and these substances are excellent adjunct treatment options. Differential fractionation, separation of active ingredients from these extracts, and investigations to ascertain the active ingredients' mode of action are ongoing[47].

As per one research group investigation has provided as evidence of Quorum Quenching (QQ) action by ε-PL, MSKE, and GLE on *S. aureus* in general and MRSA in particular, as an appealing

adjuvant therapy and anti-virulence therapy for MRSA infections[48].

Nonetheless, both the cathodic polarization theory and direct electron transport from the metal into the cell are now regarded as contributing to MIC. When bacteria are starved of an organic carbon source, it has been claimed that conductive pilis are one of the strategies for transferring electrons into the cell's cytoplasm, and that bacteria make pili to connect to steel substrate. Recent research has discovered that QS is involved in electron transfer in microbial fuel cells, syntrophic-microbial electron transfer, and direct interspecies electron transfer mediated by pili between syntrophic oxidizers and methanogens.

This led to the question of whether a similar scenario occurs in corrosion caused by direct metal-microbe electron transmission. The second investigation employed methyl eugenol QSI at a concentration of 100 ppm in a natural pond water system and found that treated SS316L had less biofilm formation and more corrosion resistance than untreated SS316L[48].

Using *Desulfo vibrio vulgaris* and *Desulfo bacterium*, the relationship between QS and MIC in the marine environment was investigated. In comparison to freshwater, it was discovered that increased corrosion rates induced by these bacteria in the marine environment were associated with higher sulphate reduction, higher AHL production rates, and higher rates of biofilm development.

The findings were verified genetically using the reverse transcription quantitative polymerase chain reaction (RT-qPCR) approach, which revealed that genes involved in QS and biofilm formation were considerably elevated under saline conditions. However, the probability of bacterial viability reduction after adding QSIs at sub-inhibitory concentrations has not been established. As a result, it's unclear whether the decrease in biofilm biomass and AHL production was caused by QS suppression or by bacteria that were no longer viable.

The effect of QS activation and inhibition on biofilm formation and carbon steel corrosion was studied using D. vulgaris as a model strain. The findings imply that using QSIs to prevent SRB-induced corrosion in ecologically sensitive areas is a good idea. This was corroborated by electrochemical tests and weight loss, which revealed that treating the samples with AHL caused a quick rise in the corrosion rate, but QSI treatment caused a slower increase[49].

After introducing AHL or QSIs to the bacteria, this work focused on transcriptome analysis of specific genes thought to be involved in sulphate reduction and biofilm formation. QS stimulation by adding AHLs resulted in overexpression of genes involved in lactate and pyruvate metabolism, sulphate reduction, electron transfer, and biofilm formation, whereas QS inhibition resulted in down regulation of same genes. External AHLs were used to stimulate QS, and there was no evidence that the bacteria were capable of regulating the QS system utilizing AHls produced by the bacteria.

Because the specific mechanism of the QS in SRB is yet unknown, more research on the association between microbial influenced corrosion and QS could be done using bacteria with a well-studied QS system as a model. Huang and colleagues took a different strategy, mixing SsoPox W263I quorum quenching lactonase enzyme with silica gel and using the resulting mixture to coat steel coupons. Magnesium peroxide, surfactin, capsaicin, gramicidin, and the QQ lactonase coating additives were tested for their capacity to prevent bio-corrosion. The lactonase coating was found to be the most stable and to have the best corrosion prevention activity of all the materials studied. However, despite the fact that lactonase is a QQ enzyme, it couldn't provide any direct evidence that QSIs of their bacteria are the mechanism that led to a reduction in corrosion rate. Furthermore, the lactonase concentration of 100 ng/mL was chosen based on preliminary results of its ability to reduce corrosion tubercles, not on sub-inhibitory concentration microbial studies, and the bacteria's viability after treatment was not confirmed[50].

To prevent corrosion, it's crucial to understand MIC mechanisms. More controlled lab research utilizing QS model organisms like *P. aeruginosa* and *B. subtilis* could be done to investigate the role of QS in bio-corrosion and the genes that are regulated by QS and play a role in electron uptake. The QS inhibition strategy has the potential to create bacteria-repellent surfaces, work in tandem with other antibacterial agents, and boost antibacterial agent penetration into biofilms. The use of QQ enzymes, particularly those isolated from marine bacteria and plants, can be a promising solution to many biofilm-related problems in various industries as they have a broad spectrum, high stability, and thermo stability in hard environments such as highly saline conditions.

The development and manufacturing of transition-state analogues of the auto-inducer synthase enzymatic

process, as well as the assessment of these molecules as CepI inhibitors. One of these compounds inhibits CepI effectively, establishing a new class of inhibitor for an undeveloped antibacterial target[51].

The discovery of a quorum sensing (QS) mechanism in bacterial pathogens to coordinate virulence and biofilm development has prompted a quest for safe, stable, and non-toxic anti-QS chemicals derived from natural products. Wherever another study has been stated that, ethanoic extracts of *Hemidesmus indicus* (L.) *Schult* (root), *Holarrhena antidysenterica* (Roth) A.DC. (Bark), *Mangifera indica L*. (seed), *Punica granatum L*. (pericarp), and *Psoralea corylifolia L*. (seed) inhibited violacein production in *Chromobacterium violaceum* (CV12472 and CVO26), *C. violaceum* CV31532 and *Pseudomonas aeruginosa* (PAO1) strains to varied degrees. Also, a considerable reduction in swarms was seen when compared to the control. The suppression of violacein synthesis and swarming motility might be owing to direct or indirect interference on QS by active ingredients, or to the interaction impact of several phyto-compounds present in the extracts. In conclusion, these plant extracts could be chosen for activity guided fractionation in order to identify and define the active component[52].

Conclusion

Progressive emergence of resistance to regular antibiotics in several bacterial pathogens threatens the hope and future of the present antimicrobial era. The evolution of antibiotic resistance in microbial pathogens emphasizes why it is crucial to discover novel ways to avoid and control infectious diseases. Since the first discovery of QS more than forty years ago, the understanding of mechanisms of a several QS systems and admiration for the significance of QS pathogenesis of many bacterial species have soared. Currently, the research is mainly focused on how single-celled bacterial pathogens utilize QS, a community regulatory system to coordinate microbial behaviour among family members so as to achieve an upper hand in pathogen-host and microbe- microbe interactions. A part from the significant progress in recognizing QS systems, new QS inhibition mechanisms have been exposed that obstruct successfully with microbial QS; these mechanisms have been in a broad variety of organisms including both eukaryotes and prokaryotes. QS Inhibiting compound synthesized chemically produced naturally by certain eukaryotic hosts or produced by genetically engineered transgenic plants all have either a positive or negative effect on the expression of bacterial phenotypes controlled by QS. The investigations on bacterial QS have approved numerous ideal targets for drug design as well as agricultural, industrial and medical applications. The QS inhibitors act by blocking the key steps of QS such as signal creation, signal accumulation and signal reception. These QS inhibitors are very effective and promising in basic research and biotechnological applications.

Several studies in recent years have demonstrated that quorum quenching-based approaches have significant antibacterial potential especially for the medical devices. Currently, research gaps have been discovered about the possible resistance mechanisms that bacteria may develop in response to quorum quenching-based treatment. As we have seen with antibiotics, resistance is a phenomenon that resulted in the bacterial evolution under a selection pressure setting that promotes the advancement of resistant strains. Although only a few QS inhibitors, such as azithromycin, have been shown to reduce growth, many others have a weak or insignificant impact. Quorum quenching enzymes may be suitable since they have low side effects and a high inhibitory efficiency against biofilms. Nonetheless, quorum-sensing inhibition, in addition to traditional antibiotics, remains a viable alternative for broadening the therapeutic arsenal for the treatment of bacterial infections. The combined effect of these strategies on bacterial physiological properties revealed that quorum interference-based approaches are appropriate for reducing bacterial virulence and restoring antibiotic resistance by reducing biofilm formation and bacteriophage resistance, paving the way for future combinational therapies. Further investigations are needed to establish the effects of these strategies on both individual bacterial species and their population.

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Conflict of interest

All authors declare no conflict of interest.

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