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Natural Products May Present an Optimum Control Strategy to Quorum-Sensing Mediated Membrane Biofouling

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Abstract

Quorum-sensing (QS) constitutes a bacterial cell-to-cell communication system based on production and secretion of signalling molecules called autoinducers (AIs), which accumulate in the extracellular environment when high cell densities are reached. Despite its numerous applications, QS plays a pivotal role in bacterial biofilm formation, leading to membrane biofouling, which is a major challenge in membrane-related water treatment systems. Interruption of QS (quorum-quenching (QQ)) using natural products may present a break-through in the fight against membrane biofouling. These natural products can form a better alternative to antibiotics which are characterized with resistance. In QQ, killing of the fouling organisms or limiting their growth is not the target but denying them of their ability to 'communicate' and form biofilms. In this review, bacterial quorum system and inhibitory effects of some natural products on QS-mediated traits such as biofilm formation have been explored in order to identify a better alternative of combating biofouling.

Keywords: Quorum-sensing; biofilms; biofouling; natural products; quorum-quenching.

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1. Introduction

Water treatment techniques such as membrane bioreactor (MBR) and reverse osmosis (RO) are faced with the challenge of membrane biofouling: coverage of membrane surfaces due to undesirable development of biofilms [1]. It has been established [2] that biofouling is directly linked to bacterial quorum-sensing (QS), which refers to a process of cell to cell communication and regulation that is population density-dependent and enables bacteria to adapt to their external environment [3]. Interrupting QS (Quorum-Quenching) (QQ) may present a promising approach in combating membrane biofouling. Strategies currently used to control biofouling mostly spin around physical cleansing of biofilms and incorporation of antimicrobial substances such as peptides and nitrofurazones [4]. Use of these chemicals is associated with resistance, environmental pollution and non-specificity [5]. Adopting QQ using natural products (a whole of parts of microorganisms, animals and plants with distinct pharmacological and/or biological effects) [6] as an alternative can be apt since the life of the bacteria is not the target but their ability to form and express biofilms. This paper aims to explore the concept, applications and implications of QS; as well as QQ potential of some natural products with a goal to identify a better anti-fouling alternative which would be safe, convenient, eco-friendly, time and cost-effective.

2. Materials and Methods

2.1 Biofilms on Membranes: Formation, Composition and Development

Microorganisms in most water systems tend to adhere to surfaces and grow at the expense of nutrients in the water phase, forming biofilms. These biofilms are encapsulated within a self-developed matrix called extracellular polymeric substances (EPS) and adhere to a living or inert surface. They are characterized by surface attachment, structural heterogeneity, genetic diversity and complex community interactions [7]. This gel structure (EPS) protects bacteria from hydraulic shearing and lethal attacks of antimicrobials [8]. Biofilms comprise of bacterial species with varying metabolic capabilities, displaying community level properties that are distinct from the planktonic cells [9]. The composition and functions of biofilms are driven by interactions between the microbial species. Understanding the dynamics of interspecies interaction within biofilms is challenging, yet important in order to control and regulate key ecosystem functions, including engineering of highly stable and sustainable microbial communities for water treatment. Biofilm formation begins with transport and attachment of bacteria to the membrane surface [9].

2.2 Transport of Microorganisms to the Membrane Surface

Fluid dynamic forces are the major mechanisms for transporting microorganisms to membrane surfaces. In spiral wound reverse osmosis (RO), the spacer between the membrane envelopes is designed to promote turbulence and assists in transporting the feed water back to the bulk stream. However, in creating turbulence, areas with low flow are developed just downstream from each crossmember in the spacer and thus fouling can build up in these areas. Matter that is caught in the spacer is trapped until the flow pattern changes. During this time, other forces are in operation. For example, Brownian motion will assist in transporting non-motile cells to the vicinity of the membrane surface and motile cells which exhibit chemotaxis will advance to the membrane

surface where nutrients are concentrated [10].

2.3 Microbial Attachment on Membrane Surfaces

Attachment of microbial cells in biofilm formation is mediated by electrokinetics and hydrophobic interactions which are followed by cellular growth and multiplication at the expense of soluble nutrients in the feed water or adsorbed organic matter on the membrane. The EPS anchor the cells to the substratum and stimulate microbial colonization of the membrane outer layer [10]. This attachment is affected by factors such as nature of the membrane material, roughness and charge of the membrane surface, hydrophobicity [7], electrolyte concentration [11], pH [10], ionic strength milieu, drag back-diffusion transport and cross-flow velocity [12]. Following the attachment, growth and metabolism of bacteria, biofilm development ensues, followed by its limitation by fluid shear forces to achieve a steady state fouling resistance.

2.4 Membrane Biofouling

This is an organic fouling which results from accumulation of microorganisms on wetted surfaces of the membranes and their complex interactions with the membrane material, dissolved substances and fluid flow parameters. Membrane biofouling is a critical issue as it compromises the efficiency of water treatment methods such as MBR and RO, causing a decline in plant performance. This phenomenon is highly challenging to control [7] with high operational costs of adopting antifouling strategies [10].

2.5 Effects of Biofouling on Membrane Systems

According to [7], the effects of biofouling on membrane systems include:

- Membrane flux decline which results from the formation of a low-permeability biofilm.
- Increased differential pressure to maintain production rate due to biofilm resistance.
- Membrane biodegradation caused by acidic by-products at the membrane surface.
- Increased salt passage and reduced quality of the product water from dissolved ions.
- Increased energy consumption because of a relatively high pressure to overcome biofilm resistance.

2.6 Challenges in Controlling Biofouling

Biofouling control is a major challenge in membrane filtration systems. The reactivity of EPS with solutes hinders the back-diffusion of these solutes (from membrane surface to the bulk phase across the biofilm), contributing to an increase in trans-membrane pressure and flux decline [13]. During membrane cleaning, EPS act as a diffusion barrier, retarding convective flow and transport of antimicrobials to microbes in the biofilm [14]. The soluble microbial products (SMP) are among the most recalcitrant naturally occurring organic foulants [15] as they accumulate on membranes, blocking their pores [16]. The amphoteric nature of protein-like materials enables them to form a cake/gel layer in colloidal form [17], making fouling difficult to overcome.

2.7 Quorum-Sensing System

Before they can exert any useful or detrimental effect to man or the environment, bacteria 'communicate' socially among themselves using AIs in the process of QS [18]. This phenomenon was first discovered in a marine bacterium *Vibrio fischeri* (now *Aliivibrio fischeri*), where it regulated bioluminescence development in symbiotic "light" organs of squids from *Euprymna* and *Sepiola* [3].

2.8 Mechanism of Quorum-Sensing

Quorum-Sensing is based on synthesis, release and uptake of AIs in the surrounding medium, whose concentration correlates with the density of secreting bacteria within the vicinity [5]. This precedes the interaction of AIs with a transcriptional regulator directly or through the activation of a sensor kinase [19]. The QS signaling molecules (Ais) have been broadly divided into three [20]:

- Acyl-homoserine lactones (AHLs) produced by Gram-negative bacteria
- Oligopeptides or autoinducing peptides (AIP) used by Gram-positive bacteria.
- Autoinducer-2 (AI-2) employed by both Gram-positive and Gram-negative bacteria

Figures 1 and 2 depict the general structures of some bacterial autoinducers:

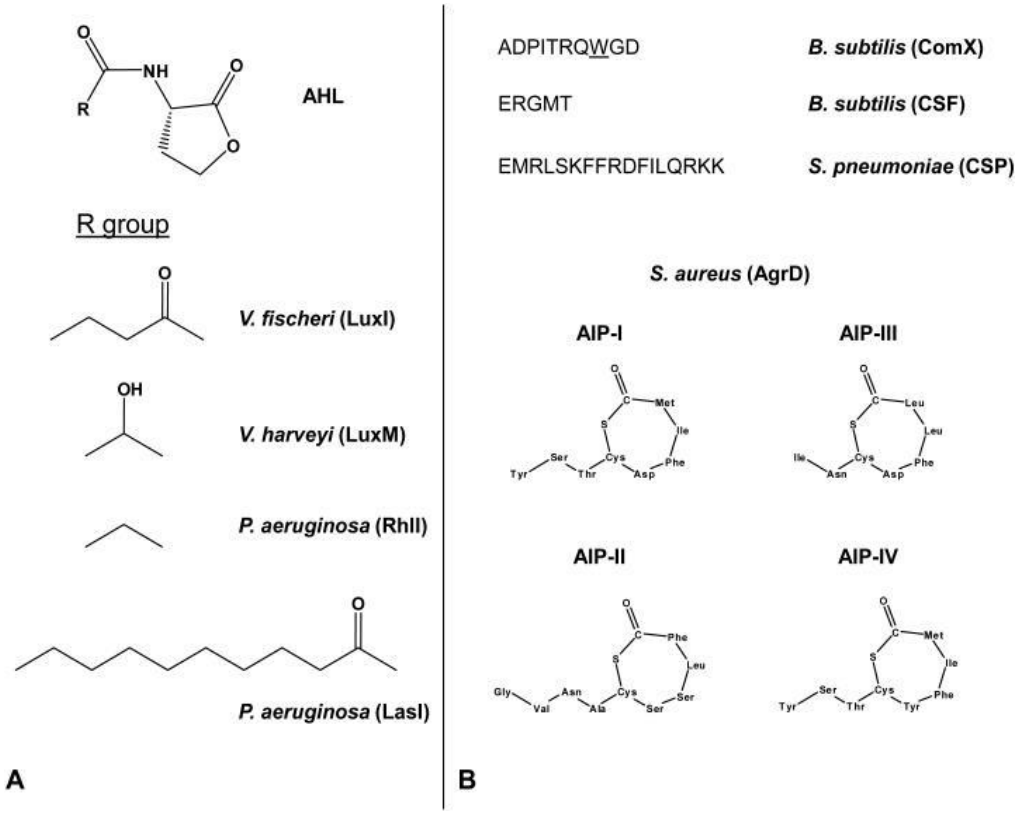

Figure 1: Structure of Bacterial Autoinducers A and B [21]

(A) Homoserine lacton autoinducers produced by different Gram-negative bacteria. (B) Amino acid sequences of three peptide autoinducers, Com X, CSF and CSP, produced by Gram positive bacteria. The underlined

tryptophan in *B. subtilis* COM X is isoprenylated. The four different AIPs are produced by *S. aureus*.

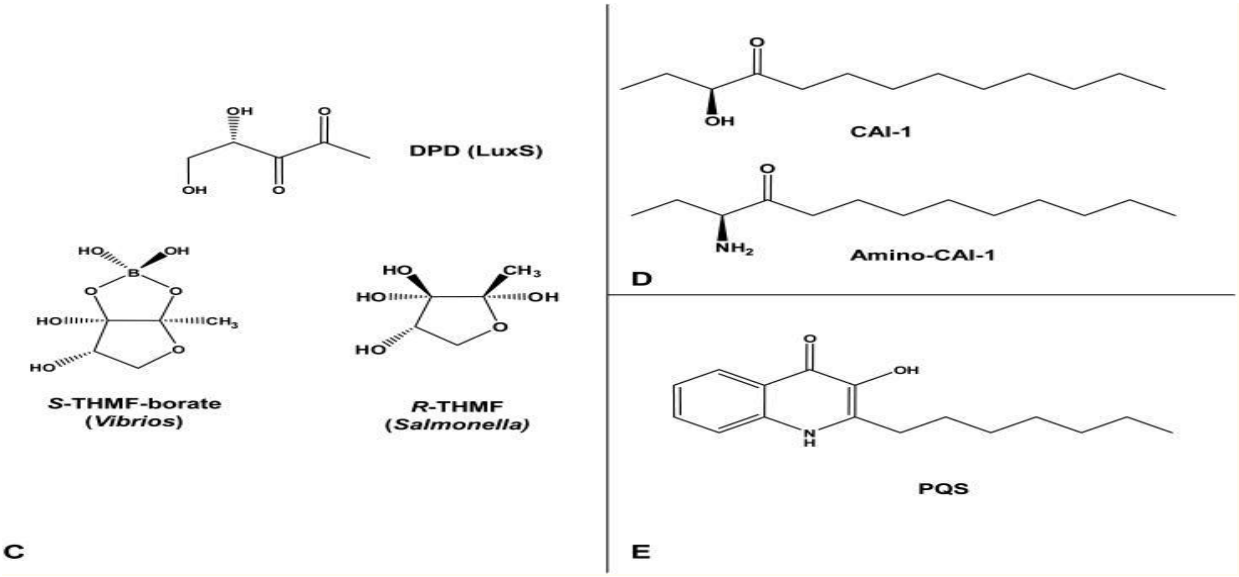

Figure 2: Structure of bacterial autoinducers C, D and E [21]

(C) the DPD, a precursor to AI-2. In the Boron, AI-2 exists as S-THMF-borate. In the absence of Boron, AI-2 exists as R-THMF. (D) Structure of *V. cholerae* CAI-1 and Amino-CAI-1. (E) Structure of the PQS autoinducer of *P. aeruginosa.* Generally, Gram-positive bacteria mainly use the oligopeptide signaling systems whereas Gram-negative bacteria primarily use the LuxR/I-type QS system (Reading and Sperandio, 2005). A list of some QS signaling molecules which function phenotypically as local sensors is provided in Table 1.

Table 1: Quorum-Sensing Signaling Molecules and Phenotypic Control in some Bacteria

Autoinducer	Producing bacteria	Phenotype(s) controlled
AHL	*C. violaceum, V. fischeri, P. aeruginosa, A. hydrophila*	Pigmentation, bioluminescence, exopolysaccharide production, biofilm formation and virulence factor.
Autoinducer-2 (AI-2)	*V. harveyi, E. coli, Y. pestis*	Bioluminescence, biofilm formation, motility and virulence factor.
4,5-dihydroxy-2,3-pentanedione	*S. typhimurium* enteric serovar	Virulence factor
Cyclic dipeptides/ Diketopiperazines (DKP)	*P. putida* WCS358, *P. aeruginosa*	Cross activates QS biosensors
(a) Cyclo(L-Pro-L-Tyr)		
(b) Cyclo(L-Phe-L-Pro)	*P. putida* WCS358, *P. aeruginosa*	Cross activates QS biosensors
(c) Cyclo(L-Leu-L-Pro)	*P. putida* WCS358	Cross activates QS biosensors
(d) Cyclo(L-Leu-L-Val)	*P. putida* WCS358	Cross activates QS biosensors
Quinolone (2-heptyl-3-hydroxy-4-quinolone)	*P. aeruginosa*	Antibiotic production
Diffusible factor (DSF)	*X. campestris*	Endoglucanase production
Gram-positive bacteria Autoinducing peptide (AIP1-AIP4)	*S. aureus*	Cross-signaling between strains and species, Biofilm formation, Virulence factor

Source: [5]

2.9 Applications of Quorum-Sensing System in Small and Large Scale Perspectives

2.10 Pathogen Diagnostics and Therapeutics using Biosensors

It has been recommended (Steindler and Venturi, 2007) that QS signals should be used as markers to check for the occurrence of pathogenic bacteria in both clinical and environmental settings. Quorum-sensing can be used in the engineering of whole cell microbial biosensors to distinguish pathogenic microorganisms present in the environment from diseased hosts; and to produce engineered bacteria capable of attacking cancer cells. For example, QS based amplification models have been applied to engineer biosensing circuits to find the occurrence of pathogenic microorganisms in contaminated groundwater, dairy and meat products. A standard AHL biosensor contains an AHL responsive transcriptional regulator (also a cognate promoter), which directs the transcription of a reporter gene [22].

2.11 Management of Cancer

According to [23], *C. violaceum* produces a pigment (violacein) via QS, which can be used in treatment of colon cancer. Additionally, *P. aeruginosa* QS signal 3-oxo-C12- HSL has been found to reduce proliferation and induce apoptosis to breast cancer cell lines in humans [24].

2.12 Biocontrol

Since QS bacteria form a main component in the rhizosphere community, some QQ enzymes have been reported to decrease bacterial virulence against plants [25].

2.13 Recombinant Gene Expression

Quorum-sensing has been used to control gene expression and cellular growth. [26] discussed some of the advancements in the control of gene expression through the perception of possible gene therapy applications. For instance, a regulated transcription switch has been generated based on the QS process. Following its release and accumulation in the immediate external environment, the AHL serves as a cognate transcription factor which activates TraR belonging to the LuxR family of transcriptional activators. Similarly, binding the *Agrobacterium tumefaciens* QS signal 3-oxo-C8-HSL results in proper folding of TraR which becomes capable of binding an 18-bp long specific DNA sequence, called Tra box [26].

2.14 Current Trends in Quorum-Sensing Systems

2.15 Bacterial Quorum-Sensing: A New Target for Anti-Infective Immunotherapy

The emergence of antibiotic-resistant bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa* calls for a new approach in combating infections. [27] highlighted the current trends in preventing bacterial infections using QQ strategies against *P. aeruginosa* and *S. aureus*, suggesting that QS unveils

attractive targets for discovery of novel anti-infective agents, including immunotherapeutic.

2.16 Quorum-System and Antibiotic Resistance

Extensive and abusive use of antibiotics have led to their resistance. The finding that many pathogens rely on QS to synchronize microbial activities essential for infection and survival in the host suggests a promising disease control strategy, i.e. quenching microbial QS (QQ). The QQ mechanism plays important roles in microbe-microbe and pathogen-host interactions and used to develop and formulate a new generation of antimicrobials.

2.17 Chromobacterium violaceum: A Biosensor Bacterial Species of Quorum-Sensing

Chromobacterium violaceum is an aquatic, gram-negative facultatively anaerobic, non-spore forming coccobacillus bacteria [28]. It grows readily on nutrient agar at 28-37℃ [23], producing a compound: homoserine lactone, which induces production of violacein via the AHL receptor CviR [29].

2.18 Applications of Quorum-Quenching in Control of Membrane Biofouling

It was established [30] that QQ can reduce membrane biofouling in water treatment plants. Recently, QQ was tested for its ability to mitigate biofouling in RO membranes used in water desalination [27]. Additionally, QQ was applied to control biofouling on hulls of shipping vessels and bio-corrosion of oil production wells [31]. Generally, QQ is gaining more recognition as a method of controlling biofouling in water treatment plants [32] and incorporating natural products could make this approach a more efficient one.

2.19 Natural Products

Natural products are substances with pharmacological or biological effects which can be:

- an entire organism that has not been subjected to any kind of processing or treatment other than a simple process of preservation (such as drying)
- part of an organism such as leaves or flowers of a plant, isolated animal organ etc.
- an extract or exudates of an organism
- pure compounds isolated from plants, animals or microorganisms such as alkaloids, coumarins, flavonoids, glycosides and lignin among others [6].

2.20 Natural Products as Quorum-Sensing Inhibitors (QSIs)

Many natural products have been identified [33] to inhibit QS not necessarily affecting bacterial growth. For example, vanillin, furanones and flavonoids interfere with bacterial QS and inhibit biofilm formation [19]. One major advantage of natural compounds (especially those from plants) is that they are structurally similar to QS signalling molecules and thus, can easily antagonize them as depicted in figure 1. They also possess the ability to degrade LuxR/LasR signal receptors [34].

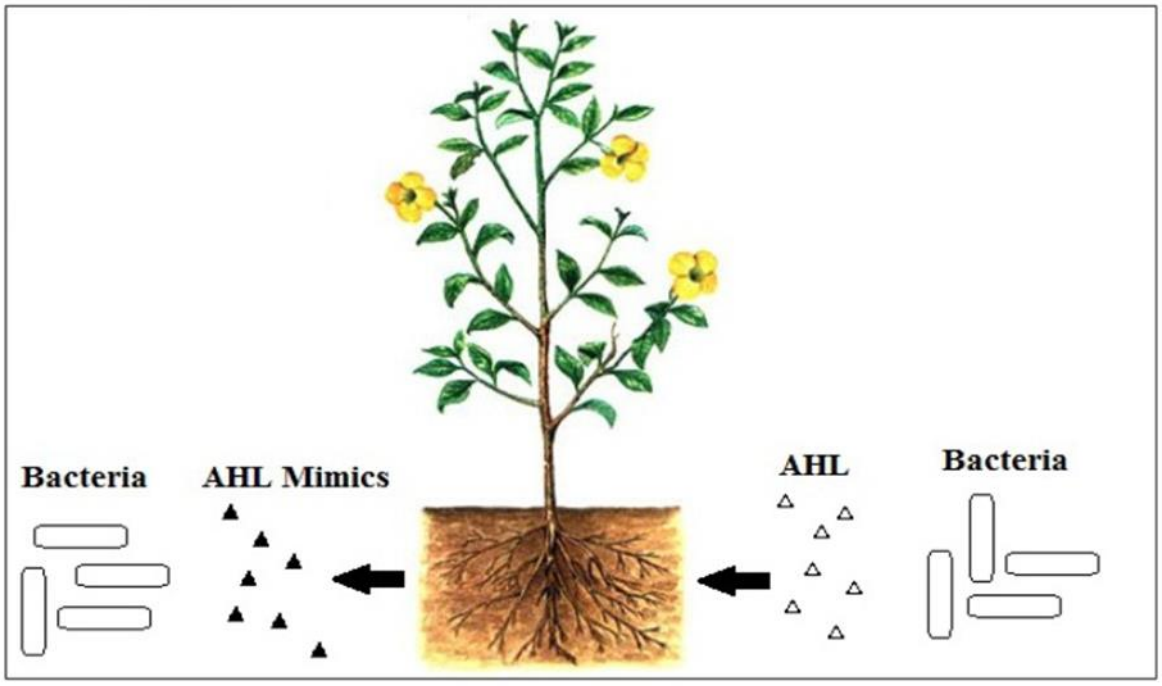

Figure 1: QS interaction between plants and bacteria

Source: [35].

A list of some QSIs derived from plants, fungi, algae and bacteria is provided in Table 2:

2.21 Role of Natural Products in Control of Membrane Biofouling

Since natural products have advantages of nontoxicity and low risk of resistance, they can be exploited as better antifouling agents. For instance, addition of natural AQS compounds in Centers for Disease Control and Prevention's (CDC's) biofilm reactor suggests that control of membrane biofouling could be achieved by incorporation of natural QSIs. Thus, engineered membranes with natural compounds are expected to be useful in designing efficient water treatment systems with economic feasibility [36]. Various plant extracts including *Capsicum chinense* (habanero: chilli), *Solanum lycopersicum* (tomato), *Coronilla varia* (crown vetch), *Glycine max* (soybean), *Nymphaeaceae odorata* (water lily) and some medicinal plants of southern Florida were found to possess AQS activities. Furocoumarin derived from grape fruit was found to inhibit QS mediated biofilm formation in *E. coli* and swarming motility in *P. aerugionsa* PAO1. Limonoids from sour orange seeds such as isolimonic acid, ichangin and deacetyl nomilinic acid 17 β-D-glucopyranoside were found to inhibit AI-2 mediated QS in *V. harveyi*. The structural resemblance of furocoumarin and limonoids with autoinducer molecules in the furan moiety was discovered as being responsible for competitive QS inhibition [21].

Table 2: List of Some Natural Products Used as QS Inhibitors

Natural compound(s)	Source	QS activity
Furanone/ 2(5H)-Furanone	Macroalga (*Delisea pulchra*)	Mimics AHL signal by occupying the binding site on putative regulatory protein which results in the disruption of QS-mediated gene regulation. Inhibits biofilm formation in *Aer. Hydrophila*. Represses LuxR protein dependent expression of P(luxI)-gfp(ASV) reporter fusion. Inhibits virulence factor in *E. coli* XL-1.
Naringin (4'5-diOH-Flavone-7-rhgluc)	Citrus extract	Decreases QS mediated biofilm formation and swimming motility in *Y. enterocolitica.*
Penicillic acid (3-Methoxy-5-methyl-4-oxo-2,5-hexadienoic acid)	*Penicillium sp.*	Down-regulates QS genes for biofilm formation in *P. aeruginosa*.
Chlorogenic acid (3-Caffeoylquinic acid)	Plant extract (*Moringa oleifera*)	Inhibits QS-regulated violacein production in *C. violaceum* 12472.
Garlic	Garlic extract	Interferes with expression of QS-controlled virulence genes in *P. aeruginosa*
Furocoumarin/ Psoralen (7H-Furo[3,2g][1]benzopyran-7-one)	Grapefruit juice and extract (*Psoralea corylifolia* L.)	The structural resemblance of furan moiety results in QS-mediated inhibition of biofilm formation in *E. coli*. Inhibits QS-mediated swarming motility in *P. aerugionsa* PAO1.
Epigallocatechin gallate (Epigallocatechol)	Green tea (*Camellia sinensis* L.)	This compound has gallic acid moiety and specifically blocks AHL-mediated biofilm formation in *S. aureus* and *B. cepacia.* Inhibits transfer of conjugative R plasmid in *E. coli*.

Source: [5]

3. Conclusion

Quorum-sensing has a wide range of applications but could lead to biofouling, which has a lot of environmental consequences especially in water treatment systems. Understanding the role of natural products as QSIs could be a milestone in addressing the challenge of membrane biofouling. While QQ using natural products seems an attractive approach for biofouling control, practical researches are encouraged to demonstrate its safety and efficacy.

4. Constraints/Limitation of the Study

The major limitation of this study was the difficulty faced in accessing some highly impactful published reaches which would have made our work richer and more meaningful.

References

[1]. P. Le-Clech. "Membrane Bioreactors and their uses in Wastewater Treatments". Applied Microbiology and Biotechnology, vol. 88, pp. 1253-1260, Jun. 2010.

[2]. J.Y. Li, Y.M. Cui, L.L. Chen, M. Gu, J. Li, F. J. Nan and Q. Z. Ye. "Mutations at the S1 Sites of Methionine Aminopeptidases from Escherichia coli and Homo sapiens Reveal the Residues Critical for Substrate Specificity". Journal of Biology and Chemistry, vol. 279, pp. 21128-21134, Aug. 2004.

[3]. D. Deryabin, A. Galadzhieva, D. Kosyan and G. Duskaev. "Plant-derived Inhibitors of AHL-Mediated Quorum-Sensing in Bacteria: Modes of Action". International Journal of Molecular Sciences, vol. 20, pp. 5588-55910, Jan. 2019.

[4]. A.L. Hook, C.Y. Chang and J. Yang. "Combinatorial Discovery of Polymers Resistant to Bacterial Attachment". Nature Biotechnology, vol. 30, pp. 868-875, Feb. 2012.

[5]. H. Lade, D. Paul and J. H. Kweon. "Quorum-Quenching Mediated Approaches for Control of Membrane Biofouling". International Journal of Biological Sciences, vol. 10, pp. 550-565, Dec. 2014.

[6]. V.P. Bulugahapitiya. Plants Based Natural Products Extraction, Isolation and Phytochemical Screening Methods. Matara, Sri Lanka: Indika Graphics, 2013, pp. 1-93.

[7]. A.F. Ismail, K.C. Khulbe and T. Matsuura. "RO Membrane Fouling, in Reverse Osmosis, 3rd ed., vol. 3. Elsevier, USA, 2019, pp. 189-220.

[8]. 8.Membrane Solutions. "Types of membrane fouling". Internet: www.membrane-solutions.com/News_1224.htm, Jun. 2018, Aug. 2021.

[9]. S. Elias and E. Banin. "Multi-species Biofilms: Living with Friendly Neighbors". Federation of European Microbiological Societies (FEMS) Microbiology, vol. 36, pp. 990-1004, Aug. 2012.

[10]. T. Nguyen, F. A. Roddick and L. Fan. "Review Biofouling of Water Treatment Membranes: A Review of the Underlying Causes, Monitoring Techniques and Control Measures". Membranes, vol. 2, pp. 804-840, Jun. 2012.

[11]. N. Park, B. Kwon, I.S. Kim and J. Cho. "Biofouling Potential of Various NF Membranes with Respect

to Bacteria and their Soluble Microbial Products (SMP): Characterization, Flux Decline and Transport Parameters". Journal of Membrane Science, vol. 258, pp. 43–54, Oct. 2005.

[12]. S.T. Kang, A. Subramani, E. M. V. Hoek, M. A. Deshusses and M. R. Matsumoto. "Direct Observation of Biofouling in Cross-flow Microfiltration: Mechanisms of Deposition and Release". Journal of Membrane Science, vol. 244, pp. 51–165, Jul. 2004.

[13]. A.S. Kim, H. Chen and R. Yuan. "EPS Biofouling in Membrane Filtration: An Analytic Modelling Study". Journal of Colloidal Interface Science, vol. 303, pp. 243–249, Oct. 2006.

[14]. G. Allison, T. Maira-Litrán and P. Gilbert. "Antimicrobial Resistance of Biofilms". In Biofilm: Recent Advances in Their Study and Control. Amsterdam, The Netherlands, Evan, L.V., Ed.; Harwood Academic Publishers, 2000, pp. 149–166.

[15]. N. Her and G. Amy. "Identification and Characterization of Foulants and Scalants on NF Membranes", in Proc. AWWA Membrane Technology Conference, 2003, pp. 25.

[16]. F. Meng, S. R. Chae, A. Drews, M. Kraumer and H. S. Shin. "Recent Advances in Membrane Bioreactors (MBRs): Membrane Fouling and Membrane Materials". Water Resource, vol. 43, pp. 489–1512, Dec. 2009.

[17]. G. Amy. "Fundamental Understanding of Organic Matter Fouling of Membranes". Desalination, vol. 231, pp. 44–51, Jun. 2008.

[18]. M. Romero, A. Martin-Cuadrado, A. Roca-Rivada, A. M. Cabello and A. Otero. "Quorum-Quenching in Cultivable Bacteria from Dense Marine Coastal Microbial Communities". Federation of European Microbiological Societies (FEMS) Microbiology Ecology, vol. 75, pp. 205–217, Feb. 2010.

[19]. S. Choudhary and C. Schmidt-Dannert. "Applications of Quorum-Sensing in Biotechnology". Applied Microbiology and Biotechnology, vol. 86, pp. 1267-1279, Apr. 2010.

[20]. N.C. Reading and V. Sperandio. "Quorum-Sensing: The Many Languages of Bacteria". Federation of European Microbiological Societies (FEMS) Microbiology Letters, vol. 254, pp. 1–11, Jul. 2005.

[21]. W.L. Ng and B.L. Bassler. "Bacterial Quorum-Sensing Network Architectures". Annual Review of Genetics, vol. 43, pp. 197–222, May 2009.

[22]. L. Steindler and V. Venturi. "Detection of Quorum-Sensing N-acyl Homoserine Lactone Signal Molecules by Bacterial Biosensors". Federation of European Microbiological Societies (FEMS) Microbiology Letters, vol. 266, pp. 1-9, Jun. 2007.

[23]. L.L. Kodach, C.L. Bos, N. Durán, M.P. Peppelenbosch, C.V. Ferreira and J.C. Hardwick. "Violacein Synergistically Increases 5-fluorouracil Cytotoxicity, Induces Apoptosis and Inhibits Akt-mediated Signal Transduction in Human Colorectal Cancer Cells". Carcinogenesis, vol. 27, pp. 508-5016, Nov. 2006.

[24]. T. Li, D. Wang, N. Liu, Y. Ma, T. Ding, Y. Mei et al. "Inhibition of Quorum-Sensing Controlled Virulence Factors and Biofilm Formation in Pseudomonas fluorescens by Cinnamaldehyde". International Journal of Food Microbiology, vol. 269, pp. 98–106, Jun. 2018.

[25]. U.K. Essays. "Quorum-Sensing and its Importance to Biotechnology". Internet: www.ukessays.com/essays/biology/quorum-sensing-and-its-importance-to biotechnology-biology-essay.php?vref=1, Sep. 20, 2017 [Sep. 11, 2021].

[26]. C. Toniatti, H. Bujard, R. Cortese and G. Ciliberto. "Gene Therapy Progress and Prospects:

Transcription Regulatory Systems". Nature, vol. 11, pp. 649-657 Apr. 2004.

[27]. H.S. Oh, C.H. Tan, J.H. Low, M. Rzechowicz, M.F. Siddiqui and H. Winters. "Quorum-Quenching Bacteria can be used to Inhibit the Biofouling of Reverse Osmosis Membranes". Water Resource, vol. 112, pp. 29–37, Sep. 2017.

[28]. I.C. Siqueira, J. Dias, H. Ruf, E.A. Ramos, E.A. Maciel, A. Rolim et. al. "Chromobacterium violaceum in Siblings, Brazil". Emerging Infectious Diseases, vol. 11, pp. 1443–1445, Jan. 2005.

[29]. S. Dobretsov, M. Bayer, S. Gunasekera, P. Proksch and V.J. Paul. "Inhibition of Marine Biofouling by Bacterial Quorum-Sensing Inhibitors". Biofouling, vol. 27, pp. 893–905, Aug. 2012.

[30]. J.H. Huang, Y.H. Shi, G.M. Zeng, Y.L. Gu, G.Q. Chen and L. X. Shi. "Acyl-homoserine Lactone-based Quorum Sensing and Quorum Quenching Hold Promise to Determine the Performance of Biological Wastewater Treatments: An Overview". Chemosphere, vol. 157, pp. 137–151, Apr. 2016.

[31]. Z. U. Rehman and T. Leiknes. "Quorum-Quenching Bacteria Isolated from Red Sea Sediments Reduce Biofilm Formation by Pseudomonas aeruginosa". Frontiers in Microbiology, vol. 9, pp. 1354, Feb. 2018.

[32]. J. Bzdrenga, D. Daude, B. Remy, P. Jacquet, L. Plener and M. Elias. "Biotechnological Applications of Quoru- Quenching Enzymes". Chemico-Biological Interactions, vol. 267, pp. 104–115, Jan. 2017.

[33]. K. Ponnusamy, D. Paul and J. H. Kweon. Inhibition of Quorum Sensing Mechanism and Aeromonas hydrophila Biofilm Formation by Vanillin". Environmental Engineering Science, vol. 26, pp. 1359-1363. Sep. 2009.

[34]. M. Teplitski, U. Mathesius and K. P. Rambaugh. "Perception and Degradation of N-acyl Homoserine Lactone Quorum Sensing Signals by Mammalian and Plant Cells". Chemical Reviews, vol. 111, pp. 100-116, Aug. 2011.

[35]. C. L. Koh, C. K. Sam, W. F. Yin, L. Y. Tan, T. Krishnan, Y. M. Chong et al. "Plant-Derived Natural Products as Sources of Anti-Quorum Sensing Compounds". Sensors, vol. 13, pp. 6217–6228, Feb. 2013.

[36]. L. D. Chambers, K. R. Stokes, F. C. Walsh and R. J. Wood. "Modern Approaches to Marine Antifouling Coatings". Surface Coatings Technology, vol. 201, pp. 3642-3652 Mar. 2006.