Quorum Sensing and Quorum Sensing Inhibitors of Natural Origin

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Abstract Now, infectious bacteria represent the worldwide health threat. Treatment with antimicrobial agents becomes ineffective with the time, especially with the massive development of antimicrobial resistance. For instance, there should be alternatives, and one of the main approaches to control bacterial virulence is quorum sensing (QS). QS is a bacterial communication system that controls the expression of bacterial virulence factors including secretion of exoenzymes, bacterial toxins, biofilm, and bacterial motility. Bacteria secret QS signals that control bacterial quorum and associated virulence factors. These signals are mainly acyl homoserine lactones (AHLs) in Gram-negative bacteria, autoinducing peptides in Gram-positive bacteria, and AI-2 signals in both. Therefore, QS is a promising target to control bacterial pathogenicity and enhance bacterial inactivation by the immune system. Many quorum sensing inhibitors have been developed that either block QS receptors, inhibit the biosynthesis of QS signals, or degrade QS signals. Various quorum sensing inhibitions (QSI) have been identified from natural sources such as plant extracts, pure compounds, natural enzymes, marine organisms, fungi, bacteria, and herbs. Plants are considered as a rich source of QSI inhibitors either, edible plants, fruits, spices, essential oils, medicinal plants. Also, several pure extracts exhibited QSI activity, such as terpenoids, flavonoids, and phenolic acids. This chapter highlights the QSI activities of natural products and how they affect QS-regulated virulence. Also, the influence of natural products on the expression of QS-regulatory network will be discussed, with focus on their advanced applications in the elimination of microbial virulence and suppression of bacterial pathogenicity.

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1 Introduction

The number of different microorganisms in the adult human body was evaluated to be at least ten times more than the number of human cells (Walter et al. 2011). A majority of these microorganisms are commensal and may even play an important role in maintaining our health and well-being (Gerritsen et al. 2011). They can live inside the human body and silently work, but they can turn on us and become "pathogenic" with too many virulence factors and cause diseases if our immune systems are weakened. Additionally, pathogenic bacteria in our environment frequently infect us. Our immune system successfully destroys microorganisms in most cases; however, at other times, our defenses cannot. Antibiotic use has been the only treatment choice for bacterial infections that for almost a century (Davies et al. 2006). Firstly, antibiotics were identified as substances produced by microorganisms that inhibit the growth of other microorganisms. With continuous and excessive use of antibiotics through the years, antibiotics were abused and overused, and this led to a serious consequence: multiple-drug resistance (MDR). The World Health Organization (WHO) identified multiple-drug resistance (MDR) as one of the top ten global public health challenges facing humanity as they lost their efficacy in the treatment of pathogenic infections (Rather et al. 2017). Therefore, the pharmaceutical industries need to develop new approaches to combat bacterial pathogens. Many pathogens that affect people, plants, animals, and aquatic life rely on bacterial communication between cells (Bruhn et al. 2005). These communication systems are called "quorum sensing" (QS) which is considered to be the key regulator of virulence factors (Williams et al. 2007). Therefore, any disruption of QS will prevent the release of virulence factors which consequently affect the pathogenicity of microorganisms. This is an innovative and effective strategy to control infectious bacterial diseases (Dong et al. 2007; Muzammil et al. 2023).

QS controls the virulence factors by regulating gene expression through autoinducer (AI) production. AIs are small organic signaling molecules that are primarily produced during the stationary phase (Czajkowski and Jafra 2009). Once the growth reaches a certain threshold level, these molecules act as mirrors that reflect the inoculum size density and control the expression of associated genes (Elgaml et al. 2014). AIs can be categorized into three classes: autoinducing peptides (AIPs), autoinducer-1 (AI-1), and autoinducer-2 (AI-2). AI-1 is known as N-acylated L-homoserine lactones (AHLs) which are the most prevalent class of QS signaling molecules in Gram-negative bacteria (Geske et al. 2008). In Gram-positive bacteria, AIPs are the main autoinducers (Sturme et al. 2002). AI-2 is used by both Gram-negative and Gram-positive bacteria and is produced in intraspecies, so it is known to be a "universal" AI (Lowery et al. 2008; Alves et al. 2023).

Quorum sensing inhibition (QSI) is achieved by too many pathways; blocking bacterial receptors, inhibiting the biosynthesis of QS signal, and degrading of QS signal in the extracellular environment. QSI strategy is an innovative and potent alternative to antibiotics use and it is thought to be less likely result in the emergence of resistance (Miller and Bassler 2001). However, according to the latest studies, it is difficult to predict this consequence, and it is probably influenced by too many factors (Cornforth et al. 2014). Designing de novo quorum sensing inhibitors (QSIs) can be opportune to draw inspiration from nature as it has long been believed that natural products are a good source of vital antibacterial agents that can be utilized to treat a variety of pathogenic diseases (Howes et al. 2020). In this review, we highlight natural QSIs from many different sources and how they affected QS-regulated virulence genes expression.

Everything Starts in Nature

Nature is always the key; it introduces a massive source of drugs. More than half of all prescribed drugs are originated from natural sources (Harper 2001; Marris 2006). Similarly, many QSIs were isolated from many natural sources such as marine organisms, fungi, plants, and herbs due to the natural competition. They exhibited a high potency in inhibiting and disrupting the bacterial QS mechanism (Rasmussen and Givskov 2006). Here, we provide a list of the most potent naturally occurring anti-QS that have been identified from a variety of diverse habitats.

1.1 Plants

Plants harbor a high density of microbial communities. So, they developed many defense mechanisms against pathogenic organisms. They display an extensive range of therapeutic purposes in conventional medicine. The therapeutically effective plant-isolated active ingredients should be safe for human cells. Toxicological studies on these active substances must be carried out to avoid their toxicity. The aim to detect and study the biological processes and mechanisms behind their therapeutic effects has increased. Biologically active components of natural resource, especially those produced from plants, have thus far prompted the creation of brand-new medicines for the treatment of a variety of diseases. QS system manipulation by plants is thought to be a form of protection against microbial pathogens because plants lack an immune system, unlike animals and humans. This forced researchers to hypothesize additional defense mechanisms to overcome the pathogenic strains infection (Koh et al. 2013). Plant extracts were reported to act as QSI. Plant chemicals often target the bacterial QS system in three different pathways (Fig. 1)**:** by degradation of the signaling molecules, blocking the synthesis of AIs, or by targeting the receptors of the signals (Koh et al. 2013).

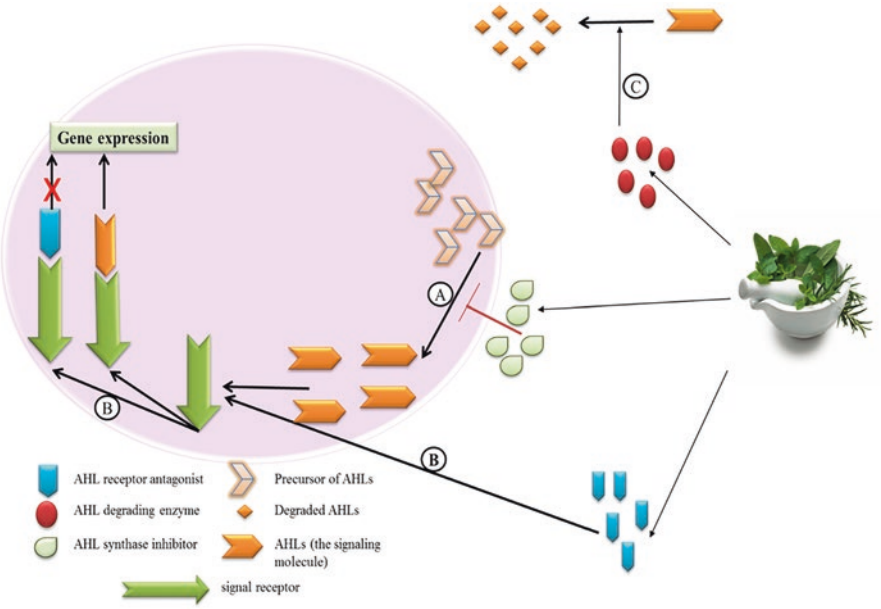

Fig. 1 Mechanisms of quorum sensing inhibition by plants secondary metabolites through blocking the synthesis of AIs (A), targeting the receptors of the signals (B), and degradation of the signaling molecules (C)

1.1.1 Edible Plants

All plant's diversity approved efficacy against QS signaling systems of pathogenic bacteria. For example, some plants used for nutrition exhibited QSI potency as *Medicago truncatula Gaertn* plant extract could inhibit the QS against *Chromobacterium violaceum* CV026, *Escherichia coli* JM109, *Pseudomonas aeruginosa*, and *Sinorhizobium Meliloti* (Gao et al. 2003). Also, *Pisum sativum* was reported to reduce violacein pigment in *C. violaceum* and swarming and motility in *P. aeruginosa* PA01 (Fatima et al. 2010)**.** Methanolic extract of *Capparis spinosa* inhibited QS and virulence in *E. coli*, *C. violaceum, S. marcescens*, *P. mirabilis*, and *P. aeruginosa* PA01 (Abraham et al. 2011). Erucin and sulforaphane compounds isolated from *Brassica oleracea* (broccoli) plant inhibited *P. aeruginosa* PA01 virulence factors (Ganin et al. 2013). *Phaseolus vulgaris* (bean) and *Oryza sativa* (rice) inhibited the biofilm formation in *Sinorhizobium fredii* SMH12 and *Pantoea ananatis* AMG501 (Pérez-Montaño et al. 2013). Additionally, myristic acids and pantolactone isolated from *Allium cepa* (onion) inhibited *P. aeruginosa* virulence factors (Abd-Alla and Bashandy 2012).

1.1.2 Fruits

Fruits also showed potent QSI activity against QS-regulated virulence genes. For example, the methanolic extract of *Mangifera indica* (mango) reduced the pyocyanin, elastase, chitinase, total protease, swarming motility, and exopolysaccharide (EPS) production by 89% 76%, 55%, 56%, 74%, and 58%, respectively, in *P. aeruginosa* PAO1 at 800 μg/mL (Kim et al. 2019). *Vitis* sp. (grape), total extracts of *Rubus idaeus* (raspberry), and *Vaccinium angustifolium* Aiton (blueberry) inhibited violacein production in *C. violaceum* (Kalia 2013). The limonoids in orange seeds including deacetyl nomilinic acid glucoside, ichangin, and isolimonic acid inhibited the biofilm formation in *V. harveyi* (Vikram et al. 2010)**.** Similarly, aqueous extracts of edible fruits such as *Musa paradisiaca*l (banana), *Ananas comosus* (pineapple), and *Manilkara zapota* (sapodilla) showed QSI activity against violacein pigment in *C. violaceum*, pyocyanin, biofilm formation, and protease in *P. aeruginosa* PA01(Musthafa et al. 2010). Biofilm formation of *Yersinia enterocolitica* was inhibited by the peel extract of *Punica granatum* (pomegranates) (Oh et al. 2015). *Psidium guajava* (guava) could reduce the biofilm production in *P. aeruginosa* PAO1 and violacein pigment synthesis in *C. violaceum* (Vasavi et al. 2014). Similarly, it inhibited quorum sensing mediated virulence factors of *Staphylococcus aureus* (Divyakolu et al. 2021).

1.1.3 Spices

Spices exhibited to be a potent source of QSIs. For instance, curcumin, which is produced from *Curcuma longa* inhibited the expression of virulence genes in *P. aeruginosa* PA01 (Rudrappa et al. 2008). Furthermore, curcumin was evaluated for its ability to disrupt mature biofilms in uropathogenic strains. It was discovered to reduce QS-dependent virulence factors such as extracellular polymeric substance formation, alginate production, and swarming motility. Curcumin was found also to make *P. aeruginosa* PA01 more susceptible to common antibiotics (Packiavathy et al. 2014). Besides, the effects of cinnamaldehyde and its derivatives were reported to be effective QSI in QS-regulated processes, including biofilm formation in *P. aeruginosa* and AI-2-mediated QS in several *Vibrio* species (Brackman et al. 2008). Additionally, it was discovered that extracts from various plant components including the leaves, flowers, fruit, and bark of *Combretam albiflorum*, *Laurus nobilis*, and *Sonchus oleraceus* had anti-QS properties (Al-Hussaini and Mahasneh 2009). *Allium sativum* (garlic) extract inhibited β-galactosidase in *Agrobacterium tumefaciens* NTL4 and violacein production in *C. violaceum* (Bodini et al. 2009). Moreover, *Vanilla planifolia* aqueous methanolic extract inhibited violacein pigment in *C. violaceum* CV026 (Choo et al. 2006).

1.1.4 Essential Oils

Essential oils showed some anti-QS properties, and the production of violacein in *C. violaceum* CV026 was significantly affected by the QSI properties of the essential oils extracted from *Piper brachypodon Benth*, *P. caucasanum Bredemeyer*, and *P. bogotense* (Olivero V et al. 2011). Similarly, methanol and hexane extracts of clove inhibited violacein pigmentation in *C. violaceum* CV026. Chloroform and methanol clove extracts dramatically decreased the amount of bioluminescence in *E. coli* [pSB1075] that is produced when cultivated with N-3-oxododecanoyl-L-homoserine lactone. While virulence factors of *P. aeruginosa* PAO1, such as pyocyanin pigment synthesis, were suppressed by the hexane extract (Krishnan et al. 2012). Eugenol is the key component of clove extract as it exhibited anti-QS properties and inhibited the virulence factors of *P. aeruginosa* and *E. coli* biosensors at subinhibitory concentrations (Zhou et al. 2013).

1.1.5 Medicinal Plants

Recent studies revealed that medicinal plants are a very potent source of QSIs. This potency is modulated by the secondary metabolites production. These metabolites are classified mainly into three main classes; terpenoids, phenolic acids, and flavonoids (Bouyahya et al. 2022).

Terpenoids

Terpenoids demonstrated remarkable antibacterial activity through a variety of pathways, including QS inhibition. Many terpenoids, including eugenol, carvacrol, linalool, D-limonene, and -pinene, have inhibitory effects via various QS mediators. For example, eugenol showed significant effects on methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from food handlers (Al-Shabib et al. 2017), as well as biofilms of clinical isolates of *P. mirabilis*, *S. marcescens*, and *P. aeruginosa* (Packiavathy et al. 2012). Interestingly, an additional study showed that eugenol hindered *P. aeruginosa* from producing its virulence factors such as elastase, pyocyanin, and the development of biofilms (Zhou et al. 2013; Al-Shabib et al. 2017; Rathinam et al. 2017). Moreover, eugenol had a notable impact against (AIs) and significantly reduced the formation of biofilm of *P. aeruginosa* PAO1 by 65.6% (Rathinam et al. 2017). Recently, other studies demonstrated that eugenol decreases the production of N-(3-oxododecanoyl)-L-homoserine lactone (3-oxo-C12-HSL) and C4-HSL N-acyl homoserine lactone signal molecules, pyocyanin, and swarming motility in *P. aeruginosa* by 50% at sub-MIC (Lou et al. 2019). Besides, eugenol reduced the expression of QS-regulated genes by 65%, 61%, and 65% for lasI, rhlI, and rhlA, respectively, and by 36% for biofilm formation (Lou et al. 2019).

Similar to this, carvacrol displayed a QSI activity against QS and biofilm development. Recent research demonstrated that carvacrol inhibited the development of biofilms in *P. aeruginosa* at very low concentrations (0.9–7.9 mM) and reduced the synthesis of pyocyanin by 60% (Tapia-Rodriguez et al. 2017). Furthermore, another study reported that subinhibitory concentrations (<0.5 mM) of carvacrol inhibited biofilm formation in *S. aureus* 0074, *Salmonella enterica* subsp., and *S. Typhimurium* DT104 (Burt et al. 2014).

Phytol is a well-known diterpene and was reported as QSI. Specifically, this substance inhibited the biofilm formation in *S. marcescens* and *P. aeruginosa* PAO1 (Pejin et al. 2015; Srinivasan et al. 2016, 2017). Phytol inhibited prodigiosin, protease, and biofilm formation by 92%, 68%, and 64%, respectively in *S. marcescens* at a concentration of 10 μg/mL (Srinivasan et al. 2016).

Another terpene that has demonstrated anti-QS action is called sesquiterpene lactone. This substance inhibited the activity of QS mediators in *C. violaceum* and *P. aeruginosa* ATCC 27853 (Amaya et al. 2012; Aliyu et al. 2021). It was reported that sesquiterpene lactones belonging to goyazensolide and isogoyazensolide chemical families approved QSI activity and inhibited the production of AHL. Also, oleanolic aldehyde coumarate inhibited biofilm formation in *P. aeruginosa* and all lasI/R, rhlI/R regulated genes (Rasamiravaka et al. 2015). Other terpenoids as linalool inhibited the biofilm formation of *A. baumannii* (Alves et al. 2016; Wang et al. 2018).

Flavonoids

The second classes of secondary metabolites found in medicinal plants are flavonoids. Recent studies revealed that this chemical group has an antibacterial impact through various mechanisms of action, including inhibition of QS and its main traits, like the development of biofilm. Epigallocatechin is one of the flavonoids, it showed antibiofilm activity against *S. typhimurium* (Wu et al. 2018; Hosseinzadeh et al. 2020) and disrupted the QS activity of *Streptococcus mutans* biofilms. It also reduced motility and decreased AI-2-regulated virulence factors activity (Castillo et al. 2015). Additionally, epigallocatechin inhibited QS and the formation of biofilm in *S. aureus* and *Burkholderia cepacia* (Huber et al. 2003), *Listeria Monocytogenes* (Nyila et al. 2012), and *Eikenella corrodens* (Matsunaga et al. 2010). Besides, naringenin inhibited biofilm formation in *S. mutans* and downregulated mRNA expression of luxS, gtfC, gtfB, comE, and comD (Yue et al. 2018). Moreover, this compound inhibited the swarming and motility in *C. violaceum* (Truchado et al. 2012).

Quercetin exerts antagonistic effects on bacterial signaling systems, and has been shown to have an important role as QSI (Vikram et al. 2010). For instance, it inhibited the biofilm formation of *E. coli* and *V. harvei* (Vikram et al. 2010). Also, it inhibited the violacein pigment production in *C. violaceum* and QS-regulated phenotypes in *P. aeruginosa* PAO1 (Al-Yousef et al. 2017). Other flavonoids like naringenin showed QSI activity against *P. aeruginosa* and inhibited elastase and

pyocyanin virulence factors (Hernando-Amado et al. 2020). Meanwhile, morin flavonoids inhibited EPS production, biofilm formation, and motility in *S. aureus* (Chemmugil et al. 2019). In addition, methoxyisoflavone inhibited the violacein pigment in *C. violaceum* and pyocyanin, protease, hemolysin, and biofilm in *P. aeruginosa* clinical isolates, PAO1, and PA14 (Naga et al. 2022). On the other side, kaempferol inhibited adhesion-related gene expression (Ming et al. 2017). Taxifolin flavonoids also showed a significant QSI activity on *P. aeruginosa* and reduced elastase and pyocyanin production (Vandeputte et al. 2011).

Phenolic Acids

Several natural resources, including medicinal plants release phenolic acids as secondary metabolites. Numerous studies showed that these phenolic compounds have anti-QS properties. In two *Pectobacterium* species, *P. carotovorum* and *P. aroidearum*, salicylic acid has been found to interfere with the QS system, influence QS machinery, and changed the expression of bacterial virulence factors (Joshi et al. 2016). Additionally, it decreased the intensity of the AHL signal and reduced the expression of several QS genes. Salicylic acid treatment significantly decreased the biofilm formation of *P. aeruginosa* as well as twitching, swarming, and motility (Chow et al. 2011). Similarly, salicylic acid modulated 103 virulence-related gene families and decreased AHL production and biofilm formation in *A. tumefaciens* (Yuan et al. 2007). On the other hand, rosmarinic acid (RA) at 750 μg/mL decreased elastase, hemolysin, and lipase production in *Aeromonas hydrophila* and inhibited the development of biofilms. The virulence genes ahh1, aerA, lip, and ahyB were also downregulated (Rama Devi et al. 2016). Also, RA inhibited the QS-regulated virulence factors in *P. aeruginosa*, it inhibited elastase, pyocyanin, and biofilm formation (Walker et al. 2004; Corral-Lugo et al. 2016; Fernández et al. 2018). Cinnamic acid is another phenolic acid with known biofilm and QS inhibitory properties. It effectively prevented *P. aeruginosa* from producing the QS-dependent virulence factors and biofilm formation at sublethal concentrations without any effect on viability (Rajkumari et al. 2018). Additionally, research revealed that cinnamic acid inhibited the virulence gene expression of *P. aroidearum* and *P. carotovorum* (Joshi et al. 2016). Cinnamic acid also decreased the intensity of the AHL signal and suppressed the production of QS genes. Similar effects were reported when *C. violaceum* ATCC12472 was exposed to two cinnamic acid derivatives, 4-dimethylaminocinnamic acid (DCA) and 4-methoxycinnamic acid (MCA) (Cheng et al. 2020). DCA and MCA reduced the production of violacein, chitinase, and hemolysin in *C. violaceum* and decreased the levels of N-decanoyl-homoserine lactone (C10-HSL).

Researchers reported that chlorogenic acid (CA) significantly reduced *P. aeruginosa* virulence factors such as biofilm formation, swarming, elastase, protease, pyocyanin, and rhamnolipid (Wang et al. 2019). Also, p-coumaric acid inhibited the QS-related virulence genes of *P. chlororaphis*, *C. violaceum* 5999, and *A. tumefaciens* NTL4 (Bodini et al. 2009)**.** In addition, it inhibited violacein pigmentation in

C. violaceum (Chen et al. 2020). Another QSI phenolic acid is caffeic acid which showed antibiofilm activity in *S. aureus* in addition to hemolysin inhibition activity (Luís et al. 2014). Besides, phenylacetic and ellagic acid were reported to be efficient against the biofilm-forming bacteria *B. cepacia* (Huber et al. 2003) and *P. aeruginosa* (Musthafa et al. 2012).

2 Fungal Quorum Sensing Inhibitors

Fungi inhabit a wide range of ecosystems and interact with other organisms, such as microorganisms, animals, and plants. They are almost cosmopolitan in nature. Additionally, they can live in extreme habitats. Organisms that cohabit in nature as partners have evolved tools to fight one another, including chemicals, enzymes, and metabolites (Sharma and Jangid 2015; Almeida et al. 2022). In soil, bacteria and mycorrhizal fungi work together closely. Fungi have inherent defenses against a bacterial population that have formed or evolved as a result of their close association. These could be for space, nutrition, or pathogenicity. Furthermore, they are known to produce a number of secondary metabolites such as enzymes, chemicals, and mycotoxins (Pitt 2000; Frisvad et al. 2008). Even so, there is little information available on fungal QSIs. So, finding fungal QSI potency isolated from varied habitats, such as endophytes and marine fungi may help.

Fungi are well-known to produce a variety of quorum sensing molecules (QSMs). For example, *Candida albicans* produces farnesol and tyrosol. Farnesol is also produced by a majority of dimorphic yeasts with a significant impact on their morphogenesis (Shirtliff et al. 2009; Weber et al. 2010). It exhibited antimicrobial activity against *Fusarium graminearum* (Semighini et al. 2006), *Paracoccidioides brasiliensis* (Derengowski et al. 2009), *Staphylococcus epidermidis*, *S. aureus* (Cerca et al. 2012), and other bacteria (Pammi et al. 2011). It was reported to act as an adjuvant against *S. epidermidis* when combined with antibiotics (Pammi et al. 2011). On the other hand, farnesol produced by *C. albicans* was reported to inhibit biofilm formation, which is regulated by QS (Ramage et al. 2002). It showed efficacy in protecting mice from candidiasis (Hisajima et al. 2008). A comparable study on *C. parapsilosis* and *C. tropicalis* revealed that farnesol at high concentrations reduced the formation of biofilms (Laffey and Butler 2005; Zibafar et al. 2015).

Additionally, many fungal secondary metabolites showed QSI activities. For instance, secondary metabolites of *Tremella fuciformis*; *Tremella* is a member of the Basidiomycota family *Tremellaceae*, also known as "jelly fungi." *T. fuciformis* inhibited QS in *C. violaceum* CVO26 and inhibited the production of violacein pigment. This pigment is regulated by QS and AHL signaling molecules. It was inhibited by different concentrations (0.2%–0.8%) of *T. fuciformis* extracts without any effect on viability and growth (Zhu and Sun 2008). Also, *Phellinus Igniarius* which is classified as a plant pathogen was reported to have anti-QS activity (Zhu et al. 2012) as well as anticancer, antidiabetic, and antioxidant characteristics (Lung et al. 2010). Additionally, heterocyclic compounds that synthesize the pigments of

Auricularia auricula could bind to the active site of receptor proteins and inhibit the AHL-regulated signaling mechanism (Zhu et al. 2011; Almeida et al. 2022). Similarly, its total extract reduced the biofilm formation of *Escherichia coli* by 73% (Li and Dong 2010).

Mycotoxins were reported to have QSI activity. Penicillic acid mycotoxin which is produced by *Penicillium radicola* and patulin which is produced by *P. coprobium* inhibited QS in *P. aeruginosa* by targeting the LasR and RhlR proteins (Rasmussen et al. 2005b). Additionally, a mouse with *P. aeruginosa* infection recovered faster after receiving patulin treatment, and it was more susceptible to tobramycin antibiotic (Rasmussen et al. 2005b). Also, a lot of promises exist for metabolites with antibacterial activity in endophytic fungi that inhabit a plant host. So, some endophytic fungi were isolated from *Ventilago madraspatana* plant (Rajesh and Rai 2013; Lima et al. 2022).

3 Marine Organisms Are a Potent Source of QSIs

Before the emergence of the first plants on the land about half a billion years ago, life existed primarily in the oceans for almost three billion years and it was at this point when QS molecules and their inhibitors started to perform their distinct roles. Numerous marine bacteria, fungi, algae, and bryozoans have been identified as QSIs, in addition to corals and sponges. For example, marine cyanobacteria are one of the richest sources of physiologically active and structurally distinct natural compounds. The family of halogenated furanones that were isolated from the marine alga *Delisea pulchra* has attracted a lot of attention and is considered to be one of the most effective and widely used natural QSI.

3.1 Algae

In the aquatic environment, beneficial and pathogenic bacteria coexist in close contact with eukaryotes including algae, protozoa, fungi, and plants. Eukaryotes have inevitably evolved several defense mechanisms for interacting with bacteria, such as creating secondary metabolites like as QSIs (Kjelleberg and Steinberg 2002; Rasmussen et al. 2005a; Dudler and Eberl 2006). For example, the red macroalga *Delisea pulchra* was the source of the first identified QSI and it exhibited a strong antifouling activity (Givskov et al. 1996). A variety of secondary metabolites like halogenated furanones were detected at the algae surface and were approved to be the main cause of the QSI activity (Dworjanyn et al. 1999). They are similar in structure to AHL, these halogenated furanones differ in having a furan ring rather than a homoserine lactone ring. The crude extract of *D. pulchra* approved efficacy against the human pathogenic bacteria; *Proteus mirabilis* and inhibited the motility

and swarming activity (Gram et al. 1996). The natural compound that has received the greatest attention to date is the halogenated furanones as it exhibited high QSI activity in AHL-controlled expression in various Gram-negative bacteria (Rasmussen et al. 2000; Hentzer and Givskov 2003) and also inhibited AI-2 signaling molecules (Ren et al. 2001). The disruption of AI-2 QS by natural and synthetic brominated furanones has been shown to protect *Artemia franciscana* shrimp from pathogenic isolates of the species *Vibrio Harveyi*, *V. campbellii*, and *V. parahaemolyticus* (Defoirdt et al. 2006). Furthermore, it was demonstrated that natural furanone inhibited the pathogenic *V. harveyi* strain from producing the toxin T1 and luminescence, both of which are QS-regulated against farmed shrimp (Manefield et al. 2000). Besides, it was shown that the natural furanone attenuated the adverse effects of various pathogenic *V. harveyi* strains in the rotifer *Brachionus plicatilis* (Tinh et al. 2007b; Tinh et al. 2007a). These findings demonstrated the ability of furanones to function as antivirulence compounds in several microbial marine ecosystems.

3.2 Bacteria

According to studies, a variety of bacteria can suppress the QS of other bacteria by producing quorum-quenching enzymes (QQEs) such as acylase and lactonase enzymes (Kalia 2013). A bacterial flora was isolated from the gut of white shrimp *Penaeus vannamei*. Then, it was cultivated with AHLs as the sole nitrogen and carbon source. It was discovered that the enrichment cultures accelerated the growth of rotifers in vitro exposed to pathogenic *V. harveyi* and degraded its signaling molecules in vitro (Tinh et al. 2007b). Similarly, other bacterial QSIs were isolated from the gut of *Lates calcarifer* and *Dicentrarchus labrax* fish (Van Cam et al. 2009). Some bacteria can serve as antagonists by releasing substances that interfere with QS signaling systems. For instance, 35 out of 88 actinomycetes stains prevented biofilm formation of *V. vulnificus*, *V. harveyi*, and *V. anguillarum* without any effect on their growth (You et al. 2007). Similarly, borrelidin, behenic acid, and 1H-pyrrole-2-carboxylic acid isolated from *Streptomyces coelicoflavus* KJ855087 inhibited QS-regulated virulence factors of *P. aeruginosa* PAO1(Hassan et al. 2016). In a cocultivation study, phenethylamine compounds were produced by *Halobacillus salinus* C42 inhibited *V. harveyi* bioluminescence. Also, these compounds inhibited several QS regulated phenotypes in Gram-negative bacteria, including luminescence in *V. harveyi,* violacein pigment in *C. violaceum* CV026, and fluorescence in *E. coli* JB525 reporter strain (Teasdale et al. 2009).

Similarly, 11 bacterial strains that were isolated from Palk Bay sediments inhibited the QS signaling systems in *C. violaceum* ATCC 12472 and *C. violaceum* CV026 (Nithya et al. 2010). Moreover, the marine isolated bacteria *Bacillus pumilus* significantly inhibited *P. aeruginosa* PAO1 virulence factors (Nithya et al. 2010). It inhibited LasB elastase by 84%, LasA protease by 76%, caseinase by 70%, pyocyanin by 84%, and pyoverdine, as well as biofilm formation by 87%. *Bacillus*

pumilus S8-07 approved QSI activity against virulence factors of *Serratia marcescens*. It exhibited a highly significant reduction in biofilm formation by 61%, hemolytic activity by 73%, prodigiosin by 90%, and caseinase by 92% (Nithya et al. 2010).

Another example of marine *Bacillus* sp. strain was isolated from the coastal region of Calimere showed a potency as QSI was reported by Musthafa and coauthors (2011). *Bacillus* sp. SS4 inhibited the violacein pigment production in *C. violaceum* by 86% and reduced the virulence factors of *P. aeruginosa* PAO1 by 88%, 68%, 65%, 68%, and 86% for biofilm, LasA protease, total protease, elastase, and pyocyanin, respectively.

3.3 Other Marine Organisms as QSIs

Aquatic invertebrates and sponges as well as marine algae and bacteria can produce QSIs that may hinder QS systems (Husain and Ahmad 2015). For example, the bryozoan *Flustra foliacea* from the North Sea excretes brominated alkaloids that lowered the signal intensity of various QS phenotypes by 20% to 50%. Additionally, the metabolites suppressed QS-regulated phenotypes of *P. aeruginosa* such as protease production (Peters et al. 2003). Furthermore**,** the sponge *Luffariella variabilis* exhibited a potent QS inhibition in LuxR-regulated systems. The inhibitory effect of this sponge was discovered to be mediated by manoalide, monoacetate, and secomanoalide secondary metabolites production (Skindersoe et al. 2008). Expression of virulence gene in *S. marcescens* and the violacein synthesis in *C. violaceum* were used to test the QSI activity of marine sponges which were collected from Palk Bay, India. Among 29 tested marine sponges, methanol extract of *Clathria atrasanguinea, Aphrocallistes bocagei*, and *Haliclona* (*Gellius*) *megastoma* inhibited the violacein production in *C. violaceum* ATCC 12472 and CV026. Besides, these sponge methanol extracts inhibited the virulence factors of *S. marcescens* PS1 such as biofilm formation, protease, hemolysin, and prodigiosin pigment production (Annapoorani et al. 2012)**.**

4 Natural Enzymatic Degradation of QSMs

Another major class of natural QSIs is enzymes. All organisms; mammals, plants, fungi, archaea, and bacteria have all been reported to participate in the production of QQEs. So, enzymatic degradation has arguably received the most attention to date (Romero et al. 2015). Many species of bacteria with enzymatic QSI activity have been identified so far (Table 1). The widespread enzymatic QSI activity among bacteria shows that disrupting bacterial communication is essential to giving bacterial populations a strategic advantage over the competition. There are now three primary groups of AHL QQEs based on the modification process. The first is the

Table 1 Quorum quenching enzymes produced by bacterial strains

Organism	Activity	Enzyme	Reference
Agrobacterium tumefaciens	Lactonase	AttM	Zhang et al. (2002)
	Lactonase	AiiB	Carlier et al. (2003)
Anabaena sp.	Acylase	AiiC	Romero et al. (2008)
Arthrobacter nitroguajacolicus	PQS	Hod	Pustelny et al. (2009)
Anabaena sp.	Acylase	AiiC	Romero et al. (2008)
Bacillus megaterium	Oxidoreductase	CYP102A1	Chowdhary et al. (2007)
Bacillus sp.	Lactonase	AiiA	Dong et al. (2001)
Brucella melitensis	Acylase	AibP	Terwagne et al. (2013)
Chryseobacterium sp.	Lactonase	AidC	Wang et al. (2012)
Geobacillus kaustophilus	Lactonase	GKL	Chow et al. (2010)
Kluyvera citrophila	Acylase	KcPGA	Mukherji et al. (2014)
Klebsiella pneumoniae	Lactonase	AhlK	Park et al. (2003)
Mesorhizobium loti	Lactonase	MLR6805	Funami et al. (2005)
Microbacterium testaceum	Lactonase	AiiM	Wang et al. (2010)
Mycobacterium avium	Lactonase	MCP	Chow et al. (2009)
Ochrobactrum sp.	Acylase	AiiO	Czajkowski et al. (2011)
	Lactonase	AidH	Mei et al. (2010)
Pseudoalteromonas byunsanensis	Lactonase	QsdH	Huang et al. (2012)
Rhodococcus erythropolis	Lactonase	QsdA	Uroz et al. (2008)
Rhizobium sp.	Lactonase	DlhR	Krysciak et al. (2011)
	Lactonase	QsdR1	
Solibacillus silvestris	Lactonase	AhlS	Morohoshi et al. (2012)
Sulfolobus solfataricus	Lactonase	SsoPox	Merone et al. (2005)

lactonase enzyme, which breaks down the ester linkage in the homoserine lactone ring of metalloproteins AHL (Dong et al. 2000, 2001) (Fig. 2). These enzymes break down all signals regardless of acyl side chain substitutions and size, making them the ones with the widest diversity of AHL specificity. The second category is the acylase enzyme which breaks down the AHL amide linkage, releasing the corresponding homoserine lactone ring and free fatty acid (Lin et al. 2003). Acylases exhibit more substrate selectivity than lactonases, which could be a result of their ability to detect the signal's acyl chain. The oxidoreductases are the third class of known AHL QQEs; unlike acylase and lactonase activities, they oxidize or reduce the acyl chain of the AHLs instead of destroying them. The signals are not degraded by these reactions, but the alterations change the specificity and this consequently affects signal and receptor interaction.

Fungi are well known for producing extracellular enzymes such as cellulases, proteases, amylases, and others that can be used to degrade bacterial biofilms. For example, some enzymes extracted from *Trichoderma viride*, *Aspergillus niger*, and *Penicillium* species approved their efficacy as QSIs and degraded the biofilm of *P. aeruginosa* (Gautam et al. 2013).

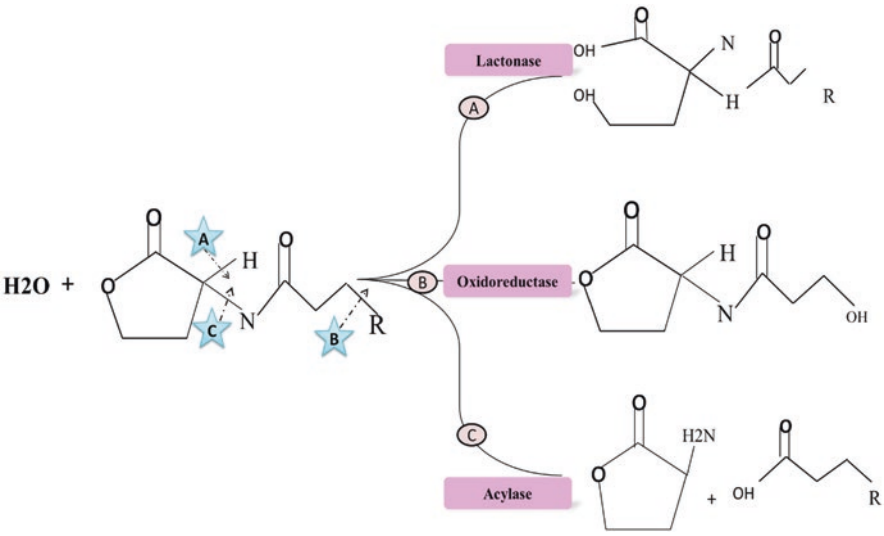

Fig. 2 Mechanisms of action of lactonase enzyme; A, oxidoreductase enzyme; B, and acylase enzymes; C

5 Conclusions

This review shows how we might draw inspiration from nature to focus on bacterial communication networks in the battle against diseases. Many other molecular entities that can interfere with bacterial virulence have been found in recent research, and many more are expected to be found in the near future. Anti-QS is crucial for combating infections because it does not put selection pressure on the population and is unlikely to lead to a resistance issue. For a better understanding of the processes involved, in vivo investigations in relevant animal models are required. It is crucial to thoroughly examine the organism's pathogenicity mechanisms, including their relationship to QS.

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