

## Review

# Quorum Quenching Mediated Approaches for Control of Membrane Biofouling

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## Abstract

Membrane biofouling is widely acknowledged as the most frequent adverse event in wastewater treatment systems resulting in significant loss of treatment efficiency and economy. Different strategies including physical cleaning and use of antimicrobial chemicals or antibiotics have been tried for reducing membrane biofouling. Such traditional practices are aimed to eradicate biofilms or kill the bacteria involved, but the greater efficacy in membrane performance would be achieved by inhibiting biofouling without interfering with bacterial growth. As a result, the search for environmental friendly non-antibiotic antifouling strategies has received much greater attention among scientific community. The use of quorum quenching natural compounds and enzymes will be a potential approach for control of membrane biofouling. This approach has previously proven useful in diseases and membrane biofouling control by triggering the expression of desired phenotypes. In view of this, the present review is provided to give the updated information on quorum quenching compounds and elucidate the significance of quorum sensing inhibition in control of membrane biofouling.

Key words: quorum quenching, quorum sensing inhibition, natural compounds, wastewater treatment, biofouling, membrane bioreactor.

## Introduction

Wastewater treatment has become an issue of global concern as scientific community strives for ways to keep environment clean. Different conventional as well as advanced treatment processes such as activated sludge, rotating biological contactor or sequencing batch reactor and membrane bioreactor (MBR) have been in use to treat industrial and municipal wastewaters. Among them, MBR is now accepted as a technology of choice for various wastewater treatments. MBR is state-of-the-art high quality wastewater treatment technology consisted of common bioreactors with membrane filtration units for biomass retention [1]. Recent technological innovations and significant membrane cost reduction have allowed the MBRs to become an established treatment

system for industrial and municipal wastewaters [2]. MBRs have emerged as an effective solution to transform wastewaters into high quality effluent suitable for discharge into surface waterways or to be reclaimed for irrigation purpose. The other advantages of MBR include small footprint, modular design, easy retrofit and ease of operation with high automation potential [2, 3]. As a result the use of MBR for treating domestic sewage, landfill leachate, hospital wastewater, restaurant wastewater, petrochemical wastewater and high-concentration industrial wastewater has significantly increased and the widening of application areas will occur in future [4]. To date, the MBR wastewater treatment technology is being successfully applied at number of locations

around the world. It is expected that MBR use for wastewater treatment will be sustained in future and further acceleration will depend on its better performance. The major players involved in the commercial production of MBR unit include CNC-Siemens, Zenon-GE, Mitsubishi-Rayon, Tory, Kubota, Motimo etc [4].

Despite numerous advantages of MBR over conventional wastewater treatment processes, there are some challenges faced by technology that may restrict its wider applications. These are; pretreatment of wastewater to remove hairs, lint, fibrous materials and other debris, high operational costs due to the use of anti-fouling strategies applied to the system, lack of long-term performance, clogging of aerators and so on [5, 1]. One of the major drawback and process limitation of MBR is clogging of membrane surface during the filtration. This phenomenon termed as 'membrane fouling' is the coverage of membrane surfaces by deposition of soluble and particulate materials onto and into the membrane which lead to a loss in permeability. The fouling of membrane initiated with the attachment of soluble microbial products (SMP), bacteria and other colloidal particles onto the membrane surface. The early bacterial attachment, subsequent growth and colonization across the overall membrane surface result into biofilm formation. The developed biofilms are highly heterogeneous and consist of both water-permeable and non-permeable substances. Biofilms lead to several adverse effects on MBR performance such as significant reduction in hydraulic performance, transmembrane pressure (TMP) increase, loss of system productivity, shorten membrane lifespan and increased operation cost; which makes biofouling becomes one of the most challenging issues facing further MBR developments.

To make the MBR as an option of choice for wastewater treatment, it is necessary to overcome the problem of membrane biofouling. Various perspectives including causes, characteristics, mechanism of fouling and methods of control have been investigated previously [6]. More recent, different physico-chemical and biological strategies have been attempted to control membrane biofouling. Most strategies for reducing MBR biofouling are focused on the physical cleaning of membrane surfaces, modification of existing membranes and incorporation of antibiotics or antimicrobial compounds in MBRs [6, 7]. Different antimicrobial compounds have been extensively tried to control membrane biofouling such as nitrofurazone, chlorhexidine, silver salts, polymerized quaternary ammonium surfactants, anionic nanoporous hydrogels and antibacterial peptides [8]. However, some antimicrobial compounds are also toxic to non-target organisms and pollute the aquatic envi-

ronment. A major challenge presented by formed biofilms is that the bacteria living within biofilms have higher protection against antimicrobial compounds and are markedly more tolerant to such control treatments [9]. Such complex structure of biofilms require excess use of antibiotics or synthetic antimicrobials which results in emergence of multi-antibiotic resistance among them. However, the control of biofouling does not mean the killing bacteria or limiting its growth but to block the expression of biofilm forming phenotypes. Quorum sensing, a way of bacterial population density-dependent cell to cell communication and phenotype regulation is known to associate with biofilm formation [10, 11]. Thus unlike antibiotics, interrupting quorum sensing may represent a novel alternative approach to combat membrane biofouling.

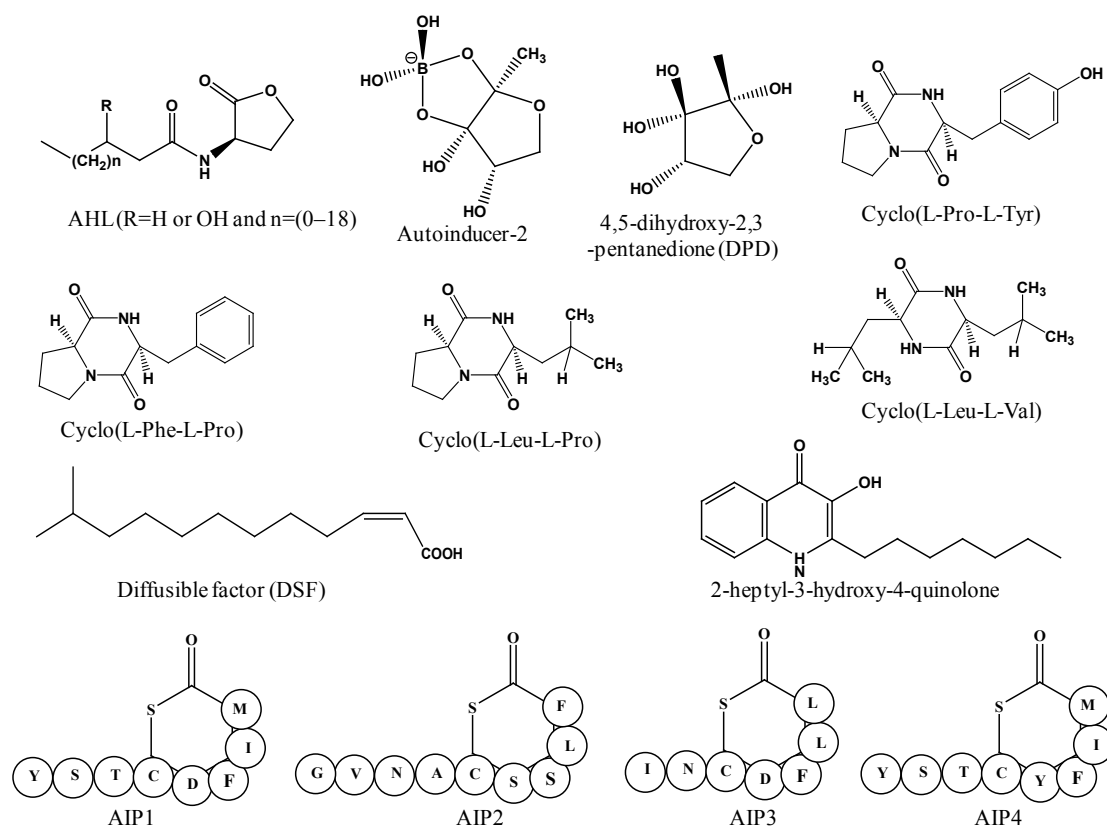
Recently, interest in controlling membrane biofouling through use of quorum quenching mediated approaches has increased among scientific communities. Since quorum sensing controls a range of biological functions associated with biofilms, this approach has the potential in controlling membrane biofouling. In quorum quenching, the targets are not essential for bacterial survival and therefore are not subject to adverse effects observed like due to conventional antibiotics [12-15]. It has been reported that a variety of natural compounds such as vanillin, furanones, flavonoids, curcumin etc. and few enzymes showed considerable quorum quenching activity against biofouling bacteria without interfering with its growth [16-21]. Moreover, the concept of bead-entrapped quorum quenching bacteria has been introduced to MBR as a new biofouling control paradigm [22]. In view of this, the present review is focused to cover all the important aspects of quorum quenching mediated approaches for control of membrane biofouling. Understanding the previous studies on quorum quenching compounds will help to design non-antibiotic biofouling control strategies and give pointers for best practices.

## Quorum sensing system

Bacteria use the language of small diffusible signaling molecules called autoinducers to communicate and assess their population densities in a process called quorum sensing. The sensing mechanism is based the synthesis, release and uptake of autoinducers in the surrounding medium, whose concentration correlates to the density of secreting bacteria in the vicinity. The basic mechanism of QS involves the interaction of autoinducer with a transcriptional regulator, either directly or through activation of a sensor kinase [23]. Both the Gram-positive and Gram-negative bacteria use species-specific au-

toinducers for activation of quorum sensing system. A variety of quorum sensing signaling molecules functions as local sensors to communicate population densities in bacteria. These signaling molecules and their receptors have been broadly divided into three major classes: *N*-acyl homoserine lactones (AHLs), which vary in the length and oxidation state of the acyl side chain and produced by Gram-negative bac-

teria; oligopeptides or autoinducing peptides (AIP), consisting of 5-34 amino acids residues, are generally used by Gram-positive bacteria; autoinducer-2 (AI-2), a ribose derivative [4,5-dihydroxy-2,3-pentanedione] employed by both Gram-positive and Gram-negative bacteria for interspecies communication (Figure 1 and Table 1) [24, 25].



**Figure 1.** Structures of bacterial quorum sensing signaling molecules, representing three major classes of autoinducers; *N*-acyl homoserine lactones, autoinducer-2 and autoinducing peptides 1 to 4.

**Table 1.** Quorum sensing signaling molecules and phenotypes controlled in Gram-negative and Gram-positive bacteria.

Autoinducer(s)	Producing bacteria	Phenotype(s) controlled	Ref.
Gram-negative bacteria			
<i>N</i> -acyl homoserine lactone (AHL)	<i>V. fischeri</i> , <i>P. aeruginosa</i> , <i>C. violaceum</i> , <i>Aer. hydrophila</i>	Bioluminescence, Exopolysaccharide production, Biofilm formation, Virulence factor, Pigmentation	[30-35]
Autoinducer-2 (AI-2)	<i>V. harveyi</i> , <i>E. coli</i> , <i>Y. pestis</i>	Bioluminescence, Biofilm formation, Motility, Virulence factor	[36-39]
4,5-dihydroxy-2,3-pentanedione	<i>Sa. enteric</i> serovar <i>typhimurium</i>	Virulence factor	[40, 41]
Cyclic dipeptides/ Diketopiperazines (DKP)	<i>P. putida</i> WCS358, <i>P. aeruginosa</i>	Cross activates QS biosensors	[42, 43]
(a) Cyclo(L-Pro-L-Tyr)			
(b) Cyclo(L-Phe-L-Pro)	<i>P. putida</i> WCS358, <i>P. aeruginosa</i>	Cross activates QS biosensors	[42, 43]
(c) Cyclo(L-Leu-L-Pro)	<i>P. putida</i> WCS358	Cross activates QS biosensors	[42]
(d) Cyclo(L-Leu-L-Val)	<i>P. putida</i> WCS358	Cross activates QS biosensors	[42]
Quinolone (2-heptyl-3-hydroxy-4-quinolone)	<i>P. aeruginosa</i>	Antibiotic production	[44-46]
Diffusible factor (DSF)	<i>X. campestris</i>	Endoglucanase production	[47]
Gram-positive bacteria			
Autoinducing peptide (AIP1-AIP4)	<i>Sta. aureus</i>	Cross-signaling between strains and species, Biofilm formation, Virulence factor	[28, 29, 48, 49]

A numbers of structurally diverse autoinducers have been identified in Gram-positive and Gram-negative bacteria. Most of them are either small (<1000 Da) organic molecules or peptides with 5-20 amino acids [26, 27]. Gram-negative bacteria employ AHL, 2-heptyl-3-hydroxy-4-quinolone, fatty acid methyl esters, long-chain fatty acids and a group of inter-convertible furanones derived from DPD called AI-2. The ribose derivative AI-2 is also produced by Gram-positive bacteria, but these organisms generally prefer linear, modified or cyclic peptides AIP made by *Staphylococcus sp* [28, 29]. The diffusible factor c-butyrolactones produced by *Streptomyces sp.* is structurally related to AHLs, as both classes belong to butanolides. In general, AHLs produced by Gram-negative bacteria and AIP from Gram-positive bacteria are often engaged in quorum sensing signaling and have been most intensively investigated. Many of these quorum sensing signal molecules are chemically diverse and species specific, while some of them can be recognized by inter-species communication. Such signal molecules exhibit biological properties far beyond their role in coordinating gene expression in producer strain. It is speculated that quorum sensing system allows bacteria to listen the communication signals from other bacteria and exploit this information to its own advantage.

Most of Gram-negative bacteria use AHLs to regulate quorum sensing mediated behaviors, while Gram-positive bacteria prefer linear, modified or cyclic peptides such as the AIP to control quorum sensing phenotypes. The quorum sensing systems regulate the coordination of population behavior to enhance nutrient availability, collective defense against other antagonizing organisms or community escape from adverse conditions [27]. Since the discovery of quorum sensing regulation in bacteria, numerous such systems have been described. These quorum sensing systems regulates diverse functions in both Gram-negative and Gram-positive bacteria, which include biofilm formation, virulence factor, bioluminescence, motility patterns, exopolysaccharide production, antifungal or antibiotic production, endoglucanase production, pigmentation, competence, plasmid conjugal transfer, cross-signaling between strains and species etc.

### **AIP mediated quorum sensing in Gram-positive bacteria**

Several Gram-positive bacteria are known to use modified peptides also called AIP as signaling molecules to regulate different phenotypes such as virulence (agr system in *Staphylococcus sp.*), bacteriocin production (pin and ssp systems in lactic acid bacteria) and competence (com system in *B. subtilis*) [50-52].

The AIP are generated by cleavage from larger precursor peptides and subsequent modification with substitution of isoprenyl groups to form lactone and thiolactone rings [53]. When the extracellular concentration of AIP becomes high, that binds to cognate membrane-bound two-component histidine kinase receptors. Which further lead into induction of receptor's kinase activity and transcription of genes in the quorum sensing regulon [54]. In case of some Gram-positive bacteria, the AIP are detected by membrane-bound two component signal transduction system [55, 50]; as the bacterial cell membrane is impermeable to peptides the specialized transporters are required to secrete AIP. Certain species of Gram-positive bacteria use AIP to regulate the production of virulence factors and biofilm formation [48, 49]. The human pathogen *Sta. aureus* uses the paradigmatic Agr system to regulate adhesion and production of virulence factors [54]. It is also reported that AIP-mediated quorum sensing has been used to regulate bacterial competence and conjugation in *Sta. aureus* and *Ent. faecalis* respectively [56]. Thus, the evolution of AIP-mediated quorum sensing system in pathogenic bacteria could have been an effective therapeutic strategy for the control of virulence and biofilms in diseases. However, there is one report available suggesting the involvement of AI-2 mediated quorum sensing in membrane biofouling; where reduced AI-2 was positively correlated to the reduced fouling resistance of nylon membranes [57].

### **AHL mediated quorum sensing in Gram-negative bacteria**

The best-studied quorum sensing systems in Gram-negative bacteria use LuxI-type enzymes, which produce AHLs as small diffusible signal molecules that get bind and activate members of the LuxR transcriptional activator protein family [58, 59]. AHL based quorum sensing system functions through three key components: i) AHL signal molecules, ii) AHL synthase protein for synthesis of AHL signals, and iii) a regulatory protein which responds to surrounding concentration of AHL signal [60]. This process initiated with the synthesis and release of AHL signals into the surrounding environment which accumulates in a cell-population-density-dependent manner. When the concentration of AHL signals reaches at higher level; the quorum sensing cells starts responding allowing them to regulate the production of secondary metabolites and control the expression of quorum sensing genes. A majority of Gram-negative bacteria regulates various phenotypes through the secretion and detection of such signaling molecules. However the efficacy of expression of quorum sensing phenotypes depends upon the pres-

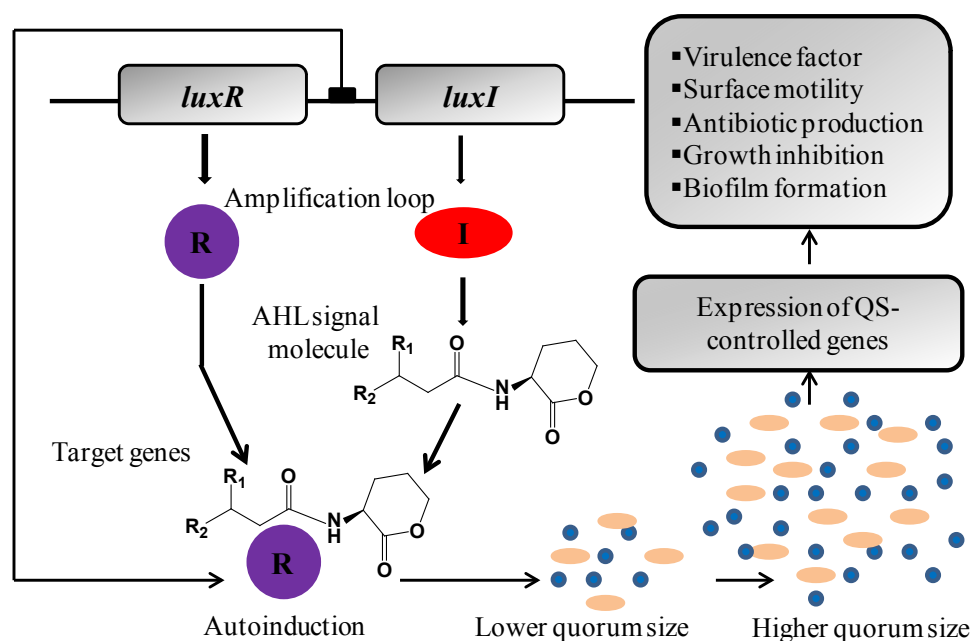
ence or absence of surrounding cells. Using quorum sensing bacteria can act to express a specific set of genes responsible for variety of physiological behaviors including bioluminescence, antibiotic production, extracellular polymer production, biosurfactant synthesis, sporulation, release of virulence factors and biofilm formation (Figure 2) [61-66].

The use of biosensor systems to detect quorum sensing signaling molecules has led to the discovery of broad range of AHLs as produced by diverse Gram-negative proteobacteria belonging to  $\alpha$ ,  $\beta$ , and  $\gamma$  subdivisions [26]. The AHLs biosensors system consist of a quorum sensing-controlled promoter fused to a reporter such as *lacZ* or *lux* or *gfp* operon [67, 68, 34] or pigment induction e.g. violacein in *C. violaceum* [31]. These biosensor strains have a functional R protein but lack the AHL synthase; thus the promoter activity depends on the presence of exogenous AHL [69]. Use of biosensor strains revealed that wide genera of Gram-negative bacteria produce a broad range of AHL molecules ranging from C4 to C18-carbon acyl side chains and either an oxo, a hydroxy, or no substitution at the third carbon. The acyl chain varies in length, saturation level, and oxidation state. In most cases, the acyl chain has an even number of carbon (C4-C18), although some AHLs with odd carbon (C5-C7) have been investigated [70, 71]. Examples of AHLs producing bacteria includes species of *Aer-*

*omonas*, *Acidithiobacillus*, *Acinetobacter*, *Agrobacterium*, *Brucella*, *Burkholderia*, *Erwinia*, *Enterobacter*, *Chromobacterium*, *Mesorhizobium*, *Pseudomonas*, *Ralstonia*, *Rhodobacter*, *Rhizobium*, *Serratia*, *Sinorhizobium*, *Vibrio* and *Yersinia* [27]. Many of these bacteria have ability to produce multiple AHLs due to the presence of more AHL synthase and thus can regulate different phenotypes.

## Quorum sensing and biofouling

Quorum sensing and biofilm formations are the central and interconnected feature of bacterial social life [72-74]; which enables bacteria to organize their activities at the population level and switch from acting as individual cells to concentrated multi-cellular structure in the form of biofilms [75]. Biofilms are the matrix enclosed bacterial cells attaching to each other or to surfaces [76]. Such complex multi-layer structure of defined architecture helps bacterial communities to live in a sessile and protected environment [77, 78]. The formation of biofilm is linked to a number of interacting processes beginning with secretion of signal molecules, solute diffusion, cell to cell or cell to solute interactions, EPS matrix production, colonization, surface attachment and maturation [79].



**Figure 2.** The LuxR/AHL-mediated quorum sensing regulation of multiple gene expressions in Gram-negative bacteria. The 'R' and 'I' genes are homologues of the LuxR and LuxI genes in which the 'R' protein is the AHL receptor and signal transducer while I protein is AHL signal synthase. The I protein is responsible for the production of AHLs. After synthesis, AHLs get diffuse (short chain) or pumped out (long chain) of the bacterial cell into the surrounding medium prior to being taken up into nearby bacterial cells. The AHL activate R protein by direct binding to make AHL/R protein complex which rapidly increases I gene expression and hence AHL production. At a certain level of bacterial cells, the quorum sensing system becomes fully activated which leads to R-mediated expression of quorum sensing target genes.

The bacterial biofilms are ubiquitous in nature and exist on all type of surfaces in water and wastewater treatment systems, which may play beneficial as well as detrimental roles. The presence of biofilms or attached bacterial cells on filtration membranes is highly prevalent and often adversely affects its efficiency. The robust biofilms are needed for treatment of wastewater by trickling filters, granular sludge and moving bed biofilm reactors [6, 80]. However, deposition of biofilms and associated extracellular polysaccharides (EPS) on membrane surfaces decreases filtration flux and causes permeability loss [81, 82]. The non-degraded organic matters, microbial flocs and SMP are also considered as potential foulants [83, 84], but the formation of biofilms on membrane surfaces is the major contributor in membrane biofouling and is the main obstacle restricting the development of MBR technology for advanced wastewater treatment.

The role of AHL-mediated quorum sensing in the development of specialized biofilm structure is best understood in *P. aeruginosa* [85]. The genes and quorum sensing regulatory circuits associated with initial cell-surface interactions and biofilm maturation are also identified in some bacteria [77]. Numerous links have been made between quorum sensing and biofilm formation, which includes direct demonstration of *Aeromonas sp.*, *Pseudomonas sp.* and *Xanthomonas sp.* AHLs-mediated phenotypes important to biofilm formation in water treatment systems [85-88]. The relationship between *P. putida* adhesions to different membrane surfaces was found to be a AHLs-mediated quorum sensing trait [89]. Xia et al. [90] demonstrated that diffusion of exogenous 3-oxo-C8-HSL increased the growth rate of *P. aeruginosa* cells on ultra-filtration membrane biofilm and had no influence on EPS of biofilm. The quorum sensing system might enhance the growth of neighboring bacterial cells in contact with membrane surfaces into biofilm and may influence the structure and organization of biofilm. The results of the study also showed that quorum sensing system has a significant relation with protein production. A correlation between AHLs production and biofilm formation was reported among activated sludge bacterial isolates; where biosensor assay with *C. violaceum* 026 and *A. tumefaciens* A136 confirms the ability of *Aeromonas*, *Enterobacter*, *Serratia*, *Leclercia*, *Pseudomonas*, *Klebsiella*, *Raoultella* and *Citrobacter sp.* to produce AHLs and form biofilms on polystyrene surface [91].

In addition to this, several studies have linked presence of AHLs with biofilm formation and addressed the problem of membrane biofouling in MBRs [82, 89, 92]. The chromatographic analysis of MBR sludge using HPLC technique has identified the

presence of several AHLs molecules. Recently HPLC analysis of MBR sludge has suggested the presence of 3-oxo-C8-HSL and C8-HSL in MBR activated sludge [22]. Moreover, HPLC characterization by Lade et al. [91] detected eight different AHLs v.z. C4-HSL, C6-HSL, C8-HSL, 3-oxo-C8-HSL, C10-HSL, C12-HSL, 3-oxo-C12-HSL and C14-HSL in activated sludge collected from MBR treating wastewater. Yeon et al. [93] detected C6-HSL and C8-HSL from mixed cultured biocake derived from fouled MBR treating wastewaters. These studies suggest that AHLs-mediated quorum sensing is extensively regulating biofilm formation. Though AHLs have been detected in activated sludge and biofouling bacteria, the precise role in membrane biofouling is not clear. Further investigation need to be carried out to understand the exact role of AHLs in various stages of biofouling. Still, membrane biofouling is persistent problem in MBR treating wastewaters and interfering with quorum sensing system may eliminate it and thus increase its efficiency.

## Quorum quenching and biofouling control

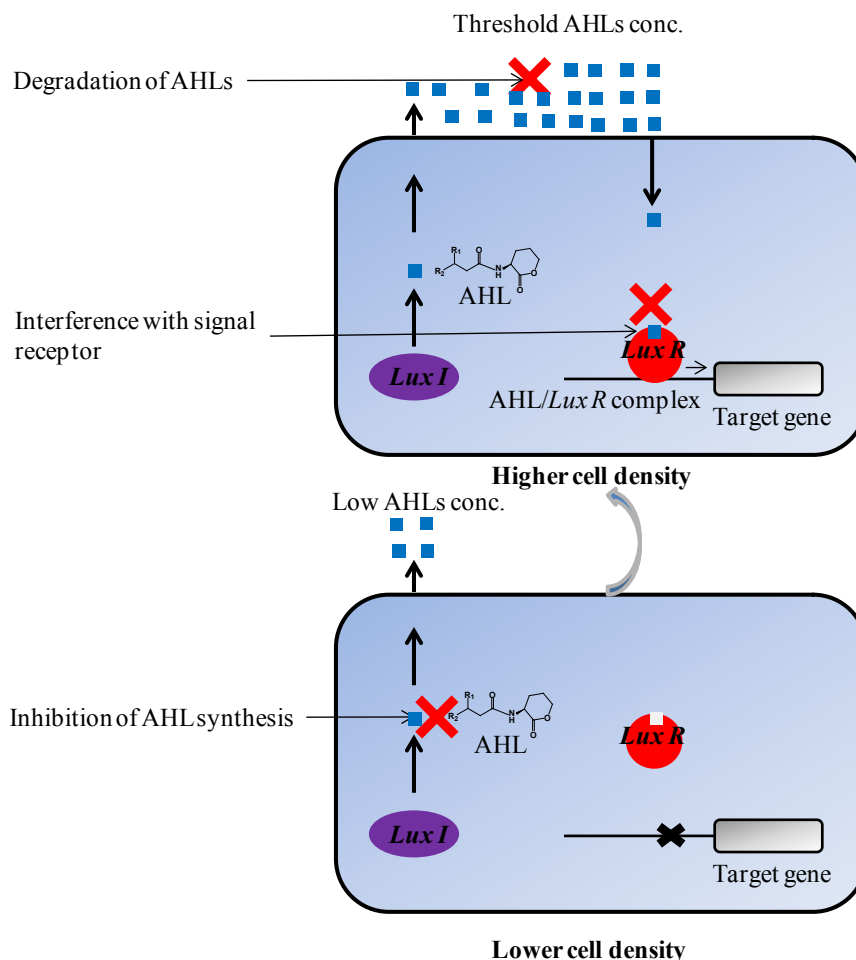
The quorum quenching refers to a process by which autoinducer-mediated quorum sensing is interrupted [94]. Quorum sensing helps bacteria to coordinate community-based behavior, but it is not essential for survival or growth. Thus, interference with quorum sensing may lead to the inhibition of desired phenotypes such as formation of biofilms. The large numbers of aquatic bacteria are Gram-negative and employ AHLs-mediated quorum sensing as their major language to coordinate population behavior [95, 10]. Since quorum sensing is involved in formation of biofilms, targeting quorum sensing has offered a novel way to combat membrane biofouling without killing or inhibiting bacterial growth [96].

There are several quorum quenching strategies available through which the process of quorum sensing can be interrupted which includes; i) Inhibition of AHL synthesis by blocking the LuxI-type synthase proteins [97, 98] ii) Enzymatic destruction of AHLs molecules by AHL-acylase and AHL-lactonase that will prevent them from accumulating [99, 33, 100] and iii) Interference with signal receptors or blockage of formation of AHL/LuxR complex [101, 102] (Figure 3). In addition to this, quorum quenching has previously proven to be a primarily target both for quorum sensing signal synthase and sensor or response regulator proteins involved [12-15]. These strategies can be applied to achieve inhibition of AHLs-mediated quorum sensing in Gram-negative and AIPs-mediated quorum sensing in Gram-positive bacteria. However, as the membrane biofouling is

mainly associated with AHLs-mediated quorum sensing, our focus in this review is on inhibition of AHLs-mediated quorum sensing.

The traditional practices of biofouling control are based on antimicrobial compounds or antibiotics that kill or inhibit bacterial growth. However bacterial survival is essential for decomposition of contaminants and a major concern with the use of antimicrobial agent is development of multi-drug resistance

among bacteria exposed [103]. This leads the way for an intense search of non-antibiotic compounds that can specifically block AHL-mediated biofouling trait without interfering with growth. It is envisioned that some natural compounds and enzymes can control the AHLs-mediated biofilm formation without affecting bacterial growth and also reduce the risk of multi-drug resistance.



**Figure 3.** Inhibition of quorum sensing in Gram-negative bacteria by various mechanisms. Three quorum quenching strategies have been used for attenuating AHL-mediated phenotypes; (i) Inhibition of AHL synthesis (ii) Degradation of AHL signal molecules (iii) Interference with signal receptor.

## Natural compounds as QSI

Many natural compounds of plant origin are well known for antimicrobial activities [104], and also shown to inhibit quorum sensing while not affecting bacterial growth. The mammalian cells, plant and algae are known to secrete the novel class of such non-antibiotic quorum quenching compounds which either activate or inhibit bacterial quorum sensing [105, 106]. Traditional medicinal plants are one of the most promising sources in search for natural quorum sensing inhibitory compounds. Several compounds of natural origin which can interfere with bacterial

quorum sensing system and inhibit biofilm formation have been identified as secondary metabolites produced by algae, fungi, bacteria and higher plants. A major advantage of natural compounds is that it ruins the problem of bacterial resistance to conventional antibiotics, as it specifically interferes with expression of specific traits. The natural compounds are structurally similar to those of quorum sensing signal molecules and thus antagonize them and also have ability to degrade LuxR/LasR signal receptors [107, 108]. A summary of the known natural quorum sensing inhibitory compounds derived from plant, fungi, algae and bacteria is provided in Table 2.

**Table 2.** Natural compounds as quorum sensing inhibitors.

Natural compound(s)	Source	QS activity	Ref.
Furanone/ 2(5H)-Furanone/	Macroalga ( <i>Delisea pulchra</i> )	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 <i>Aer. hydrophila</i>	[109, 17]
(5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone.	Macroalga ( <i>Delisea pulchra</i> )	Repress LuxR protein dependent expression of P(luxI)-gfp(ASV) reporter fusion. Inhibit virulence factor in <i>E. coli</i> XL-1.	[110]
Ajoene (1-Allyldisulfanyl-3-(prop-2-ene-1-sulfinyl)-propane)	Garlic extract ( <i>Allium sativum</i> )	Disrupts QS-regulated bioluminescence in <i>V. harveyi</i> by interacting with Hfq protein. Inhibit swarming motility and biofilm formation in <i>E. coli</i>	[111, 112]
Iberin (1-Isothiocyanato-3-(methylsulfinyl)propane)	Horseradish extract ( <i>Armoracia rusticana</i> )	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 <i>P. aeruginosa</i> PAO1	[113, 114]
Sulforaphane (1-Isothiocyanato-4-(methylsulfinyl)butane)	Boroccoli	Inhibit expression of QS-regulated <i>lasB-gfp</i> and <i>rhlA-gfp</i> genes responsible for virulence factor in <i>P. aeruginosa</i>	[115]
Erucin (4-methylthiobutyl isothiocyanate)	Boroccoli	Reduce the expression of <i>lasI-luxCDABE</i> reporter in <i>P. aeruginosa</i>	[116]
Naringin (4'5-diOH-Flavone-7-rhgluc)	Citrus extract	Reduce the expression of <i>lasI-luxCDABE</i> reporter in <i>P. aeruginosa</i>	[116]
Naringenin (4',5,7-Trihydroxyflavanone)	Malagasy bark extract ( <i>Combretum albiflorum</i> )	Decrease the QS mediated biofilm formation and swimming motility in <i>Y. enterocolitica</i>	[18]
Taxifolin/ Distylin (dihydroquercetin)	Malagasy bark extract ( <i>Combretum albiflorum</i> )	Reduces production of pyocyanin and elastase in <i>P. aeruginosa</i> PAO1. Also inhibit 3-oxo-C12-HSL and C4-HSL synthesis driven by <i>lasI</i> and <i>rhlII</i> genes	[117, 118]
Morin (2',3,4',5,7-Pentahydroxyflavone)	Malagasy plant extract ( <i>Combretum albiflorum</i> )	Reduces production of pyocyanin and elastase in <i>P. aeruginosa</i> PAO1	[117]
Patulin/ Clavacin (4-Hydroxy-4H-furo[3,2-c]pyran-2(6H)-one)	Grapefruit ( <i>Artocarpus heterophyllus</i> )	Inhibit LasR and RhlR dependent protease, elastase and hemolysin in <i>P. aeruginosa</i> PAO1	[119, 120]
Penicillic acid (3-Methoxy-5-methyl-4-oxo-2,5-hexadienoic acid)	<i>Penicillium sp.</i>	Targets the RhlR and LasR proteins. Down-regulates QS genes for biofilm formation and virulence in <i>P. aeruginosa</i>	[121]
Vanillin (4-Hydroxy-3-methoxybenzaldehyde)	<i>Penicillium sp.</i>	Down-regulates QS genes for biofilm formation in <i>P. aeruginosa</i>	[121]
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)	Vanilla beans extract ( <i>Vanilla planifolia Andrews</i> )	Interfere with AHL receptors. Inhibit C4-HSL, C6-HSL, C8-HSL, 3-oxo-C8-HSL. Inhibit biofilm formation in <i>Aer. hydrophila</i>	[122, 123, 16]
L-canavanine (L- $\alpha$ -Amino- $\gamma$ -(guanidinoxy)-n-butyric acid)	Crown gall cells	Control conjugation of pTic58 by regulating expression of the arc operon in <i>A. tumefaciens</i>	[124]
Gamma-aminobutyric acid (GABA) (4-Aminobutanoic acid)	Seed exudates ( <i>Medicago sativa</i> )	Inhibit the expression of QS-regulated phenotype exopolysaccharide II production in <i>Si. meliloti</i>	[125]
Rosmarinic acid (R-O-(3,4-Dihydroxycinnamoyl)-3-(3,4-dihydroxyphenyl) lactic acid)	Plants ( <i>Arabidopsis sp.</i> )	Induce the expression of attKLM operon to stimulate inactivate 3-oxo-C8-HSL by <i>A. tumefaciens</i> lactonase AttM	[126, 127]
Salicylic acid (2-Methyl-5-tert-butylsalicylic acid)	Sweet basil ( <i>Ocimum basilicum</i> )	Inhibit protease, elastase, hemolysin production, biofilm formation and virulence factor in <i>P. aeruginosa</i>	[119, 108, 128]
Chlorogenic acid (3-Caffeoylquinic acid)	Plant phenolic secondary metabolite	Inhibit the expression of vir regulon in <i>A. tumefaciens</i> . Also stimulates AHL-lactonase expression which degrades AHLs.	[129]
Allin (2-Amino-3-[prop-2-ene-1-sulfinyl]-propionic acid)	Plant extract ( <i>Moringa oleifera</i> )	Inhibit QS-regulated violacein production in <i>C. violaceum</i> 12472	[130]
Ursolic acid (3beta-Hydroxyurs-12-en-28-oic acid)	Garlic extract ( <i>Allium sativum</i> )	Inhibit QS-regulated gene expression by interacting with receptors in <i>P. aeruginosa</i> and make biofilm sensitive to antibiotics.	[113, 131]
Ellagic acid (Benzoic acid)	Plant extract ( <i>Sambucus chinensis</i> )	Inhibit biofilm formation by suppressing cysteine synthesis in <i>E. coli</i>	[132, 133]
$\alpha$ -Hydroxybutyric acid (2-hydroxy-butanoic acid)	Fruit extract of <i>Terminalia chebula</i> Retz.	Down-regulate the expression of virulence gene in <i>P. aeruginosa</i> PAO1. Reduces biofilm formation and swarming motility in <i>B. cepacia</i>	[134, 135]
Epigallocatechin gallate (Epigallocatechol)	<i>Arabidopsis exudates</i>	Induce the expression of attKLM-lacZ fusion in <i>A. tumefaciens</i>	[136]
Pyrogallol (1,2,3-Trihydroxybenzene)	Green tea ( <i>Camellia sinensis</i> L.)	This compound has gallic acid moiety and specifically block AHL-mediated biofilm formation in <i>Sta. aureus</i> and <i>B. cepacia</i> .	[135, 137-139]
Cinnamon oil/ Cynamaldehyde (trans-Cinnamaldehyde)	Plant extract ( <i>Punica granatum</i> )	Inhibit transfer of conjugative R plasmid in <i>E. coli</i>	[140, 141]
Furocoumarin/ Psoralen (7H-Furo[3,2-g][1]benzopyran-7-one)	Plant extract ( <i>Cinnamomum zeylanicum</i> )	Inhibit AI-2 mediated bioluminescence in <i>V. harveyi</i>	[140, 141]
Urolithin (3,8-Dihydroxy-benzo[c]chromen-6-one)	Grapefruit juice and extract ( <i>Psoralea corylifolia</i> L.)	Interfere with AI-2 based QS and decreases the DNA-binding ability of LuxR protein to reduce virulence in <i>V. spp.</i> Reduces LuxR-mediated transcription from the PluxI promoter which influences biofilm formation in <i>P. aeruginosa</i>	[142, 143]
		The structural resemblance of furan moiety results in QS-mediated inhibition of biofilm formation in <i>E. coli</i> . Inhibit QS-mediated swarming motility in <i>P. aeruginosa</i> PAO1	[144, 145]
	Ellagitannin-rich extract from Pomegranate	Inhibit C6-HSL and 3-oxo-C6-HSL associated biofilm formation in <i>Y. enterocolitica</i> . Inhibit QS-mediated swarming motility in <i>E. coli</i>	[146, 147]



Curcumin (E,E)-1,7-bis(4-Hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	From <i>Curcuma longa</i>	and <i>P. aeruginosa</i> PAO1 Down-regulates virulence factors and biofilm initiation genes in <i>P. aeruginosa</i> PAO1 and inhibit its phenotype expression. [19]
$\alpha$ -D-galactopyranosyl-(1 $\rightarrow$ 2)-glycerol (floridoside) (N), Betonicine (O), and Isethionic acid	Red alga ( <i>Ahnfeltiopsis flabelliformis</i> )	Attenuate QS-dependent EPS production, swarming motility and biofilm formation in uropathogenic <i>E. coli</i> , <i>P. aeruginosa</i> , <i>Pr. mirabilis</i> and <i>S. marcescens</i> . [148]
Musaceae	Musaceae extract ( <i>Musa paradisiaca</i> )	Inhibit C8-HSL mediated QS in <i>A. tumefaciens</i> NTL4 [149]
Garlic	Garlic extract	Inhibit QS-mediated elastase production and biofilm formation in <i>P. aeruginosa</i> PAO1 [150]
<i>Piper betle</i>	<i>Piper betle</i> extract	Interferes with expression of QS-controlled virulence genes in <i>P. aeruginosa</i> [121]
<i>Cuminum cyminum</i>	<i>Cuminum cyminum</i> extract	Inhibit QS-mediated biofilm formation in <i>P. aeruginosa</i> [151] Reduce LuxR dependent biofilm formation and swarming motility of <i>P. aeruginosa</i> [152]

A promising group of natural QSI is the halogenated furanones produced by the Australian red alga, *Delisea pulchra* which inhibit AHLs-mediated gene expression by interfering with AHL signal from its reporter protein [153, 110]. Halogenated furanones are also known to inhibit quorum sensing by destabilizing and accelerating the turnover of LuxR which then impairs its ability to bind DNA and initiate transcription [154]. It has now been shown that furanones inhibits AHLs as well as AI-2 based quorum sensing system as they are structural mimics of lactones and tetrahydrofuran rings of quorum sensing system [112]. The marine alga *Delisea pulchra* produces furanones in central vesicle gland cells and secrete to the fronds to prevent bacterial colonization and thereby macro-fouling [155]. Furanones are structural analogues to short-chain AHLs and appears to interact directly with LuxR-type receptors [156]. Thus, they inhibit AHL-mediated quorum sensing and subsequent biofilm formation in some Gram-negative bacteria such as *P. aeruginosa*, *V. harveyi* and *E. coli* [122, 157-160, 112]. A natural compound (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H)-furanone produced by marine alga has been shown to inhibit swarming motility and biofilm formation in *E. coli* at concentration non-lethal to planktonic growth [112, 111].

Flavonoids are widely distributed in the plant kingdom and are known for their numerous and determinant roles in plant physiology, metabolism and development of plant-rhizobia interactions. For the human health perspective, flavonoids have shown their roles as anti-oxidant, anti-inflammatory and anticancer agents [161]. In addition to these health benefits, flavonoids such as kaempferol, naringenin, quercetin and apigenin have been reported as inhibitors of AHL and AI-2 mediated pathogenic traits in *P. aeruginosa* PAO1, *E. coli* O157:H7 and *V. harveyi* [117, 162, 163]. Quercetin and naringenin were found to inhibit quorum sensing based biofilm formation in *V.*

*harveyi* BB886 and *E. coli* O157:H7 [163]. Flavonones naringenin and taxifolin derived from Malagasy plant *Combretum albiflorum* attenuates the production of QS-controlled virulence factors in *P. aeruginosa* PAO1 [117]. Moreover, Flavan-3-ol catechin from the bark of same plant reduce the production of quorum sensing regulated virulence factors- pyocyanin, elastase and biofilm formation in *P. aeruginosa* PAO1 without affecting growth [118]. In addition, reduction in expression of several quorum sensing controlled genes i.e. lasI, lasR, rhlI, rhlR, lasA, lasB, phzA1 and rhlA was also reported with these compounds. Truchado et al. [18] reported the quorum sensing inhibitory effects of an orange extract enriched in O-glycosylated flavanone naringin, which diminished the levels of lactones secreted by pathogenic *Y. enterocolitica* and decreased quorum sensing mediated biofilm maturation without affecting bacterial growth. The naringin was also found to inhibit swimming motility and induce the transcription levels of *yenR*, *flhDC*, and *fliA* in *Y. enterocolitica*.

A sulfur-rich QSI compound ajoene have been identified from garlic extract, which can block the quorum sensing regulated production of rhamnolipids resulting in phagocytosis of biofilms. This compound also targets Gac/RSM part of quorum sensing system and lowers the expression of two small regulatory RNAs, RsmY and RsmZ in *Pseudomonas aeruginosa* PAO1 [114]. Another isothiocyanate containing sulfur-rich compound iberin extracted from horseradish has shown strong QSI activity [115]. A recent study identified sulforaphane QSI from broccoli extract, which covalently bind to cys79 residue in the 3-oxo-C12-HSL binding pocket of LasR in *P. aeruginosa* [116, 164]. An arginine analog L-Canavanine derived from seeds exudates of *Medicago sativa* has shown to serve as a nitrogen source for seed germination and also inhibit growth of certain bacteria and phytophagous insects [165]. This compound incorporates in place of L-arginine into nascent pro-

tein chains during synthesis and results in altered protein structure and function leading to death of target bacteria [165, 125].

More recently, various plants extract including habanero (chilli), tomato, crown vetch, soybean, water lily, *Daucus carota* subsp. *sativu*, *Medigo sativa*, *Pisum sativum* seedling, *Allium cepa*, *Allium sativum*, *Lycopersicon esculentu*, *Medicago truncatula*, vanilla, *Piper betle*, *Cuminum cyminum* and some medicinal plants of southern Florida were found to possess anti quorum sensing activities [121, 156, 166, 110, 167, 151, 152, 168]. A cyclic disulphur compound having strong antagonistic effect on LuxR-based quorum sensing has been identified from garlic extract [121, 169]. Furocoumarin derived from grapefruit was found to inhibit quorum sensing mediated biofilm formation in *E. coli* and swarming motility in *P. aeruginosa* PAO1 [144, 145]. Limonoids from sour orange seeds such as isolimononic acid, ichangin and deacetyl nomilinic acid 17  $\beta$ -D-glucopyranoside were found to inhibit AI-2 mediated quorum sensing in *V. harveyi* [170]. The structural resemblance of furocoumarin and limonoids with autoinducers molecule in the furan moiety was found to be responsible for competitive quorum sensing inhibition [171, 172].

It is expected that fungi can produce QSI compounds as they have co-existed with quorum sensing bacteria from millions of years. In a recent study two QSI compounds were identified as penicilic acid and patulin produced by *Pe. radiccicola* and *Pe. coprobium* respectively [121]. The DNA microarray-based transcriptomics showed that penicilic acid and patulin respectively targets 60% and 45% quorum sensing genes in *P. aeruginosa* suggesting the RhIR and LasR quorum sensing regulators [173, 121].

Therefore natural QSI offer a potential solution to the multidrug resistance associated with traditional antibiotics or antimicrobial compounds. Several comprehensive reviews on natural compounds that antagonize quorum sensing are available [174, 161]. However, further investigation is required to identify the potential QSI present in natural sources and mechanism they employ to antagonize quorum sensing. Use of natural QSI may lead to the development of novel non-antibiotic agent which will target at the inhibition of desired traits like biofilm formation or virulence factor rather than killing the bacteria.

### Natural compounds for control of membrane biofouling

Natural QSI have advantages of nontoxicity, high antifouling potential and low risk of bacterial resistance development. These compounds have mostly been applied to pathogenic bacteria; however some recent studies showed that control of membrane

biofouling could also be achieved by incorporation of natural QSI. An early example of the addition of natural quorum sensing compound in a CDC biofilm reactor (Center for Disease Control) was provided by Poonusamy et al. [175]. The author successfully used vanillin for combating *Aer. hydrophila* biofilms on five different membrane surfaces. Vanillin was also reported to inhibit the short and long-chain AHL-mediated quorum sensing leading to the reduction of *Aer. hydrophila* biofilm on polystyrene surface [16]. The Piper betle extract has been found to mitigate membrane biofouling in ultrafiltration MBR treating textile effluent [176]. In another study Piper betle extract has shown the reduction in biofilm formation and EPS production caused by *P. aeruginosa* and bacterial consortium without raising the selective pressure for the growth of microorganisms [151]. These results reveal that Piper betle extract could be used as a potential anti-quorum sensing agent for mitigation of membrane biofouling. The correlation between membrane biofouling and quorum sensing activity demonstrated that Piper betle extract could inhibit AIs production and reduce EPS and biofilm formation [177]. These evidences suggest that incorporation of natural QSI on membrane surfaces and addition in MBRs could be an effective strategy for control of membrane biofouling. Such artificial quorum sensing regulatory systems might help to mimic the problem of membrane biofouling without disturbing bacterial growth. Thus, engineered membranes with natural compounds are expected to be very useful in plant scale MBR and in designing of wastewater treatment systems with economic feasibility.

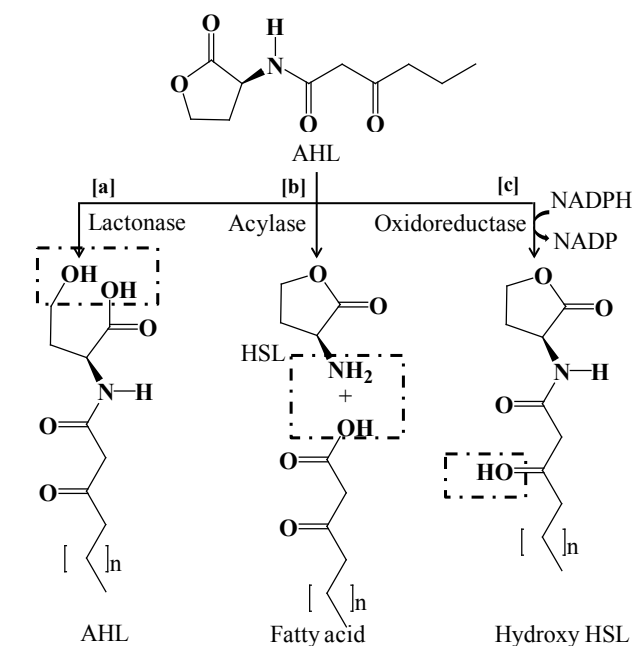
### Enzymes as QSI

Complete degradation or inactivation of AHL signal molecules can be achieved by quorum quenching enzymes. Two major classes of enzymes that degrades AHLs signal molecules are reported, which includes lactonases that open the homoserine (HSL) ring [178, 158, 179] and acylases that cleave the acyl side chain from the HSL ring [99, 180]. Another class of enzyme oxidoreductase has also been known to catalyze the oxidation or reduction of acyl side chain [181, 182] (Figure 4).

In nature, several AHLs degrading enzymes have been reported from large number of bacteria, fungi, plants and legumes. A broad spectrum of AHLs degrading AHL-acylases are produced by *Ralstonia sp.* XJ12B and *P. aeruginosa* PAO1 [99, 183]. Few examples of bacterial AHL acylases reported includes AiiD from *Ralstonia sp.* XJ12B [99], AhlM from *Streptomyces sp.* [184], PvdQ and QuiP from *P. aeruginosa* PAO1 [183, 185, 33] and AiiC from *Anabaena sp.* PCC7120 [185]. The acylases HacA and HacC produced by *P.*

*syringae* B728a have shown to degrade quorum sensing signal AHLs [187]. AHL-acylase produced by *Streptomyces sp.* has been shown to possess an ability to degrade specific AHLs having 6 or more acyl chains [184].

The other quorum quenching enzyme AHL-lactonases have been reported from various bacteria and fungi. The most promising bacteria producing AHL-lactonase are strains belonging to diverse *Bacillus sp.* such as *B. cereus*, *B. subtilis* and *B. thuringiensis* [188-191]. However, *B. thuringiensis* present a unique property as it does not produce quorum sensing signals but has AHL-lactonase activity [192]. The other bacterial lactonases includes AttM from *A. tumefaciens* c58 [179], AiiA from *Bacillus sp.* 240B1 [158], AiiB from *A. tumefaciens* [193], QIcA from *Acidobacteria sp.* [194] and AidH from *Ochrobactrum sp.* T63 [195]. A fungal quorum quenching enzyme gluconolactonase has been reported from *As. niger* IAM 2094 [196]. The legume alfalfa, clover, lotus, peas and yam bean shown to contains AHL degrading enzyme lactonase [197-199]. A summary of the known quorum quenching enzymes is provided in Table 3.



**Figure 4.** Degradation mechanism of quorum sensing signal molecule N-acyl homoserine lactone by quorum quenching enzymes. (a) Lactonase open the HSL ring (b) Acylase cleaves the acyl side chain from HSL ring or hydrolyze the amide linkage (c) Oxidoreductase catalyzes the oxidation or reduction of acyl side chain.

**Table 3.** Enzymes as quorum sensing inhibitors.

Enzyme class/ Name	Source/ Producing strain	AHLs degradation	Ref.
<b>AHL-acylase</b>			
Acylase I	Porcine (Kidney)	C4-HSL, C6-HSL, C8-HSL, 3-oxo-C10-HSL, 3-oxo-C12-HSL	[88, 200, 201]
AiiD	<i>Ralstonia sp.</i> XJ12B	C4-HSL, C6-HSL, C8-HSL	[20, 202-204]
AiiC	<i>Anabaena sp.</i> PCC7120	3-oxo-C8-HSL, 3-oxo-C10-HSL, 3-oxo-C12-HSL	[99]
PvdQ	<i>Pseudomonas sp.</i> strain PAI-A	C4-HSL, C14-HSL	[186]
HacA	<i>P. syringae</i> strain B728a	C10-HSL, 3-oxo-C10-HSL, C12-HSL, 3-oxo-C12-HSL, C14-HSL, C16-HSL	[183, 33]
HacB	<i>P. syringae</i> strain B728a	C8-HSL, C10-HSL, C12-HSL	[187]
Aac	<i>R. solanacearum</i> GMI1000	C6-HSL, C8-HSL, C10-HSL, C12-HSL	[187]
Aac	<i>Shewanella sp.</i> strain MIB015	C7-HSL, C8-HSL, 3-oxo-C8-HSL, C10-HSL	[205]
AhlM	<i>Streptomyces sp.</i> strain M664	C8-HSL, C10-HSL, C12-HSL	[206]
QuiP	<i>P. aeruginosa</i>	C8-HSL, C10-HSL, 3-oxo-C12-HSL	[184]
QuiP	<i>P. aeruginosa</i>	C6-HSL, C8-HSL, C10-HSL, C12-HSL	[207]
n.d.	<i>Pseudomonas sp.</i> 1A1	C6-HSL, C8-HSL, 3-oxo-C8-HSL, 3-oxo-C10-HSL, C10-HSL, 3-oxo-C12-HSL, C12-HSL	[208]
<b>AHL-lactonase</b>			
Lactonase	Human (Airway epithelia)	3-oxo-C12-HSL	[209]
Gluconolactonase (GL)	<i>As. niger</i> IAM 2094	Lactone ring hydrolysis	[196]
AttM	<i>A. tumefaciens</i> c58	3-oxo-C8-HSL	[179]
AiiA	<i>Bacillus sp.</i> 240B1	C8-HSL	[158, 210]
AiiA	<i>B. anthracis</i> (Ames strain)	C6-HSL, C8-HSL, C10-HSL	[211]
AiiA	<i>B. cereus</i> and <i>B. mycoides</i>	C6-HSL, C8-HSL, C10-HSL	[189]
AiiA	<i>B. thuringiensis</i>	3-oxo-C6-HSL, C6-HSL, C8-HSL	[212]
AiiB	<i>A. tumefaciens</i> C58	3-oxo-C6-HSL, C6-HSL, C8-HSL, C7-HSL, 3-oxo-C8-HSL, C8-HSL	[213]
AiiB	<i>A. tumefaciens</i>	C4-HSL, 3-oxo-C6-HSL, C6-HSL, 3-oxo-C8-HSL, C8-HSL, C10-HSL	[193]
GKL	<i>Ge. kaustophilus</i> strain HTA426	C6-HSL, 3-oxo-C8-HSL, C8-HSL, C10-HSL, 3-oxo-C12-HSL	[214]
AiiM	<i>M. testaceum</i> StLB037	3-oxo-C6-HSL, C6-HSL, 3-oxo-C8-HSL, C8-HSL, 3-oxo-C10-HSL, C10-HSL	[215]
MCP	<i>My. avium</i> subsp. <i>paratuberculosis</i> K-10	C7-HSL, C8-HSL, 3-oxo-C8-HSL, C10-HSL, C12-HSL	[216]
PPH	<i>My. tuberculosis</i>	C4-HSL, 3-oxo-C8-HSL, C10-HSL	[217]
AidH	<i>Ochrobactrum sp.</i> T63	C4-HSL, C6-HSL, 3-oxo-C6-HSL, 3-oxo-C8-HSL, C10-HSL	[195]

AhIS	<i>So. silvestris</i> StLB046	C10-HSL	[218]
SsoPox	<i>Sul. solfataricus</i> strain P2	3-oxo-C8-HSL, C8-HSL, 3-oxo-C10-HSL, 3-oxo-C12-HSL	[219, 220]
QsdA	<i>Rho. erythropolis</i> W2	3-oxo-C6-HSL, C6-HSL, 3-oxo-C8-HSL, C8-HSL, 3-oxo-C10-HSL, C10-HSL, 3-oxo-C12-HSL, C12-HSL, 3-oxo-C14-HSL, C14-HSL	[221]
QIcA	<i>Acidobacteria</i> sp.	3-oxo-C6-HSL, C6-HSL, C7-HSL, 3-oxo-C8-HSL, C8-HSL, 3-oxo-C10-HSL, C10-HSL	[194]
AhID	<i>Arthrobacter</i> sp. IBN110	C4-HSL, 3-oxo-C6-HSL, C6-HSL, C8-HSL, 3-oxo-C10-HSL, C10-HSL	[222]
<b>Oxidoreductase</b>			
P450BM3	<i>B. megaterium</i> CYP102A1	Oxidizes; C12-HSL, 3-oxo-C12-HSL, C14-HSL, 3-oxo-C14-HSL, C16-HSL, C18-HSL, C20-HSL.	[181]
n.d.	<i>Burkholderia</i> sp. strain GG4	Reduces; 3-oxo-AHL to corresponding 3-hydroxy derivatives.	[207]
n.d.	<i>Rho. erythropolis</i> W2	Converts C8-HSL to C14-HSL to corresponding 3-hydroxy derivatives	[182]

n.d.: Not determined.

## Enzymatic control of membrane biofouling

Enzymatic inactivation of AHL molecules has recently been proved to be a promising approach for the control of membrane biofouling. The quorum quenching enzymes AHL-acylase and AHL-lactonase have shown their potential to be used as quorum quenching agent in biofouling control. Xu et al. [201] reported that formation of *Aer. hydrophila* biofilm on polystyrene surface would be reduced by Acylase I. In another study it was found that 5 µg/ml of Acylase I dose results into 60% and 73% reduction of *Aer. hydrophila* and *P. putida* of biofilms on polystyrene surface [20]. In order to overcome the loss of enzyme during operation and ensure the slow release, immobilization of Acylase I on nanofiltration membrane was carried out by Kim et al [203]. The results of the laboratory-scale nanofiltration system demonstrated that newly developed acylase-immobilized membrane could inhibit quorum sensing between bacteria and biocake, thereby reducing biofouling. In addition to this, Lee et al. [223] developed an effective anti-fouling system by immobilizing quorum quenching acylase in magnetically separable mesoporous silica. The engineered system was found to effectively alleviate the biofilm maturation of test strain *P. aeruginosa* PAO1 on a membrane surface and thereby enhanced its filtration performance even under harsh conditions of high organic load and low enzyme dose. The synergistic action between enzymatic regulation of quorum sensing molecules and nanobiocatalytic enzyme stabilization has proven its high potential towards simple and effective antifouling solution in MBR. However, the exact mechanism by which the enzymatic quorum quenching can mitigate the biofilm formation in MBR is not yet fully investigated.

Yeon et al. [204] developed acylase attached magnetic particles to inhibit quorum sensing in MBR treating wastewaters. They found that immobilized enzymatic particles has reduced the biofilm formation

and enhanced membrane permeability for prolonged period. A major advantage using enzymatic quorum quenching approach is that it only influences sludge characteristics and biofouling, while not impacting pollutant degradation [202]. The mass production of quorum quenching enzymes by engineering gene network in bacteria whose expression is under quorum sensing system could be a futuristic approach for prolonged inhibition of membrane biofouling [224, 23]. Recently, a microporous membrane encapsulated with AHL-lactonase producing recombinant *E. coli* has been successfully used for the control of biofouling by interspecies interference in MBR [21]. In another study, a microbial-vessel containing quorum quenching bacteria encapsulated inside a porous hollow fiber membrane was found to inhibit membrane biofouling in an external submerged MBR treating synthetic wastewater [225].

## Conclusions

Biofouling, a consequence of various microbial activities is a complex process in MBR treating wastewaters. Recent studies have proved evidence that quorum sensing, which was earlier known for pathogenesis, may also play key role in membrane biofouling. AHLs-based quorum sensing system associated with Gram-negative bacteria is known to have a potential role in biofilm formations. Understanding the mechanism of AHLs-based quorum sensing system in wastewater microbiology can help in targeting quorum sensing and addressing the problem of membrane biofouling. Natural compounds as QSI could act as a 'silver bullet' to solve the problem of membrane biofouling as this has great potential towards inhibiting biofilm formation without affecting bacterial growth.

## Abbreviations

*Aer.*: *Aeromonas*; *A.*: *Agrobacterium*; *As.*: *Aspergillus*; *B.*: *Bacillus*; *C.*: *Chromobacterium*; *E.*: *Escherichia*; *Ent.*: *Enterococcus*; *Ge.*: *Geobacillus*; *M.*: *Microbacterium*;

*My.: Mycobacterium; Pe.: Penicillium; P.: Pseudomonas; Pr.: Proteus; R.: Ralstonia; Rho.: Rhodococcus; Rho.: Rhodospirillum; S.: Serratia; Sa.: Salmonella; Sta.: Staphylococcus; Si.: Sinorhizobium; So.: Solibacillus; Sul.: Sulfolobus; V.: Vibrio; X.: Xanthomonas; Y.: Yersinia.*

## Competing Interests

The authors have declared that no competing interest exists.

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