Journal of Experimental Biology and Agricultural Sciences, April - 2022; Volume – 10(2) page 278 – 293

Journal of Experimental Biology and Agricultural Sciences

http://www.jebas.org

ISSN No. 2320 – 8694

Bacterial biofilms: role of quorum sensing and quorum quenching

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Received – January 24, 2022; Revision – March 24, 2022; Accepted – April 27, 2022
Available Online – April 30, 2022

DOI: http://dx.doi.org/10.18006/2022.10(2).278.293

KEYWORDS

Bacterial biofilms

Multi-drug resistance

N-acyl homoserine lactones

Quorum sensing

Quorum quenching

ABSTRACT

Bacterial biofilms provide an adjustable strategy to manage themselves in the existing conditions. Biofilms of pathogenic bacteria act as a reservoir for various device and non-device related diseases which are tough to cure. Exposure to a high dose of antibiotics is not an appropriate solution to this problem as high antibiotic concentrations lead to the generation of Multi-drug resistant strains as well as affect the human body. So, it is needed to bypass the use of antibiotics to prevent bacterial biofilms. In this context, Quorum Sensing (QS) may be a potential target since biofilm formation is regulated by QS. N-acyl homoserine lactones (N-AHL) act as predominant QS signal molecules in Gram-negative bacteria. Counteraction of the QS-regulated activities using quorum quenching may be an alternative way to combat biofilm formation in bacteria. Quorum sensing inhibitors (QSIs) and QQ enzymes play a significant role in this regard either by interference with the signal generation, perception, or by degradation, and chemical modification, respectively. Many quorum quenching enzymes have been reported from bacteria. Extremophilic bacteria have also been reported to produce potent quorum quenching enzymes which can effectively break down N-AHLs.

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Peer review under responsibility of Journal of Experimental Biology and Agricultural Sciences.

Production and Hosting by Horizon Publisher India [HPI] (http://www.horizonpublisherindia.in/).
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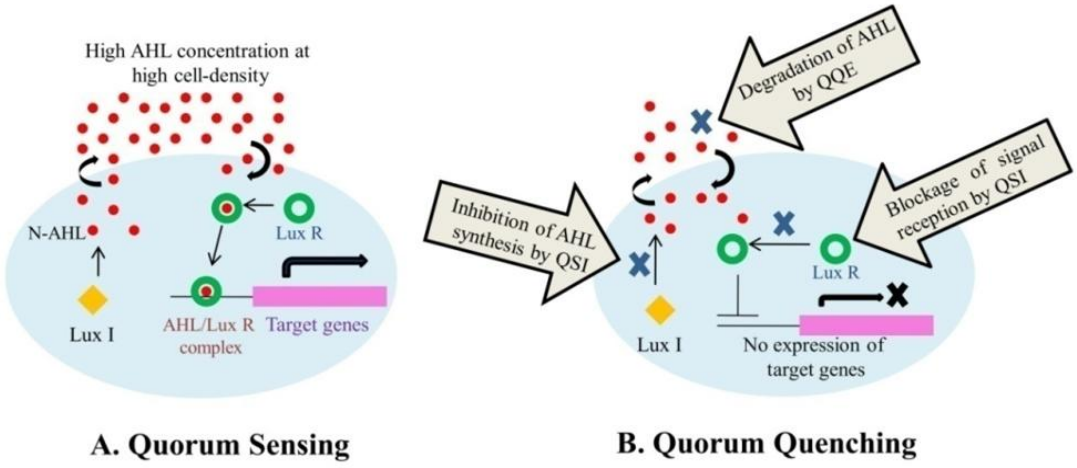
GRAPHICAL ABSTRACT



1 Introduction

Flexibility in gene expression and adaptability in changing environments allow cosmopolitan distribution of bacteria. Most of them can interchange between planktonic mode of growth to bio-film mode according to the need of life. Bio-films are matrix-enclosed bacterial populations adhered to each other or to the surface. Bio-films contain a complex assembly of polysaccharides, proteins, DNA and lose aggregation of sessile cells embedded in a hydrated matrix made up of extracellular polymeric substances. Most of the pathogenic bacteria such as *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Burkholderia cepacia*, *Klebsiella pneumonia*, *Acinetobacter baumanii* etc. produce biofilms, virulence factors which are associated with pathogenicity. Biofilms also act as a reservoir for pathogenic bacteria in aquaculture (Small and Pagenkopp 2011). Although planktonic bacteria show higher cell growth and reproduction (Rabin et al. 2015), bacterial bio-films represent a strategy of growth either to survive in harsh conditions or to accommodate themselves in a nutrient-rich favorable niche.

2 Bacterial Biofilm Associated Human Diseases

It is reported that more or less 65% of all bacterial infections are related to biofilms (Lewis et al. 2011) including both device-related and non-device associated diseases. Biofilms of pathogenic bacteria help them to survive in hosts and make chronic infections resulting in persistent inflammations and tissue damage (Lebeaux et al. 2013). Some examples of non-device associated infections are Cystic Fibrosis, Chronic Obstructive Pulmonary Disease Urinary Tract Infections, Endocarditis, Chronic Otitis Media, Chronic Rhinusinusitis, Dental Plaque, Dental Caries, Periodontitis, Ostiomyelitis (Lebeaux and Ghigo 2012). Bacterial biofilms also inhabit on or within implantable medical devices such as contact lenses, endotracheal tubes, prosthetic cardiac valves, vascular grafts, pacemakers, vascular central catheters, urinary catheters, breast implants, orthopedic implants, prosthetic joints etc. (Jefferson 2004). Thus biofilms of pathogenic bacteria formed on medical devices, human tissue organs directly affect public health and the economy.

3 Insight into conditions, development, and structure of bacterial biofilms

The process of biofilm formation is cyclic and dynamic (Jefferson 2004). Different external cues play important role in biofilm formation. Inside and outside the host body, nutrient deficiency, oxidative stress, osmotic stress, high temperature, pH change, high concentration of drugs, host immune responses etc. trigger the biofilm mode of growth in bacteria from that of planktonic mode. Slow and/or no growth of the biofilm inhabitants during such stresses allows bacterial survivability (Kırmusaoğlu 2016). On the other hand, a surplus of nutrients also promotes biofilm development as high C/N ratio enhances EPS production and biofilm formation in Pseudomonads, *Vibrio cholerae*, *Escherichia coli* and Streptococci (O'Toole et al. 2000; Jefferson et al. 2004). Here EPS acts as a reservoir of carbon sources which may serve as storage during starvation. Thus, biofilms help in the colonization of bacteria in suitable, favorable niches as well as provide support in unfavorable conditions (Jefferson 2004).

Biofilm formation starts with the initial reversible attachment of planktonic cells to biotic/abiotic surface(s). This is achieved by various non-covalent interactions such as van der Waals, electrostatic and hydrophobic interactions between bacterial cells and surface(s). Here flagella and pili assist initial attachment of bacterial cells to the surface. It is reported that rough, hydrophobic surfaces coated with various organic materials are most suitable for

initial reversible attachment (Donlan 2002). Then irreversible attachment is achieved by extracellular polymeric substances (EPS) production (Rabin et al. 2015). During irreversible attachment, several physiological and structural changes take place including non-motility of attached cells (Sauer et al. 2002). The second phase is the multiplication of bacterial cells on surfaces along with the increasing synthesis of EPS matrix. The continuous growth of sessile bacterial cells form microcolonies and achieve mushroom or pillar-shaped structures (Kaplan 2010). The biofilm matrix holds the cell mass together, acts as a structural scaffold and provides physical strength to biofilms (Rabin et al. 2015). Sometimes mature biofilms may be mono-layered consisting of cells in porous EPS or multi-layered with loosely bound micro-colonies held together in EPS matrix and intermingled with void spaces, fluid-filled channels and water channels (Chmielewski et al. 2003) which act together as circulatory system in biofilms (Kaplan 2010). eDNA is released from lyzed cells as well as actively secreted via the Type IV secretion system (Hamilton et al. 2005). eDNA plays a crucial role in biofilm attachment and adhesion (Rabin et al. 2015). Rhamnolipids help in the micro-colony formation and circulatory channel maintenance in biofilms (Pamp and Tolker-Nielsen 2007). Mostly, multi-layered biofilms have heterogeneity in terms of the spatial distribution of metabolically active cells which are resulted from diffusion limitation of nutrients, oxygen, secondary metabolites, signal molecules and antimicrobials (Jefferson 2004). Such local variation also results in the different growth rates of biofilm inhabitants with a difference in gene expression. Metabolically active fast-growing cells reside in the upper surface layer of biofilm whereas low metabolically active slow-growing cells remain in deeper parts of biofilm. Such metabolically different heterogeneous cells exhibit a wide range of responses to each antimicrobial agent and antibiotic. Some cells become dormant with no growth. These are called persistor cells (Kırmusaoğlu 2016). Persistor cells remain as disease reservoirs in biofilms which can change into infectious particles once antibiotic stresses have been removed (Rabin et al. 2015).

Biofilm dispersal is the last phase of biofilm formation. Nutrient depletion not only triggers the formation of biofilms but also leads to biofilm dispersal where detached cells search for a new source of nutrients and colonize there (O'Toole et al. 2000). Biofilm dispersion is equally important as biofilm formation in bacterial survival and dissemination behind which there are several internal as well as external factors as seen in Figure 1. Active dispersal takes place by bacteria themselves using an enzymatic breakdown of EPS matrix, biofilm substrates, central hollowing followed by seeding dispersal (Kaplan et al. 2003b; Ma et al. 2009), changes in nutrient availability, Oxygen tension, temperature and pH (Karatan and Watnick 2009). Decrease in Cyclic Diguanyl Monophosphate (c-di-GMP) downregulates EPS production and induces biofilm dispersion in several genera *viz. P. aeruginosa*, *P. fluorescence*, *Shewanella oneidensis*, *E. coli* and *Vibrio* sp. (Simm et al. 2004; Thormann et al. 2005; Morgan et al. 2006; Newell et al. 2009; Boehm et al. 2009; Yildiz and Visick 2009). Rhamnolipids are amphipathic, extracellular surfactants that reduce cohesiveness of cell to cell, cell to the matrix, and cell-surface interaction triggering central hollowing,

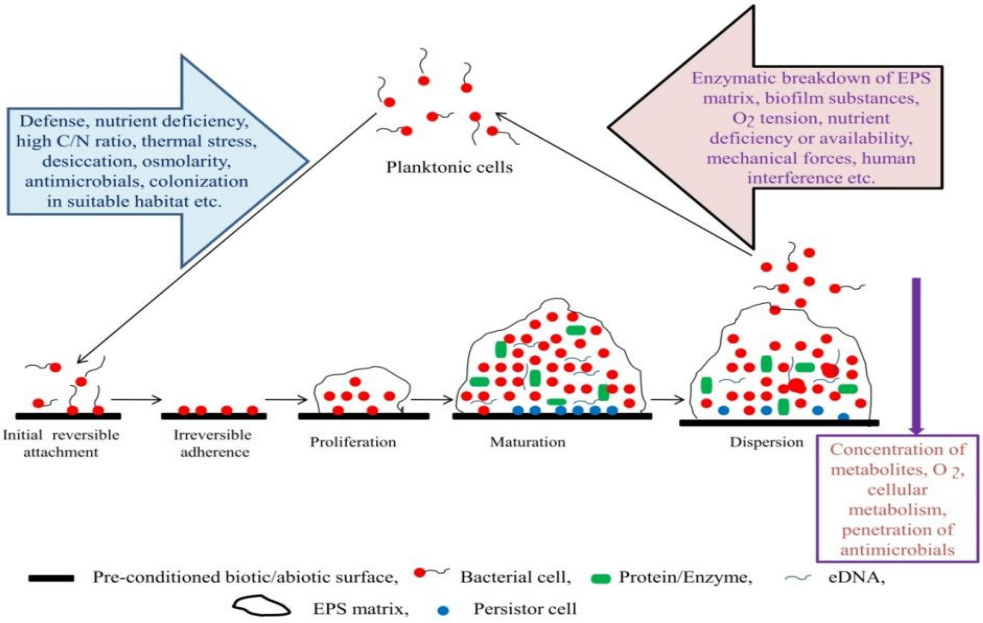


Figure 1 Different stages of biofilm formation showing the effect of various internal and external factors behind biofilm formation and dispersion along with concentration gradients of AHL during the development of biofilm

seeding dispersal and cell detachment followed by biofilm dispersion in a non-specific manner. Rhamnolipids also disrupt matrix components and form central cavities leading to biofilm dispersal (Pamp and Tolker-Nielsen 2007). Exogenous rhamnolipids are also responsible for the dispersion of biofilms in both wild-type and mutant *P. aeruginosa* (Boles et al. 2005; Dong et al. 2008). On the other hand, passive dispersion is achieved by mechanical forces like fluid shear, abrasion (collision between solid particles within biofilm), phagocytosis, increased Nitric Oxide level (due to anaerobic respiration in deeper parts) and human interferences (Kaplan 2010). The process of biofilm formation along with the responsible factors is summarized in figure 1.

4 Molecular Regulation of Bacterial Biofilm Formation

In bacteria, biofilm formation is a complex genetic process in which several genes play different functions at different times. Some genes regulate the initial adherence of bacteria to biotic/abiotic surface(s), Some genes are responsible for the development of proper biofilm architecture while few genes mediate biofilm dispersal. External cues trigger the expression of a subset of genes that initiate biofilm formation. This generates different micro-environment within biofilm that alter further gene expression leading to biofilm maturation and so on. Table 1 shows the involvement of some genes during different stages of biofilm formation.

Table 1 List of various genes and proteins along with their functions responsible for biofilm formation in bacteria

Name of the gene/protein	Function	Reference
operon, *csgDEFG and csgBA*	Curli synthesis, required for primary adherence to abiotic surfaces and formation of multilayered cell clusters in *E. coli*	Prigent-Combaret et al. 2000
Catabolite Repression Control protein (Crc)	Type IV pili synthesis in *P. aeruginosa*, primary adhesion via twitching motility	O'Toole et al. 2000
cupA gene of *cup* gene cluster	Initial adhesion of cells to inert surfaces by fimbriae in many bacteria	Vallet et al. 2001
degU, flaA, flgL motB	Flagella synthesis, flagella structure and motility in *Listeria. monocytogenes*,	Gueriri et al. 2008; Todhanakasem and Young 2008; Lemon et al. 2007
Bap protein	Surface attachment in *L. monocytogenes* and *S. aureus*	Cucarella et al. 2001; Jordan et al. 2008
relA and *hpt*	Exertion of stringent response during starvation after surface attachment in *L. monocytogenes*	Taylor et al. 2002
pel	Production of glucose-rich exopolysaccharide Pel in *P. aeruginosa* strain PA14	Friedman and Kolter 2004a
psl	Synthesis of mannose-rich exopolysaccharide Psl in *Pseudomonas aeruginosa* strains ZK2870	Friedman and Kolter 2004b
algC	Synthesis of alginates,lipopolysaccharides, Pel and Psl exopolysaccharides in *P. aeruginosa*	Ma et al. 2012
gbp	Biosynthesis of Glucan binding protein (Gbp) which maintain biofilm architecture by tight association of bacteria with EPS in *Streptococcus mutans*	Lynch et al. 2007
GbpA	Synthesis of glucosyltransferase which mediate synthesis of sucrose-dependent exopolysaccharides during biofilm formation in *Streptococcus mutans*	Loo 2003
tasA	Formation of strong insoluble fibrous protein that keep sessile cells together and helps biofilms to withstand destructive forces in *Bacillus subtilis*	Romero et al. 2010
Fap (Amyloid protein)	Induction of cell aggregation and biofilm formation in *Pseudomonas* spp	Dueholm et al. 2013
Dispersin B (DspB)	Acts as glycoside hydrolase which is EPS matrix-degrading enzyme in *Actinobacilllus actinomycetemcomitans*	Kaplan et al. 2003a
alpP	Encodes Lysine hydrolase enzyme which generates H_2O_2 leading to cell death in microcolonies followed by dispersal in *Marinomonas mediterranea, Chromobacterium violaceum*, and *Caulobacter crescentus*.	Mai-Prochnow et al. 2008
rhaAB	Production of Rhamnolipids which induce central hollowing and seeding dispersal in *P. aeruginosa*	Boles et al. 2005
RpoN (σ54)	Induces the expression of *rhlI* gene which synthesizes rhamnolipids	Heurlier et al. 2003

5 Impact of bacterial biofilm on their hosts

Bacterial biofilms have 100 to 1,000 fold higher tolerance toward antibiotics than their free-floating counterparts. Biofilms of pathogenic bacteria lead to the emergence of Multi-Drug Resistance (MDR) property among them which create serious problems in medical treatment. It is observed that the development of MDR strains of biofilm forming pathogen is due to a higher rate of lateral gene transfer in biofilms than in their planktonic counterparts (Madsen et al. 2012). Increased transfer of genes responsible for antibiotic resistance in *S. aureus* and other bacteria is reported in bio-films (Savage et al. 2013). A recent study also showed that many MDR strains of Enteroccoi, resistant to several conventional antibiotics, have biofilm forming capacity which leads to chronic infections (Haruna et al. 2022). Not only that, biofilms show high resistance to antimicrobial agents by various mechanisms. Some mechanisms of antibiotic resistance are as follows.

i. Slow growth rate and Stringent Response (Nguyen et al. 2011; Abebe 2020), local variation and heterogeneity inside biofilms (Kırmusaoğlu 2016; Abebe 2020) assist antimicrobial resistance.

ii. Biofilm-specific efflux pumps (Gills et al. 2005; Zhang and Mah 2008) lead to no penetration or very short retention of antimicrobial agents within the biofilm (Stewart and Costerton 2001; Van Acker et al. 2014).

iii. The charge of matrix polysaccharides and secreted antibiotic-degrading enzymes cause binding and/or deactivation of antibiotics (Walters et al. 2003; Bagge et al. 2004; Abebe 2020).

iv. Antibiotic resistance is also exerted by altering target sites as well as hindering the diffusion of antibiotics across the EPS matrix itself (Abebe 2020).

v. Persistor cells in the biofilm also play a significant role in tolerance to a high concentration of antibiotics as persistor cells go to a dormant stage so house-keeping processes remain completely shut off (Dufour et al. 2010).

In addition to antimicrobial resistance, bio-films exert resistance to the host immune system (Hall Stoodley and Stoodley 2009). Alginates of biofilm matrix polysaccharides restrict phagocytosis by IFN-γ-activated macrophages in *P. aeruginosa* (Leid et al. 2005) while PMN toxin *viz*. Rhamnolipid B in *P. aeruginosa* kills neutrophils (Jensen et al. 2007). Apart from bio-film mediated antimicrobial resistance, intrinsic antibiotic resistance is a well-known phenomenon in bacteria such as in *Burkholderia cepacia*. Treatment with multiple combinations of drugs is reported to kill MDR strains like *B. cepacia* isolated from cystic fibrosis patients. Although some of the tested isolates raised resistance to such combined antibiotic treatments (Dales et al. 2009). Moreover, long-term use of single or multiple combinations of antibiotics causes harmful effects on the human body. Beneficial microflora of the human body become extremely affected by such treatments. Some other side-effects of antibiotics are failure of multi-organ like liver, kidney; allergy; development of autoimmune diseases, destruction of hemoglobin etc.

6 Quorum Sensing and Role in Biofilm Formation

Biofilm formation in bacteria represents a cooperative action where inhabitants of the biofilms are interconnected to each other. It seems that they communicate and mediate structural and physiological changes accordingly. Quorum Sensing (QS) play important role in this context. QS is reported to control various stages of biofilm formation including irreversible attachment, EPS synthesis, formation of pillar-like structures and fluid channels, maturation, dispersal etc. The relationship between QS and biofilm formation in *P. aeruginosa* was studied. They showed that the *lasI/lasR* system is involved in biofilm differentiation and proper development of biofilm architecture in *P. aeruginosa* on abiotic/biotic surfaces (Davies et al. 1998). A *lasI-rhlI* double mutant strain of *P. aeruginosa*, defective in 3-oxo-C_{12} HSL and 3-oxo-C_4 HSL synthesis, respectively, showed reduced expression of *pel* gene resulting in defective unstructured biofilms. However, exogenous application of 3-oxo-C_{12} HSL restored wild-type phenotype which indicated direct involvement of AHLs in biofilm formation (Sakuragi and Kolter 2007). Another mutant study in *B. cepacia* strain H111 was done to investigate the involvement of AHLs in biofilm formation. Two mutant strains *viz*. H111-I, defective AHL synthase *cepI* (responsible for AHL synthesis) and H111-R, defective *cepR* (receptor of AHL and transcription regulator) show significantly reduced biofilm formation with defective biofilm architecture. Mutant strains H111-I and H111-R restore wild-type phenotype when supplemented with exogenous AHLs. Moreover, this study also reported that AHLs are required in biofilm maturation rather than initial attachment (Huber et al. 2001). Uropathogenic strain of *E. coli* isolated from UTI samples also showed the involvement of N-AHLs in biofilm formation (Taghadosi et al. 2015). The expression and amount of various AHL molecules in *E. coli* increased gradually along with increasing biofilm biomass and weight. AHL concentration was highest during the activation and maturation stage of biofilm development (Hu et al. 2016).

AHLs not only play important role in biofilm formation but they are also required for biofilm dispersion. Δ*lasI/rhlI* double mutant strain of *P. aeruginosa* cannot produce C_4-HSL and does not show central hollowing and seeding dispersal (Purevdorj-Gage et al. 2005). C4-HSLs promote rhamnolipid biosynthetic gene *viz. rhaA* leading to dispersal in *P. aeruginosa* PAO1 biofilm (Davey et al. 2003).

Rhamnolipds also mediate interspecies signaling pathways. The cooperation of Rhamnolipids and 3-oxo-C_{12} HSL of *P. aeruginosa* promote biofilm dispersal in *E. coli* (Bhattacharjee et al. 2016). A recent study also showed that 3-OC12-HSL significantly increased the number of persister cells in *P. aeruginosa* PAO1 during the logarithmic phase (Möker et al. 2010).

From the above-mentioned statements, it is clear that quorum sensing has a significant role in biofilm formation. In some bacteria, AHL is required for initiation of biofilm formation while some others use AHLs for biofilm maturation and/or dispersion. Although biofilm formation is a beneficial feature in bacteria, it creates a serious problem in conventional treatment particularly for biofilm-forming notorious pathogens. Biofilm formation protects them from antibiotics and antimicrobial agents by various mechanisms mentioned above. So scientists are looking for new alternative approaches which can bypass antibiotics and antimicrobials. Quorum quenching may be a trustful alternate strategy in this context. Before discussing quorum quenching, it is important to know about quorum sensing.

Quorum sensing (QS) is a cell-density-dependent synchronized program in bacteria by which bacteria respond accordingly to the changing environment to manage themselves (Fuqua and Greenberg 2002; Whitehead et al. 2001). Bacteria mediate several biological activities via quorum sensing e. g., swarming motility, aggregation, horizontal gene transfer, competence, virulence factor synthesis, antibiotic production, luminescence, biofilm formation, sporulation etc. (Fuqua and Greenberg 2002; Swift et al. 2001; Williams et al. 2007). In pathogenic bacteria, pathogenicity, production of virulence factors, secondary metabolites, exoenzymes, toxins and endospore formation are also under the control of QS. QS Signal molecules are produced and secreted by bacteria constitutively. At high cell density, bacteria sense the extracellular concentration of particular QS signaling molecules. Mostly, Auto-Inducing Peptides (AIPs) and butyro-lactones are QS signal molecules in Gram-positive bacteria while N-Acyl homosertine lactones (N-AHL) with variable acyl side chains (species specific) in Gram-negative bacteria predominantly (Whitehead et al. 2001). However, *X. campestris*, *S. typhimurium* and *S. pneumoniae* secrete DSF, AI-2 and CSF as QS signal (Hornby et al. 2001; Waters and Bassler 2005). N-acylhomoserine lactone molecules are made up of two parts: an identical homoserine lactone ring and a variable acyl side chain. Different bacteria produce a diverse array of Acyl homoserine lactones, their diversity comes from the length of the acyl side chain which may be saturated or unsaturated with or without C-3 substitution (Fuqua and Greenberg 2002; Swift et al. 2001). AHLs are synthesized by LuxI synthase and AHL receptors belong to the LuxR family of transcription regulators and are secreted by diffusion (LaSaree and Federle 2013).

7 Quorum Quenching

Quorum quenching is the counter-acting mechanism to interrupt QS-mediated activities. Interference with quorum sensing may result in the prevention of desired phenotypes without imposing selective pressure on them. As QS-mediated activities are not associated with bacterial house-keeping machinery, so, biofilm formation and pathogenicity can be managed by QQ (Lade et al. 2014). Quorum quenching agents inhibit some particular traits in bacteria that are not house-keeping processes, so bacteria don't need to overcome the inhibitory action of quorum quenching agents. The chance of getting resistance against them is less. However, some reports are also available about resistance against quorum quenching.

7.1 Quorum quenching Agents

Quorum quenching agents are broadly categorized into two classes: quorum sensing inhibitors (QSIs) and quorum quenching enzymes (QQEs). QSIs disrupt QS by competitive inhibition, antagonism, mimicry of QS signal molecules or by interfering in QS signal synthesis, secretion and perception (Grandclément et al. 2016). The first reported QSI was halogenated furanone obtained from *Delisea pulchra* (Givskov et al. 1996). QQEs cleave/or modify the QS signal molecules. AiiA (Lactonase) is the first reported quorum quenching enzyme from *Bacillus* sp. 240B (Dong et al. 2000). As quorum quenching enzymes act in the extracellular environment without entering the cell, the tendency of getting resistant is less likely than QSIs which either interact within cells or on the cell surface. Although QQ enzymes are less stable they make their application limited (Lu et al. 2021).

7.1.1 Quorum sensing inhibitors (QSIs)

There are several types of Quorum sensing inhibitors (QSIs) isolated from different bacteria. Halogenated furanone of *Delisea pulchra* inhibits QS-mediated swarming and surface colonization by *Serratia liquefaciens* (Givskov et al. 1996). In *E. coli*, swarming motility and biofilm formation was inhibited by (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2-(5H)-furanone (Ren et al. 2001). Recently 3-methyl-2(5H)-furanone and 2′-hydroxycinnamic acid are reported to inhibit biofilm formation in *K. pneumonia* ATCC 13884 up to 67.38% and 65.06% respectively. Further experiments showed that these compounds irreversibly affect the adhesion phase of the *K. pneumonia* ATCC 1388 (Cadavid and Echeverri 2019). Embeline and piperine inhibited the biofilm formation in *Streptococcus mutans* by interfering with signal perception involved in the QS pathway (Dwivedi and Singh 2016). 2, 6-Di-*tert*-butyl-4-methylphenol (DTBMP) was isolated from marine cyanobacterium *Chroococcus turgidus.* DTBMP effectively inhibited the bioluminescence in *V. harveyi* while biofilm related other

virulence characteristics such as exopolysaccharide production, hydrophobicity index, swimming and swarming motility in three major pathogenic vibrios: *V. harveyi*, *V. parahaemolyticus* and *V. vulnificus* were also inhibited by DTBMP (Santhakumari et al. 2018). Some QSIs which are produced by extremophilic and mesophilic bacteria are represented in Table 2 below.

7.1.2 Quorum quenching enzymes

Quorum quenching enzymes include AHL-lactonase, AHL-acylase and oxidoreductase (Fetzner 2015). AHL-lactonase and acylase chemically degrade the ester linkage of lactone ring and amide bond of Acyl homoserine lactone, respectively. However, the

Table 2 Example of some QSIs with their producer organisms

Quencher bacteria	QSIs	Reference
Marine bacterium *Halobacillus salinus*	N-(2'-phenylethyl)-butyramide	Teasdale et al. 2009
	3-methyl-N-(2'-phenylethyl)-butyramide	
Hexane, Dichloroethane, and Butanol extracts of *Marinobacter* sp. SK-3 and *Halomonas* sp. SK-1	Cyclo-(L-Pro-L-Phe) [DKP]	Abed et al. 2013
	Cyclo-(L-Pro-L-Leu) [DKP	
	Cyclo-(L-Pro-L-isoLeu) [DKP]	
	Cyclo-(L-Pro-D-Phe) [DKP]	
Staphylococcus delphini	N-(2'-phenylethyl)-urea	Chu et al. 2013
	N-[2-(1H-indol-3-yl)ethyl]-urea	
Rheinheimera aquimaris QSI02	Cyclo(Trp-Ser (diketopiperazine factor)	Sun et al. 2016
Oceanobacillus sp. XC22919	2-methyl-N-(2′-phenylethyl) butyramide	Chen et al. 2019
	3-methyl-N-(2′-phenylethyl)-butyramide	
	benzyl benzoate	
Vibrio neptunius	3-Methyl-*N*-(2′-Phenylethyl)-Butyramide	Meschwitz et al. 2019

Table 3 Name of some quorum quenching enzymes reported from mesophilic bacteria

Rhodococcus erythropolis W2	Oxidoreductase and acylase	Both oxidoreductase and amidolytic activity, degradation of short-chain AHLs, reduction of pathogenicity of *Pectobacterium carotovorum* in potato tubers.	Uroz et al. 2005
Shewanella sp. MIB015	AHL acylase	Degradation of long acyl AHLs, heterologous expression in fish pathogen *Vibrio anguillarum* reduced biofilm formation.	Morohoshi et al. 2008
P. aeruginosa PAO1	PvdQ (AHL-acylase)	*P. aeruginosa* virulence in *C. elegans*, swarming and production of elastase, pyocyanin were significantly reduced by PvdQ	Huang et al. 2003; Papaioannou et al. 2009
Bacillus sp. A196	$AiiA_{A196}$ Lactonase (thermostable)	Highest activity at 10 ºC-40 º C at pH 8.0, also stable at 70 º C for 1hr, resistance to proteases and carp intestinal juices, oral administration of $AiiA_{A196}$ in Zebrafish attenuated infection of *Aeromonas hydrophila.*	Cao et al. 2012
B. licheniformis DAHB1	AiiA lactonase	Inhibit of severe Gastroenteritis disease and mortality of Indian white shrimps infected by *Vibrio parahaemolyticus* DAHB1, resistance to acidic intestinal juice, and proteases of the shrimps which make it effective to be used in shrimp aquaculture.	Vinoj et al. 2014
Alteromonas stellipolaris PQQ-42	Ahl lactonase	Prevention of AHL accumulation, production of chitinase, protease, and swirming motility in many *Vibrio* spp. in a fish hatchery, reduction of the tissue damage of the coral *Oculina patagonica* infected with aquaculture pathogen *V. mediterranei* Vibc-Oc-097.	Torres et al. 2016
Kurthia huakui LAM0618^T	AiiK lactonase	Heterologous expression of AiiK exhibited variable substrate spectrum, resistance to great resistance to α-chymotrypsin protease K and trypsin. AiiK significantly inhibited biofilm formation and attenuated extracellular proteolytic activity, pyocyanin synthesis of *P. aeruginosa* PAO1	Dong et al. 2018
Bosea sp. F3-2	AidB lactonase	Thermostability up to 80ºC, maximum enzymatic activity at 60ºC. Heterologous expression attenuates pyocyanin production and pathogenicity in *P. aeruginosa* and *P. carotovora*, respectively	Zhang et al. 2019

enzyme oxidoreductase chemically modifies the AHL without degradation (Liu et al. 2017). These enzymes are very effective against QS-mediated gene expression. Many AHL-lactonase, acylase and oxidoreductase enzymes have been reported from mesophilic as well as extremophilic bacteria. Only a few of them possess both AHL-lactonase and AHL-acylase enzymes as in *Deinococcus radiodurans*, *Photorhabdus luminescens*, *Hyphomonas neptunium* and *Rhodococcus erythropolis* W2 (Kalia et al. 2011). Many reported QQ enzymes can effectively degrade AHLs and attenuate the virulence of pathogenic bacteria. Some quorum quenching mesophilic bacteria, their QQ enzyme, and quorum quenching properties are presented in table 3.

Although a lot of Quorum quenching enzymes are reported by various laboratories, the potentiality of enzymes can be limited by cost, activity level or compatibility with recent biotechnological and industrial plants (Rémy et al. 2016). The exploitation of extremozymes has, therefore, achieved a considerable interest to fulfill the requisites such as tolerance in high temperatures, pH stability, production optimization, wide solvent range etc. (Mayer et al. 2015). There are few reports on the quorum quenching enzymes isolated from halophiles and thermophiles which show high affectivity. Some of these quorum quenching extremozymes are listed below in Table 4.

Actinomycetous bacteria are also reported to possess quorum quenching activity. For example, marine Actinomycete strain A66 extracts were observed to reduce biofilm formation in *V. harveyi* at a concentration of 2.5% (v/v). Strain A66 reduced the number of microcolonies and attenuated biofilm architecture. It was found

Table 4 Name of some quorum quenching enzymes reported from extremophilic microorganisms

Sulfolobus islandicus (Hyperthermophilic archaeon)	sisLac lactonase	Member of Phosphotriesterase like Lactonase (PLL) family, optimum pH and temperature 7 to 10 and 85°C, respectively, preference for medium length (C8, C10) of acyl chain AHLs,	Hiblot et al. 2012
Sulfolobus solfataricus (hyperthermophilic archaeon)	SsoPox lactonase	Member of PLL family, a bifunctional enzyme with organophosphate hydrolase and PLL Lactonase, reduction of virulence factor, elastase pyocyanin production in *P. aeruginosa* by SsoPox –Lactonase	Ng et al. 2011
Thalassomonas sp. PP2-459 (Marine)	Qqenzyme other than lactonase	Reduction of AHLs with different acyl chains in *Halomonas anticariensis* FP35^T and aquaculture pathogen *V. anguillarum* ATCC 1926^T	Torres et al. 2013
Tenacibaculum sp. Strain 20J	AHL lactonase	Member of phosphotriesterase (PTE) family, a cell-bound soluble AHL-lactonase having the capacity to degrade both short and long-chain Ahls. reduction of pathogenicity of the fish pathogen *Edwardsiella tarda* ACC 35.1 which otherwise causes Septicaemia Edwardsiellosis.	Romero et al. 2014
Tenacibaculum sp. 20J (marine bacterium)	Aii20J lactonase (thermostable)	Unspecified and broad substrate range, retention of activity at 80 ° C, pH range 3-9, resistance to protease K and alpha-chymotrypsin, reduction of cell viability, and glutamate-dependent acid resistance in *E. coli* K-12.	Mayer et al. 2015
P. flavipulchra JG1	PfmA acylase	Degradation of AHLs with long side chain, reduction of production virulence facts (protease, pyocyanin) in *Vibrio anguillarum* VIB72 and *P. aeruginosa* PAO1. PfmA also increased the survivality of *Artemia* sp. (model animal) infected with *P. aeruginosa*.	Liu et al. 2017
Salinicola salaria MCCC1A01339 (halophilic bacterium)	AhlX lactonase	Highly stable, broad substrate specificity, ~100% activity at 60ºC after 2 hr incubation, retention of 60% activity at 25% NaCl, dried AhlX powder generated by a spray-dry process at 80-120ºC temperature reduced infection of *Erwinia carotovora* on potato slices and Chinese cabbage.	Liu et al. 2019
Stenotrophomonas maltophilia	QQ enzyme	Inhibition of AHL accumulation, reduction by enzymatic activity in *Pectobacterium carotovorum* CECT 225^T and *Vibrio coralliilyticus* VibC-Oc-193 in the co-cultivation experiment. Reduction in potato tuber maceration and mortality of *Artemia salina* by *P. carotovorum* and *V. coralliilyticus*, respectively.	Reina et al. 2019
Psychrobacter strain M9-54-1	AhaP Acylase	Wide range of unsubstituted and substituted AHLs (C4-HSL to C14-HSL) at 4°C, 15°C, and 28°C. Reduction of swarming motility and cytotoxic galactophilic lectin synthesis in *P. aeruginosa* PAO1. Decrease in mortality of brine shrimps infected by *Vibrio coralliilyticus* VibC-Oc-193	Reina et al. 2021
Reinheimera aquimaris, Acinetobacter junii, Pseudomonas sihuiensis, Ruegeria atlantica and *Microbulbifer echini*	QQ enzyme other than AHL Lactonase	Degradation of all AHLs in *Vibrio coralliilyticus* along with a reduction in virulence factors synthesis increased survivality of *Artemia salina*	Reina et al. 2022

that strain A66 inhibited the *Vibrio* biofilm formation at both the initiation and maturation stages. At a concentration of 2.5% (v/v), the inhibition rate of crude extract was 99.3% while the degradation rate was 75.6% (You et al. 2007). Quorum quenching activity is also reported in Coral Associated Bacteria (CAB). Crude extract of *B. horikoshii* (E6), isolated from the coral *Acropora digitifera* restricted biofilm formation in clinical M serotypes of *S. pyogenes* at very low concentrations [10–50 µg mL^{-1}] (Thenmozhi et al. 2009). In another study, *Bacillus firmus* and *Vibrio parahemolyticus* which were isolated from *Acropora digitifera*, have shown quorum quenching activity against Methicillin-Resistant *S. aureus* (MRSA) and Methicillin Susceptible *S. aureus* (MSSA). *B. firmus* and *V. parahemolyticus* significantly reduced the synthesis of EPS and hemolysin which resulted in inhibition of biofilms (80–87%) formed by both MRSA and MSSA. Furthermore, CAB extracts strongly decreased Cell Surface Hydrophobicity (CSH) of *S. aureus* which mediates adherence of the bacteria to substrata during biofilm formation (Gowrishankar et al. 2012).

7.1.3 Application of QQ Bacteria

Nowadays application of crude QQ enzymes on pathogenic bacteria and medical devices has been reported to attenuate biofilm formation. Immobilization of SsoPox Lactonase enzyme isolated from thermophilic archaeon *Sulfolobus solfataricus* onto the nano alumina membrane showed increased activity up to 25% as compared to control set. Application of Membrane immobilized SsoPox reduced pyocyanin synthesis and elastase activity when added to *P. aeruginosa* PAO1 culture (Ng et al. 2011). Catheter functionalization was investigated using a silicon catheter coated with AHL Acylase of *Aspergillus melleus*. Adhesion of *P. aeruginosa* ATCC 10145 was strongly inhibited in comparison to the control set. Moreover, biofilm formation was also reduced up to 50% in acylase-coated catheters (Ivanova et al. 2015a). The combination of acylase and amylase on multi-layer coatings of urinary catheters reduced biofilm formation in *P. aeruginosa* and *S. aureus*, respectively (Ivanova et al. 2015b). Immobilization of quorum quenching bacteria was done in magnetic nanocomposite beads (IMN) and significant degradation of C6-HSL was achieved (Kaur and Yogalakshmi 2022). Another study showed that QSIs restricted antibiotic-induced resistance mutation in *E. coli* which indicated combination of QSIs and antibiotics may be effective to inhibit bacterial growth (Ning et al. 2021).

8 Alternate strategy for inhibition of biofilm formation

8.1 Use of Bacteriophages

There are some other regulatory factors regarding biofilm formation in bacteria apart from quorum sensing. Second messengers like c-di-GMP and cAMP mediate different physiological processes during biofilm formation (Ha and O'Toole 2015; Sutrina et al. 2015; Jenal et al. 2017; Sutrina et al. 2019). Regarding such factors, quorum quenching may not be the sole weapon for controlling biofilm formation. Engineered T7 phage showed a reduction of bacterial count in *E. coli* biofilm when polysaccharide degrading enzyme, Depolymerase gene *dspB* was incorporated within its genome (Lu et al. 2007). Another engineered T7 phage containing AHL Lactonase gene *aiia* (derived from *B. anthracis*) showed effective degradations of AHLs in many bacteria along with effective cell lysis in the specific host (Pei and Lamas-Samanamud 2014). Sometimes cocktails of phages targeting various cell receptors, have been used to prevent phage resistance (Chan et al. 2013; Pires et al. 2017) as some reports showed re-growth of single phage-treated bacterial biofilms (Pires et al. 2017; Tan et al. 2019). A combination of phage and antibiotics is another way to get rid of phage-resistant host variants (Verma et al. 2009). Although bacteriophages cannot be used in human, animal as well as commercial aspects due to a lack of regulations (Fauconnier 2017) and license (Ferriol-González and Domingo-Calap 2020). Treatment of single Bacteriophages as well as bacteriophage cocktails have been used in medical devices such as urinary catheters and ultra-specific host bacteria (Curtin and Donlan 2006; Goldman et al. 2009; Fu et al. 2010).

8.2 Use of EPS matrix-degrading enzymes

Enzymatic breakdown of biofilm matrix is another approach to control bacterial biofilms. Cellulase enzymes obtained from *A. niger* (C1184-Sigma Aldrich) as well as partially purified Cellulase enzyme of *Bacillus* sp. DGV19 (EU053862.1) has significantly reduced biofilm formation in *Burholderia cepacia* on sterile discs made up of polyvinyl chloride (PVC), polystyrene, glass slides and polycarbonate (Rajasekharan and Ramesh 2013). Another experiment showed that an extracellular α-amylase isolated from marine bacteria *Bacillus subtilis* S8-18 not only inhibited biofilm formation but also degraded pre-formed mature biofilms of Methicillin-Resistant *S. aureus* (MRSA), *P. aeruginosa* and *V. cholerae* (Kalpana et al., 2012). Further 1:1 mixture of commercially purchased cellulase and amylase enzymes reduced EPS biomass of *S. aureus* and *P. aeruginosa* monoculture and co-culture biofilms making the biofilm more susceptible to conventional antimicrobial agents as well as increasing the release of lanktonic cells from biofilms both *in vitro* and *in vivo* (Fleming et al. 2017). Alginate lyase, Lysostaphin and Dispersin B also showed effective inhibition of biofilms of various pathogenic bacteria when treated alone or in combination with antibiotics (Alkawash et al. 2006; Donelli et al. 2007; Kolkai et al. 2009). DNase and proteases have also capability to break down EPS matrix components as well (Eckhart et al. 2007; Saggu et al. 2019).

Conclusion

Biofilm formation, particularly in pathogenic bacteria has appeared as a threatening problem in conventional treatment. Disruption of QS-mediated biofilm formation in pathogenic bacteria, therefore, may show a trustful alternate strategy to control this particular feature instead of the application of excess antibiotics. Many QSIs and QQ enzymes are reported from mesophilic as well as extremophilic microorganisms which can attenuate QS signals, biofilm formation, virulence, pathogenicity etc. of pathogenic bacteria *in vitro* conditions. Recent experiments have been done to control biofilm formation in medical devices which otherwise cause further infection of patients. Apart from quorum quenching, other strategies such as phage therapy, enzymatic breakdown of EPS matrix etc. are also effective to combat the problem of biofilm formation in pathogenic bacteria. The application of these strategies may control biofilms of pathogens actively. A combination of QSIs or QQ enzymes with EPS degrading enzymes may be used in aquaculture to manage QS-mediated bacterial infection. QQ bacteria may also be used as probiotics or as food supplements which may improve disease management and survivality of organisms in aquaculture. Though bacteriophages can't be used in humans and animals for their inherent allergenicity; a combination of bacteriophages with EPS degrading enzymes or QQ enzymes may be used in membrane bioreactors during wastewater management to combat bio-fouling. On the other hand, quorum quenching enzymes along with EPS degrading enzymes can be immobilized on medical devices to attenuate medical device-associated diseases in hospitals. Purified QQ enzymes or their heterologous expression in probiotic bacteria can be used in pharmaceutical industries for the production of new medicines as well. Thus, quorum quenching may a suitable tool for the treatment of MDR pathogenic strains as well as biofilm-forming bacteria in various fields where biofilms create serious problems to handle. Exploration of quorum quenching enzymes with a better biotechnological application can lead to novel techniques in wastewater management, aquaculture, agriculture and most importantly conventional chemotherapy in medical science.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding information

This work is supported by the Council of Scientific & Industrial Research (CSIR), Government of India.

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